Magnetic Resonance Imaging-Guided Laser Thermal Ventral Capsulotomy for Intractable Obsessive-Compulsive Disorder

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BACKGROUND: Obsessive-compulsive disorder (OCD) is a disabling condition characterized by intrusive thoughts and repetitive behaviors. A subset of individuals have severe, treatment-resistant illness and are nonresponsive to medication or behavioral therapies. Without response to conventional therapeutic options, surgical intervention becomes an appropriate consideration.

OBJECTIVE: To report clinical outcomes and the safety profile of bilateral ventral anterior capsulotomy for OCD using magnetic resonance (MR)-guided laser interstitial thermal therapy (LITT) in 10 patients followed for 6 to 24 mo.

METHODS: A total of 10 patients underwent LITT for severe OCD; 1 patient withdrew prior to follow-up. LITT is a minimally invasive ablative technique performed with precise targeting and use of thermography under MR guidance. Lesions of the ventral anterior limb of the internal capsule by other techniques have been shown to be efficacious in prior studies.

RESULTS: A total of 7 of the 9 patients were considered full responders (77.8%; Yale-Brown Obsessive-Compulsive Scale change ≥35%). Adverse effects included transient apathy/amotivation postsurgery (2 patients). One patient had a small tract hemorrhage where the laser fiber traversed the cerebral cortex as well as persistent insomnia postsurgery. One individual died after a drug overdose 7 mo postsurgery, which was judged unrelated to the surgery.

CONCLUSION: LITT ventral capsulotomy was generally well tolerated, with promising evidence of effectiveness in the largest such series to date. Results were comparable to those after gamma knife ventral capsulotomy, as well as ventral anterior limb deep brain stimulation.

KEY WORDS: Obsessive-compulsive disorder, Psychiatric neurosurgery, Magnetic resonance imaging, Capsulotomy, Lesion, Ablation

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Obsessive-compulsive disorder (OCD) is a chronic condition characterized by intrusive thoughts (obsessions) and repetitive behaviors (compulsions). The estimated lifetime prevalence is 2.3%.[1] Medical therapy with serotonin reuptake inhibitors and cognitive behavioral therapy are the first-line treatments.[2-11] Despite adequate treatment, only 39% of patients enter full or partial remission in long-term follow-up.[12] For a carefully selected subset of individuals with documented nonresponse to standard treatments,[13,14] surgical intervention should be considered.

Neurosurgery for OCD was developed empirically against a historic paucity of

ABBREVIATIONS: GAF, Global Assessment of Functioning; **GKVC,** gamma knife ventral capsulotomy; **IC,** internal capsule; **LITT,** laser interstitial thermal therapy; **LVC,** LITT ventral capsulotomy; **MADRS,** Montgomery-Asberg Depression Rating Scale; **MNI,** MontrealNeurological Institute; **OCD,** obsessive-compulsive disorder; **RF,** radiofrequency; **SOFAS,** Social and Occupational Functioning Assessment Scale; **YBOCS,** Yale-Brown Obsessive-Compulsive Scale

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efficacious medical and psychotherapeutic interventions. The advent and maturation of OCD surgery is inseparable from the history of stereotactic neurosurgery and its undertaking to more precisely localize targets and minimize lesion volume, thereby reducing adverse effects.[15] The pathoanatomic models of OCD that emerged later, implicating thalamocortical and thalamostriatal networks, are concordant with empirically derived surgical targets.[16-22] Our initial work hypothesized that a single bilateral lesion of the pathways in the anterior limb of the internal capsule (IC) that connected the medial and orbital frontal cortex, the head of the caudate, and the midline thalamus would be efficacious. However, after an initial series of 15 patients, it became clear that a slightly larger bilateral lesion targeting the bottom third of the IC would be necessary for improved outcomes.[23]

Surgical technique can be divided into ablation and electrical neuromodulation (eg, deep brain stimulation; DBS). Within the first category, radiofrequency (RF) anterior capsulotomy or cingulotomy offers patients with refractory OCD a full or partial response in two-thirds of cases.[24] The largest series examining lesions for intractable OCD using noninvasive stereotactic gamma radiation was reported by our group with similar results.[23] However, radiation-induced lesions are less predictable than thermally induced lesions, such as by RF or laser thermal energy. There is also potential for longer term side effects related to high-dose radiation exposure in a relatively young sample. Our prior work has demonstrated the risk for radiation-induced cysts.[23] We therefore sought to understand whether laser thermal lesions were a viable approach in this population.

