Title

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Journal

Biological Psychiatry, 84(5)

ISSN

0006-3223

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Publication Date

2018-09-01

DOI

10.1016/j.biopsych.2017.11.034

Peer reviewed

Archival Report

Biological Psychiatry

Gamma Ventral Capsulotomy in Intractable Obsessive-Compulsive Disorder

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ABSTRACT

BACKGROUND: Despite the development of effective pharmacologic and cognitive behavioral treatments for obsessive-compulsive disorder (OCD), some patients continue to be treatment-refractory and severely impaired. Fiber tracts connecting orbitofrontal and dorsal anterior cingulate cortex with subcortical nuclei have been the target of neurosurgical lesions as well as deep brain stimulation in these patients. We report on the safety and efficacy of ventral gamma capsulotomy for patients with intractable OCD.

METHODS: Fifty-five patients with severely disabling, treatment-refractory OCD received bilateral lesions in the ventral portion of the anterior limb of the internal capsule over a 20-year period using the Leksell Gamma Knife. The patients were prospectively followed over 3 years with psychiatric, neurologic, and neuropsychological assessments of safety and efficacy, as well as structural neuroimaging.

RESULTS: Thirty-one of 55 patients (56%) had an improvement in the primary efficacy measure, the Yale-Brown Obsessive Compulsive Scale, of ≥35% over the 3-year follow-up period. Patients had significant improvements in depression, anxiety, quality of life, and global functioning. Patients tolerated the procedure well without significant acute adverse events. Five patients (9%) developed transient edema that required short courses of dexamethasone. Three patients (5%) developed cysts at long-term follow-up, 1 of whom developed radionecrosis resulting in an ongoing minimally conscious state.

CONCLUSIONS: Gamma Knife ventral capsulotomy is an effective radiosurgical procedure for many treatment-refractory OCD patients. A minority of patients developed cysts at long-term follow-up, 1 of whom had permanent neurological sequelae.

Keywords: Anterior capsulotomy, Efficacy, Frontostriatal circuits, Gamma Knife, Obsessive-compulsive disorder, Safety

https://doi.org/10.1016/j.biopsych.2017.11.034

Obsessive-compulsive disorder (OCD) affects 1% to 2% of the population worldwide (1–3). The illness has a serious impact on employment, marital satisfaction, and quality of life (4). Eighty percent of patients seeking treatment report that their symptoms have seriously impacted their lifetime work capacity, and 15% of patients are disabled. Despite advances in the pharmacologic and behavioral treatment of OCD (5–7), 3% to 5% of patients with OCD remain severely impaired and refractory to treatment (8,9). Neurosurgery is a recognized option for these treatment-refractory patients. The Leksell Gamma Knife (Elekta Instrument AB, Stockholm, Sweden) is a radiosurgical instrument that allows noninvasive stereotactic lesions to be precisely placed deep in the brain, significantly reducing the risk of infection, hemorrhage, or seizure compared with procedures requiring craniotomy. Rylander (10) and Leksell (11) were the first to report on the efficacy and safety of gamma capsulotomy for intractable OCD. Additional trials from the Karolinska group found that 60% to 70% of patients were much or very much improved (12,13). However, the neuroanatomic placement and the number and volume of the lesions in the capsule were large, widely variable, and not hypothesis driven (14). Long-term follow-up studies of these cohorts have demonstrated significant neuropsychological impairment (15).

Positron emission tomography studies of OCD have demonstrated that abnormal regional metabolism between caudate, orbitofrontal cortex, and thalamus are mitigated after treatment with medication or behavior therapy (16–19). Resting-state functional magnetic resonance imaging (MRI) studies have consistently shown increased orbitofrontal–striatal connectivity in OCD (20,21). We selected our initial target based on where the orbital and anterior cingulate efferents ran in the anterior capsule of nonhuman primates (22). More recently, diffusion imaging studies have confirmed the location of these fibers in the human anterior capsule (23).

We report the results of the largest, systematic prospective follow-up study to date of the efficacy and safety of gamma ventral capsule/ventral striatal capsulotomy (GVC) in the treatment of 55 severely ill, intractable obsessive-compulsive patients.

ISSN: 0006-3223

METHODS AND MATERIALS

Study Design and Subjects

Our initial hypothesis was that a single bilateral lesion in the anterior limb of the internal capsule that carried the afferent and efferent fibers connecting the medial and orbital frontal cortex, the head of the caudate, and the midline thalamus would be equally efficacious to the previously studied larger lesions, while minimizing adverse effects. Fifteen patients were entered into this initial phase of the study (single shot). One patient in this group demonstrated significant improvement and did not require a second procedure. A second patient in this group withdrew from the study after experiencing no improvement after the first shot. The remaining 13 patients went on to a second-stage procedure because of a lack of response to the first procedure (single shot repeated). Forty additional patients were subsequently treated with two shots bilaterally in one session (double shot). Follow-up assessments were completed at 3, 6, 12, 24, and 60 months after the procedure. Because of the level of functional impairment caused by their severe OCD and related Axis I disorders, ongoing behavioral treatment and pharmacologic treatment were allowed after the procedure to optimize treatment response. Medications were held constant for the 6 weeks before and 6 months after radiosurgery.

Baseline Assessments

Candidates for the study were assessed by the primary investigator (SAR), a neurologist (SPS), and a neuropsychologist (PJM or NCM). Each assessment included a comprehensive review of psychiatric history obtained by direct interview of the patient, family, and treatment providers and a review of all available records. The suitability of participants for inclusion into the study was reviewed by an independent board whose members included an ethicist, two psychiatrists, a minister, a lawyer, a nurse, and a member of the National Alliance for the Mentally Ill.

