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Treatment Outcomes of Gamma-Knife Radio Surgery in Refractory Obsessive-Compulsive Disorder

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ABSTRACT

Background: Obsessive-compulsive disorder (OCD) is a common disease that has negative effects on functionality, and 10% of the patients do not respond to first-line treatments. Gamma-knife radiosurgery (GKRS) has been used in patients with treatment-resistant OCD, but the data on long-term outcomes are still unsatisfactory.

Methods: In this study, 12 patients who underwent GKRS between 2005 and 2020 were evaluated retrospectively. Anterior capsulotomy was performed using two 4-mm isocenters at the midputaminal point of the anterior limb of the internal capsule on each side with a maximum radiation dose of 140-180 Gy. Patients were followed up with the Yale-Brown Obsession and Compulsion Scale (Y-BOCS), Montgomery-Asberg Depression Rating Scale (MADRS), and Brief Psychiatric Rating Scale (BPRS) on the first, third, and sixth months.

Results: After the procedure, a 35% reduction was observed in the overall Y-BOCS scores, and full response rate was 50%. There was a 49.5% decrease in the MADRS scores and a 57.8% decrease in the BPRS.

Conclusion: GKRS is an effective and non-invasive procedure with favorable side effects in treatment-resistant OCD with selected patients.

ARTICLE HISTORY

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KEYWORDS: Anterior capsulotomy, Gamma Knife, obsessive-compulsive disorder, radiosurgery, treatment resistance

INTRODUCTION

OCD is characterized by 2 major symptoms which are obsessions (repetitive and unwanted thoughts, images, or urges) and compulsions (repetitive behaviors) that emerge in response to these obsessions. With a lifetime prevalence of 1-3%, OCD is one of the ten physical and mental diseases that have a global burden of disease worldwide.[1] Bimodal distribution of the age at onset is seen with 2 peaks, in late childhood/early adolescence and early adulthood.[2]

Due to obsessions and compulsions, daily functions are impaired in social, occupational, and family issues. This impairment is more prominent in severe OCD, and in patients with a Y-BOCS score over 20, psychosocial functions and quality of life are reported to be more affected.[3] The most common lifetime diagnosis comorbid with OCD is depression, with a rate of 50.5%, and the lifetime prevalence of suicide attempt is reported as 9%.[4] It is important but extremely difficult to predict suicidal behaviors in patients at such at risk,[5] and lifetime depressive episode is stated as one of the predictors of suicide attempt among patients with OCD.[6]

First-line treatments of OCD include selective serotonin reuptake inhibitors (SSRI) and/or cognitive-behavioral therapy (CBT). An insufficient response to the combination of these treatments with optimal dosage and duration points out a refractory to treatment. This corresponds to 10% of patients that fail to respond to conventional treatments including augmentations.[7] Neuroanatomical pathologies in OCD include abnormal activity and connectivity within the orbitofronto-striato-pallido-thalam ic network with increased activity in the orbitofrontal cortex (OFC), the supplementary motor area (SMA), the cingulate gyrus, and the caudate.[8] It has been also reported that after medication or behavioral therapy, the activity of these regions returns to normal levels[9] in patients responsive to treatment. However, non-response to treatment creates a challenge to the clinician as well as the patient. Various treatment options such as transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS),[10] or deep brain stimulation (DBS)[11] that target these brain regions come up as a treatment option in treatment refractor patients. Besides, neurosurgery is

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another option that has been used in the last 2 decades for treatment-resistant OCD as in other psychiatric diseases.[12]

Anterior capsule is one of the targets used in psychosurgery via damaging white matter tracts of the network that have an increased activity.[13] Therefore, a bilateral stereotactic lesion is achieved in the anterior limb of the internal capsule. Anterior capsulotomy can be achieved by both thermoregulation or Gamma-knife radiosurgery (GKRS).[14] GKRS is a non-invasive procedure applied with a helmet-like device mounted on the patient's head. High-energy gamma rays emitted from the radioactive isotope of cobalt that are surrounded hemispherically in this device provide sharply limited lesions in targeted regions of the brain.[15]

Although the literature examining GKRS in treatment-resistant OCD has expanded over time, it still consists of case series and small sample-sized studies,[15] and there has been only one randomized control study comparing the effectiveness of GKRS with a sham application.[16] The evidence of the literature in this field has some contradictions in terms of patient selection criteria, applied neurosurgery techniques, and the way of evaluating treatment response. In a recent systematic review, response rates at experienced centers were reported as one-half to two-third with limited and favorable side effects.[15]

In this study, it was aimed to retrospectively evaluate long-term follow-up results of patients diagnosed with treatment-resistant OCD who underwent GKRS in a tertiary clinic with specialized psychiatry and neurosurgery departments. Gamma Knife has been present since 2005 in Gazi University Faculty of Medicine, and GKRS for treatment of OCD has been first applied in 2005.[17] We hypothesized that patients with OCD would have exhibited greater reduction in YBOCS scores and also supposed that MADRS scores would have decreased after GKRS.

