Original Investigation

# Gamma Ventral Capsulotomy for Obsessive-Compulsive Disorder
## A Randomized Clinical Trial

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**IMPORTANCE** Select cases of intractable obsessive-compulsive disorder (OCD) have undergone neurosurgical ablation for more than half a century. However, to our knowledge, there have been no randomized clinical trials of such procedures for the treatment of any psychiatric disorder.

**OBJECTIVE** To determine the efficacy and safety of a radiosurgery (gamma ventral capsulotomy [GVC]) for intractable OCD.

**DESIGN, SETTING, AND PARTICIPANTS** In a double-blind, placebo-controlled, randomized clinical trial, 16 patients with intractable OCD were randomized to active (n = 8) or sham (n = 8) GVC. Blinding was maintained for 12 months. After unblinding, sham-group patients were offered active GVC.

**INTERVENTIONS** Patients randomized to active GVC had 2 distinct isocenters on each side irradiated at the ventral border of the anterior limb of the internal capsule. The patients randomized to sham GVC received simulated radiosurgery using the same equipment.

**MAIN OUTCOMES AND MEASURES** Scores on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) and the Clinical Global Impression-Improvement (CGI-I) Scale. Response was defined as a 35% or greater reduction in Y-BOCS severity and "improved" or "much improved" CGI-I ratings.

**RESULTS** Three of 8 patients randomized to active treatment responded at 12 months, while none of the 8 sham-GVC patients responded (absolute risk reduction, 0.375; 95% CI, 0.04-0.71). At 12 months, OCD symptom improvement was significantly higher in the active-GVC group than in the sham group (Y-BOCS, $P = .046$; Dimensional Y-BOCS, $P = .01$). At 54 months, 2 additional patients in the active group had become responders. Of the 4 sham-GVC patients who later received active GVC, 2 responded by post-GVC month 12. The most serious adverse event was an asymptomatic radiation-induced cyst in 1 patient.

**CONCLUSIONS AND RELEVANCE** Gamma ventral capsulotomy benefitted patients with otherwise intractable OCD and thus appears to be an alternative to deep-brain stimulation in selected cases. Given the risks inherent in any psychiatric neurosurgery, such procedures should be conducted at specialized centers.

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Obsessive-compulsive disorder (OCD) has a lifetime prevalence of 2% to 3% in the general population.[1] A small proportion of patients with OCD have chronic, severe, and disabling symptoms, despite all available conventional treatments.[1,2] For such individuals, psychiatric neurosurgery remained an option. For more than 5 decades, ablation (typically cingulotomy or capsulotomy) has been most used. In uncontrolled trials and case reports, these ablations yielded treatment efficacy of 22% to 76% and 40% to 80%, respectively.[3-7]

The recent emergence of deep-brain stimulation (DBS) has garnered considerable attention, with open series and small randomized clinical trials, typically of DBS of the ventral internal capsule, suggesting benefit.[8-10] Although DBS has advantages (eg, reversibility, individualized stimulation parameters, and faster treatment responses) over its ablative counterparts, experience shows that ablation is comparatively less expensive and imposes a less burdensome follow-up regimen on patients over the long term. Therefore, studies of ablative techniques remain needed. In particular, gamma ventral capsulotomy (GVC), applied at Brown University, the University of Pittsburgh, and the University of Virginia, represents a refinement of the noninvasive Gamma Knife radiosurgery first used at the Karolinska Institute in 1976 that originally included a larger lesion within the internal capsule.[7,11-13] In an open pilot study conducted at the University of São Paulo, 5 patients with intractable OCD underwent GVC. After a 3-year follow-up period, 3 of 5 patients were classified as full responders and 1 was classified as a partial responder, with none of the patients having experienced any serious adverse events.[14,15] Here, we present the results of a double-blind, placebo-controlled, randomized clinical trial of GVC designed to evaluate the efficacy and safety of the technique.

## Methods

The study was approved by the research ethics committees of the University of São Paulo School of Medicine and the Institute of Neurological Radiosurgery, Santa Paula Hospital, as well as by the Brazilian National Commission of Research Ethics. All patients gave written informed consent in sessions that were recorded on video and later reviewed by an independent review panel appointed by the Regional Medical Board of São Paulo. The review panel confirmed the appropriateness of the surgical intervention and that patients adequately understood the risks and benefits associated with the study.[16]

### Participants

The criteria for inclusion, exclusion, and refractoriness are described in eTable 1 in the Supplement. All of the patients selected had a primary diagnosis of OCD according to the *DSM-IV*.[17] Detailed history taking from previous medical records, clinicians, and family revealed that the patients selected had gained minimal or no benefits from previous treatments for OCD. All patients had a history of treatment with multiple pharmacologic approaches at maximum doses (eg, clomipramine hydrochloride, 300 mg/d; fluoxetine hydrochloride, 80 mg/d; paroxetine hydrochloride, 60 mg/d; sertraline hydrochloride, 200 mg/d; and fluovoxamine maleate, 300 mg/d). They also had attended at least 20 sessions of cognitive-behavioral therapy (involving exposure and response prevention techniques), without lasting improvement (**Table 1**). The appropriateness of their previous pharmacologic and cognitive-behavioral therapy regimens was verified by a psychiatrist (A.C.L.) and by a behavior therapist (M.E.M.) (eAppendix 1 in the Supplement).

### Randomization and Masking

A statistician used sampling selection with the statistical software NCSS PASS 2008 to generate the randomization list. We randomly assigned patients, in blocks of 4, to 1 of 2 groups: active treatment (ATa), in which patients underwent GVC, and sham treatment (ST), in which patients underwent a sham procedure (**Figure 1**).

Radiosurgical planning (placing the radiosurgical targets on each patient's magnetic resonance images [MRIs] in stereotactic space with the GammaPlan software) was done the day before surgery. Only the radiosurgical team (a neurosurgeon, a radiotherapist, a physicist, and a nurse) had access to the randomization status of each patient immediately before the beginning of the radiosurgical procedures, when patients were already sedated. For the sham group, the total duration of the sham surgery was calculated based on the patient's gamma planning. Just after each procedure, patients were sent to a postoperative surgical ward, whose medical team was blind to the allocation status of every patient. Patients were discharged from the hospital the day after surgery. The psychiatric team and all outcome raters were not allowed to assist the radiosurgical procedures and they had no access to the medical records at Santa Paula Hospital.