History of medication compliance was obtained by interview with the treating psychiatrist, patient, and family. The maximal dose of medications varied because of the patients' ability to tolerate adverse effects. However, no patient failed to receive less than the maximal recommended doses for at least 10 weeks of two or more serotonin reuptake inhibitors. Patients who were poorly compliant with medication or exposure treatment were not entered into the study. A list of clinical assessment measures is shown in the Supplement. A comprehensive neuropsychological battery was obtained at baseline. All patients accepted into the study provided informed consent for radiosurgery and clinical follow-up (see the Supplement for specific inclusion/exclusion criteria).

Radiosurgical Technique

The first 37 patients were treated with the Leksell Gamma Knife model U, while the remainder were treated with the model C. For the single shot repeated group, in the coronal plane, the initial bilateral single target was located centrally in the capsule, one-third of the distance dorsally from the capsule's most ventral extension and in the axial plane adjusted so the posterior part of the 20% isodose line transected the genu of the capsule. The second stage target (single shot repeated) was defined immediately ventral to the first stage shot in the center of the capsule. Individual variation in the anatomy of the anterior limb of the internal capsules as they coursed through the corpus striatum necessitated minor alterations in targeting. The double shot group received two shots bilaterally, targeted to cover the ventral third of the anterior capsule/ventral striatum, that were consistently placed 8 to 10 mm anterior to the posterior border of the anterior commissure. Target locations in the coronal and axial planes and the distribution of actual volumes at 1-year follow-up are presented in the Supplement.

Follow-up Assessments

Baseline MRIs were obtained on all patients. Follow-up clinical scans were obtained in most cases. The typical appearance of the lesions is illustrated in Figure 1. In the initial (single shot

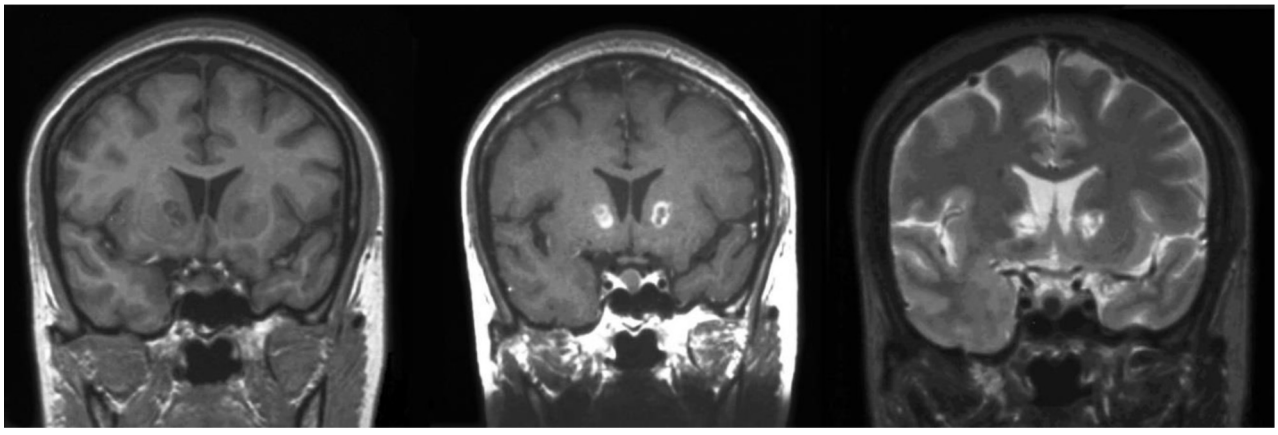

Figure 1. (Left panel) T1-weighted magnetic resonance imaging scan (coronal projections) taken 8 months postsurgery showing double shot bilaterally in the ventral portion of the internal capsule. (Middle panel) T1-weighted postgadolinium magnetic resonance imaging scan showing ring enhancement around the lesion. (Right panel) T2-weighted magnetic resonance imaging scan at same time point showing interstitial edema surrounding the lesion.

repeated) cohort, 1 of 13 patients who received a second-stage procedure failed to develop a lesion in the targeted location. This single patient subsequently received a third-stage procedure that targeted the same area that was identified for the second-stage lesion. MRI follow-up 6 months after the third-stage lesion revealed a characteristic ring-enhancing lesion at the target. All other patients developed necrotic lesions that were consistent with the target location by the 6-month assessment.

Outcome data were obtained at 3, 6, 12, 24, and 36 months postprocedure. Clinician ratings were ascertained from patients and corroborated with interviews with family members (see Supplement for a description of follow-up measures).

Data Analyses

Our primary outcome analysis used linear mixed effects regression models evaluating the significance of change in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores from baseline to 6, 12, 24, and 36 months for the single shot repeated group (therefore, after the second procedure), and baseline to 6, 12, 24, and 36 months for the double shot group. The repeated assessments are parameterized to reflect the amount of change in outcome for each follow-up compared to baseline levels. A secondary categorical outcome analysis was the number of responders at follow-up. Responder criteria were a ≥35% improvement from baseline on the Y-BOCS. We also classified patients as partial responders by an improvement of ≥25% on the Y-BOCS. The last observations from patients who dropped out prematurely were carried forward in the analyses. We completed linear mixed effects analysis of change in outcomes for the Hamilton Depression Rating Scale, Beck Depression Inventory, Hamilton Anxiety Rating Scale, and Global Assessment of Functioning (GAF) for the separate groups. Categorical clinical variables were analyzed with χ^2. Planned covariates included age and gender. Using adjusted linear mixed effects models, we examined relationships between baseline clinical characteristics and changes in primary outcomes by including model terms for average level of premorbid functioning, the presence or absence of consistent social supports, age of major symptom onset, and principal symptom category. A carry forward analysis of percentage improvement of mean and medians on last follow-up is given in Supplemental Table S2.

