Results of Gamma Knife anterior capsulotomy for refractory obsessive-compulsive disorder: results in a series of 10 consecutive patients

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OBJECTIVE Obsessive-compulsive disorder (OCD) is a severe psychiatric condition. The authors present their experience with Gamma Knife radiosurgery (GKRS) in the treatment of patients with OCD resistant to any medical therapy.

METHODS Patients with severe OCD resistant to all pharmacological and psychiatric treatments who were treated with anterior GKRS capsulotomy were retrospectively reviewed. These patients were submitted to a physical, neurological, and neuropsychological examination together with structural and functional MRI before and after GKRS treatment. Strict study inclusion criteria were applied. Radiosurgical capsulotomy was performed using two 4-mm isocenters targeted at the midputaminal point of the anterior limb of the capsule. A maximal dose of 120 Gy was prescribed for each side. Clinical global changes were assessed using the Clinical Global Impression (CGI) scale, Global Assessment of Functioning (GAF) scale, EQ-5D, Beck Depression Inventory (BDI), and State-Trait Anxiety Inventory (STAI). OCD symptoms were determined by the Yale–Brown Obsessive Compulsive Scale (Y-BOCS).

RESULTS Ten patients with medically refractory OCD (5 women and 5 men) treated between 2006 and 2015 were included in this study. Median age at diagnosis was 22 years, median duration of illness at the time of radiosurgery was 14.5 years, and median age at treatment was 38.8 years. Before GKRS, the median Y-BOCS score was 34.5 with a median obsession score of 18 and compulsion score of 17. Seven (70%) of 10 patients achieved a full response at their last follow-up, 2 patients were nonresponders, and 1 patient was a partial responder. Evaluation of the Y-BOCS, BDI, STAI-Trait, STAI-State, GAF, and EQ-5D showed statistically significant improvement at the last follow-up after GKRS. Neurological examinations were normal in all patients at each visit. At last follow-up, none of the patients had experienced any significant adverse neuropsychological effects or personality changes.

CONCLUSIONS GKRS anterior capsulotomy is effective and well tolerated with a maximal dose of 120 Gy. It reduces both obsessions and compulsions, improves quality of life, and diminishes depression and anxiety.

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KEYWORDS obsessive-compulsive disorder; Gamma Knife radiosurgery; capsulotomy; functional neurosurgery

OBSESSIVE-COMPULSIVE disorder (OCD) is a challenging psychiatric condition.²⁸ This mental disorder presents intrusive, anxiety-provoking thoughts and ritualized behaviors manifesting in many different forms. These forms can include self-mutilation, negative

social behaviors, impaired functioning, and need for hospitalization. Some patients may be severely affected and become resistant to standard pharmacological, psychiatric, and behavioral therapy. Based on neuroimaging studies, models of cortico-striato-thalamo-cortical dysfunction

ABBREVIATIONS BDI = Beck Depression Inventory; CGI = Clinical Global Impression; CGI-I = CGI-Improvement subscale; CGI-S = CGI-Severity subscale; DBS = deep brain stimulation; GAF = Global Assessment of Functioning; GKRS = Gamma Knife radiosurgery; OCD = obsessive-compulsive disorder; STAI = State-Trait Anxiety Inventory; STAI-S = STAI-State; STAI-T = STAI-Trait; Y-BOCS = Yale–Brown Obsessive Compulsive Scale.

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FIG. 1. Axial (A) and coronal (B) T2-weighted images, and T1-weighted sagittal image (C), showing the prescription isodose (yellow line) and 12-Gy isodose (green line). Figure is available in color online only.

have been hypothesized to underlie the pathophysiology of OCD, providing a basis for modulation or effects on this circuitry.^{23,24} According to this evidence, the ventral anterior internal capsule has been considered an appropriate target for such modulation, with good results over the long term.^{2,13,19,20,29}

The utility of Gamma Knife radiosurgery (GKRS) in the anterior limb of the internal capsule was first described at the Karolinska Institute, showing target effects and reporting significant symptomatic relief in 80% of the cases.^{11,14} To this point, only one randomized clinical trial and a few case series have confirmed these encouraging results.² However, the precise volume and the maximal radiation dose appropriate for anterior capsulotomy remain subjects of debate. In this retrospective study, we evaluate our experience with GKRS anterior capsulotomy in treating patients with severe OCD. The radiological, clinical, and neuropsychological results were taken into account with the aim of reporting the efficacy and safety of the procedure.