Patients and investigators were blinded for the first 12 months of follow-up, after which the ST-group patients were given the option of receiving AT. The group of patients that opted to undergo GVC was designated the ATb group. Changes to medication regimens were not allowed in the month preceding surgery and were allowed during the follow-up period only if strictly necessary. All patients were encouraged to participate in 20 sessions of cognitive-behavioral therapy at the third month after surgery.

### Procedures

A stereotactic frame was attached to the patient's head, following which axial and coronal MRI scans were obtained for target localization and dose planning. Targets were defined at the ventral portions of the anterior limb of the internal capsule, 7 to 10 mm rostral to the posterior border of the anterior commissure. Prior to each surgery, calculations were made by 3 of the authors (a neurosurgeon and 2 psychiatrists) and reviewed by another 2 (a psychiatrist and a neurosurgeon). We used a double-shot technique, in which 2 distinct isocenters were planned and irradiated on each side of the midline (2 on 1 hemisphere and then 2 on the other hemisphere, in this sequence). The targets were irradiated by cross-firing 201 collimated converging beams of gamma radiation, with the intended volume of necrosis defined by the 50% isodose line and

Table 1. Baseline Demographic and Clinical Features of the Patients Selected

| Patient Statistic | Age, y | Age at OCS Onset, y | Duration of OCD, y | Treatment History | | | Y-BOCS Score | Follow-up, mo | Comorbidities | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | No. of Medications | No. of SRIs | No. of CBT Trials | | | Other Axis I Disorders | Axis II Disorders |
| ST1[a,b,c,d,e] | 34 | 22 | 8 | 14 | 8 | 1 | 37 | NA | MDD (recurrent) | OCPD, histrionic PerD |
| ST2[a,b,e,f,g] | 43 | 17 | 20 | 13 | 5 | 1 | 38 | 24 | MDD (single episode), PD (without agoraphobia) | None |
| ST3[b,e,f,h,i] | 25 | 12 | 10 | 16 | 7 | 1 | 32 | NA | MDD (single episode), SocPh, BDD, BED | Borderline PerD, OCPD |
| ST4[b,e,h,j,k] | 53 | 13 | 38 | 12 | 4 | 1 | 32 | NA | MDD (recurrent), AD (complete remission), SpecPh, GAD | OCPD |
| ST5[b,e,f,g,h] | 38 | 9 | 29 | 12 | 4 | 1 | 38 | NA | None | Avoidant PerD |
| ST6[b,f,h,i,l] | 26 | 14 | 9 | 7 | 3 | 1 | 32 | 12 | MDD (single episode), alcohol abuse (complete remission) | Avoidant PerD, OCPD |
| ST7[b,d,f,h,l] | 24 | 11 | 13 | 15 | 7 | 2 | 40 | 45 | MDD (single episode), GAD | None |
| ST8[a,b,f,k,l] | 30 | 20 | 10 | 16 | 4 | 2 | 29 | 30 | Psychotic disorder NOS (past), trichotillomania | Dependent PerD, OCPD, paranoid PerD |
| ATa1[a,b,c,i,m] | 34 | 21 | 13 | 19 | 7 | 1 | 35 | 86 | MDD (recurrent) | OCPD |
| ATa2[b,f,h,i,l] | 26 | 13 | 7 | 16 | 6 | 1 | 30 | 56 | MDD (recurrent), GAD | None |
| ATa3[b,c,g,h,m] | 35 | 11 | 24 | 9 | 5 | 1 | 30 | 48 | None | None |
| ATa4[e,f,h,i,n] | 34 | 6 | 20 | 14 | 5 | 1 | 31 | 72 | MDD (recurrent), SocPh | Avoidant PerD, OCPD |
| ATa5[a,b,d,e,j] | 55 | 7 | 40 | 12 | 5 | 2 | 36 | 55 | MDD (single episode) | OCPD |
| ATa6[b,e,f,h,i] | 21 | 15 | 5 | 15 | 7 | 2 | 30 | 56 | None | Dependent PerD |
| ATa7[a,b,e,f,i] | 24 | 17 | 7 | 4 | 3 | 1 | 32 | 51 | MDD (single episode), GAD | OCPD |
| ATa8[b,f,g,h,l] | 28 | 5 | 15 | 9 | 3 | 1 | 36 | 12 | MDD (single episode), SocPh, BDD, IED | Avoidant PerD, OCPD, paranoid PerD |
| ST group, median | 32 | 13.5 | 11.5 | 13.5 | 4.5 | 1 | 34.5 | | | |
| Mean (SD) | 34.1 (10.1) | 14.8 (4.5) | 17.1 (11.0) | 13.1 (2.9) | 5.3 (1.8) | 1.3 (0.5) | 34.8 (4.0) | | | |
| ATa group, median | 31 | 12 | 14 | 13 | 5 | 1 | 31.5 | | | |
| Mean (SD) | 32.1 (10.6) | 11.9 (5.7) | 16.4 (11.6) | 12.3 (4.8) | 5.1 (1.6) | 1.3 (0.5) | 32.5 (2.7) | | | |
| *P* value | .71 | .75 | .61 | .79 | >.99 | >.99 | .17 | | | |

Abbreviations: AD, alcohol dependence; ATa, active treatment (blinded phase); BDD, body dysmorphic disorder; BED, binge-eating disorder; CBT, cognitive-behavioral therapy; GAD, generalized anxiety disorder; IED, intermittent explosive disorder; MDD, major depressive disorder; NA, not applicable; NOS, not otherwise specified; OCD, obsessive-compulsive disorder; OCPD, obsessive-compulsive personality disorder; OCS, obsessive-compulsive symptoms; PD, panic disorder; PerD, personality disorder; SocPh, social phobia; SpecPh, specific phobia; SRIs, serotonin reuptake inhibitors; ST, sham treatment; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale.