METHODS

Subjects and Study Design

All files of the patients who underwent GKRS for OCD in Gazi University Faculty of Medicine from 2005 to 2020 were scanned. Ethics committee approval was received from the Ethics Committee of Gazi University (2021-283). A total of 23 patient files were accessed. Eleven patients were excluded due to insufficient data on file. Eventually, 12 patients were examined in terms of sociodemographic and clinical variables, cranial MR images, scale scores, and possible complications. In Gazi University Faculty of Medicine, GKRS has been applied to patients with treatment-resistant OCD with the collaboration of psychiatry and neurosurgery clinics since 2005. The decision to perform GKRS has been made by 2 psychiatrists and a neurosurgeon. Patient selection for GKRS was made based on recommended criteria for OCD surgery[18-20] as follows: age 18-60 years and who provide informed consent, at least a 5-year history of serious OCD symptoms reducing quality of life and activities of daily living, meeting the DSM-IV or DSM-V criteria of OCD diagnosis, Y-BOCS score > 25 and disease evaluated as treatment-refractory by at least 2 psychiatrists, failure of both psychopharmacological treatment (at least 2 SSRIs or serotonin-norepinephrine reuptake inhibitors (SNRI) and clomipramine) at maximum doses with enough time and psychotherapy (CBT).

Psychiatric Evaluation and Follow-Up

All patients were evaluated with neuropsychological test battery including Stroop test, Wisconsin Card Scoring test, and Ray Auditory Verbal Learning test. YBOC-S was used to determine baseline levels and in the follow-ups of all patients. It was observed in patient files that some of the patients were additionally evaluated with the Brief Psychiatric Rating Scale (BPRS) and Montgomery-Asberg Depression Rating Scale (MADRS). The patients were evaluated with these scales at baseline, first, third, and sixth month of follow-ups.

GKRS Procedure and Neurosurgical/Neuroradiological Follow-Up

Frame application was performed on the day of the treatment under local anesthesia. Radiosurgery was delivered with the Elekta Gamma-Knife Perfexion unit (Elekta AB). Thin-sliced volumetric T1-weighted MR images of the entire brain, and T2-weighted MR images centered on the on the region of the anterior limb of the internal capsule were obtained (Figure 1). Anterior capsulotomy was performed using two 4-mm isocenters at the midputaminal point of the anterior limb of the internal capsule on each side with a maximum radiation dose of 140-180 Gy (Table 1). After the procedure, patients were briefly clinically/neurologically observed and discharged on the same day. Neurosurgical and neuroradiological follow-up of the patients was performed with MRI 6 months after GKS.

Statistical Analysis

The research data were evaluated by Statistical Package for the Social Sciences (SPSS) version 23.0 (IBM SPSS Corp.; Armonk, NY, USA). The demographic and clinical characteristics of the study cohort were summed by descriptive statistics (frequency, mean, and standard deviation). Repeated measure analysis was used to compare the measurements obtained at different times. $P < .05$ were considered statistically significant.

RESULTS

Sociodemographic characteristics of the participants are shown in Table 2. The mean age was 30.75±4.92 years. In this study, 58.3% of the participants were female. Half of them were single and most of the participants (83%) were educated from high school or university.