Methods

All patients were treated with GKRS at Ruber International Hospital. Data have been collected in a prospectively maintained database approved by the Ruber International Hospital review board. From this database, all patients who had been treated (after a multidisciplinary evaluation) for severe OCD refractory to any pharmacological and behavioral treatments were identified. Their cases have been retrospectively reviewed.

Patient Selection

Patients eligible for GKRS are chronic patients (OCD lasting at least 5 years) with symptoms that do not allow the patient to have a normal life, according to his/her own mental status and emotions. Symptoms have to be categorized by at least two psychiatrists as refractory to all possible treatments, with a total Yale–Brown Obsessive Compulsive Scale (Y-BOCS) score ≥ 24 , stable at least 12 months before GKRS without any evidence of anatomical abnormalities on pretreatment structural and functional MRI. A written informed consent form was signed by the patient and by his/her legal representative if necessary. Pa-

tients included in the study were submitted to a physical, neurological, and neuropsychological examination before the radiosurgical procedure.

Clinical Assessment

The severity of obsessive-compulsive symptoms was determined by the Y-BOCS.⁷ Depression and anxiety symptoms were measured by Beck Depression Inventory (BDI) and State-Trait Anxiety Inventory (STAI). Clinical global changes were assessed by the Clinical Global Impression (CGI) scale, Global Assessment of Functioning (GAF) scale,^{3,10} and quality of life (EQ-5D).^{5,6}

Response after GKRS was defined as an improvement of at least 35% in Y-BOCS score from baseline.⁴ Patients with an improvement between 25% and 35% were considered as partial responders. Patients who achieved a Y-BOCS score ≤ 8 were considered to be recovered.

GKRS

All patients were hospitalized the day before the treatment. Frame application was performed the following day under local anesthesia. Radiation was delivered with the Elekta Gamma Knife Unit (Model 4C until September 2007, and Perfexion model from October 2007 onward). Radiosurgical capsulotomy was performed using two 4-mm isocenters at the midputaminal point of the anterior limb of the internal capsule bilaterally, at the most ventral portion. Isocenters were located using volumetric T1-weighted MR images of the entire brain, and T2-weighted axial and coronal slices centered on the region of the anterior limb of the internal capsule. A maximal dose of 120 Gy was prescribed for each side (Fig. 1). Patients were discharged the same day of treatment after a brief period of clinical and neurological observation. After GKRS, patients were regularly followed by their treating psychiatrist and general practitioner. Whenever possible, patients were assessed at the neurosurgical clinic in Ruber International Hospital. A neuroradiological follow-up evaluation was performed with standard and functional MRI at 6 months, 1 year, and then yearly until the fifth year after GKRS, together with a new neuropsychological evaluation when possible. If the patient was unable to return to our department, MRI was per-

formed locally and images were sent to our hospital to be analyzed by the neurosurgeon and the neuroradiologist. Finally, neurosurgeons and neuropsychologists at Ruber International Hospital periodically telephoned patients to evaluate them.

Statistical Analysis

Due to the small number of samples, clinical assessment at last follow-up was the main imputation method. Continuous variables were examined for homogeneity of variance by the Kolmogorov-Smirnov test. For continuous variables, results were reported as median (range, mean, standard deviation). Statistical analyses of categorical variables were performed using the chi-square or Fisher exact test as appropriate. Statistics of means and medians were calculated using the Wilcoxon matched-pairs signed-rank test. A logistic regression and bivariate correlation were performed to analyze possible predictive parameters. A probability value less than 0.05 was considered to indicate statistical significance and all reported probability values are 2-tailed. All calculations were performed using the SPSS statistical package (version 21, IBM Corp.).

Results

Patient Characteristics

Ten patients with medical refractory OCD (5 women and 5 men), who underwent GKRS anterior capsulotomy between 2006 and 2015 at Ruber International Hospital in Madrid, Spain, were included in this study (Table 1).

Before GKRS, the median Y-BOCS score was 34.5 (range 24–38, mean 32.7 ± 4.8) with a median obsession score of 18 (range 15–18, mean 17.3 ± 1) and compulsion score of 17 (range 8–20, mean 16.3 ± 3.6). The median BDI score was 20; half of the patients were rated as mildly depressed, 2 as moderately depressed, and 3 as severely depressed. The median STAI-Trait (STAI-T) at GKRS was 65, while the median STAI-State (STAI-S) was 52. The median GAF score was 40.5, indicating serious to major impairment in several areas. The median CGI-Severity subscale (CGI-S) score was 6, indicating a group of patients markedly or severely ill. All patient characteristics are summarized in Table 1.