[a] Female.

[b] White.

[c] Married.

[d] Education level = college, discontinued.

[e] Unemployed.

[f] Single.

[g] University educated.

[h] Male.

[i] High school educated.

[j] Divorced.

[k] Education level = high school, discontinued.

[l] Not in the labor force.

[m] Employed.

[n] Mixed race/ethnicity.

a maximum dose of 180 Gy at the 100% point, using 4-mm collimators, in a Gamma Knife model B (Elekta Inc).

In the ATa group, double bilateral lesions were created. Patients in the ST group received simulated radiosurgery with a fake treatment chamber attached to the front of the Gamma Knife unit (eFigure 1 in the Supplement). This was done to ensure blinding, despite the fact that all of the patients were sedated throughout the procedure. For ST patients, the shield-

ing doors of the Gamma Knife were kept closed during the entire procedure.

### Outcome Measures

Patients were systematically assessed by blinded raters in the first year and by unblinded raters thereafter. Assessments were made prior to the procedure and at postprocedure week 2, as well as at postprocedure months 1, 2, 3, 6, 9, and 12. Thereafter, patients were assessed at least once a year, if possible. Assessment instruments included the Structured Clinical Interview for *DSM-IV* Axis I Disorders,[17] the Structured Interview for *DSM-IV* Personality,[18] the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS),[19] the Dimensional Y-BOCS (DY-BOCS),[20] the Beck Anxiety Inventory (BAI),[21] the Beck Depression Inventory (BDI),[22] the Clinical Global Impression-Improvement,[23] the Global Assessment of Functioning scales,[17] the Systematic Assessment for Treatment Emergent Events scale,[24] and the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36).[25] Prior to the procedures and 12 months later, all patients underwent neuropsychological testing (eTable 2 in the Supplement). Response was defined as a 35% or greater reduction in the Y-BOCS score (relative to the baseline score) and a Clinical Global Impression-Improvement rating of 1 ("very much improved") or 2 ("much improved").

### Statistical Analysis

Last observation carried forward was the primary imputation method because of the small samples. We also conducted sensitivity analyses for the main outcome measures. The variables were summarized using descriptive statistics. For age, age at OCD diagnosis, duration of OCD in years, and initial Y-BOCS scores, we used the Mann-Whitney *U* Test.

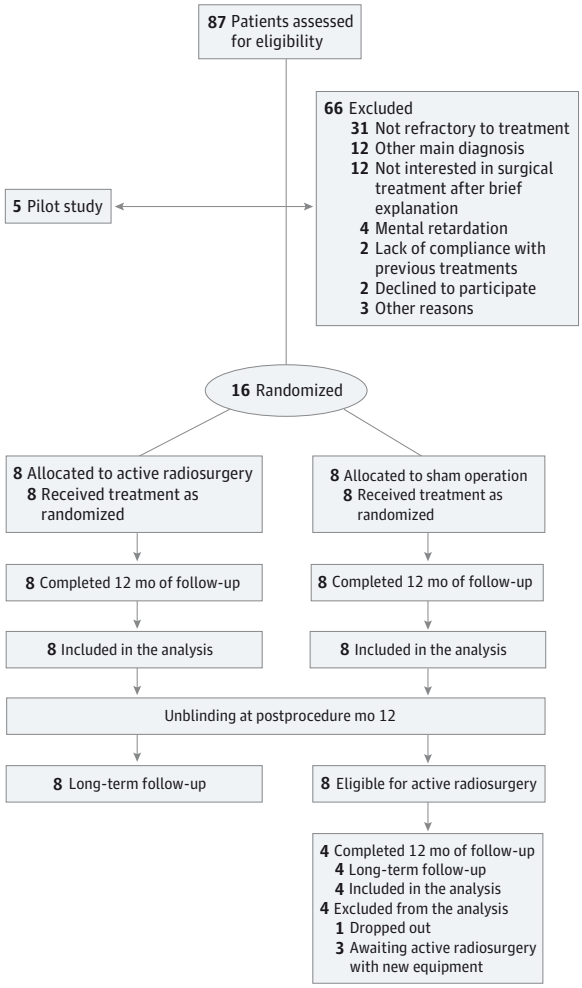
For the ATa and ST groups, beta distributions (normalized likelihoods) were determined for the frequency of no improvement at postprocedure month 12 (Clinical Global Impression-Improvement score >2) and for the probability that there was a difference between the frequencies of these groups.[26] We performed longitudinal analysis considering the postoperative gain (percentage of change) in comparison with the initial measurements, using the Wilcoxon rank sum test, for the following outcome measures: Y-BOCS, DY-BOCS, BAI, BDI, Global Assessment of Functioning, and SF-36 domain scores. In terms of neuropsychologic performance, independent group comparisons (ST vs ATa) were analyzed by the Mann-Whitney *U* test, whereas paired-group comparisons (preoperative vs postoperative scores) were made using the Wilcoxon signed rank test. Values of $P < .05$ were considered statistically significant.

## Results

### Clinical Features

Between 2004 and 2008, we evaluated 87 patients with intractable OCD but only 21 met our criteria for surgery (Figure 1). The first 5 patients were enrolled in an open pilot study.[14] The remaining 16 were subsequently included in the present trial. Demographic data are summarized in Table 1. Groups were similar for sex, marital status, level of education, occupation, age, age at onset of obsessive-compulsive symptoms (OCS), and duration of OCD. The median number of medication trials was 13.0 and 13.5 in the ATa and ST groups, respectively (Table 1).

