



Characteristics of Patients With Intractable Obsessive-Compulsive Disorder With High/Low Responsiveness to Gamma Knife Surgery

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Objective Obsessive-compulsive disorder (OCD) is a psychiatric condition that causes significant distress and social costs and often follows a chronic course with frequent relapses. Approximately 20% of patients do not respond to medication or cognitive behavioral therapy; gamma knife surgery (GKS) has been proposed as a treatment option for these patients. However, research on GKS for OCD patients is rare.

Methods In this study, 10 patients with treatment-resistant OCD underwent GKS, and the treatment response and side effects were assessed. The improvement in patients' obsessive-compulsive symptoms was evaluated using the Yale-Brown Obsessive Compulsive Scale (YBOCS) scores following GKS. Additionally, the characteristics distinguishing the groups with favorable responses to GKS from those with less favorable responses were examined.

Results GKS was well tolerated, and patients demonstrated a statistically significant reduction in YBOCS scores before and after GKS ($p=0.016$). Patients that responded to GKS exhibited distinct characteristics from those who did not respond. Patients who responded poorly tended to present an earlier age of onset, a longer duration of illness, more frequent hospitalizations, poorer social functioning, and a greater incidence of suicide attempts/thoughts.

Conclusion This study not only demonstrated that GKS is a safe and effective treatment method for intractable OCD but also revealed characteristics distinguishing patients who respond well to GKS from those who do not. These results may aid in the selection of patients for future application of GKS.

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Keywords Obsessive compulsive disorder; Gamma knife surgery; Intractable OCD.

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a common psychiatric condition, with a lifetime prevalence of up to 3%. OCD typically manifests at an early age, follows a chronic course, and is characterized by infrequent complete remission and frequent relapses.¹ OCD often cooccurs with other mental dis-

orders, such as depression, leading to significant distress through repetitive intrusive thoughts and consequent compulsive actions, increasing suicide rates and impairing daily functioning.² Pharmacotherapy with serotonin uptake inhibitors and cognitive behavioral therapy are the first-line treatments for OCD, but a considerable proportion of patients (approximately 20%) are reportedly resistant to these treatments.^{3,4}

In the treatment of intractable OCD, clinicians frequently encounter significant challenges that underscore the limitations of conventional pharmacotherapy.⁵ Despite the availability of various serotonin reuptake inhibitors and cognitive behavioral therapies, a substantial subset of patients remain resistant to these interventions.⁶⁻⁹ This resistance not only highlights the complex neurobiological underpinnings of OCD but also underscores the urgent need for alternative therapeutic strategies to address the debilitating impact of this disorder on individuals' lives.

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Recent advances in neurosurgical techniques have opened new possibilities for treating psychiatric disorders that are refractory to standard medical interventions. Among these, gamma knife surgery (GKS), a form of stereotactic radiosurgery, has emerged as a promising modality for targeting specific brain regions implicated in the pathophysiology of OCD.^{10,11} GKS is a method that employs the radioactive isotope cobalt-60 to locally destroy tissue.¹² Unlike traditional open brain surgery, GKS is minimally invasive and involves focusing high-intensity gamma rays on specific areas of the brain, thereby minimizing damage to surrounding healthy tissues.^{10,13-16} This precision offers a compelling advantage, especially in the delicate landscape of the human brain, where surgical interventions must be executed with the utmost care.

The rationale for employing GKS in the treatment of intractable OCD is grounded in a growing body of neuroimaging and neuroanatomical research that has identified the cortico-striato-thalamo-cortical circuit as a critical locus of dysfunction in OCD.¹⁷⁻¹⁹ Alterations in the activity and connectivity of this circuit are thought to contribute to the characteristic obsessions and compulsions of the disorder. By selectively targeting areas within this circuit, GKS has the potential to modulate aberrant neural pathways, thereby alleviating the symptoms of OCD without the need for ongoing medication or the risks associated with more invasive surgical procedures.^{20,21}

However, current research on GKS for patients with intractable OCD is limited.^{11,13-16,22} At present, predicting the prognosis for patients with intractable OCD who undergo GKS is challenging. While previous studies indicate that approximately 60%–70% of patients achieve a partial response, little is known about which patients with intractable OCD respond well to GKS.^{14,23,24} Therefore, research into determining which patient groups respond favorably to GKS is necessary to aid in patient selection and to reduce societal costs. This study aimed to explore the changes in obsessive-compulsive symptoms in ten individuals who underwent GKS and the characteristics of these patients according to their responsiveness, thereby providing a basis for predicting a favorable outcome.