Radiosurgical Data

The median total time of exposure to radiation was 288.6 minutes (range 147.5–374.4 minutes, mean 268.3 ± 76.3 minutes) with a median radiation rate from the ^{60}Co sources of 1.76 Gy/min (range 1.47–3.36 Gy/min, mean 2.1 ± 0.77 Gy/min). The prescription dose was 84 Gy at 70% with a maximal dose of 120 Gy for all patients. The median volume of parenchyma included in the prescription isodose was 109.4 mm³ on average on the left side (range 100–175 mm³, mean 119.7 ± 26 mm³) and 108.5 mm³ (range 85–153 mm³, mean 108.5 ± 21.6 mm³) on the right anterior limb of the internal capsule. Sensitive structures such as the optic nerves and lenses were protected, maintaining radiation below a safe threshold. The median total V₁₂ was 5.8 cm³ (range 5.11–7.5 cm³, mean 6 ± 0.8 cm³).

TABLE 1. Clinical and demographic characteristics of patients included in the study

Characteristic	Value (%)	Mean (SD)	Median (range)
Sex (M/F)	5/5	—	—
Age at diagnosis, yrs	—	25 (10.7)	22 (16–56)
Age at treatment, yrs	—	41.2 (10.7)	38.8 (27–65)
Family history	5 (50)	—	—
Duration of OCD, yrs	—	15.3 (6.8)	14.5 (6–26)
Psychiatric hospitalization	3 (30)	—	—
Comorbidity	7 (70)	—	—
Bipolar	1 (10)	—	—
Major depression	6 (60)	—	—
Generalized anxiety	2 (20)	—	—
Dependence	1 (10)	—	—
Personality disorder	2 (20)	—	—
Eating disorder	1 (10)	—	—
Tics	1 (10)	—	—
Suicide attempts	1 (10)	—	—
Category of OCD			
Doubts/checking	2 (20)	—	—
Contamination/cleaning	2 (20)	—	—
Order/symmetry	1 (10)	—	—
Hoarding	2 (20)	—	—
Taboo thoughts	6 (60)	—	—
Employment status			
Unemployed	5 (50)	—	—
Employed	4 (40)	—	—
Retired	1 (10)	—	—
Therapy			
Pharmacological	10 (100)	—	—
Behavioral	9 (90)	—	—
Electroconvulsive	2 (20)	—	—
Familial situation			
Single	5 (50)	—	—
Married	3 (30)	—	—
Divorced	2 (20)	—	—
Education			
Poor	3 (30)	—	—
High school	5 (50)	—	—
University	2 (20)	—	—
Y-BOCS score		32.7 (4.8)	34.5 (24–38)
Severe (24–31)	3 (30)	26.33 (2.5)	26 (24–29)
Extreme (32–40)	7 (70)	35.43 (1.7)	35 (33–38)
BDI score	—	23.4 (9.9)	20 (14–44)
STAI-T score	—	64.2 (9.4)	65 (48–77)
STAI-S score	—	54.3 (15.8)	52 (33–80)
GAF score	—	40.8 (7.1)	40.5 (32–53)
CGI-S score	—	5.7 (0.7)	6 (5–7)
EQ-5D score	—	26.5 (10.5)	25 (20–55)

FIG. 2. Line graph showing Y-BOCS changes for each patient and aggregated mean $\pm$ SEM. Figure is available in color online only.

Clinical Assessment

The median clinical follow-up duration was 26 months (range 6–116 months, mean 41 months). Seven patients (70%) achieved a full response to the GKRS anterior capsulotomy at their last follow-up. The patient with the shortest follow-up (6 months) was classified as a partial responder (Y-BOCS reduction between 25% and 35%). Two patients were classified as nonresponders because they did not meet remission or response criteria. Between these two patients, patient 1 showed a complete response (100%) at the 12-month follow-up, but had a relapse 41 months after GKRS (Fig. 2). This patient was later treated using radiosurgical bilateral cingulotomy.