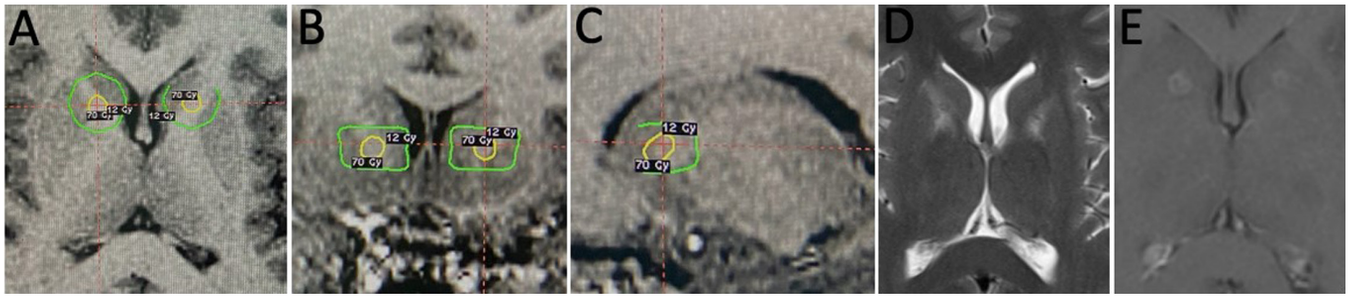

Figure 1. a-e. Axial (a), coronal (b), and sagittal (c) T1-weighted images showing the prescription isodose (yellow) and 12-Gy isodose (green). Images 6 months after GKRS: axial T2-weighted (d) and postcontrast T1-weighted (e) images showing the lesion in the anterior limb of the internal capsule. Note the focal ring of enhancement corresponding to the location of each isocenter (e).

Table 1. Maximum Radiation Dose and Number of Shots of the Patients Included in the Study

Patient No.	Max Radiation Dose (Gy)	Number of Shots
1	160	Double
2	160	Double
3	140	Double
4	140	Double
5	140	Double
6	140	Double
7	140	Double
8	140	Double
9	180	Single
10	180	Single
11	180	Double
12	180	Single

Table 2. Sociodemographic Characteristics of the Participants

Patient No.	Age	Gender	Marital Status	Education
1	25	Female	Single	High school
2	30	Male	Single	University
3	28	Male	Married	High school
4	40	Male	Married	University
5	38	Female	Married	Primary school
6	28	Female	Married	High school
7	25	Female	Single	University
8	29	Male	Single	University
9	31	Female	Married	Primary school
10	27	Female	Single	High school
11	32	Male	Married	High school
12	36	Female	Single	University

Table 3 shows the clinical variables of the participants. The mean age at onset of the disease was 16.58±6.37 years. The mean duration of the disease was 13.83±6.02 years. Hypertension, Hepatitis B carrier state, and epilepsy were physical comorbidities seen in 3 patients.

When looking at the treatment history of the patients, all of them had used at least 2 SSRIs or SNRI; of those, 2 patients had used 4 SSRIs and 3 patients had used 3 SSRIs. Three patients had used venlafaxine combination with SSRI. Eleven patients had used antipsychotics, clonazepam, or buspirone for augmentation. The most commonly used antipsychotics were quetiapine (in 10 patients), risperidone (in 6 patients), amisulpride (in 5 patients), and aripiprazole (in 4 patients). In 1 patient, 25 sessions of rTMS had been applied for OCD and 2 patients had Electroconvulsive therapy (ECT) for 21 and 12 sessions, respectively. CBT had been applied to all patients.

The scale scores of the patients are given in Table 4. All of the patients had baseline and follow-up Y-BOCS scores; in 8 patients BPRS and in 6 patients MADRS had been additionally applied. According to cut-off scores of MADRS (9 for mild, 29 for moderate, and 36 for severe depression),[21] all of the 6 patients had baseline depression; half of those had moderate and the other half had mild depression. After GKRS, depressive symptoms of 2 patients had remitted and 4 had mild depression. In other words, there was a 49.5% reduction in the mean MADRS scores which were 24.8 at baseline and 12.5 at the last follow-up. The mean BPRS scores of the 8 patients was 25.3 at baseline, and it was 10.7 after GKRS. The BPRS is recommended as a useful tool in evaluating treatment response in psychiatric diseases,[22] and it showed a 57.8% decrease in symptoms of the patients in our study.

The change in Y-BOCS scores of each patient is shown in Figure 2 and the change in the mean Y-BOCS is shown in Figure 3. It can be observed that there was a 35% reduction in the overall Y-BOCS scores ($F = 134{,}136$, $P < .001$). Half of the patients met the criteria for a full response (a greater than 35% improvement in the Y-BOCS score). No side effects were observed related to the treatment except headache in 2 patients.

