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SURGERY

Gamma Knife Surgery (GKS) for the Treatment of Obsessive-Compulsive Disorder (OCD) Refractory to Pharmacological Therapy: State of the Art and Review of the Literature

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Abstract

Obsessive-compulsive disorder (OCD) is a psychiatric condition characterised by ritualised behaviours and anxiety-stimulating thoughts. In severe cases, refractory to medical treatments, symptoms can have a substantial impact on patient's social life, with important direct and indirect costs. Radiosurgery (gamma knife surgery (GKS)) and functional neurosurgery (deep brain stimulation (DBS)) have been employed as therapeutic approaches for the more severe cases of the disorder. This systematic review aims to evaluate use of GK for OCD refractory patients. The main biomedical databases (PUBMED, EMBASE, SCOPUS and Cochrane) were investigated for English-written studies regarding the use of surgical treatments in case of medically refractory OCD. Special attention was given to the patient number, approach, outcomes and complications. A high response after the procedures was seen by the use of gamma knife (GK) treatment (48.26%). It has been noted that gamma knife radiosurgery (GKRS) anterior capsulotomy shows positive and effective responses to treating refractory OCD. Furthermore, there is low evidence of GKRS capsulotomy to be effective to decreasing depression and anxiety symptoms and improving the quality of life. The main complications after the radiosurgical treatment were mood disturbances, lethargy, insomnia, cerebral oedema, gastrointestinal symptoms, radiation necrosis, weight/appetite changes and brain cysts. Although the pharmacological advancements favoured the treatment of OCD patients, the general management is still complex and presents several difficulties. In a selected group of patients refractory to pharmacological treatments and cognitive behavioural therapy, radiosurgical intervention (GKS) is seen to be a valid solution. The review of the literature presented shows that GKRS is a valid alternative in the treatment of refractory OCD.

Keywords Obsessive-compulsive disorder · Gamma knife radiosurgery · OCD · GKRS

Abbreviations

GK	Gamma knife
GKS	Gamma knife surgery
GKC	Gamma knife capsulotomy
GKRS	Gamma knife radiosurgery
OCD	Obsessive-compulsive disorder
DBS	Deep brain stimulation
Y-BOCS	Yale-Brown Obsessive-Compulsive Scale

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Introduction

Obsessive-compulsive disorder (OCD) is defined as a common, chronic and long-lasting disorder in which a person has uncontrollable, reoccurring obsessions and compulsions that the patient feels the urge to repeat over and over [14]. OCD is characterised by a wide range of signs and symptoms; such diversity and severity of symptoms makes the diagnosis difficult. Gold standard treatment for a patient newly diagnosed with OCD consists in the use of pharmacological agents such as serotonin reuptake inhibitors (SRIs), selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants

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(TCAs), which seem to be beneficial in most of the cases [16]. However, there is a percentage of patients, in some cases reported to be up to 40%, with a high level of severity and who are refractory to pharmacological therapy [2]. Those patients are characterised by difficulty in everyday life to the point that they are unable to keep an employment, causing also important indirect costs for the society [11].

From several years, neurosurgical (mainly consisting of neuromodulation techniques) and radiosurgical approaches have been used for the treatment of severe and medically refractory cases of OCD. According to the literature, several surgical targets have been proposed as a possible treatment, among which some fibres of the orbito-fronto-striato-thalamocortical tract, ventral striatum, anterior internal capsule, nucleus accumbens and subthalamic nucleus [7]. These targets have been recognised thanks to previous studies, which have shown that, in these areas mentioned, there are increased brain activities in OCD patients [7, 12, 14].

With the purpose to assess the state of the art of the neurosurgical treatment in refractory patients, the authors performed a review of the literature.

Method

In order to perform a review of the literature about gamma knife in the treatment of medically refractory obsessive-compulsive disorder, two of the authors (IZ. and AL.) searched the main biomedical databases (PUBMED, EMBASE, SCOPUS and Cochrane) with a systematic approach, using terms related to gamma knife capsulotomy (GKC) and OCD.

The databases were searched for English language articles published up to January 2019. The MeSH terms include "neurosurgery", "Obsessive-compulsive disorder", "OCD", "Gamma knife", "Functional neurosurgery", alone or in combination. The abstracts were reviewed for each paper. Duplicates were removed. Exclusion criteria included the following: animal studies, incomplete studies from conference presentations, studies not related to the treatment of pharmacological refractory OCD, studies that did not concern neurosurgery, studies where full text was not available, studies that did not define the OCD and editorials or letters to the editor. In case it was needed, the authors also refer to the online supplementary information for specifics. We have considered all the types of studies (both retrospective and prospective). Publications that were written in a language different from English were excluded, even though the abstract was in English. The patients that were affected by OCD but a consequence of other conditions were not considered. We focused our effort in the attempt to analyse and see the number of patients, approaches, outcomes and complications presented.