Laser interstitial thermal therapy (LITT) is a minimally invasive ablative technique performed with precise stereotactic targeting and near-real-time magnetic resonance imaging (MRI) guidance and thermography. Compared to RF thermal lesions, LITT lesions appear to have different morphology, with more distinct boundaries.[25] Therefore, a simple extrapolation of prior RF lesion experience to LITT may or may not be appropriate. Currently, LITT is most widely applied to epilepsy and brain tumors.[26-28] Anterior cingulotomy using LITT has been reported for chronic pain.[29,30] An initial open-label report[31] found that 4 OCD patients improved by 3 mo after LITT ventral capsulotomy (LVC). We report here the largest series with longer follow-up, after LVC.

METHODS

Patients

A total of 10 patients with intractable OCD underwent LVC. A total of 6 patients had never received neurosurgery, and 3 had received a prior single-shot gamma knife ventral capsulotomy (GKVC), which had proven ineffective. In 1 patient, double-shot GKVC was followed by durable improvement and later resurgence of severe OCD. One individual with prior GKVC refused follow-up and was therefore excluded. The study was approved by the Institutional Review Board (IRB), allowing for the use of clinical records and neuroimaging for research. All participants gave written informed consent.

Inclusion/Exclusion Criteria

Patients underwent extensive review through our program's Psychiatric Neurosurgery Program, as part of the clinical standard of care for treatment of severe, treatment-resistant OCD. All patients were referred by their local treating clinician. Review included extensive psychiatric and medical records. After initial record collection, patients received a baseline in-person screening. Patients were between 18 and 70 yr of age, judged to have severe, treatment-resistant OCD, had undergone documented trials of pharmacological and exposure/response prevention treatments without adequate benefit, and were medically healthy. Patients were selected for surgery by the Psychiatric Neurosurgery Committee, consisting of a psychiatrist, a neuropsychologist, a neurologist, a behavior therapist, a neurosurgeon, and a community representative. The members of the neurosurgery treatment team advised this group, but did not make the final decision.

Measures

Outcome measures were either administered by a licensed psychologist or a trained assistant, either in person or over the telephone. Measures were administered at baseline, 3, 6, 12, and 24 mo postsurgery. Assessments included the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition,[32] Yale-Brown Obsessive-Compulsive Scale (YBOCS),[33,34] YBOCS Symptom Checklist,[35] Global Assessment of Functioning (GAF),[36] Social and Occupational Functioning Assessment Scale (SOFAS),[37] Montgomery-Asberg Depression Rating Scale (MADRS),[38] Hamilton Depression Rating Scale,[39] Hamilton Anxiety Rating Scale,[40] Beck Depression Inventory,[41] and Beck Anxiety Inventory.[42]

Surgical Procedure

Patients underwent a 2-stage procedure consisting of fiducial placement followed by lesion approximately 10 d later. Surgical planning was undertaken using FHC Waypoint Software (FHC Inc, Bowdoin, Maine). A computed tomography (CT) with fiducials in-place was merged with a preoperative MRI and planning was performed using T1 postcontrast and T2 images. Targets were the bilateral ventral anterior ICs about 8 to 10 mm anterior to the posterior border of the anterior commissure, the same location previously used for GKVC.[23] Targeting was based upon the visualized structure of the IC on MRI. For patients with prior lesions, the lesion was expanded in the coronal plane of the IC, to ultimately ablate the bottom third of the capsule. All new patients were targeted to lesion the bottom third of the IC in the coronal plane.