Figure 1. CONSORT Diagram of Sham and Active Treatment Groups




### Double-Blind Phase

Information regarding the integrity of the blinding can be found in the Supplement (eTables 3 and 4). During the 12-month blinded phase, 3 of 8 patients (37.5%) in the ATa group (patients ATa3, ATa6, and ATa7) met response criteria, whereas there were no responders in the ST group (**Table 2**; eTable 5 in the Supplement), giving an absolute risk reduction of 0.375 (95% CI, 0.04-0.71) or a number needed to treat of 2.667 (95% CI, 1.408-25.303). Beta distributions[26] indicated an 87.6% higher probability of no improvement in the ST group than in the ATa group and statistically significant differences between the groups in terms of total Y-BOCS and DY-BOCS scores ($P = .046$ and $P = .01$, respectively; **Figure 2**; Tables 2, **3**, and **4**; eFigures 2 and 3 in the Supplement). A subitem of the DY-BOCS (OCD impairment scores) was also significantly lower in the ATa group ($P = .02$). Sensitivity analysis demonstrated that only with a worst-case-scenario imputation (ie, if all ST-group patients dropped out and achieved remission and all ATa-group

Table 2. Y-BOCS Scores, CGI-I Scores, and Response Status at 12 Months After Sham or Active Gamma Ventral Capsulotomy and at the Most Recent Assessment after Gamma Ventral Capsulotomy

| Patient, Statistic | Preoperative Y-BOCS | Postoperative Month 12 | | | | Follow-up, mo | Most Recent Assessment | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Y-BOCS | Decrease, % | CGI-I | Response Status | | Y-BOCS | Decrease, % | CGI-I | Response Status |
| ST1[a] | 37 | 35 | 5.4 | 4 | Nonresponder | NA | NA | NA | NA | NA |
| ST2 | 38 | 30 | 21.1 | 3 | Nonresponder | 24 | 32 | 15.8 | 4 | Nonresponder |
| ST3[a] | 32 | 32 | 0.0 | 5 | Nonresponder | NA | NA | NA | NA | NA |
| ST4[a] | 32 | 30 | 6.3 | 4 | Nonresponder | NA | NA | NA | NA | NA |
| ST5[a] | 38 | 40 | −5.3 | 4 | Nonresponder | NA | NA | NA | NA | NA |
| ST6 | 32 | 29 | 9.4 | 3 | Nonresponder | 12 | 29 | 9.4 | 3 | Nonresponder |
| ST7 | 40 | 27 | 32.5 | 3 | Nonresponder | 45 | 36 | 10 | 4 | Nonresponder |
| ST8 | 29 | 32 | −10.3 | 4 | Nonresponder | 30 | 29 | 0 | 4 | Nonresponder |
| ATa1 | 35 | 28 | 20.0 | 3 | Nonresponder | 86 | 14 | 60.0 | 2 | Responder |
| ATa2 | 30 | 16 | 46.7 | 3 | Nonresponder | 56 | 11 | 63.3 | 3 | Nonresponder |
| ATa3 | 36 | 22 | 38.9 | 2 | Responder | 48 | 10 | 72.2 | 1 | Responder |
| ATa4 | 31 | 30 | 3.2 | 3 | Nonresponder | 72 | 20 | 35.5 | 2 | Responder |
| ATa5 | 36 | 25 | 30.6 | 3 | Nonresponder | 55 | 32 | 11.1 | 3 | Nonresponder |
| ATa6 | 30 | 1 | 96.7 | 1 | Responder | 56 | 12 | 60.0 | 1 | Responder |
| ATa7 | 32 | 11 | 65.6 | 2 | Responder | 51 | 9 | 71.9 | 1 | Responder |
| ATa8 | 36 | 34 | 5.6 | 5 | Nonresponder | 12 | 34 | 5.6 | 5 | Nonresponder |
| ATb1 | 35 | 0 | 100.0 | 1 | Responder | 82 | 0 | 100.0 | 1 | Responder |
| ATb3 | 32 | 32 | 0.0 | 4 | Nonresponder | 67 | 0 | 100.0 | 1 | Responder |
| ATb4 | 30 | 23 | 23.3 | 3 | Nonresponder | 65 | 25 | 43.3 | 3 | Nonresponder |
| ATb5 | 40 | 40 | 0.0 | 4 | Nonresponder | 12 | 40 | 0.0 | 4 | Nonresponder |
| ST group, median | 34.5 | 31 | 5.8 | 4 | | | | | | |
| Mean (SD) | 34.8 (4.0) | 31.9 (4.1) | 7.4 (13.9) | 3.8 (0.7) | | | | | | |
| ATa group, median | 33.5 | 23.5 | 34.7 | 3 | | | 13 | 60.0 | 2 | |
| Mean (SD) | 33.3 (2.8) | 20.9 (11.0) | 38.4 (31.4) | 2.8 (1.2) | | | 17.8 (10.0) | 47.4 (26.7) | 2.3 (1.4) | |
| *P* value[b] | | | .046 | | | | | | | |
| ATb group, median | 33.5 | 27.5 | 11.7 | 3.5 | | | 12.5 | 71.7 | 2 | |
| Mean (SD) | 34.3 (4.3) | 23.8 (17.3) | 30.8 (47.4) | 3.0 (1.4) | | | 16.3 (19.7) | 60.8 (48.6) | 2.3 (1.5) | |

Abbreviations: ATa, active treatment (blinded phase); ATb, active treatment (of former sham treatment–group patients, unblinded phase); CGI-I, Clinical Global Impression-Improvement Scale; NA, not applicable; ST, sham treatment; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale.

[a] Ultimately (after unblinding) became ATb.

[b] ST group vs ATa group.

patients dropped out and had no improvement) the results would not be significant for the observed difference between groups.

At month 12, the active and sham groups did not differ statistically in terms of anxiety (BAI) ($P = .46$) and depression (BDI) ($P = .17$), as seen in Tables 3 and 4. In 3 ATa-group patients (ATa2, ATa4, and ATa8), BDI scores worsened after 12 months of follow-up. Those same 3 patients were nonresponders at postoperative month 12. Consequently, the mean BDI scores at month 12 tended to be higher in the ATa group than in the ST group. Furthermore, there were no statistically significant differences between the ST and ATa groups in the SF-36 scores.

## Secondary Active Treatment

After unblinding, 7 of 8 ST-group patients opted to receive active treatment. Four of 7 subsequently underwent GVC (the previously designated patients ST1, ST3, ST4, and ST5 became ATb1, ATb3, ATb4, and ATb5, respectively). The patient ATb1 became a responder at post-GVC month 6.