Results

The results of the search are summarised in the PRISMA flow chart (Fig. 1). The authors found a total of 171 publications on PUBMED; the papers found were complementary with the studies found on the other databases searched. The studies found have been widely screened by 2 of the authors (IZ. and AL.), finding 75 studies fitting for the purpose of the review. Of the 75 articles, fourteen were non-English articles, nineteen were editorials or letters to the editor, fifteen were laboratory studies, three were case reports and ten were reviews/meta-analyses. The remaining 14 studies have been analysed.

Results have been summarised in Table 1. A total of 14 studies were included, for a total of 235 patients. A small fraction of the patients were affected by other important conditions, like skin-picking disorder (1), GAD or phobias (6), anxiety neurosis (17) and chronic anxiety (4). When indicated, the mean follow-up reported was 48.35 months (5.4–139.6 months).

The main grading score used to define the severity of OCD was the so called Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), which is a 10-item scale designed to measure the severity and type of symptoms in patients with OCD. This scale is still useful in tracking OCD symptoms at intake and during/after treatment.

As stated above, to assess the level of severity of the mean preoperative Y-BOCS, the value was 34.1, while the last one after the surgery was 17.39. A high level of response was reported; in particular, the gamma knife treatment brought benefits to 111 patients (48.26%).

In Table 2, complications due to the treatment were reported. Eighteen patients (7.83%) reported mood disturbances, 9 (3.91%) had neurological problems, 1 patient (0.43%) was affected by lethargy, 5 (2.17%) by insomnia, 17 patients (7.39%) had cerebral oedema, 8 (3.48%) gastrointestinal symptoms, 2 cases (0.87%) of radiation necrosis, 14 patients (6.09%) with weight/appetite changes, 4 cases of brain cysts (1.74%) after treatments and 7 (3.04%) other complications not specified.

At last it was noticed by the authors that the criteria used to define any eventual benefits from the radiosurgical treatment were usually loose.

Discussion

Obsessive-compulsive disorder is a type of mental health disorder, with a prevalence of 1.6% [3]. Clinically, these patients present with repetitious ideas and behaviours that they feel forced to do [21, 22]. Even though it can present at any age, the characteristic symptoms of OCD are usually exhibited by the age of 30 years [3].

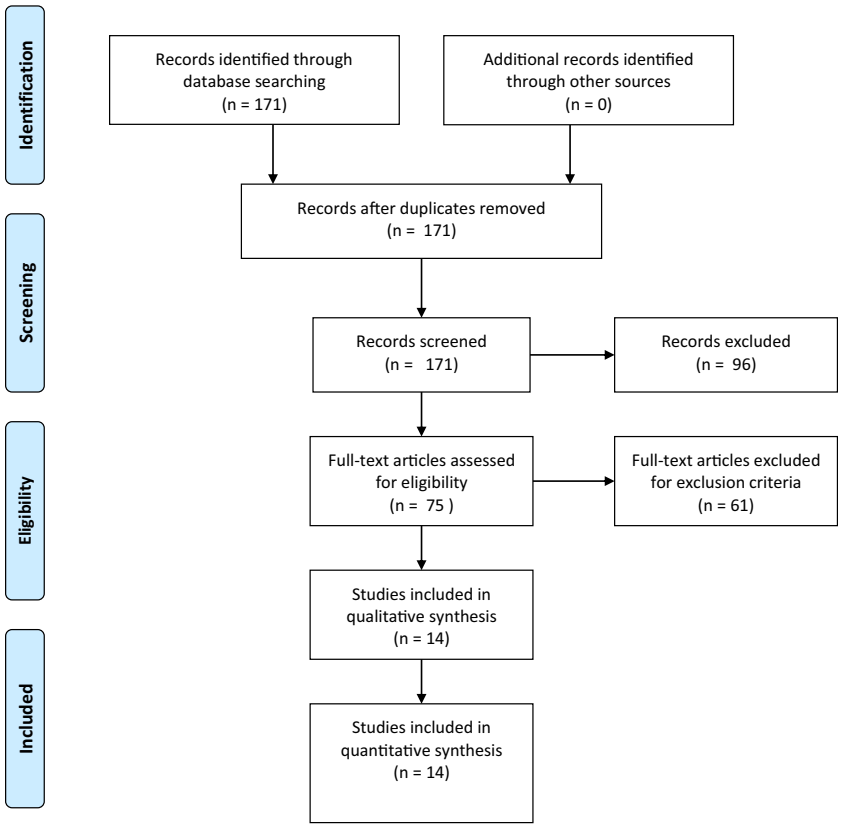

Fig. 1 PRISMA flow diagram

The Y-BOCS is one of the most used tools to assess and analyse the progress of OCD. The scale is subdivided based on severity of the disease: (1) subclinical OCD = 0–7; (2) mild = 8–15; (3) moderate = 16–23; (4) severe = 24–31; and (5) extreme = 32–40 [6].