Patients were brought to the operating room and positioned within an intraoperative CT scanner (AIRO, BrainLab AG, Munich, Germany). After induction of general anesthesia, a three-dimensional (3D) printed stereotactic platform (Star-Fix, FHC Inc) was affixed to the fiducials, 3.2 mm burr holes were made using a drill guide inserted into the platform, and fiber optic catheters (Visualase, 3 mm circumferential aperture, Medtronic Inc, Dublin, Ireland) were introduced bilaterally through guides in the platform. CT scan (registered to preoperative MRI) was then obtained to confirm catheter placements.

Patients were transported to an extraoperative MRI scanner (1.5T Magnetom Espree, Siemens Healthcare GmbH, Erlangen, Germany). Patients were positioned within the scanner and the fiber optic catheters were connected to fiber optic cables as well as a pumped saline cooling circuit. Background anatomic images were obtained to demonstrate the precise position of the catheters in the coronal plane, and sagittal or axial planes. These were registered to magnetic resonance (MR) thermometry images on the Medtronic Visualase control system.

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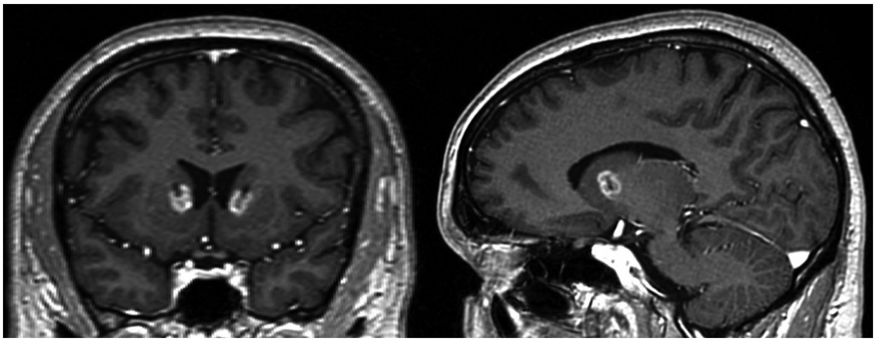

FIGURE 1. *Immediate postoperative T1 postcontrast coronal (left) and sagittal (right) images.*

TABLE 1. Demographic and YBOCS Outcome Information for All Participants

Patient	Age	Comorbid diagnoses	Gender	Baseline YBOCS	3 mo	6 mo	9 mo	12 mo	24 mo	% YBOCS change at the time of last follow-up	Responder classification
Repeated surgeries[a]											
1	53	MDD, GAD, PTSD (past)	M	36	33	38	36	–	–	0	Non
2	42	MDD, GAD, dysthymia	M	32	20	18	23	21	14	−56.25	Full
3	67	MDD	F	30	–	17	–	–	–	−43.44	Full
Initial surgeries											
4	29	Persistent DD, SUD (past), AUD (past)	M	30	11	14	–	–	–	−53.33	Full
5	28	MDD, social phobia	F	33	–	21	18	29	21	−36.36	Full
6	46	MDD, GAD	F	32	31	29	33	–	–	3.125	Non
7	21	Excoriation, mood DD, ADHD	M	36	29	28	30	22	–	−38.89	Full
8	39	MDD, PTSD (past)	F	31	25	14	–	17	–	−45.16	Full
9	23	MDD, OCPD	F	26	14	12	11	7	–	−73.08	Full

[a] Repeated surgeries include patients who have had prior gamma knife capsulotomy with insufficient response.
MDD = major depressive disorder, GAD = Generalized Anxiety Disorder; PTSD = Post-Traumatic Stress Disorder; Persistent DD = Persistent Depressive Disorder, SUD = Substance Use Disorder; AUD = Alcohol Use Disorder; Mood DD = Mood Dysregulation Disorder; ADHD = Attention Deficit Hyperactivity Disorder; OCPD = Obsessive-Compulsive Personality Disorder.