## Open Long-term Follow-up

For the ATa and the ST/ATb groups, the mean duration of follow-up was 54.5 and 56.5 months, respectively. Two patients (ATa8 and ATb5) declined long-term assessments. Three patients who were initially nonresponders (ATa4, ATa1, and ATb4) subsequently became responders during the long-term follow-up (at post-GVC months 14, 24, and 36, respectively). All responders retained that status at their most recent follow-up visits. Ultimately, 5 of 8 patients (62.5%) in the ATa group became responders, as did 2 of 4 patients (50%) in the ATb group (eTable 5 in the Supplement). They were also generally less impaired in terms of social functioning at the most recent follow-up (eTable 6 in the Supplement). Among the pa-

tients who did not receive active GVC, OCD remained refractory to treatment in all cases (mean [SD] follow-up, 29.5 [17.2] months).

Some medication changes were needed during the double-blind and the open long-term follow-up phases mostly owing to increasing levels of depression and nonspecific anxiety or after medication-related adverse events (the Supplement provides details). However, changes were similar between the groups and they did not seem to have significantly influenced the response to treatment (eTable 7 in the Supplement).

As to postoperative MRI scans, patient ATb4 exhibited an unusually brisk reaction to GVC, whereas patient ATa8 (a nonresponder) showed only small lesions at month 12 (details in the Author Material). Other patients demonstrated adequately conformed lesions (eFigure 4 in the Supplement).

### Safety

As seen in **Table 5**, most adverse events were transient. However, after the double-blind phase, 2 patients (ATa5 and ATb4) with a history of subclinical hypomanic symptoms subsequently developed manic episodes (at post-GVC months 3 and 9, respectively), which were controlled by adding mood stabilizers to the treatment regimens. Another patient (ATb1) developed drug dependence 4 years after surgery, although she had no history of drug abuse. The most serious adverse event occurred in patient ATb4, in whom MRI revealed a substantial area of radiation-induced perilesional edema at post-GVC month 8. This was accompanied by delirium, confabulation, and visual hallucinations that responded to corticosteroids within a few days. However, memory deficits and executive function impairment persisted for 5 months. Ultimately, the patient returned to his baseline level of neuropsychological functioning. At month 54, that same patient was a nonresponder and had developed a 6-mm-diameter asymptomatic brain cyst (eFigure 5 in the Supplement). Neuropsychological performance remained stable.

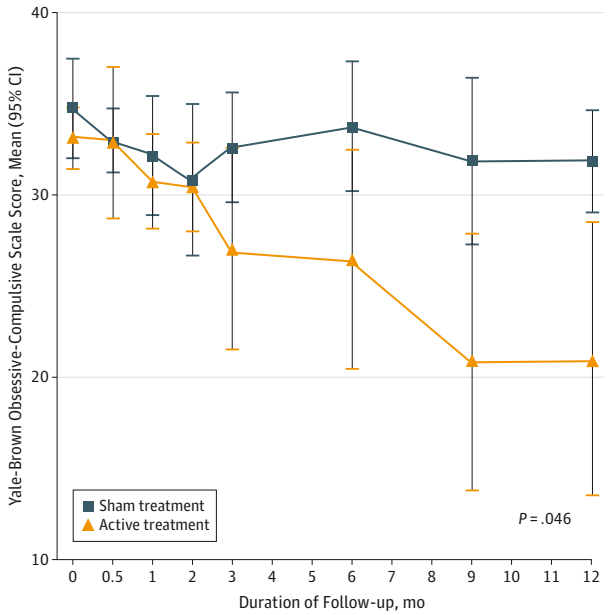
None of the other patients experienced any significant adverse neuropsychological effects or personality changes (eAppendix 2 and eTable 8 in the Supplement).

## Discussion

To our knowledge, this is the first double-blind, placebo-controlled, randomized clinical trial of ablative neurosurgery for the treatment of a psychiatric disorder. The masking methods—sedation during procedures, a sham Gamma Knife chamber, and only the radiosurgery team being unmasked—are unique in the literature.

Our results are consistent with previous, long-term open studies (most case reports) of OCD neurosurgery. Response rates reported for radiofrequency capsulotomy and gamma capsulotomy are 44% to 79% and 55% to 80%, respectively, compared with 22% to 76% for cingulotomies.[4-6,27-34] Randomized clinical trial efficacy tends to be lower than case series. Here, the response rate in the month-12 blinded portion (37.5%) was lower than in previous open studies, although it climbed to 58.3% in the open-label phase. There is no comparable controlled trial of DBS with a masked phase duration of 12 months. However, randomized trials of ventral capsular/ventral striatal (VC/VS) DBS found an at least 35% reduction of blind Y-BOCS scores in 1 of 4 (25%)[35] to 2 of 6 (33%)[8] and 3 of 4 (75%) patients.[36] Greenberg et al[37] also described long-term experience with VC/VS DBS at 4 centers. Ten of 21 patients (48%) showed a more than 35% reduction in Y-BOCS severity after 12 months of open follow-up compared with 4 of 8 patients (50%) here. As to other DBS techniques, 1 of 10 (10%),[38] 8 of 14 (57%),[10] and 6 of 16 (38%)[9] patients showed a more than 35% reduction of blind Y-BOCS scores, with accumbens DBS (targeting pathways overlapping those of VC/VS DBS and GVC)[10,38] and subthalamic DBS,[9] respectively. However, the time course for improvement is earlier in DBS (eAppendix 2 in the Supplement).

Figure 2. Mean (95% CI) Yale-Brown Obsessive-Compulsive Scale Scores for the Sham Treatment and Active Treatment Groups During the First 12 Months of Follow-up (Double-Blind Phase)




*P* value is for the comparison between each surgical group.

The severity of Y-BOCS improved in the ATa group during the blind phase and 37.5% of patients responded by post-GVC month 12. That proportion increased to 62.5% at post-GVC month 24, when 2 additional patients responded. Of the 4 patients in the ATb group, 2 became responders at post-GVC months 12 and 24. Therefore, of 12 patients who ultimately received GVC, 7 (58.3%) became responders. Patients who did not receive GVC did not improve, strongly suggesting the absence of a placebo effect.