DISCUSSION

In this study, 12 patients with treatment-resistant OCD were investigated retrospectively in terms of treatment

Table 3. Clinical Variables of the Participants

Patient No.	Age at Disease Onset	Duration of Disease (Years)	Physical Comorbidity	Hospitalization (N)	Family History
1	10	14	-	4	OCD
2	13	16	Hypertension	2	-
3	10	17	-	1	OCD
4	14	25	HBV	1	-
5	18	20	-	-	-
6	23	5	-	3	-
7	13	12	-	1	BAD
8	17	12	-	3	-
9	25	6	-	1	
10	11	16	Epilepsy	3	
11	15	17	-	-	
12	30	6	-	-	

Table 4. Scale Scores of the Participants at Baseline ad Follow-Ups

	Patient No.											
	1	2	3	4	5	6	7	8	9	10	11	12
Y-BOCS												
Baseline	27	33	36	30	33	34	31	22	40	40	35	27
1 month	25	17	9	14	25	27	28	16	40	36	35	27
3 months	29	14	7	9	22	25	27	12	28	35	34	26
6 months	25	15	14	8	18	15	24	5	21	37	32	26
Mean % of change	22.2	54.5	16.6	80	42.4	67.6	22.5	77.2	47.5	10	20	3.7
MADRS												
Baseline	-	-	29	35	27	30	19	9				
1 month	-	-	13	9	20	34	13	5				
3 months	-	-	14	9	16	28	14	4				
Mean % of change			27.5	77.1	44.4	46.6	42.1	55.5				
BPRS												
Baseline	15	24	29	16	30	44	29	16				
1 month	12	10	8	9	16	28	20	6				
3 month	10	8	9	8	8	24	18	8				
6 month	13	8	13	6	9	22	15	7				
Mean % of change	20	75	48.2	50	70	68.1	48.2	56.2				

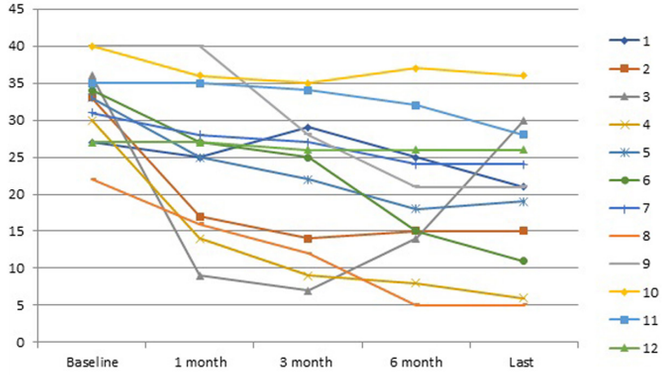

Figure 2. Change in Y-BOCS scores of each 12 participants.

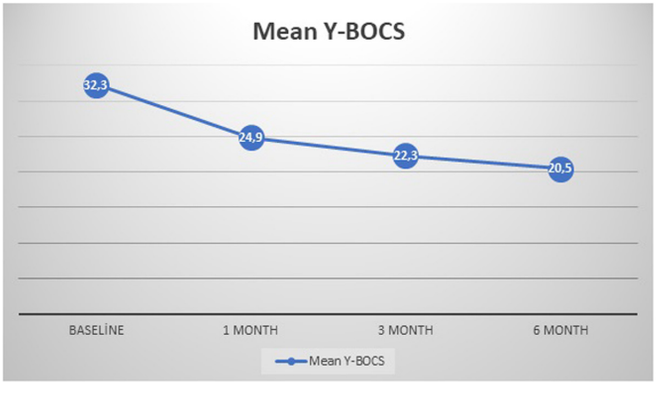

Figure 3. Change in the mean Y-BOCS scores of the participants.

outcomes of GKRS. "Full response" is mostly described in the literature as a greater than 35% improvement in the Y-BOCS score.[16,18,23] According to this, our data show a 50% full response rate of GKRS in treatment-refractory OCD. The other half of the participants also had some improvements in Y-BOCS scores but not enough for meeting the full response criteria. Remission in OCD has been defined as an endpoint Y-BOCS total score ≤ 12 or 8[20,24] and 2 patients (16.6%) in our study achieved remission according to both of the 2 cut-offs. A recent study from Turkey has reported a full response rate of 75% and a remission rate of 35% in 21 patients treated with GKRS.[20] Since the first GKRS has been performed for severe anxiety and OCD nearly 40 years ago[25], there has been mounting evidence revealing the safety and efficacy of this treatment. Rück et al.[13] reported a 56% of response rate that was based on a 35% improvement in Y-BOCS, in his long-term follow-up study with 25 patients. Similarly, Rasmussen stated that 56% of the 55 patients achieved full response during 3 years of follow-up.[26] There have been 2 randomized controlled studies investigating GKRS in OCD, one of whose focus was on the cognitive effects of GKRS. In this study, visuospatial memory performance was reported to be improved in the active treatment group than the sham group. Additionally, 37.5% of the patients of the treatment group were responders whereas there was no responder in the sham group.[14] The response rate stated in the other randomized controlled trial was 37.5% (3 of 8 patients), similarly.[16] Based on the given data, it can be concluded that the results give an overall impression that GKRS is effective in treatment refractor OCD. Nevertheless, patient selection criteria, response and remission criteria, variations in neurosurgery techniques, lack of long-term observations and consensus on how to observe these patients, and finally small samples of the studies remain as barriers to sufficient level of evidence.