Full laser power was set to 10 watts. A test dose was given briefly using 15% to 25% of this power while continuous MR thermometry was performed (6 s intervals between acquisitions) in order to visualize location, shape, and spread of heat. As noted above, targeting was based on the anatomic visualization of the IC in the coronal plane, along the length of the catheter. Once the location of the base of the catheter was determined to be appropriate within the bottom third of the IC, a lesion was created using 25% to 60% laser power. A lesion estimate was generated to guide the application of laser power and laser-on time.[43] Adjustments to catheter position were made by manually advancing or withdrawing, in order to ablate the bottom third of the IC.

Once the lesion estimates were deemed sufficient (ie, bottom third of the IC was ablated), postlesion scans were obtained using Diffusion Weighted Imaging and T1 postcontrast sequences. An example of a postablation image is presented in Figure 1. To identify lesions, postablation T1 postcontrast images were coregistered to surgical planning images and exported to AFNI.[44,45] To account for procedure-related brain shift, postcontrast postablation T1 images were nonlinearly warped to preoperative T1 images. Lesions were delineated by calculating the voxel intensity difference between preoperative T1 and postablation T1 postcontrast images. Voxels immediately adjacent to the fiber optic catheter that were ≥85th percentile of intensity difference values were considered lesioned voxels. Thus, the "active" lesion was the new lesion for all patients, not including any prior historical lesion. To "fill in" the catheter artifact, lesion voxels were padded by 10 voxels and then eroded by 10 voxels. Lesion volumes were calculated by multiplying the number

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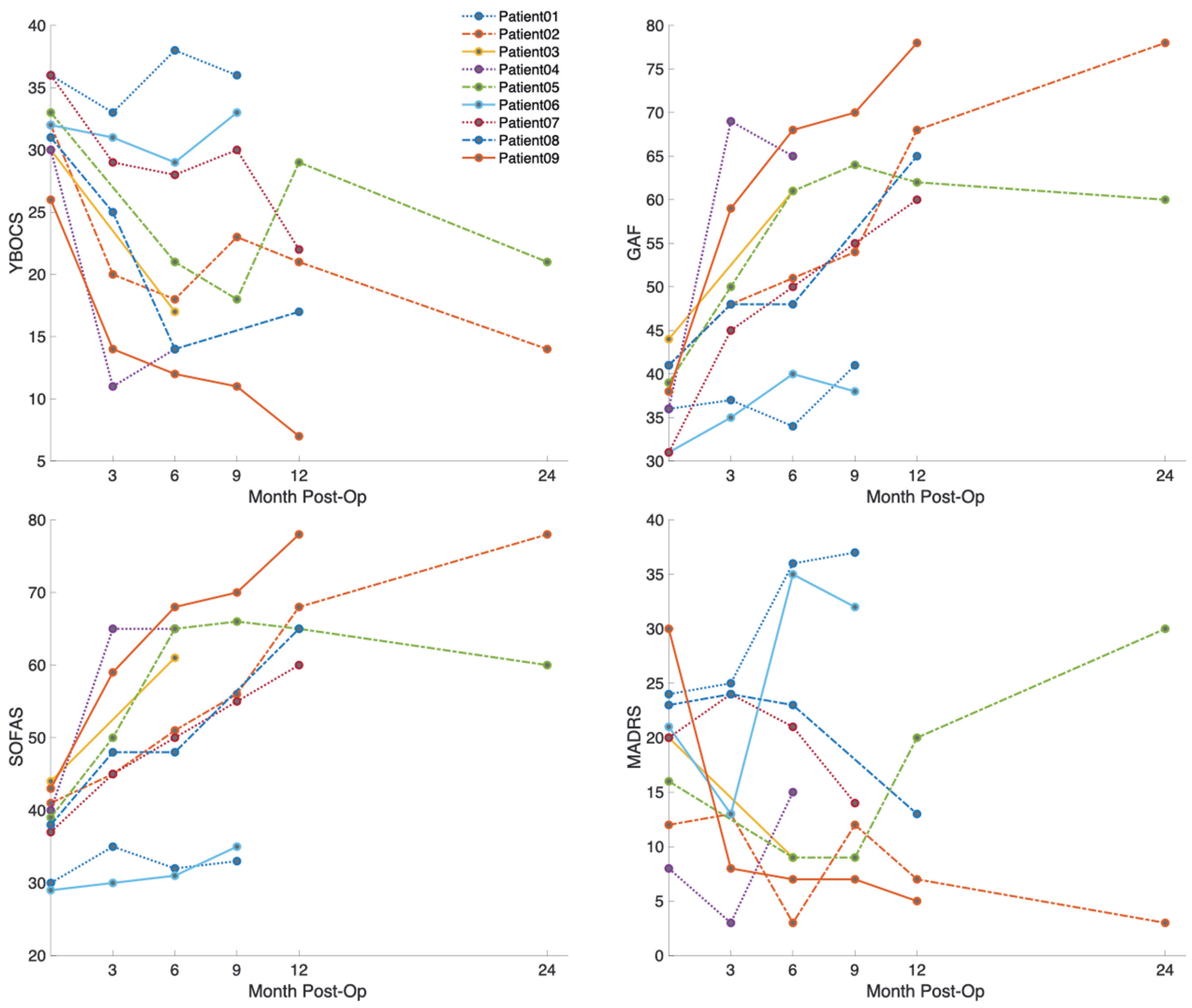