The pre-radiosurgical median Y-BOCS score of 34.5 (symptoms rated as extreme) showed a decrease to a median value of 10.5 (classified as mild) with a median score in obsession of 5 and 6 in compulsion at the last follow-up evaluation ($p = 0.007$, Wilcoxon matched-pairs signed-rank test). Obsession and compulsion scores were statistically lower at the last follow-up when compared with their value at GKRS ($p = 0.007$ and $p = 0.015$, respectively, Wilcoxon test).

The BDI score at GKRS decreased to a median value of 8.5 (minimal depression) at the last follow-up ($p = 0.009$, Wilcoxon test). The median value of STAI-T (65 at GKRS) decreased to 50.5 (minimal anxiety) at last follow-up ($p = 0.022$, Wilcoxon test). The median value of STAI-S at GKRS of 52 decreased to 38.5 ($p = 0.018$, Wilcoxon test). The median GAF value improved to 61.5 ($p = 0.005$, Wilcoxon test) with a median increase of 47%. The CGI-Improvement subscale (CGI-I) score at last follow-up was much improved with a mean value of 2.2, indicating better clinical condition and reduction of symptoms, i.e., an increase in the level of functioning but some symptoms remain. The EQ-5D had a statistically significant improvement to a median value of 67.5 ($p = 0.005$, Wilcoxon test). The median increase was 158% (range 40%–300%, mean

164% $\pm$ 93%). The Y-BOCS, BDI, STAI-T, STAI-S, GAF, and EQ-5D values at GKRS, at last follow-up, and percentage reduction/increase for each patient are reported in Table 2.

As recommended by treating psychiatrists, medical treatments related to OCD were maintained after GKRS and responders or partial responders did not require increases in doses or new medications. At the last follow-up, it was possible to reduce the doses of medication in 5 partial responders, and the 2 patients who were recovered were allowed to suspend their medical therapy by their own treating psychiatrists.

Predictive Value of Clinical Characteristics

All clinical assessment data (Y-BOCS and its subscales, BDI, GAF, STAI-S, and STAI-T) before GKRS were compared in the two subgroups of responders and nonresponders. No statistically significant differences were noted (Mann-Whitney test of two independent samples: $p = 0.833$, 0.267, 0.667, 0.267, and 0.833, respectively). Age at surgery, sex, family history of psychiatric diseases, presence of a psychiatric comorbidity, and subtype of OCD did not influence the response to GKRS in a statistically significant manner. The duration of follow-up was longer in patients who recovered compared to those who did not, without reaching a statistically significant difference.

MRI Results

The median radiological follow-up duration was 29 months (range 6–60 months, mean 29 months). Postradiosurgical MRI confirmed the exact location of the target on the anterior limb of the internal capsule indicated. On MRI, we found hypointense oval-shaped or round volumes on T1-weighted images, with hyperintense borders on FLAIR and T2-weighted images. Sometimes FLAIR and T2 hyperintensity filled the anterior limb of the internal capsule

TABLE 2. Preoperative value, last follow-up value, and percentage reduction for the Y-BOCS, BDI, STAI-T, STAI-S, GAF, and EQ-5D for all patients

Variable	Patient No.										Mean	Median	SD
	1	2	3	4	5	6	7	8	9	10			
Sex	M	M	M	M	M	F	F	F	F	F			
Preop													
Y-BOCS	26	36	24	35	38	33	35	37	29	34	32.7	34.5	4.8
BDI	14	33	17	23	32	23	17	17	14	44	23.4	20	9.9
STAI-S	33	44	60	39	80	44	75	62	44	62	54.3	52	15.8
STAI-T	48	74	62	65	71	58	70	65	52	77	64.2	65	9.4
GAF	33	32	43	34	37	38	44	49	45	53	40.8	40.5	7.1
EQ-5D	20	20	30	25	25	25	20	20	25	55	26.5	25	10.6
At last FU													
Y-BOCS	29	17	9	11	28	4	7	10	22	10	14.7	10.5	8.8
BDI	21	15	4	11	14	2	1	6	11	5	9	8.5	6.5
STAI-S	55	30	33	36	72	26	35	41	57	45	43	38.5	14.4
STAI-T	59	55	29	48	66	23	37	44	58	53	47.2	50.5	13.9
GAF	40	46	65	58	43	80	92	70	57	85	63.6	61.5	18.1
EQ-5D	60	70	65	80	35	90	80	40	50	85	65.5	67.5	19.1
% reduction													
Y-BOCS	12	-53	-63	-69	-26	-88	-80	-73	-24	-71	-53	-66	31
BDI	50	-55	-76	-52	-56	-91	-94	-65	-21	-89	-55	-60	43
STAI-S	67	-32	-45	-8	-10	-41	-53	-34	-30	-27	-15	-30	37
STAI-T	23	-26	-53	-26	-7	-60	-47	-32	-12	-31	-25	-29	27
GAF	21	44	51	71	16	111	109	43	27	60	55	47	33
EQ-5D	200	250	117	220	40	260	300	100	100	55	164	158	93
FU (mos)	41	25	21	14	6	116	106	37	27	17	41	26	38.4