METHODS

Participants

This study included all patients who were diagnosed with OCD at the outpatient Department of Psychiatry at Seoul National University Hospital (SNUH) between January 2017 and December 2023, underwent GKS, and completed at least one post-surgery evaluation. Treatment for all participants was administered through outpatient and inpatient services at the Department of Psychiatry, SNUH.

Patients were selected for GKS in accordance with estab-

lished criteria.²⁵ Each participant had a score of ≥ 20 on the Yale–Brown Obsessive Compulsive Scale (YBOCS) and had experienced symptoms of OCD for a minimum of 4 years, with the majority having endured the condition for more than 10 years. Recruitment was limited to those demonstrating inadequate responses to a minimum of three serotonin reuptake inhibitors, including clomipramine, or a combination at least two pharmacological agents, including antipsychotics or clomipramine or to individuals who participated in 20 or more hours of exposure and response prevention therapy but continued to exhibit moderate to severe symptoms. The age of the participants ranged from 18 to 75 years, and none had previously been diagnosed with any other persistent mental disorders. Prior to undergoing the surgical procedure, a structural magnetic resonance imaging (MRI) scan was performed on each patient to verify the absence of anatomical abnormalities.

Patient characteristics were collected, including sex, age, duration of illness, number of hospital admissions, psychiatric family history, history of suicide attempts, comorbid conditions, types of obsessions and compulsions, treatments received for OCD, occupation, marital status, and education level. These data are presented in Table 1.

Following the principles outlined in the Declaration of Helsinki, detailed explanations of the study were provided to the subjects, and the subjects provided written informed consent. The research protocol received official endorsement from the Institutional Review Board of SNUH (IRB No. H-2402-059-1510).

Clinical assessment

Obsessive-compulsive symptoms were assessed utilizing the YBOCS, which was administered by a psychiatrist during face-to-face interviews with the patients.^{3,26} Measurements were taken weekly for the first month following GKS, then bi-weekly until the 24th week, and monthly thereafter. Based on the outcomes of previous studies, a reduction in the YBOCS score of 35% or more was classified as full remission, a reduction of 20%–35% was classified as partial remission, and a reduction less than 20% was classified as minimal or no response.^{10,27-29} Additionally, we assessed the patients' symptoms of depression and anxiety using the Hamilton Depression Rating Scale and the Hamilton Anxiety Rating Scale.³⁰⁻³³

GKS

All patients were admitted to the hospital one day prior to undergoing GKS for a comprehensive clinical evaluation. Depending on the patient's condition, the procedure was conducted under either general or local anesthesia. GKS targeted the bilateral nucleus accumbens using stereotactic MRI, with the single shot size set at 4 mm for all patients except for one

Table 1. Clinical and demographic variables of the study participants (N=10)

	Value
Sex	
Male	7 (70)
Female	3 (30)
Age at diagnosis (yr)	19.9±5.65
Age at treatment (yr)	35.6±10.4
Duration of OCD (yr)	15.8±9.51
Psychiatric hospitalization	2.50±1.80
Family history of psychiatric disorder	7 (70)
Comorbidity	
Major depressive disorder	6 (60)
Bipolar disorder	3 (30)
Gender dysphoria	1 (10)
History of suicide attempt	2 (20)
Category of obsession	
Aggression	4 (40)
Contamination	3 (30)
Somatic	2 (20)
Sexual	1 (10)
Symmetry	1 (10)
Category of compulsion	
Checking	7 (70)
Cleaning	3 (30)
Repeating	2 (20)
Hoarding	1 (10)
Therapy	
Pharmacologic	10 (100)
Cognitive behavior therapy	10 (100)
Employment status	
Unemployed	5 (50)
Employed	2 (20)
Student	3 (30)
Marital status	
Single	6 (60)
Married	4 (40)
Education	
High school	2 (20)
University	8 (80)

Data are presented as mean±standard deviation or N (%). OCD, obsessive-compulsive disorder

patient, for whom shot sizes of 4 mm and 8 mm were used. All patients received fractionated GKS for 3 consecutive days. Most patients received 30 Gy per day at the 50% isodose level and two patients received 25 Gy per day at the 50% isodose

level. Patients were meticulously monitored for clinical and neurological side effects for two days post-surgery before discharge. The follow-up care included appointments at the psychiatry and neurosurgery outpatient departments to evaluate clinical symptoms. Between 6 and 12 months post-surgery, a follow-up MRI scan was performed to assess the outcomes of the GKS.