RESULTS

Baseline Clinical Features

Tables 1 and 2 summarize the demographic and clinical characteristics of the single shot repeated and double shot samples at baseline. The groups did not differ on any quantitative measure. Y-BOCS severity at baseline was 33.3 (standard deviation = 4.8) (single shot repeated group) and 34.2 (standard deviation = 3.2) (double shot group), considered "extreme" OCD (Table 3). On average, the time consumed by OCD symptoms was more than 8 hours per day. Consistent with severe to extreme functional impairment, baseline GAF scores for both groups were in the 30s (Table 3). The most common lifetime comorbid Axis I psychiatric conditions were major depressive disorder, dysthymia, panic disorder without agoraphobia, and social phobia. The most common Axis II diagnoses were avoidant, obsessive-compulsive personality disorder, and dependent personality disorders (see Table 3 for comorbidities). Seventy-eight percent met lifetime DSM criteria for recurrent major depressive disorder. All failed to respond to multiple trials of pharmacologic and behavioral treatments. The average age of major OCD symptom onset was 19.4 years (standard deviation = 7.9 years). The most common obsessions were aggressive and contamination thoughts. The most common compulsions were doubt/checking and cleaning.

Efficacy

Single Shot Repeated. At an average follow-up of 9 ± 0.4 months after the first stage single shot procedure, only 1 of 15 patients met criteria as a full or partial responder. As a group, these 15 patients did not improve significantly on the Y-BOCS, Clinical Global Impression Scale, or GAF either at the 6-month follow-up (B = −2.5, SE = 2.3, p = .29) or at end point of the first stage procedure (B = −2.6, SE = 2.3, p = .26). In addition, there was no significant improvement in measures of anxiety (Hamilton Anxiety Rating Scale: $F_{4,54}$ = 2.15, p = .09) or depression (Hamilton Depression Rating Scale: $F_{4,54}$ = 1.8, p = .14). Thirteen of these 15 patients went on to have a

Table 1. Demographic and Symptom Information at Baseline

Variable	Overall, n = 55	Double Shot, n = 40	Single Shot Repeated, n = 15	Between Group Comparison		
				χ^2/t	df	p
Gender, n (%)						
Female	20 (36.4)	15 (37.5)	5 (33.3)	0.00	1.00	1.00
Male	35 (63.6)	25 (62.5)	10 (66.7)			
Age, Years, Mean (SD)	33.6 (10.5)	32.8 (11.1)	35.87 (8.7)	1.09	32.04	.29
Age of Onset of Major Symptoms, Years, Mean (SD)	19.4 (7.9)	18.6 (7.7)	21.53 (8.3)	1.21	23.60	.24
Prior Functioning, n (%)				0.00	1.00	.98
Never employed	24 (43.6)	18 (45)	6 (40)			
Employed	31 (56.4)	22 (55)	9 (60)			
Family Support, n (%)				0.00	1.00	1.00
Low support	6 (10.9)	4 (10)	2 (13.3)			
High support	49 (89.1)	36 (90)	13 (86.7)			

Table 2. Symptom Information at Baseline

Variable, *n* (%)	Overall, *n* = 55	Double Shot, *n* = 40	Single Shot Repeated, *n* = 15
Primary Symptoms[a]			
Obsessions			
Aggressive	21 (38.2)	15 (37.5)	6 (40)
Contamination	20 (36.4)	16 (40)	4 (26.7)
Religious	0 (0)	0 (0)	0 (0)
Symmetry/ordering	13 (23.6)	9 (22.5)	4 (26.7)
Somatic	4 (7.2)	4 (10)	0 (0)
Hoarding	2 (3.6)	1 (2.5)	1 (6.7)
Sexual	7 (12.7)	6 (15)	1 (6.7)
Compulsions			
Cleaning	22 (40)	17 (42.5)	5 (33.3)
Checking	32 (58.2)	24 (60)	8 (53.3)
Repeating	8 (14.6)	6 (15)	2 (13.3)
Counting	0 (0)	0 (0)	0 (0)
Ordering/arranging	7 (12.7)	5 (12.5)	2 (13.3)
Hoarding	6 (16.3)	2 (5)	4 (26.7)
Miscellaneous	1 (1.8)	1 (2.5)	0 (0)
Comorbid Disorders			
Axis I			
Anorexia/bulimia	3 (5.5)	1 (2.5)	2 (13.3)
Depression	43 (78.2)	33 (82.5)	10 (66.7)
Simple phobia	2 (3.6)	0 (0)	2 (13.3)
Bipolar	2 (3.6)	1 (2.5)	1 (6.7)
Panic without agoraphobia	5 (9.1)	2 (5)	3 (20)
Dysthymia	6 (10.9)	4 (10)	2 (13.3)
Social phobia	5 (9.1)	4 (10)	1 (6.7)
Generalized anxiety disorder	3 (5.5)	3 (7.5)	0 (0)
Developmentally disabled	1 (1.8)	1 (2.5)	0 (0)
Body dysmorphic disorder	2 (3.6)	2 (5)	0 (0)
Cannabis	3 (5.5)	3 (7.5)	0 (0)
Alcohol	3 (5.5)	3 (7.5)	0 (0)
Posttraumatic stress disorder	3 (5.5)	3 (7.5)	0 (0)
Axis II			
Avoidant	23 (41.8)	16 (40)	7 (46.7)
Dependent	15 (27.3)	11 (27.5)	4 (26.7)
Narcissistic	1 (1.8)	1 (2.5)	0 (0)
OCPD	19 (34.6)	11 (27.5)	8 (53.3)
Histrionic	4 (7.2)	1 (2.5)	3 (20)
Borderline	3 (5.5)	2 (5)	1 (6.7)
Self-defeating	2 (3.6)	2 (5)	0 (0)
Paranoid	2 (93.6)	0 (0)	2 (13.3)