It was somewhat unexpected that the 2 groups did not differ in terms of depressive (BDI) and anxiety (BAI) symptoms at month 12. Other ablative procedures, such as stereotactic subcaudate tractotomy, where the target overlaps GVC, have been reported to improve depression as well as OCS. Open DBS studies have also shown significant reductions in depression and anxiety in OCD.

Table 3. Changes in Secondary Outcome Measures at 12 Months After Sham or Active Gamma Ventral Capsulotomy

| | Preoperative | | | | Postoperative, at 12 mo | | | | Decrease at 12 mo, % | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient | DY-BOCS | BDI | BAI | GAF | DY-BOCS | BDI | BAI | GAF | DY-BOCS | BDI | BAI | GAF |
| ST group | | | | | | | | | | | | |
| ST1[a] | 27 | 36 | 27 | 33 | 24 | 16 | 14 | 38 | 11.1 | 55.6 | 48.1 | 15.2 |
| ST2 | 29 | 17 | 18 | 31 | 23 | 5 | 5 | 41 | 20.7 | 70.6 | 72.2 | 32.3 |
| ST3[a] | 28 | 56 | 35 | 32 | 27 | 45 | 19 | 28 | 3.6 | 19.6 | 45.7 | −12.5 |
| ST4[a] | 28 | 33 | 7 | 26 | 22 | 22 | 7 | 32 | 21.4 | 33.3 | 0 | 23.1 |
| ST5[a] | 28 | 13 | 4 | 24 | 29 | 11 | 12 | 18 | −3.6 | 15.4 | −200 | −25.0 |
| ST6 | 27 | 4 | 0 | 35 | 23 | 3 | 3 | 49 | 14.8 | 25 | −300 | 40 |
| ST7 | 27 | 52 | 45 | 31 | 25 | 8 | 18 | 41 | 7.4 | 84.6 | 60 | 32.3 |
| ST8 | 23 | 22 | 8 | 37 | 24 | 8 | 10 | 50 | −4.3 | 63.6 | −25 | 35.1 |
| ATa group | | | | | | | | | | | | |
| ATa1 | 30 | 46 | 60 | 33 | 24 | 22 | 15 | 46 | 20 | 52.2 | 75 | 39.4 |
| ATa2 | 25 | 12 | 3 | 28 | 17 | 16 | 4 | 43 | 32 | −33.3 | −33.3 | 53.6 |
| ATa3 | 26 | 12 | 12 | 42 | 9 | 7 | 7 | 68 | 65.4 | 41.7 | 41.7 | 61.9 |
| ATa4 | 24 | 33 | 30 | 32 | 26 | 35 | 13 | 41 | −8.3 | −6.1 | 56.7 | 28.1 |
| ATa5 | 26 | 30 | 13 | 32 | 19 | 28 | 16 | 57 | 26.9 | 6.7 | −23.1 | 78.1 |
| ATa6 | 30 | 14 | 22 | 32 | 0 | 8 | 7 | 68 | 100 | 42.9 | 68.2 | 112.5 |
| ATa7 | 27 | 18 | 21 | 32 | 10 | 3 | 8 | 75 | 63 | 83.3 | 61.9 | 134.4 |
| ATa8 | 30 | 26 | 22 | 32 | 22 | 30 | 37 | 15 | 26.7 | −15.4 | −68.2 | −53.1 |
| ATb group | | | | | | | | | | | | |
| ATb1 | 24 | 16 | 14 | 38 | 0 | 24 | 12 | 62 | 100 | −50 | 14.3 | 63.2 |
| ATb3 | 27 | 45 | 19 | 28 | 28 | 35 | 17 | 10 | −3.7 | 22.2 | 10.5 | −64.3 |
| ATb4 | 22 | 22 | 7 | 32 | 20 | 20 | 7 | 54 | 9.1 | 9.1 | 0 | 68.8 |
| ATb5 | 29 | 11 | 12 | 18 | 27 | 7 | 3 | 19 | 6.9 | 36.4 | 75 | 5.6 |
| ST, median | 27.5 | 27.5 | 13 | 31.5 | 24 | 9.5 | 11 | 39.5 | 9.3 | 44.4 | 22.9 | 27.7 |
| Mean (SD) | 27.1 (1.8) | 29.1 (18.5) | 18.0 (16.2) | 31.1 (4.3) | 24.6 (2.3) | 14.8 (13.7) | 11.0 (5.9) | 37.1 (10.8) | 8.9 (10) | 46 (26) | −37.4 (137.7) | 17.5 (23.9) |
| ATa, median | 26.5 | 22 | 21.5 | 32 | 18 | 19 | 10.5 | 51.5 | 29.5 | 24.2 | 49.2 | 57.7 |
| Mean (SD) | 27.3 (2.4) | 23.9 (12.1) | 22.9 (17.1) | 32.9 (4) | 15.9 (8.9) | 18.6 (11.9) | 13.4 (10.5) | 51.6 (19.5) | 40.7 (33.6) | 21.5 (39.6) | 22.4 (55.2) | 56.9 (57.1) |
| *P* value | | | | | | | | | .01 | .17 | .46 | .08 |
| ATb, median | 26 | 19 | 13 | 30 | 24 | 22 | 10 | 37 | 8 | 16 | 12 | 34 |
| Mean (SD) | 25.5 (3.1) | 23.5 (15) | 13 (5) | 29 (8.4) | 18.8 (13) | 21.5 (11.6) | 9.8 (6.1) | 36.3 (25.6) | 28.1 (48.3) | 4.4 (38) | 25 (33.9) | 18.3 (62) |

Abbreviations: ATa, active treatment (blinded phase); ATb, active treatment (of former sham treatment–group patients, unblinded phase); BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; DY-BOCS, Dimensional Yale-Brown Obsessive-Compulsive Scale; GAF, Global Assessment of Functioning Scale; ST, sham treatment.

[a] Ultimately (after unblinding) became ATb.