Statistical analysis

In this study, YBOCS scores assessed immediately before GKS and at the most recent follow-up after surgery were compared. Initially, tests for normality were conducted using the Kolmogorov–Smirnov and Shapiro–Wilk methods. Subsequently, paired t tests were performed. Additionally, the reduction rate in YBOCS scores was calculated, and patients were divided into three groups according to the reduction rate. Due to the small sample size, consisting of a total of 10 patients, with 5, 2, and 3 patients in each group, statistical significance for differences in characteristics among groups was not evaluated. Instead, only trends were described. All calculations were performed using the SPSS statistical package (version 25, IBM Corp., Armonk, NY, USA).

RESULTS

Clinical assessment

Patients underwent GKS between March 2017 and May 2023, with an average follow-up duration of 139.5 months. Five patients achieved a full response, defined as a 35% or greater reduction in YBOCS score. Two patients exhibited a partial response, with a YBOCS score reduction between 20% and 35%, and three patients demonstrated minimal or no response. The baseline average YBOCS score was 26.2 (SD=3.22), and the average score at the last follow-up was 16.9 (SD=7.96). The baseline and last follow-up YBOCS total, obsession, and compulsion scores were normally distributed, confirming the use of paired t tests for each score category. The results of the paired t tests revealed statistically significant differences in the mean total and obsession scores before and after GKS, but compulsion scores were not significantly different (total YBOCS score $p=0.016$, $T=2.967$; obsession score $p=0.012$, $T=3.128$; compulsion score $p=0.098$, $T=1.845$). The changes in YBOCS scores by group are presented in Figure 1. The trend in YBOCS scores among patients exhibiting a full response is presented in Figure 2. For patients who demonstrate a response, the graph reveals that a period of at least 14 to 20 weeks is required before a response becomes evident and the reaction stabilizes.

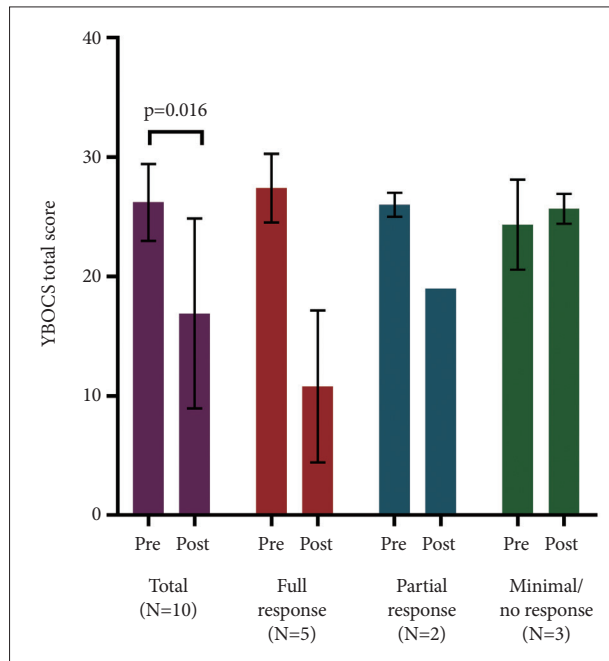


Figure 1. Changes in Yale-Brown Obsessive Compulsive Scale (YBOCS) scores according to response rate. A response rate of 35% or higher was classified as a full response, between 25 and 35% was classified as a partial response, and less than 25% was classified as minimal/no response. This classification was used to determine the average pre- and post-gamma knife surgery YBOCS scores for each group. “Pre” refers to the baseline time point, and “post” denotes the last follow-up time point. Total refers to the aggregate sum of all three groups.

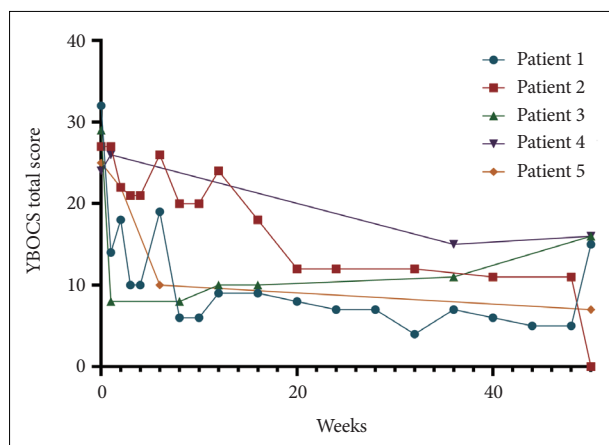


Figure 2. Trends in Yale-Brown Obsessive Compulsive Scale (YBOCS) scores by week. The progression of YBOCS scores over time, broken down by week, for patients demonstrating a response rate of more than 35% is illustrated. The final data points reflect the YBOCS scores at the time of the last follow-up.