FU = follow-up.

or extended beyond it. No correlation was found between radiological results and clinical improvement. None of the patients who underwent radiosurgery developed radiation necrosis or adverse side effects visible on MRI.

Side Effects

All patients tolerated the anterior capsulotomy well. Neurological examinations were normal in all patients at each visit. Two patients complained about loss of interest compared to their condition before GKRS. One patient gained weight during the 7 years after GKRS without reaching an obese BMI. Two patients complained about memory changes, but memory test results were normal at last follow-up. At last follow-up, none of the patients had experienced any significant adverse neuropsychological effects or personality changes.

Discussion

The possibility of anterior limb capsulotomy with GKRS was first reported at the Karolinska Institute, showing target effects and reporting significant symptomatic relief in 80% of the cases.^{11,14} Up to the present time, only one randomized clinical trial and few case series have confirmed these encouraging results.^{1,2,8,11,12,14–18,25–27} The

group from Charlottesville²⁷ believes that a bilateral single 4-mm isocenter delivering a maximum dose of 140–160 Gy is enough to show clinical improvement in patients with OCD, and reported a marked clinical improvement in 4 of 5 patients (80%) without any clinical side effects at a median follow-up duration of 24 months. The most recent study published by the group at the Karolinska Institute reported clinical results in 9 patients treated with single or double isocenters at higher doses (180–200 Gy).²⁵ The mean preoperative Y-BOCS score was 33.4, which improved to 14.2 at a mean follow-up of 136.8 months. At last follow-up, 5 patients were classified as responders. Studies at Brown University showed efficacy using an oval-shaped radiosurgical volume with two 4-mm isocenters recommended.⁹ Following this philosophy, Kondziolka et al.¹² from Pittsburgh noted significant functional improvement and a reduction in OCD behavior in 3 patients treated at a maximum dose of 140–150 Gy. At a mean follow-up of 41.7 months, 2 patients were classified as responders and no side effects were reported. In his prospective pilot study, Lopes et al.¹⁷ demonstrated clinical improvement at a mean follow-up of 48 months in 3 of 5 patients treated with GKRS capsulotomy using a double isocenter technique with a maximum dose of 180 Gy. The same group from São Paulo conducted the first and only

TABLE 3. Literature review of patients with OCD who underwent GKRS for anterior capsulotomy

Authors & Year	No. of Pts	Mean Age (yrs)	Mean FU (mos)	Max Dose, Gy (shots)	Mean Y-BOCS Score		Responders (%)
					Before GKRS	After GKRS	
Rück et al., 2008	9	43.9	136.8	180–200 (1–3)	33.4	14.2	5 (56)
Lopes et al., 2004	5	35	48	180 (2)	32	24	3 (60)
Gouvea et al., 2010	1	34	12	180 (2)	37	0	—
Kondziolka et al., 2011	3	44	42	140–150 (2)	37.3	16.3	2 (67)
Sheehan et al., 2013		38	26	140–160 (1)	32	17	4 (80)
Lopes et al., 2014–2015	12	33.9	55.2	180 (2)	33.6	17.3	7 (58.3)
Present series	10	41.2	41	120 (2)	32.7	14.7	7 (70)

Pts = patients.