There was no statistical difference in SF-36 scores between the treated and nontreated patients at month 12, a measure of quality of life. Although quality of life may improve after DBS for OCD, symptom improvements after medications are sometimes not associated with higher scores in quality of life measures.[39,40] In contrast, an individual's overall level of impairment owing to OCS, as measured by the DY-BOCS impairment scores, decreased in the treated patients, suggesting that DY-BOCS is more sensitive to OCS impairments.

For those who received the active procedure, 1 patient developed an unusually brisk radiation-induced reaction (brain edema at first and delayed brain cyst in the long-term follow-up). Rasmussen (written communication, April 2008) identified delayed brain cysts in 3 of 55 patients who underwent GVC for OCD using Gamma Knife model C, whereas no cyst formation was observed so far in the patients treated with the older model U. Of those 3 patients, 2 remained asymptomatic but the third required surgical cyst drainage to correct neurologic symptoms. Delayed cyst formation has been reported in 2.2% to 9.0% of patients undergoing radiosurgery for other conditions (primarily arteriovenous malformations), with permanent complications in 1%.[41] We cannot rule out the risk for the development of additional late cysts in our cohort. However, data in the literature indicate that this is unlikely beyond 5 years after surgery[41] and our patients have now been followed up for nearly that long (mean, 55.2 months). The images of 2 of our nonresponders (patients ATb4 and ATa8) are shown in the Supplement (eFigures 5 and 6).

The safety profile of the double-shot GVC technique used here was superior to that reported for different combinations

Table 4. Changes in Secondary Outcome Measures at the MRA After Sham and Active Gamma Ventral Capsulotomy

| | MRA | | | | | Decrease at MRA, % | | | |
|---|---|---|---|---|---|---|---|---|---|
| Patient | Follow-up, mo | DY-BOCS | BDI | BAI | GAF | DY-BOCS | BDI | BAI | GAF |
| ST group | | | | | | | | | |
| ST1[a] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| ST2 | 24 | 27 | 11 | 3 | 35 | 14.8 | 35.3 | 83.3 | 12.9 |
| ST3[a] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| ST4[a] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| ST5[a] | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| ST6 | 12 | 23 | 3 | 3 | 49 | 14.8 | 25 | −300 | 40 |
| ST7 | 45 | 24 | 8 | 18 | 41 | 11.1 | 84.6 | 60 | 32.3 |
| ST8 | 30 | 25 | 21 | 26 | 50 | −8.7 | 4.5 | −225 | 35.1 |
| ATa group | | | | | | | | | |
| ATa1 | 86 | NA | 38 | 35 | 62 | NA | 17.4 | 41.7 | 87.9 |
| ATa2 | 56 | 26 | 11 | 0 | 46 | −4 | 8.3 | 100 | 64.3 |
| ATa3 | 48 | 7 | 2 | 0 | 79 | 73.1 | 83.3 | 100 | 88.1 |
| ATa4 | 72 | 19 | 34 | 35 | 66 | 20.8 | −3 | −16.7 | 106.3 |
| ATa5 | 55 | 22 | 31 | 4 | 43 | 15.4 | −3.3 | 69.2 | 34.4 |
| ATa6 | 56 | 0 | 11 | 5 | 68 | 100 | 21.4 | 77.3 | 112.5 |
| ATa7 | 51 | 5 | 2 | 1 | 84 | 81.5 | 88.9 | 95.2 | 162.5 |
| ATa8 | 12 | NA | NA | NA | NA | NA | NA | NA | NA |
| ATb group | | | | | | | | | |
| ATb1 | 82 | 0 | 32 | 15 | 52 | 100 | −100 | −7.1 | 36.8 |
| ATb3 | 67 | 0 | 0 | 0 | 92 | 100 | 100 | 100 | 228.6 |
| ATb4 | 65 | 25 | 22 | 20 | 55 | −13.6 | 0 | 185.7 | 71.9 |
| ATb5 | 12 | 27 | 7 | 3 | 19 | 6.9 | 36.4 | 75 | 5.6 |
| ST, median | NA | 24.5 | 9.5 | 10.5 | 45.0 | 13 | 30.1 | −82.5 | 33.7 |
| Mean (SD) | NA | 24.8 (1.7) | 10.8 (7.6) | 12.5 (11.4) | 43.8 (7.1) | 8 (11.3) | 37.4 (34) | −95.4 (195.6) | 30.1 (11.9) |
| ATa, median | 55.5 | 13 | 11 | 4 | 66 | 47 | 17.4 | 77.3 | 88.1 |
| Mean (SD) | 54.5 (21.3) | 13.2 (10.5) | 18.4 (15.5) | 11.4 (16.2) | 64 (15.4) | 47.8 (42.3) | 30.4 (39.2) | 66.7 (42.3) | 93.7 (40.2) |
| ATb, median | 66 | 13 | 15 | 9 | 54 | 53 | 18 | 34 | 54 |
| Mean (SD) | 56.5 (30.6) | 13 (15) | 15.3 (14.5) | 9.5 (9.5) | 54.5 (29.8) | 48.3 (60.3) | 9.1 (83.6) | −4.5 (129.2) | 85.7 (99) |

Abbreviations: ATa, active treatment (blinded phase); ATb, active treatment (of former sham treatment–group patients, unblinded phase); BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; DY-BOCS, Dimensional Yale-Brown Obsessive-Compulsive Scale; GAF, Global Assessment of Functioning Scale; MRA, most recent assessment; NA, not applicable; ST, sham treatment.