Patient characteristics

Patients were divided into three groups according to their response rate: greater than 35%, 25%–35%, and less than 25%. Patients who exhibited a full response tend to have a shorter duration of illness (less than 10 years) and an older average age of onset (20.2 years) compared to other patients. In this

group, the patient with the highest number of hospital admissions had been admitted twice, and the average number of admissions for this group tended to be lower than the average number of admissions for other groups. Additionally, there was a higher incidence of major depressive disorder (MDD) as a comorbid condition. The majority of this group were either employed or students, with only one individual being unemployed. There was no history of suicide attempts. Of the five patients who exhibited a full response, two initially showed only a partial response and underwent a second procedure, after which they demonstrated a full response. Among these patients, one achieved full remission, with a YBOCS score of 0 at the last follow-up. Two of the five patients experienced rapid improvement in symptoms immediately following GKS, with YBOCS scores decreasing by more than half within a week. Another patient experienced a reduction in their YBOCS score to less than half of the baseline score after 6 weeks, while the remaining two patients experienced a gradual decrease in YBOCS scores over a period of more than 9 months.

The three patients who demonstrated minimal or no response had an average age at diagnosis of 14 years, indicating a tendency to develop the condition at an earlier age compared to other groups. Additionally, on average, at the time of GKS, the participants were approximately 45 years old, which was approximately 10 years older than the average age of the overall sample. All patients had a duration of illness exceeding 20 years and had been hospitalized for psychiatric treatment on four or more occasions. All three were unemployed, and two had a history of suicide attempts. Among the two suicide attempts, one patient experienced gender identity confusion, exhibited hoarding-related compulsive symptoms and was taking clozapine for severe depressive symptoms. The characteristics of each group are presented in Table 2.

Side effects

GKS was generally well tolerated. Among the entire cohort, three patients reported fatigue and exhibited an increase in sleep duration; however, these symptoms generally improved within three months. One patient complained of headaches, but these symptoms improved within one month.

DISCUSSION

This study investigated 10 patients with OCD who underwent GKS. Among these patients, five exhibited a full response, two demonstrated a partial response, and three showed minimal or no response. The baseline average YBOCS score was 26.2 (SD=3.22), and the YBOCS score measured at the last follow-up after GKS was 16.9 (SD=7.96). The overall YBOCS score demonstrated a statistically significant reduction. While

Table 2. Group-specific patient characteristics

	Full response (N=5)	Partial response (N=2)	Minimal/no response (N=3)
Sex (male/female)	3/2	1/1	3/0
Age at diagnosis (yr)	20.2±4.66	35.5±8.01	14.0±5.66
Age at treatment (yr)	30.2±11.2	35.5±7.85	44.7±3.54
Duration of OCD (yr)	10.0±9.67	14.5±2.12	26.3±2.62
Psychiatric hospitalization	1.40±0.55	2.00±2.00	4.67±0.94
Family history of psychiatric disorder	4	2	2
Baseline YBOCS score	27.4±2.87	26.0±3.77	24.3±3.77
Baseline HAM-D	12.6±4.27	11.5±5.50	19.67±5.91
Baseline HAM-A	12.8±7.05	11.0±3.00	15.7±11.6
Comorbidity			
Major depressive disorder	4	0	2
Bipolar disorder	1	1	1
Gender dysphoria	0	0	1
History of suicide attempt	0	0	2
Category of obsession			
Aggression	2	0	2
Contamination	1	2	0
Somatic	1	0	1
Sexual	0	0	1
Symmetry	1	0	0
Category of compulsion			
Checking	5	0	1
Cleaning	1	2	0
Repeating	1	0	1
Hoarding	0	0	1
Employment status			
Unemployed	1	1	3
Employed	2	0	0
Student	2	1	0
Marital status			
Single	3	1	2
Married	2	1	1
Education			
High school	1	0	1
University	4	2	2

Data are presented as mean±standard deviation or N. OCD, obsessive-compulsive disorder; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale

the obsession score showed a significant reduction, the compulsion score did not demonstrate a statistically significant reduction. This phenomenon is presumed to stem from an outlier with a increased compulsion score. This patient, who did not respond to GKS, maintained a nearly stable obsession score, but exhibited an increase in the compulsion score at post-GKS. Excluding this patient, the majority of patients ei-

ther maintained or showed a decrease in their compulsion scores prior to GKS. While there was an average decrease in total YBOCS score among the patients, the variability in score reduction resulted in an increase in the standard deviation. This indicates that the response to GKS varied among patients. The majority of patients recovered without enduring side effects, and GKS was well tolerated in all patients.