FIGURE 2. *Line graphs plotting change over time for OCD symptomology (YBOCS), general functioning (GAF, SOFAS), and depression (MADRS).*

of lesion voxels by the volume of each voxel. Lesions from previous procedures were not highlighted by contrast, and not included in total lesion volumes. For 5 participants, T1 images acquired 1 yr after surgery were coregistered to the surgical plan as described above. Because brain shift was not present in these images, postoperative T1 images only underwent additional linear coregistration with preoperative T1 images. Lesions were delineated by the same method as above. Postoperative lesion voxel clusters that overlapped with the coregistered postablation lesion were manually selected to ensure lesion volume corresponded to the LITT procedure.

To examine lesions across patients, preoperative T1 volumes were nonlinearly warped to a standard Montreal Neurological Institute (MNI) brain. Resulting warps were applied to each patient's lesion volumes. Individual YBOCS change was plotted separately at voxels corresponding to their lesion in MNI space. Average YBOCS change across patients was computed per voxel by dividing each voxel's summed YBOCS change data by the number of overlapping lesions present.

RESULTS

Behavioral Outcomes

Formal statistical analyses of clinical outcomes were not completed due to the small sample size; only descriptive analyses are reported here for those variables. See Table 1 for demographic and outcome information, and Figure 2 for line graphs of individual participants. At last follow-up, 7 of the 9 patients were

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TABLE 2. Lesion Size and Location Directly and 1 yr After Laser Ablation. Patients 1 to 3 Had Repeated Lesions, Patients 4 to 9 Had New Lesions. Coordinates Are in Native Space, Relative to the Midcommissural Point

		Immediate postoperative lesions				1 yr postoperative lesions			
Patient	Side	x	y	z	Volume (mm³)	x	y	z	Volume (mm³)
Patient 1	L	15.8	−22.3	0.2	601				
	R	12.6	−25.1	−1.3	397				
Patient 2	L	13.3	−18.2	6.9	739.5	13.9	−20.8	1.3	35
	R	13.2	−18.8	5.0	643.8	14.1	−20.1	1.9	29.2
Patient 3	L	15.2	−22.4	5.9	173.5				
	R	15	−18.8	4.4	451				
Patient 4	L	14.7	−24.4	1.7	278				
	R	14.3	−23.2	4.8	461				
Patient 5	L	10	−23.2	5.2	314	11.1	−22.5	4.1	71
	R	10.2	−23.5	4.5	350.2	9.8	−22.8	2.9	71
Patient 6	L	12.3	−22.5	7.2	889.5				
	R	9.9	−23.6	7.8	410.5				
Patient 7	L	11.1	−21.8	0.6	268.8	14.7	−22.8	2.4	162.8
	R	11	−21.4	3.8	333.2	11.3	−21	3.7	60
Patient 8	L	8.9	−21.9	1.1	491.5	11.2	−21.1	1.1	115.2
	R	8.2	−24.5	3.3	329.2	10.8	−22.5	3.6	64.5
Patient 9	L	11.2	−24.4	0.5	630.2	12.8	−24.1	−1.2	89.8
	R	10.2	−21.5	0.8	844.2	10.8	−19.7	0.4	141