OCPD, obsessive-compulsive personality disorder.
[a]Primary symptom subtype rated by patient, in conjunction with a psychiatrist and a study nurse.

second-stage procedure. Tables 3 and 4 and Figures 2 and 3 summarize the efficacy data for the single shot repeated (from second surgery) and double shot groups. At 1-year follow-up of the single shot repeated cohort, 5 of 13 (39%) patients met the criteria for being a responder, and 2 additional patients (15%) were partial responders. As a group, patients in this cohort who had failed to respond to the single-stage procedure improved significantly from baseline at each of the 24- (B = −9.0, SE = 2.4, p = .004) and 36-month (B = −13.8, SE = 2.3, $p < .001$) assessments on the Y-BOCS. Depression (Y3 vs. baseline: B = −6.5, SE = 2.5, p = .01) and anxiety (Y3 vs. baseline: B = −5.6, SE = 2.0, p = .006) scores were also significantly improved compared with baseline (Figure 2). There was significant improvement in GAF ($F_{4,54} = 11.23$, $p < .0001$) with mean increases ranging from 7.7 to 15.1 at the 12-, 24-, and 36-month follow-ups.

Double Shot. The double shot group showed significant improvement in OCD (Y-BOCS: $F_{4,130} = 70.73$, $p < .0001$), depression (Hamilton Depression Rating Scale: $F_{4,130} = 16.47$, $p < .0001$), and anxiety (Hamilton Anxiety Rating Scale: $F_{4,130} = 15.48$, $p < .0001$) compared with baseline at the 6-, 12-, 24-, and 36-month follow-up assessments (Tables 3 and 4 and Figures 2 and 3). Categorical analysis of the double shot group revealed that 13 (59%) met the responder criteria at 1 year with an additional 5 patients (23%) meeting the criteria for partial response. These gains were maintained at 2 years with 15 (69%) meeting the criteria for full responders and 5 (23%) meeting the criteria as partial responders. The double shot group had an average drop of 17.4 points in the Y-BOCS at the 36-month follow-up, while the single shot repeated group had an average drop of 14.0 points.

Table 5 shows the baseline and follow-up measures of functional status and quality of life as measured by the Sickness Impact Profile. Following the first stage procedure there was no significant improvement in any of the subscales at 6 months or at end point. Significant improvements were observed in emotional behavior (B = −16.0, SE = 4.9, p = .0020) and social interaction (B = −20.5, SE = 5.5, p = .0005) in the single shot repeated sample at 36 months of follow-up. In the double shot sample, emotional behavior (B = −14.3, SE = 4.4, p = .0017), sleep and rest (B = −21.2, SE = 5.7, p = .0003), home management (B = −26.4, SE = 4.7, $p < .0001$), communication (B = −9.8, SE = 2.6, p = .0003), social isolation (B = −19.1, SE = 4.1, $p < .0001$), recreational activities (B = −26.7, SE = 5.1, $p < .0001$), mobility (B = −11.6, SE = 3.6, p = .0016), and work (B = −24.0, SE = 5.9, p = .0001) had each improved significantly compared with baseline assessments given alpha correction for multiple comparisons.

Predictors of Outcome

In the double shot group, we examined relationships between levels of premorbid functioning (employment), symptom type, the presence or absence of consistent social supports, and age of major onset with levels of Y-BOCS and changes in levels over assessments. The presence of family support predicted overall lower Y-BOCS scores (B = 6.8, SE = 2.3, p = .052), while being male predicted a worse outcome (B = 3.7, SE = 1.6, p = .025). No other examined predictors were associated with Y-BOCS scores and no predictor interacted with time, suggesting no evidence for differential changes over time. Being employed ($F_{4,34} = 4.2$, p = .008) and having a later age of onset ($F_{4,34} = 4.7$, p = .004) were associated with greater improvement in the GAF at follow-up. No other predictors were

Table 3. Primary Outcomes for Single Shot Repeated and Double Shot Groups at Baseline and Follow-up Assessments

	Baseline		6 Months		1 Year		2 Years		3 Years	
	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*
Single Shot Repeated										
Y-BOCS	33.27 (4.82)	15	30.80 (5.98)	15	30.67 (7.59)	15	24.07 (9.29)	14	19.29 (11.25)	14
HAM-D	24.27 (8.67)	15	22.47 (7.02)	15	22.80 (8.90)	15	22.43 (13.02)	14	17.14 (13.05)	14
HAM-A	19.33 (8.49)	15	15.87 (8.77)	15	16.67 (8.67)	15	14.86 (9.49)	14	12.21 (8.92)	14
GAF	32.33 (8.42)	15	34.13 (9.13)	15	40.07 (10.25)	15	41.00 (16.50)	15	47.40 (19.87)	15
Double Shot										
Y-BOCS	34.18 (3.15)	40	23.95 (7.61)	37	20.26 (7.34)	35	17.80 (7.62)	30	16.78 (8.30)	32
HAM-D	27.65 (9.67)	40	22.03 (10.01)	37	19.17 (9.70)	35	16.17 (9.04)	30	15.81 (10.78)	32
HAM-A	19.95 (9.45)	40	14.73 (8.72)	37	13.20 (7.82)	35	11.20 (6.00)	30	11.31 (6.66)	32
GAF	38.78 (6.94)	40	46.73 (7.93)	37	51.29 (9.37)	35	55.81 (11.36)	31	58.35 (12.72)	31

GAF, Global Assessment of Functioning; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

associated with change in Y-BOCS or change in GAF over assessments (p values $> .10$).