The patient groups divided by response rate to GKS exhibited distinct characteristics. Although the small sample size limits the statistical power, generally, the group with minimal or no response to GKS showed a tendency of having the following characteristics; diagnosed with OCD at a younger age, undergoing GKS at an older age due to a longer duration of illness more admissions to psychiatric wards, a larger number of history of suicide attempts or instances of suicidal ideation, a greater proportion of patients experiencing sexual and hoarding symptoms, a higher rate of unemployment, and a greater proportion of higher education.

Although research on prognostic factors for GKS in patients with OCD is rare, comparisons with previous studies, including those on patients with treatment-resistant OCD, revealed congruencies as well as some differences. Previous research has indicated that male sex is associated with a poorer prognosis in OCD patients undergoing GKS.¹⁴ In this research, all patients within the poor response group were male, showing a trend having a higher male ratio compared to other groups. Prior research has shown that being unemployed, receiving more inpatient treatment, presenting with obsessive-compulsive symptoms related to sexual/hoarding themes, and having a younger age of onset are factors associated with a worse prognosis.⁹ These factors are consistent with the characteristics of the patient group that did not respond well to GKS in this research. Additionally, among three patients who showed minimal or no response, two had attempted suicide or experienced suicidal thoughts, which represented a higher tendency compared to other groups. This result is consistent with previous findings that indicate a poorer prognosis for patients exhibiting suicidal ideation.³⁴ However, due to statistical reasons, patients with more severe baseline symptoms may appear to show greater improvement compared to those with less severe symptoms, necessitating caution in the interpretation of certain variables.

Meanwhile, there were some discrepancies between the results of this study and previous studies on prognosis of OCD.^{9,35} More specifically, factors such as living alone, high baseline YBOCS scores, and a family history of psychiatric disorders were evaluated as predictors of poor prognosis in OCD in previous studies, but such tendencies were not observed in this study.⁹ In this study, depression scale scores tended to decrease after GKS, and the full response group had a tendency to have a higher proportion of patients with comorbid MDD. It is generally known in OCD that the presence of comorbid psychiatric conditions is associated with a poorer prognosis. However, prior studies involving GKS in OCD have reported that depression scale scores mostly decreased after the intervention.^{13,14,16} Therefore, questions remain as to whether GKS directly improves depressive symptoms, if the improvement

in obsessive-compulsive symptoms leads to an improvement in depressive symptoms, or if GKS is more effective in cases accompanied by depressive symptoms. Further research on this matter is deemed necessary.

Strengths and limitations

This paper is limited by its small sample size, which prevents it from achieving sufficient statistical power for specific analyses. However, this study has value as one of the few studies that has analyzed the outcomes of GKS in patients with intractable OCD. In particular, its significance lies in classifying patient prognosis after GKS and analyzing how the patient characteristics of each group differ. Future research building on the results of this study could involve administering GKS to a larger sample of patients with intractable OCD and evaluating how patient characteristics correlate with outcomes. This research would not only aid in understanding the neurobiology of intractable OCD but could also assist in selecting patients for GKS treatment.

Conclusions

In this study, the clinical changes and characteristics of ten patients with intractable OCD who underwent GKS targeting the nucleus accumbens were investigated. The patients' average YBOCS scores decreased significantly, and no side effects that could cause sustained functional impairment were observed. Therefore, GKS could be considered a promising treatment option for patients resistant to conventional therapies. Patients who responded well to treatment were characterized by a lack of chronicity and good functioning. The group that responded well to GKS had a later age of onset, a shorter duration of illness, fewer hospitalizations, and better social functioning. Conversely, the group that responded poorly to GKS had an earlier age of onset, a longer duration of illness, more frequent hospitalizations, poorer social functioning, and a greater incidence of suicide attempts/thoughts. These results will be helpful in predicting the prognosis of GKS and in selecting patients for GKS treatment.

Availability of Data and Material

The datasets generated or analyzed during the study are not publicly available due to the inclusion of patient personal information but can be obtained from the corresponding author upon reasonable request.

Conflicts of Interest

Jun Soo Kwon, a contributing editor of the *Psychiatry Investigation*, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

Author Contributions

Conceptualization: Jun Soo Kwon, Moonyoung Jang. Data curation: Moonyoung Jang, Ho Sung Myung. Formal analysis: Moonyoung Jang. Funding acquisition: Jun Soo Kwon, Minah Kim. Investigation: Moonyoung

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