considered full responders (77.8%; defined as YBOCS decrease of ≥35%). Baseline YBOCS score was a mean of 31.8, with a mean at last follow-up of 20.1, for an average YBOCS decrease of 36.7%.

Adverse Events

In all cases, bilateral capsulotomies were formed using a 3 mm laser window aperture, and there were no apparent surgical complications. A total of 2 individuals reported transient apathy/amotivation for several weeks postsurgery. One patient developed persistent insomnia, and the same individual had a small hemorrhage at the LITT fiber insertion point. One patient, despite a year of abstinence before surgery, died at 7 mo postop after recurrence of illicit substance use. This was considered a recurrence of a prior condition and unlikely to be the result of surgery.

Lesion Size and Placement Immediately and 12 Months Postsurgery

Immediately postsurgery (n = 9), mean left side lesion size (see Table 2) was 487.33 mm^3 (standard deviation—SD = 244.64; range 173.5-889.5 mm^3), and mean right side lesion size was 468.90 mm^3 (SD = 170.45; range 329.2-844.2 mm^3). Approximately 12 mo postsurgery (n = 5), mean left side lesion size (see Table 2) was 94.76 mm^3 (SD = 47.98; range 35.0-162.8 mm^3), and mean right side lesion size was 73.14 mm^3 (SD = 41.19; range 29.2-141.0 mm^3).

Pearson correlations were carried out; there were no correlations between YBOCS change and lesion size for either time point. Location was in the ventral portion of the anterior limb of the IC, as targeted (see Figure 3). Immediately postsurgery (n = 9; Figure 3A and 3B), left lesions had a peak overlap MNI coordinate of (x: +13, y: −11, z: −4) while the peak MNI coordinate of right lesions was (x: −11, y: −11, z: −3). Approximately 12 mo postsurgery (n = 5; Figure 3C and 3D), left lesions had a peak overlap MNI coordinate of (x: +14, y: −9, z: −4), while the peak MNI coordinate of right lesions was (x: −13, y: −10, z: −2). For voxels in MNI space with ≥2 overlapping lesions, average YBOCS change was plotted over anatomy.

DISCUSSION

We present 9 participants followed for 6 to 24 mo after LITT for rigorously defined intractable OCD. Outcomes in this study were comparable to other studies of DBS or lesions for treatment-resistant OCD. Here, 77.8% of the participants were full responders, and 22.2% had no meaningful change in YBOCS OCD severity. Adverse effects included transient apathy/amotivation postsurgery. In addition, new-onset persistent insomnia arose in a patient who had a small hemorrhage at the LITT fiber insertion point. One individual, with a prior history of substance abuse, died after an illicit substance overdose 7 mo postsurgery, an event deemed unlikely to be related to surgery. As with prior studies, particularly with GKVC, there is variability in clinical response. This variability is likely related to the typical waxing and waning course of OCD, as well as delays in response that are likely related to behavioral adjustment after surgery. In addition, many patients who are surgical