Safety

The acute effects of the Gamma Knife procedure were well tolerated, with most patients returning home the same day. Nausea and in some cases vomiting was noted in the double shot group during the third and fourth shots. These adverse effects were eliminated by administering 10 mg of intravenous dexamethasone prophylactically in patients immediately before the procedure. Most patients complained of transient postoperative headache that resolved between the second and fifth day. There was no confusion, disorientation, or incontinence noted. No clinically significant abnormalities were noted on neurologic examination at any follow-up visit, with the exception of the patient in the double shot group who developed radionecrosis.

There was considerable variation in the development of interstitial edema caused by the radiation-induced lesion across participants. Five patients (9%) developed significant edema with headache without additional complications 3 to 6 months after the procedure that required treatment with 1 month of 1 to 2 mg of dexamethasone daily as an outpatient.

Table 4. Percent Decrease in Symptoms From Baseline to 6-, 12-, 24-, and 36-Month Assessments

Time Since Surgery	<25%	25–34%	≥35%	*n*
Single Shot Repeated, *n* (%)[a]				
6 months	12 (80)	1 (6.67)	2 (13.33)	15
1 year	8 (53.33)	2 (13.33)	5 (33.33)	15
2 years	6 (40)	4 (26.67)	5 (33.33)	15
3 years	6 (40)	2 (13.33)	7 (46.67)	15
Double Shot, *n* (%)				
6 months	19 (47.5)	8 (20)	13 (32.5)	40
1 year	9 (22.5)	9 (22.5)	22 (55)	40
2 years	9 (22.5)	9 (22.5)	22 (55)	40
3 years	5 (12.5)	5 (12.5)	30 (75)	40

Any missing observations were replaced by using the last observation carried forward.

[a]Time points since second surgery.

Six patients also developed asymptomatic lacunar infarcts of the caudate that were 3 to 5 mm in diameter over the first year of follow-up, presumably because of damage to small perforating vessels. Manic episodes developed during follow-up in three patients who had histories of manic episodes. The addition of mood stabilizers resolved the manic symptoms in all cases.

The Systematic Assessment for Treatment Emergent Events was collected at baseline and during follow-up visits for all patients, and few adverse effects were found in either the single shot repeated or double shot groups. There was no significant increase in side effects over time for either group. The most commonly reported side effects were insomnia, anxiety, altered mood, poor memory/difficulties concentrating, headache, and lethargy. In most cases, these symptoms were present at baseline and may have been attributed to either baseline psychiatric symptomology (e.g., mood, anxiety, or difficulties concentrating) or the high medication levels patients were using in an attempt to control their OCD. One patient in the single shot repeated group was noted to have significant impairment in her drive and motivation after the second procedure that led to her losing her job. She improved after a course of oral dexamethasone.

Patients completed neuropsychological assessments before and after GVC. There were no patterns of pervasive cognitive decline in any patient. There was a slight improvement in overall mean scores, consistent with reduction in their OCD symptoms. A subsequent report detailing these findings is in preparation.

Brain cysts developed 3 to 5 years after GVC in 3 of 55 patients. Cysts were noted in 2 of the patients on the 5-year follow-up MRI. They were clinically asymptomatic. A third patient presented with neurological symptoms including headache, dizziness, and visual changes 10 months after radiosurgery. MRI revealed extensive bilateral edema with radionecrosis and cyst formation. The patient continued to manifest extensive edema and necrosis despite attempts to drain the cyst, a course of bevacizumab, and placement of a shunt, ultimately requiring open resection of the necrotic material. The patient subsequently sustained a fall during neurorehabilitation with a large subdural hematoma that led to posterior cerebral artery occlusion and a minimally conscious

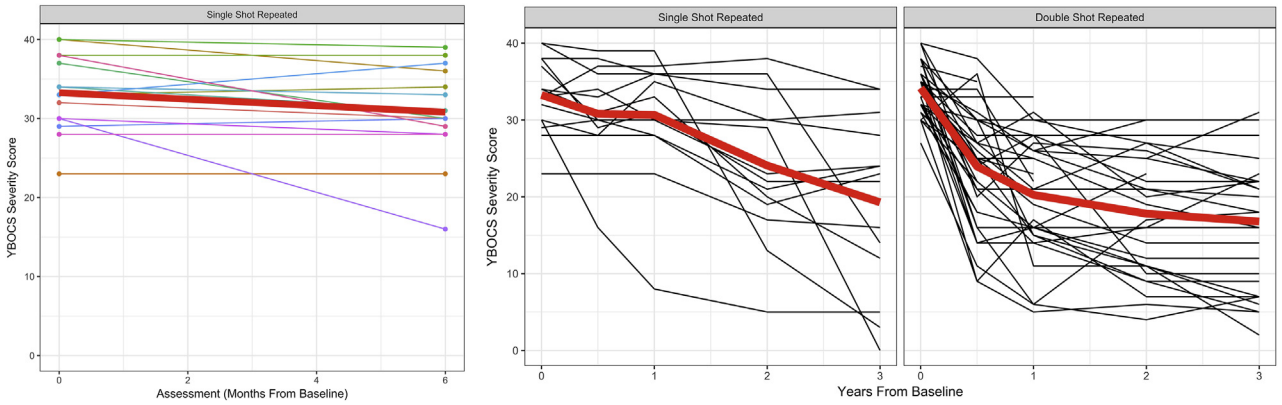

Figure 2. Overall change in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores for individuals in the single shot repeated and double shot cohorts. Note that there is significant variability in response between patients in both cohorts and that the double shot cohort responded more quickly, though the mean response at 3-year follow-up was similar.

state. All three cysts occurred after double shot radiosurgery with the model C Gamma Knife. No cysts were noted in the double shot group operated on with the model U Gamma Knife.