[a] Ultimately (after unblinding) became ATb.

of Gamma Knife and thermocapsulotomy for OCD described elsewhere.[4] We observed no permanent deleterious neuropsychologic or personality changes after 1 to 5 years of follow-up. However, the risk for delayed brain cyst development is a concern. Other adverse effects, including the manic episodes observed here, also require clinical vigilance. It is unclear whether the emergence of drug dependence in 1 patient was attributable to surgery. Given that GVC is indicated only for patients with severe impairment and for otherwise intractable cases, the (relatively low) potential for severe adverse effects might represent an acceptable risk. Such effects should be considered within the context of the adverse effects that can occur after DBS or after open ablative procedures. Studies have shown that some thermocapsulotomy patients experience postoperative epileptic seizures, delirium, emotional blunting, temporary erratic behavior, or cerebral hemorrhage. Furthermore, the use of radiation doses as high as 200 Gy, more than 2 isocenters, larger collimators, and multiple operations were highly associated with the incidence of adverse effects such as abnormal radiation necrosis or edema, apathy, memory problems, and executive dysfunctions.[4] Taken that our target lesions were smaller than those in the original gamma capsulotomy series, we expected a lower incidence of severe adverse events (eAppendix 2 in the Supplement). Our observations were in line with expectations, except for 1 case that developed a delayed-onset brain cyst.

The relative risks and burdens of GVC vs DBS bear discussion. For example, VC/VS DBS is not itself an innocuous procedure. Potential psychiatric adverse effects of DBS include induction of hypomania, as well as rapid worsening in both OCD and depression (including possible suicidality), if DBS is interrupted by battery depletion or a broken stimulating wire. Other surgical complications and adverse effects of DBS include intracerebral hemorrhage, infection, delirium, convulsions, mania, weight gain, and urinary incontinence.[8,38,39,42]

For decades, ablative neurosurgical techniques and Gamma Knife surgery have been used in the treatment of

Table 5. Adverse Effects on the Systematic Assessment for Treatment of Emergent Events Scale Up to the Most Recent Assessment

| Adverse Effect | ATa Group (n = 8) | ST Group (n = 8) | ATb Group (n = 4) |
|---|---|---|---|
| Insomnia | 2 patients, owing to hypomania and anxiety, at post-GVC mo 9 | 1 patient, for a few days after surgery | |
| Sedation | | 1 patient, in the first immediate post-procedure period | |
| Depressive symptoms | | 1 patient, first few days after the procedure | |
| Mania/hypomania | 2 patients, at post-GVC mo 3 and 9 | | |
| Visual hallucination | | 1 patient, a few hours after the procedure | 1 patient, 9 mo after surgery, for 1 wk |
| Lightheadedness | | | 1 patient, for the first 3 d after surgery |
| Delirium | | | 1 patient, 9 mo after surgery, for 1 wk |
| Perseverative behaviors | | | 1 patient, 9 mo after surgery, for 1 wk |
| Headache | 4 patients, episodic | 3 patients, episodic | 1 patient, episodic |
| Slurred speech | 1 patient, for the first 2-3 d after surgery | 1 patient, for the first 2-3 d after the procedure | 1 patient, for the first 2-3 d after surgery |
| Muscle pain | 1 patient, leg pain for the first 4 d after surgery | 1 patient, cervical and lumbar pain for 2 wk after the procedure | |
| Nausea/vomiting | 6 patients | 2 patients | 1 patient |
| Abdominal discomfort | 1 patient, for the first 3 d after surgery | | |
| Diarrhea | | 1 patient, for the first 2 d after the procedure | |
| Increased appetite | 6 patients | 3 patients | 1 patient |
| Increased weight | 5 patients | 4 patients | 1 patient |
| Skin paresthesia | 8 patients, at the insertion site of a stereotactic frame on the skull (for 1-4 wk after surgery) | 4 patients, at the insertion site of a stereotactic frame on the skull (for 1-4 wk after the procedure) | 1 patient, at the insertion site of a stereotactic frame on the skull (for 2 wk after surgery) |
| Pain/edema on the skin | 2 patients, at the insertion site of a stereotactic frame on the skull (for ≤2 wk after surgery) | 6 patients, at the insertion site of a stereotactic frame on the skull (for 1 d-4 wk after the procedure) | 2 patients, at the insertion site of a stereotactic frame on the skull (for 1-2 wk after surgery) |
| Local dermatitis | | 1 patient, at the insertion site of the stereotactic frame (for 2 wk after the procedure) | |
| Sialorrhea | 1 patient, for the first 3 d after surgery | | |
| Sore throat | 1 patient, for the first 7 d after surgery | | |

Abbreviations: ATa, active treatment (blinded phase); ATb, active treatment (of former sham treatment–group patients, unblinded phase); GVC, gamma ventral capsulotomy; ST, sham treatment.

mental disorders, with long-term follow-up providing data on safety. The lack of randomized clinical trials of ablative procedures has precluded direct comparisons between such techniques and DBS. Stereotactic ablation and DBS will very likely continue to coexist as treatment options for intractable OCD or depression. The present study provides information that is essential to weighing their potential relative risks, benefits, and burdens.

Although the size of our sample was large enough to detect a therapeutic signal, it was a small sample, especially in terms of its ability to detect adverse events. The short duration of the blinded treatment phase might also represent a limitation. Even an entire year of blinding might be suboptimal because OCS can continue to improve for 2 years after GVC, as observed here. However, extending the blinded phase could be unethical because it would expose intractably ill patients to a prolonged period without receiving a treatment that has shown promise in an open-label series and in the present trial. Another limitation of our study was that the patients were not evaluated by independent blinded raters after the first year of the randomized trial and during the long-term follow-up phase.

We terminated the study earlier than planned because our cobalt sources (half-life of 5.27 years, initially activated in 1998) were in a state of advanced decay. That prolonged our surgical procedures (and the sedation protocol), making them inconveniently and perhaps dangerously long (>12 hours).

Future studies should address the role of smaller, single-shot Gamma Knife lesions (especially on the ventral border of the internal capsule) in terms of efficacy and adverse events. A recent pilot study suggests that approach to be efficacious and safe.[7]

## Conclusions

Gamma ventral capsulotomy demonstrated significant efficacy in reducing OCS, with an acceptable incidence of severe adverse effects. As for any such procedure, the use of GVC for OCD should be restricted to specialized centers with highly experienced teams of psychiatrists and neurosurgeons committed to following up these patients systematically for many years under strict guidelines.[16,43,44] In addition, we urge that an international registry be established to collect systematic data on patient characteristics, procedures, and outcomes related to the use of GVC for the treatment of OCD.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