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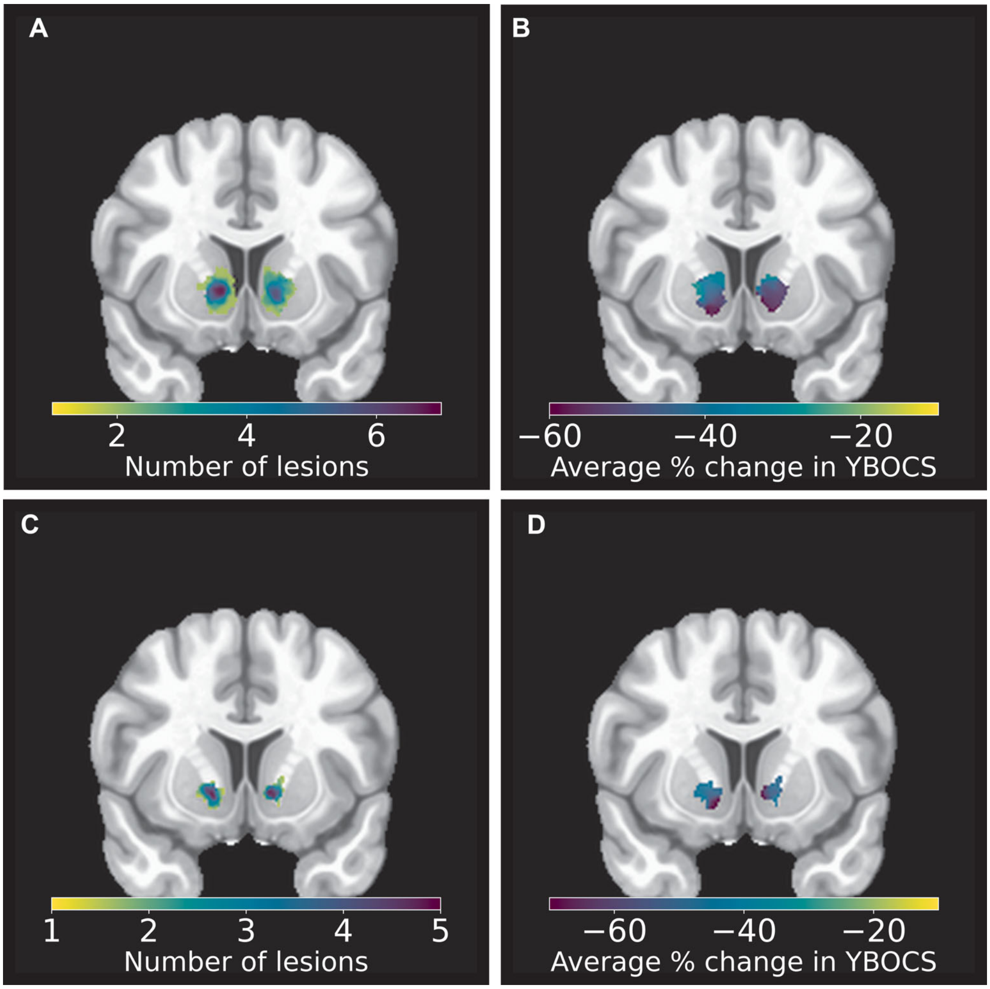

FIGURE 3. *Lesion overlaps in MNI space.* **A**, *Immediate lesion density for all 9 patients. Coronal plane shown is 11 mm anterior of the anterior commissure (midpoint of left and right peak lesion densities).* **B**, *Average change in YBOCS for voxels with ≥2 overlapping lesions. Voxels displayed are flattened to the same coronal plane as* **A**. **C**, *12-mo postoperative lesion density for 5 patients. Voxels are flattened to the same coronal plane as* **A** *and* **B**. **D**, *Average change in YBOCS for postoperative lesions. Because of the lower number of lesions, all voxels are displayed. Voxels are flattened on the same coronal plane as* **A**, **B**, *and* **C**.

candidates have experienced severe symptoms for many years, even decades, which has impacted their overall functioning. In the current study, there was a mean YBOCS decrease of 36.7% from baseline to longest follow-up. However, based on prior studies, we may expect improvement with continued follow-up. Though there may be improvements in symptoms after surgery, it may take months or even years to overcome delays in social and occupational functions.