The second aim of this study was to examine the change in depressive symptoms after GKRS, and it was observed that there was a 49.5% reduction in the mean MADRS scores of the participants. A similar observation was stated in a recent study that reported a significant decrease in depression and anxiety levels of patients treated with anterior capsulotomy.[27] In a study reviewing 14 data sets including 310 patients, the rate of patients who had significant improvement in depressive symptoms measured by Hamilton Depression Rating Scale (HAM-D), Beck Depression Inventory (BDI), or MADRS was stated as 85%.[23] It was also reported that improvement in depressive symptoms along with the symptoms of OCD continued during the 3-year follow-up.[26]

The comorbidity of depression with OCD is not a rare condition in clinical practice such that its lifetime prevalence is around 62.7-78.2%. The importance of this comorbidity is not only related to its frequent occurrence but also to suicide attempts, disability, and increased severity of symptoms caused by it.[28] In addition, depression in patients with OCD reduces treatment compliance as well as negatively affects the processes in CBT.[29] Considering the importance and consequences of this comorbidity, it can be said that the data on the underlying causes are insufficient. It is known that the main neuroanatomical regions involved in depression are dorsolateral, ventrolateral, or orbital prefrontal cortex and nucleus caudatus.[30] OCD is mainly associated with the fronto-striatal-thalamic pathway, and the orbitofrontal cortex, dorsal anterior cingulate cortex, striatum, and thalamus play a role in the development of the disease. On the other hand, the anterior limb of the internal capsule has strategic importance as it enables the connection of these brain regions.[18] For this reason, capsulotomy is the most preferred way in the neurosurgeries of OCD and also the effectiveness of different neuroablative surgeries was reported as 55% with higher response rates in capsulotomy (59%) than limbic leukotomy (47%) and cingulotomy (36%).[23] Lack of knowledge on the neuroanatomical infrastructure of depression and OCD comorbidity makes it difficult to interpret the underlying cause. Therefore, it is possible to adopt a more common observation that depressive symptoms develop secondary to the chronic and debilitating nature of OCD that significantly affects the functionality of daily life.[31] Whether the improvement in depressive symptoms seen in our study is the result of the regression in obsessive symptoms or the direct effect of the surgical intervention remains a question mark that should be revealed in future research.

The noninvasive nature of GKRS reduces possible complications related to neurosurgery. Sheehan et al.[32] reported no side effects in their study consisting of 5 patients. In another study, headaches, vertigo, weight changes, and episodic nausea/vomiting were reported as side effects that were episodic and transient.[33] Lopes also reported no permanent neuropsychologic side effect after 1-5 years of follow-up except delayed brain cyst in 1 patient.[16] A recent meta-analysis reported an increased risk of impulsivity and hypomania in DBS versus capsulotomy.[34] Overall, the most reported side effects of GKRS are headaches, cognitive deficits, and behavioral problems, and the radiation dose used in the surgery may be related to these side effects, especially headaches.[23] In our study, 2 patients had reported a transient headache following GKRS and other side effects were not observed.

The results of this study should be interpreted with some limitations. First, retrospective design limits the causal relationship and detailed observations. Since this study was performed by screening patients' files, information obtained was restricted to the records. Although follow-up of these patients was made based on some pre-agreed principles of the 2 clinics, longitudinal studies, as well as randomized-controlled studies, are thought to give more

definite data on effectivity and adverse effects of GKRS. The small sample size is another limitation; however, GKRS can be only applied in specialized clinics to patients with treatment refractor OCD with strict inclusion criteria, and this makes it very difficult to increase sample size in such studies. Some of the participants of this study were not living in the same city and could not come to further visits longer than 6 months therefore enough information couldn't be obtained about long-term results.

Despite these limitations, this second large sample-sized study from Turkey shows that GKRS is an effective technique for not only obsessive-compulsive disorder but also for depressive symptoms in treatment refractor OCD. In addition, its safety profile with mild side effects and non-invasive nature could expand its use. It is thought that, with paying specific attention to patient selection criteria, GKRS can be used safely in experienced tertiary clinics in cooperation with psychology, psychiatry, and neurosurgery departments.

Ethics Committee Approval: Ethics committee approval was received from the Ethics Committee of Gazi University (2021-283).

Informed Consent: Informed consent was obtained from all participants who participated in this study.

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