double-blind, randomized trial to determine the efficacy and safety of radiosurgery for intractable OCD;¹⁶ 16 patients were randomized and half of them underwent an active treatment, while the other half underwent a sham procedure. At 12 months, OCD symptom improvement was significantly higher in the active group than in the sham group ($p = 0.046$) with 3 patients classified as responders, strongly suggesting the absence of a placebo effect. At 54 months, 2 additional patients in the active group had become responders. Of the 4 sham-treatment patients who later received active treatment, 2 responded so that after a mean follow-up of 55.2 months, 7 of 12 patients (58.3%) were responders. In our series, we also used two 4-mm isocenters, creating an oval-shaped lesion centered on the anterior limb of the internal capsule, and prescribed a maximal dose of 120 Gy. At a mean follow-up of 40.2 months, 7 patients (70%) were responders; 3 (30%) had a Y-BOCS score ≤ 8 at last follow-up and were considered recovered, while 4 patients (40%) were categorized as in remission (Y-BOCS score between 6 and 16). The patient with the shortest follow-up (6 months) was classified as a partial responder (Y-BOCS score reduction between 25% and 35%). Two patients were classified as nonresponders because they did not meet remission or response criteria. Good response was already achieved at 12 months of follow-up with a median reduction of 56.5% from initial Y-BOCS score. We believe that response to GKRS can rely not only on the lesional effect on the internal capsule but also on a neuromodulative process on the cortico-striato-thalamo-cortical circuit within the capsule that can give a better response to pharmacological therapy; furthermore, some patients can be more radiosensitive or radioresistant than others with results that can appear later in time. Our results are consistent with previously reported response rates for GKRS capsulotomy (56%–80%, Table 3).

In the GKRS capsulotomy literature, only Lopes et al.^{1,17} and Rück et al.²⁵ also analyzed secondary efficacy variables such as anxiety, depression, and GAF score at long-term follow-up. In the Brazilian series at 12 months, the active and sham groups did not differ statistically in terms of anxiety (Beck Anxiety Index, $p = 0.46$) and depression (BDI, $p = 0.17$). In 3 actively treated patients classified as nonresponders, BDI scores worsened after 12 months of follow-up. At last follow-up, the BDI score in actively treated patients decreased from a median value of 22 to

a median value of 11, BAI decreased from a median of 21.5 to a median of 4, and the GAF score increased from a median of 32 to a median of 66. Similar results were noted at 12 months in those 4 patients who secondarily moved to active treatment, and in their pilot prospective study of 5 patients.¹⁷ The Swedish group²⁵ noted that the Montgomery-Asberg Depression Rating Scale and Brief Scale for Anxiety scores at long-term follow-up were significantly lower than at the 1-year follow-up, indicating stable improvement. The mean GAF score preoperatively was 44.3 and was not significantly higher (47.5) at long-term follow-up. None of the patients were employed at the time of long-term follow-up. Seventeen of the 23 patients were receiving daily OCD medication at long-term follow-up. In these two studies, the mean CGI-I scores at long-term follow-up were 2.3 and 2.4, respectively; we reported a similar CGI-I score of 2.2, indicating a significant improvement.

In the present study, we report a statistically significant improvement in depression ($p = 0.009$) with a median reduction of 60%. The STAI-T level was lower at last follow-up in all patients but with a significant decrease ($p = 0.022$). This improvement was also noted in the STAI-S level ($p = 0.018$). The median postoperative GAF score in our series was 61.5, showing a significantly better function in all patients after GKRS. The EQ-5D was utilized to report the personal point of view of the patient on the impact of GKRS in his/her quality of life. At last follow-up, the median EQ-5D score was significantly higher ($p = 0.005$) compared to its median value at GKRS, demonstrating that the patient also realized a positive effect of the treatment. In this series, we also demonstrated that all secondary efficacy parameters statistically improved in those patients classified as responders, while if the patient did not reach the criterion of response (Y-BOCS reduction $\geq 35\%$), the slight improvement in depression, anxiety, GAF, and EQ-5D did not reach a statistically significant result. Sheehan et al.²⁷ in their paper suggested that perhaps the position of the inferior isocenter is enough to produce a lesioning effect in the nucleus accumbens and to achieve a beneficial effect for patients with OCD. Following this suggestion, we analyzed the possible correlation between the percentage of Y-BOCS score reduction and the distance of the lower inferior isocenter on both hemispheres, or the maximal dose received by the nucleus accumbens, but no positive correlation was found between the percent-

age of Y-BOCS score reduction and the dose to the nucleus accumbens in the dominant hemisphere ($p = 0.054$).