DISCUSSION

Efficacy

We present efficacy and safety data from the largest systematic, prospective follow-up study of GVC for the treatment of intractable OCD. The overall results show that GVC is effective in reducing OCD symptoms of severely ill, treatment-refractory patients as measured by continuous or categorical carry forward measures of the Y-BOCS at 6, 12, 24, and 36 months of follow-up versus baseline for those patients who received two bilateral lesions in the ventral capsule/ventral striatum. Highly significant and correlated reductions in comorbid depression and anxiety were also observed. All patients had failed to improve with available nonsurgical treatments and had been severely ill for a minimum of 5 years. Many patients felt that after gamma capsulotomy they were able to tolerate exposure to feared situations that they routinely avoided before radiosurgery. Many surgical responders either discontinued or dramatically reduced their medications over the follow-up period. We cannot conclude that surgery alone led to the improvement in symptoms and function owing to ongoing pharmacologic and behavioral treatment that were continued for ethical considerations. There appeared to be a synergistic effect of cognitive behavioral therapy and surgery, which has been noted in other studies (24).

Only 1 of 15 patients (7%) had a significant improvement with the bilateral first stage lesion. We conclude that a single bilateral shot in the anterior midcapsular region is ineffective in intractable OCD.

The study was not a double blind controlled study, and we cannot therefore rule out the possibility of a placebo response. However, the likelihood that improvement in our single stage and double shot patients was caused by a placebo effect is unlikely because we had every expectation that the single shot lesion alone would be effective. A recent double blind study of gamma capsulotomy using the double shot target described here has demonstrated comparable efficacy for the active group and lack of efficacy for the sham condition (25). Although unlikely, our data cannot rule out the possibility that the first lesion would have been effective if we had waited longer than 9 months. However, examination of a nonsurgical OCD cohort that was matched for severity and duration of illness at baseline showed no improvement in symptoms over a comparable 5-year period (26). It is also possible that a single bilateral lesion might have been effective if placed more ventral in the capsule and striatum.

Our data suggest that targeting the longitudinal fiber tracts that contain the anterior cingular and orbitofrontal projections to the striatum, thalamus, and brain stem is key to a therapeutic response. Additional prospective diffusion imaging data are needed to confirm this hypothesis. The localization of effective stimulation to the ventral edge of the capsule in deep brain stimulation (DBS) points to the need for a future study examining the effects of a single bilateral lesion at this site. Sheehan *et al.* (27) published a case series of single bilateral GVC lesions for intractable OCD with comparable efficacy to our double shot lesions. This study awaits replication in a larger sample. There are no extant data to test whether unilateral lesions are effective.

Course of Improvement

The course of improvement of OCD symptoms after thermocapsulotomy, subcaudate tractotomy, and limbic leucotomy has been poorly documented in previous studies (28–31). Though some authors have reported acute effects that were complicated by more general states of confusion, most data appear consistent with a delayed response. One quarter of the patients in our sample experienced a transient minimal improvement in symptoms during the first 1 to 2 weeks after surgery that disappeared by the 3-month follow-up. It is unclear if this was an acute biological response to the radiation or a placebo effect. A gradual but variable improvement in the single shot repeated group that occurred primarily between 6