Our group began using GKVC for refractory OCD in 1993.[23] Given relatively wide variation in radiobiological response and resulting lesion formation across individuals and the small but notable risk of delayed adverse effects of high-dose radiation in this relatively young population, we decided to explore the option of laser thermal lesions. LITT has the advantage over RF lesions of being able to clearly see the target, and obtain a lesion estimate through a heat map. Disadvantages of LITT include the requirement for placing a fiber optic catheter directly into the target via a burr hole, and confinement to a linear trajectory for lesion creation. Laser ablation is also an invasive procedure performed under general anesthesia, conferring uncommon but real risks related to hemorrhage and anesthetic complications. During this study, 1 participant had a small hemorrhage near the insertion point. Despite anticipated advantages of the laser thermal modality, we nevertheless observed some variation in lesion size, though magnitude of variation in comparison to other surgical procedures is unknown. This is likely attributable

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to several factors, including (1) a limited portion of the linear trajectory intersecting with the intended white matter target in some cases; (2) potentially limited accuracy of the Arrhenius model of thermal ablation that is used to estimate the final lesion size during the procedure; (3) though minimal, variation in the timing of the postlesion MRI, which may influence the immediate appearance of the lesions; and (4) relatively less surgical experience and comfort with this approach. Given technical software limitations, there is no way to directly compare targeted lesion size with final lesion size. Whether variability impacted therapeutic efficacy is unclear given the lack of observed relationship between lesion size and the YBOCS, albeit in this small case series. In addition, there may be evolution of lesion size months or even years postsurgery, and may be borne out with continued imaging follow-up.

Patients with refractory OCD also have the option to undergo DBS. However, while DBS has potential advantages related to adjustability and (to a certain extent) reversibility, lesions remain a valuable option for patients for several reasons. Patients often travel to distant, experienced centers for psychiatric neurosurgery; when they return home, there may not be local expertise available to manage a DBS system, especially for a less common psychiatric indication. Additionally, the adjustability of DBS—while regarded initially as an advantage—may in fact be a drawback when there are no presently proven biomarkers for therapeutic effect and where natural fluctuations in symptoms may create an unstable feedback loop where clinicians and patients find themselves in a frustrating cycle of programming adjustments and delayed evaluation without a clear biological endpoint. Lastly, the efficacy of lesions for OCD has generally been similar to DBS, so a procedure that does not entail the risks, potential discomfort, and continued maintenance and costs associated with indwelling devices may be preferable in some cases.

CONCLUSION

Overall, we found laser thermal capsulotomy to be a safe and potentially effective therapy for intractable, debilitating OCD. Clinical outcomes were comparable to prior studies of GKVC, as well as DBS for OCD. Additional refinement of trajectories and lesioning technique may improve outcomes. A controlled trial using larger patient samples and longer-term follow-up of these patients will be necessary to establish overall efficacy, particularly for comparison with other forms of capsulotomy.

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Disclosures

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COMMENT

The authors present the largest single-institution experience with laser thermal capsulotomy for treatment of medically-refractory obsessive compulsive disorder; the documented symptomatic improvement and procedural safety appear to be same or better compared to other modalities, including deep brain stimulation, radiofrequency thermal ablation and radiosurgical lesioning.

In our (very limited; n = 10) experience with surgical OCD management, the patients would either choose approach that does not destroy brain tissue (DBS) or one that does not require creation of "holes in the skull" (radiosurgery), and the choice between perceived invasiveness and reversibility of effect appeared to be quite challenging for most patients to make.

The advantage of direct visualization of the thermal lesion with MR-thermography may prove to be clinically meaningful, and therefore one may only hope that this pioneering experience facilitates development of even less invasive surgical interventions (such as focused ultrasound) that combine such visualization with elimination of the need in skull drilling and advancing the cannulas toward the target.

I congratulate the authors with their great results and look forward to seeing longer follow up and larger clinical series.

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