When treating a psychiatric condition with GKRS, particular attention should be paid to side effects and complications. Rück et al.²⁵ reported that 50% of their patients displayed signs of primarily apathy and impaired executive function behavior; all of these patients received very high radiation doses or underwent more than 1 procedure, and 1 patient committed suicide. Lopes et al. in their randomized trial¹⁶ reported the following minor side effects: episodic headaches (4 patients), nausea/vomiting ($n = 6$), weight/appetite changes ($n = 6$), insomnia ($n = 2$), mania ($n = 2$), and transient memory problems ($n = 1$), while 1 patient developed an asymptomatic brain cyst, and another had episodes of delirium and confabulation ($n = 1$). The only side effects noted in our sample were 2 patients who complained of loss of interest, and 1 patient gained weight during the 7 years after GKRS without being obese. Two patients complained of memory changes, but memory test results were normal at the last follow-up. Recently, the Brazilian group of Lopes et al. updated their previously published results and reanalyzed visuospatial memory after GKRS ventral capsulotomy,¹ demonstrating that initial results after 1 year of follow-up suggest that the procedure is safe in terms of neuropsychological functioning and may actually improve certain domains. The risk for delayed brain cyst development, as well as manic and perseverative episodes, is a possible side effect and requires clinical vigilance.¹⁶ Pepper and colleagues²² in their literature review have shown that some patients may experience serious postoperative side effects, such as epileptic seizures, intracranial hemorrhages, neurological deficits, and cognitive changes, from emotional blunting to temporary erratic behavior or delirium after deep brain stimulation (DBS) or thermocoagulation. Rück et al.²⁵ noted that the incidence of radiation necrosis, edema, and neurological and behavioral dysfunction was more associated with the use of radiation doses higher than 200 Gy, more than 2 shots, with larger collimators, and multiple operations. Weight gain greater than 10% is statistically more probable in lesioning techniques (GKRS or thermocoagulation) than in DBS.²² The use of double-shot GKRS anterior capsulotomy is superior in efficacy and safety to that reported for different combinations of Gamma Knife and thermocapsulotomy for OCD.²⁵

In the present study, the target lesions were smaller and the maximum dose lower than other previously published case series on GKRS capsulotomy; thus we expected a lower incidence of severe adverse events. The selection of 120 Gy as the maximal dose was done empirically for OCD, but also according to some encouraging results on movement disorders. At last follow-up, none of our patients reported any significant neurological side effects or neuropsychological personality changes. Similar results were demonstrated by Nyman et al.,²¹ in which no neurological deficits or MRI anomalies were noticed and no patient committed suicide after 6 months to 9 years of follow-up. The lower incidence of severe side effects following GKRS anterior capsulotomy could make this procedure a good alternative to DBS or thermocapsulotomy.

Limitations of the Study and Future Studies

The first limitation of this study is the lack of a placebo treatment and its retrospective design, even if data have been collected in a prospectively maintained database. Although the size of our sample was large enough to detect a therapeutic effect, it was a small sample, especially in terms of its ability to detect adverse events and predictive factors, resulting in a low a priori statistical power. The different duration of follow-up within the sample might also represent a limitation, even if no statistical differences were noticed between responders and nonresponders. Finally, the absence of an independent blinded evaluation after GKRS and the decision of some patients to intentionally miss some of their scheduled follow-up appointments may represent another weakness of this study. Longer-term safety and efficacy evaluation of at least 5–10 years of follow-up should be conducted.

Conclusions

The management of patients affected by OCD is challenging. In a select group of patients with OCD refractory to medical and behavioral therapy, neurosurgical or radiosurgical intervention may be the only possible solution. Globally, our overall results are consistent with other results in the literature and suggest that GKRS anterior capsulotomy may be equally effective and better tolerated with a maximal dose of 120 Gy. GKRS anterior capsulotomy is effective not only in reducing obsession and compulsion symptoms, but also in improving quality of life and reducing the value of depression and anxiety.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Martinez-Alvarez, Spatola, Rgis. Acquisition of data: Spatola, Martnez-Moreno, Rey, Linera, Ros-Lago, Sanz, Vidal. Analysis and interpretation of data: Martinez-Alvarez, Spatola, Ros-Lago, Gutirrez, Vidal. Drafting the article: Spatola, Richieri, Rgis. Critically revising the article: Martinez-Alvarez, Spatola, Rgis. Reviewed submitted version of manuscript: Martinez-Alvarez, Spatola, Richieri, Rgis. Statistical analysis: Spatola, Rey, Gutirrez. Study supervision: Martinez-Alvarez, Richieri, Rgis.

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