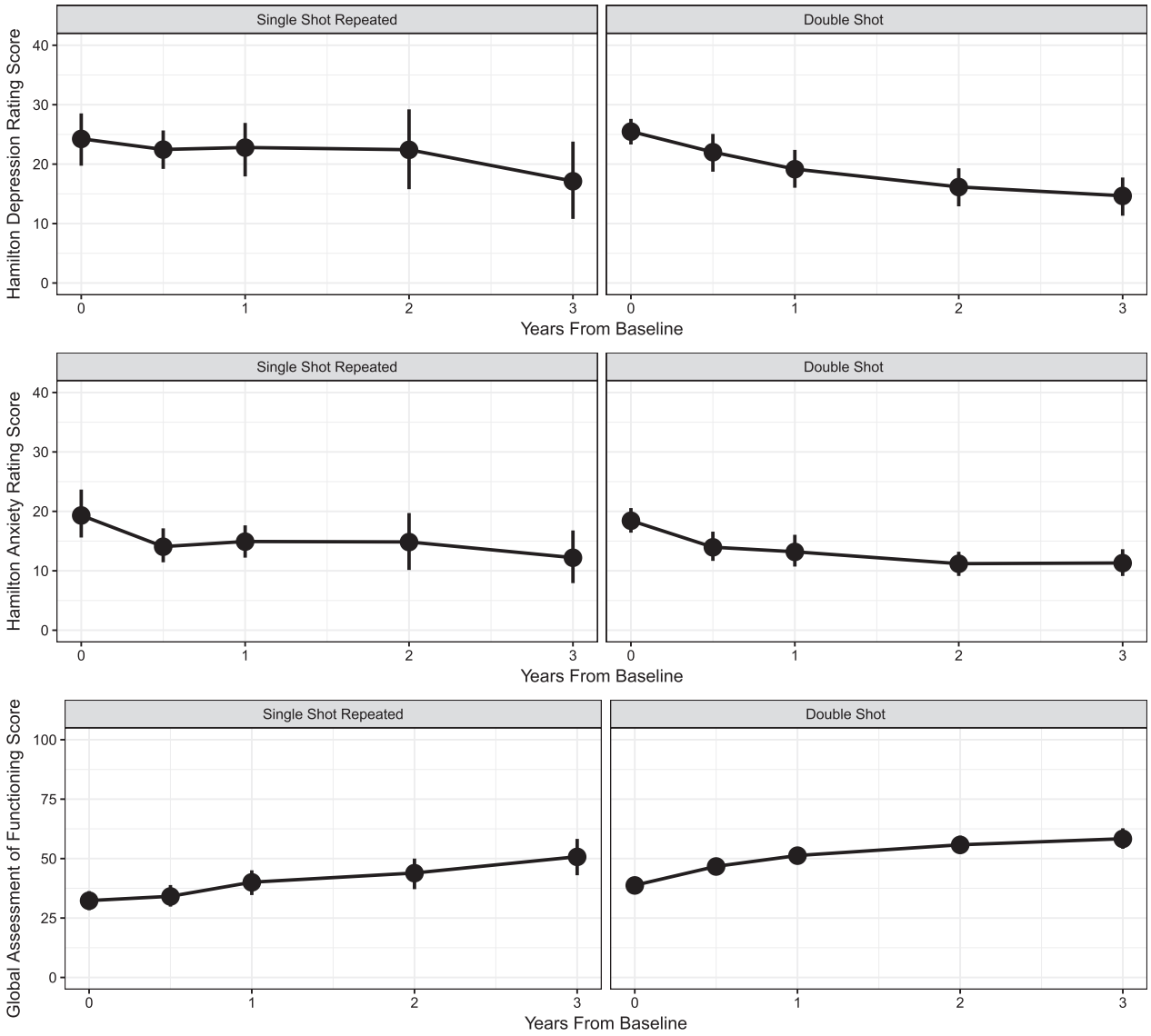

Figure 3. Overall change in depression, anxiety, and global assessment of function over 3 years showing significant improvement for the single stage and double stage cohorts.

to 12 months after surgery was observed, as opposed to an earlier response of 3 to 9 months for the double shot group. Responders reported a gradual decrease in anxiety and distress associated with the obsessions as well as concomitant decreases in the urge to ritualize, followed by a more gradual return to improved function.

Gamma Knife lesions in white matter develop slowly over weeks to months (32). Although the exact time course of radiation-induced necrosis was variable across our subjects, lesions were present in all but one patient by 3 months after radiosurgery. One possibility is that the therapeutic effect is in part caused by the radiation-induced edema that is maximal 6 to 15 months postprocedure (33). This seems unlikely, because our experience has shown that patients do not relapse when the edema resolves further into the follow-up period. Another possibility is that improvement is consistent with the time course of retrograde Wallerian degeneration in midline thalamic nuclei and orbitomedial cortex caused by the capsular lesion.

Safety

Long-term follow-up of the 37 GVCs performed with the Gamma Knife model U has demonstrated that it is a generally safe procedure with few acute or long-term side effects. In contrast to open surgeries that carry intraoperative risks of hemorrhage, seizure, and infection, gamma capsulotomy can be performed in an outpatient setting. Follow-up MRIs revealed the presence of small asymptomatic infarctions in the caudate in 2 (13%) of the single shot and 4 (10%) of the double

Table 5. Sickness Impact Scale

	Baseline		6 Months		1 Year		2 Years		3 Years	
	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*
Single Shot Repeated[a]										
Emotional behavior	42.11 (25.48)	15	34.87 (22.53)	13	32.39 (28.27)	12	32.48 (26.41)	13	24.41 (23.36)	13
Sleep and rest	36.07 (28.00)	15	31.35 (29.37)	13	33.58 (28.01)	12	30.31 (28.94)	13	24.37 (22.71)	13
Home management	40.07 (26.12)	15	39.34 (33.97)	13	26.47 (24.62)	12	24.41 (29.72)	13	26.38 (30.38)	13
Communication	12.63 (16.37)	15	13.92 (18.95)	13	9.39 (14.37)	12	5.15 (7.31)	13	2.71 (5.22)	13
Social interaction	42.65 (21.55)	15	41.39 (19.83)	13	28.08 (19.75)	12	30.07 (18.21)	13	21.25 (19.86)	13
Recreational activities	45.36 (27.36)	15	37.42 (30.84)	13	27.53 (28.81)	12	31.60 (26.76)	13	29.15 (26.88)	13
Alertness	4.40 (6.26)	15	3.28 (5.22)	13	5.38 (12.79)	12	0.32 (1.16)	13	0.76 (2.75)	13
Mobility	21.82 (18.27)	15	27.33 (20.73)	13	18.04 (21.48)	12	19.64 (20.13)	13	20.25 (21.03)	13
Work	61.82 (29.39)	15	59.32 (26.32)	13	49.92 (30.51)	12	43.96 (34.52)	13	49.35 (32.50)	13
Double Shot										
Emotional behavior	41.33 (25.89)	40	37.13 (23.23)	33	27.70 (23.15)	29	24.48 (22.22)	26	25.57 (22.58)	27
Sleep and rest	36.87 (27.03)	40	33.38 (22.94)	33	25.71 (25.60)	29	18.12 (22.69)	26	15.46 (24.59)	27
Home management	35.47 (23.24)	40	21.83 (23.61)	33	18.83 (19.81)	29	20.22 (24.50)	26	9.22 (12.45)	27
Communication	12.03 (18.50)	40	4.43 (9.05)	33	3.47 (10.47)	29	4.06 (10.93)	26	2.92 (5.52)	27
Social interaction	33.90 (22.09)	40	27.78 (22.04)	33	22.49 (18.50)	29	19.51 (17.47)	26	14.87 (16.47)	27
Recreational activities	42.11 (21.17)	40	30.68 (24.42)	33	27.93 (26.38)	29	23.63 (22.13)	26	15.02 (17.05)	27
Alertness	5.18 (9.10)	40	2.99 (6.91)	33	2.33 (5.09)	29	2.25 (4.32)	26	0.81 (2.02)	27
Mobility	20.01 (17.70)	40	17.56 (16.93)	33	11.57 (11.67)	29	9.35 (14.33)	26	8.71 (12.61)	27
Work	60.28 (22.52)	40	61.37 (21.41)	33	52.97 (28.54)	29	44.95 (32.73)	26	34.47 (33.89)	27