First-line treatment for OCD includes psychotherapy and medications, mainly SRIs, SSRIs and TCAs (like fluoxetine, sertraline and clomipramine). If these drugs are not effective, tricyclic antidepressants (TCA), such as clomipramine, have been used. Low doses of antipsychotics and benzodiazepines can be added in case of necessity.

However, a small percentage of patients showed to be refractory to medical therapy. A Karolinska neurosurgical group, more than 2 decades ago, was able to demonstrate the safety and efficacy of stereotactic capsulotomy for pharmacologically refractory OCD [13, 15]. In their study, they considered 24 patients that showed a significant symptomatic relief in 80% of the cases [13]. The same group also observed an important correlation between changes in brain metabolism on PET and changes in personality scores [15].

In the recent years, the interest toward the use of radiosurgical procedures for the treatment of medically refractory OCD is increasing [10]. This can be seen by the recent publication of different studies on this topic. Miguel et al. [11] published a study where they perform a literature review, detailing how the procedure has changed over the years. In their work, they also highlighted the possible complications, which became lesser present thanks to the evolution of the targeting strategies. They concluded stating that gamma ventral capsulotomy is a reliable treatment option for selected cases of OCD. Sheth [20] instead published a commentary in which he analysed the present literature and focused on the future directions of such procedures; he outlined that changes in the geometry of the cobalt-60 sources over subsequent models of the gamma knife apparatus produced changes in the isodose geometry, modifying the doses per volume of tissue, possibly explaining why cyst development only occurred in patients treated after the change of gamma knife apparatus. In his study, he also paid attention to the fact that clinical responses are quite variable across patients (more than 1 or 2 years).

Despite the promising results obtained by Lopes et al. first in their prospective study [8] and then in their randomised controlled trial [9] in the radiosurgical treatment of medically refractory OCD, up to now, only few centres around the world are using gamma knife radiosurgery for this pathology [5]. Several reasons have been adduced to the unsatisfactory spread of this novel technique, which goes under the label of "psychiatric surgery"; first of all, there is the reluctance on the part of psychiatrists to refer patients and also the social stigma that patients and also some clinicians show for neurosurgery for psychiatric diseases (NPD). Other reasons that did not allow the hoped widespread are the lack of funding, the perceived experimental nature of currently available treatment options, such as DBS, and the historic misuse of

Table 1 Summary of papers considered in the review

Study	Technique	Patients	Diagnosis (*n*)	Mean time of follow-up (FU) (months)	Mean pre-op Y-BOCS (SD)	Mean last FU Y-BOCS (SD)	Last FU improvement (%)	Responders	Complications	Response criteria
Rylander et al.	GK capsulotomy	9	OCD (5); "chronic anxiety" (4)	5.4	NA	NA	NA	5/9 (55.5%)	NA	Loose response criteria
Lindquist et al.	GK capsulotomy	17	OCD and "anxiety neurosis" (17)	84	NA	NA	NA	5/7 (71.4%)	Lethargy (1)	NA
Kihlström et al.	GK capsulotomy	11	OCD (5); GAD or phobias (6)	NA	NA	NA	NA	4/11 (36.4%)	Severe fatigue (3), signs of frontal lobe syndrome (apathy, fatigue, loss of initiative and occasional disinhibition) (2)	Loose response criteria
Rasmussen et al.	Gamma ventral capsulotomy, single and double shots	35	OCD (35)	NA	NA	NA	NA	1/15 (6.7%) (single shot), 5/13 (second, additional shot), 10/18 (double shot)	Headache and cerebral oedema (3/15 additional isocenter), asymptomatic caudate infarctions (2/15 additional isocenter), mania (1/15 additional isocenter); headache and cerebral oedema (3/20 double shot), mania (2/20 double shot), apathy and amotivation (1/20 double shot)	≥ 35% reduction in Y-BOCS
Lippitz et al.	GK capsulotomy	10	OCD (10)	NA	NA	NA	74.6 (42.7)	7/10 (70%)	NA	≥ 50% reduction in Y-BOCS
Rück et al.	GK capsulotomy	9	OCD (9)	139.6	33, (3.4)	14.3 (12.1)	55.8 (36.3)	5/9 (55.6%)	Chronic brain oedema (1), radiation necrosis with sequelae (1), cognitive changes (1), apathy (2), urinary incontinence (1), seizures (1), sexual disinhibition (1)	≥ 35% reduction in Y-BOCS
Lopes et al.	Gamma ventral capsulotomy, double shots	5	OCD (5)	48	32.2 (1.48)	20.6 (12.3)	36.4 (37.9)	3/5 (60%)	Weight changes (4)	≥ 35% reduction in Y-BOCS + CGI scores
Kondziolka et al.	Gamma ventral capsulotomy, double shots	3	OCD (2); skin-picking disorder (1)	41.6	37.3 (2.9)	16.3 (8.6)	55.1 (26.3)	2/3 (66.7%)	NA	NA
Rasmussen et al.	Gamma ventral capsulotomy, single and double shots	55	OCD (55)	NA	NA	NA	NA	1/15 (6.7%) (single shot), 5/13 (38.5%) (second, additional	Asymptomatic brain cysts (2), symptomatic brain cyst (1, with headache,	≥ 35% reduction in Y-BOCS