[a]Data refer to time after second repeated shot, which occurred 9 months after the first shot.

shot subjects. These patients have shown no demonstrable adverse effects on neurologic, psychological, or psychiatric status at the 10-year follow-up. Individual variation in sensitivity to radiation was seen in this study as has been found previously (32–34). Four of 55 patients developed headache caused by more extensive edema postsurgery. They were treated with dexamethasone and had complete resolution of symptoms. Manic episodes developed during the follow-up in 3 patients who had histories of manic episodes, and the addition of mood stabilizers resolved the manic symptoms in these cases.

There were no adverse effects of GVC on personality or neuropsychological function at follow-up with the exception of 1 patient with apathy and a second with radionecrosis. It remains possible that the overall improvement in OCD may be masking subtle cognitive deficits related to surgery in individual patients.

Patients 38 to 55 received identical lesions in terms of placement and dose (maximum 180 Gy) using the model C Gamma Knife. It was noted on long-term follow-up that 3 of these patients developed cysts with the model C Gamma Knife that were not seen in the first 36 patients operated on with the model U Gamma Knife. One of these patients developed severe radionecrosis with extensive edema requiring an open drainage procedure. A fall in rehab resulted in a subdural hematoma and an ongoing minimally conscious state. In collaboration with radiobiologists at Oxford, we have subsequently determined that the dose volume distributions at 10 and 20 Gy were larger for the model C versus model U Gamma Knife, which may explain the genesis of the cysts. We are currently evaluating the feasibility of replicating the gamma model U isodose distribution with the Perfexion Model Gamma Knife and reducing the maximal target dose.

Comparison to Other Neurosurgical Procedures for OCD

Studies have consistently demonstrated the efficacy of cingulotomy, capsulotomy, gamma capsulotomy, and DBS of the capsule and adjacent ventral striatum for intractable OCD (35). Thermocapsulotomy or gamma capsulotomy of the entire anterior limb in the coronal plane has been demonstrated to carry a significant risk of long-term adverse effects on personality and psychologic function (36). This does not appear to be the case in patients undergoing the more limited GVC based on experiences from our cohort, followed out for as long as 20 years. In a comparable follow-up study of 34 patients who received cingulotomy for treatment of refractory OCD, 32% of the patients met criteria for full response and 14% for partial response at a mean follow-up time of 32 months (37).

A recent meta-analysis identified 20 studies reporting on 170 patients; 62 patients who underwent DBS of the ventral capsule/ventral striatum or the nucleus accumbens, and 108 patients who underwent anterior capsulotomy. There was a 40% decrease in Y-BOCS score in patients treated with DBS compared with a 51% decrease for those who underwent anterior capsulotomy (38). No difference in complication rates was noted. DBS has the theoretical advantage of being a reversible therapy with adjustable parameters. However, in practice, few patients are explanted because of the additional risks of the procedure. DBS is more expensive (39) and also has the disadvantage of requiring frequent battery replacement

and physician visits to adjust stimulation parameters. A disadvantage of using the Gamma Knife is some unpredictability regarding the individual response to a standard dose of radiation. One adverse event (radionecrosis with cysts, open drainage, and a subsequent fall during rehabilitation resulting in a subdural hematoma and a continued minimally conscious state) was severe. Closer attention to minimizing isodose volume distributions outside the target and lower maximal but still biologically effective doses may help minimize risk. Further study is warranted of smaller bilateral lesions and/or reduced radiation dose to an even more precisely defined ventral target. A study of 4 patients who underwent highly focused ultrasound to the capsule has shown mean improvements of 33% in Y-BOCS score in the first 6 months (40). This methodology is noninvasive and offers the advantage of allowing for observation of lesion development in real time.

Conclusions

In summary, our results show that GVC is an effective noninvasive therapy for severely ill patients with intractable OCD. Our clinical data have important implications for guiding future translational studies directed toward increasing our understanding of the pathophysiology of OCD. While the procedure is well tolerated by the majority of patients, there is a small but significant risk of the development of radionecrosis using high-dose radiation. Standardizing the isodose volumes and biologically effective doses while examining the efficacy of a lower maximal dose should be the subject of future studies.

ACKNOWLEDGMENTS AND DISCLOSURES

We thank Per Mindus, a former colleague and friend, for the many contributions to this study and for pioneering the use of gamma capsulotomy for intractable obsessive-compulsive disorder. We thank Brittney Blanchette and Lauren Bruguera for their support in preparation of the manuscript. Part of the data from this study was presented in abstract form at the American College of Neuropharmacology meeting in 2013 and subsequently published in *Neuropsychopharmacology* that same year.

CL has received financial compensation for consulting work performed for Elekta Instrument AB, the manufacturer of the Gamma Knife. The other authors report no biomedical financial interests or potential conflicts of interest.

ClinicalTrials.gov: Safety and Effectiveness of Gamma Capsulotomy in Intractable OCD; https://clinicaltrials.gov/ct2/show/NCT01849809; NCT01849809.

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Received Feb 17, 2017; revised Sep 26, 2017; accepted Nov 17, 2017.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.biopsych.2017.11.034.

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