Table 1 (continued)

Study	Technique	Patients	Diagnosis (*n*)	Mean time of follow-up (FU) (months)	Mean pre-op Y-BOCS (SD)	Mean last FU Y-BOCS (SD)	Last FU improvement (%)	Responders	Complications	Response criteria
								shot), 13/22 (59.1%) (double shot)	dizziness and visual changes, requiring drainage), headaches and cerebral oedema (10), apathy and amotivation (1)	
SheehaN et al.	Gamma ventral capsulotomy, single shot	5	OCD (5)	22.2	32.4 (1.5)	16.2 (8.3)	50.5 (23.3)	4/5 (80%)	NA	NA
Lopes et al.	Gamma ventral capsulotomy, double-shot	16	OCD (16)	NA	34.8 (4)	NA	NA	0/8 (0)	Increased appetite and weight (4) (sham group)	≥ 35% reduction in Y-BOCS + CGI scores
				54.5	32.5 (0.7)	17.8 (10)	46.8 (26)	2/8 (25)	Manic episode (2), delirium + perseverations for 1 week (1), increased appetite and weight (6), memory deficits for 10 months (1), asymptomatic brain cyst (1), substance abuse (1) (all operated patients)	NA
				55.2	33.1 (3.3)	17.3 (13.1)	51.4 (33.5)	7/12 (58.3)		NA
Peker et al.	Gamma ventral capsulotomy, single and double shots	10	OCD (10)	9	38	16	NA	7 (70)	NA	NA
Spatola et al.	GK anterior capsulotomy	10	OCD (10)	NA	32.7 (4.8)	10.5	NA	7 (70)	0	≥ 35% reduction in Y-BOCS + CGI scores
Gupta et al.	GK Ventral Capsulotomy	40	OCD (40)	24	35	27.5 (10.8)	NA	18/40 (45%)	10 (25%) had mood disturbance. 3 (7.5%) had neurological complications. 5 (12.5%) cases of insomnia. 8 (20%) cases of gastrointestinal symptoms. 1 (2.5%) radiation necrosis with oedema	≥ 35% reduction in Y-BOCS + CGI scores

Table 2 Summary of complications reported

Type of complication	*n* cases (%)
Mood disturbances	18 (7.83)
Neurological disturbances	9 (3.91)
Lethargy	1 (0.43)
Insomnia	5 (2.17)
Cerebral oedema	17 (7.39)
Gastrointestinal symptoms	8 (3.48)
Radiation necrosis	2 (0.87)
Weight/appetite changes	14 (6.09)
Brain cyst	4 (1.74)
Other	7 (3.04)

neuromodulation. At last, we should remember that particular procedures of functional neurosurgery are usually only performed in the academic centres, limiting in a certain way the access to the patients [10]. Even though there is an important gap among neurosurgeons and psychiatric patients, which could be reduced with a more effective way of communication, a strong collaboration between neurosurgeons and psychiatrists should be encouraged, since the latter are usually the "reference point" of psychiatric patients.

In the recent years, the use of deep brain stimulation (DBS) for the treatment of medical refractory OCD was also approved by the FDA. Several neuroanatomical targets have been considered for DBS; the main structures targeted are the nucleus accumbens, subthalamic nucleus, ventral internal capsule/ventral striatum and anterior internal capsule, showing a satisfactory result in 50% of the cases analysed [1]. Even though the results were promising, complications, like intracerebral haemorrhage, have been reported [1].

Both DBS and gamma knife radiosurgery (GKRS) present technical advantages in the treatment of OCD, like the reversibility and mobilisation of stimulation over time with regard to BDS and the fact that the lesion is permanent and does not require adjustment over time and there is no surgical opening in the case of GKRS. From an economic point of view, there are some considerable advantages to take in account, like the reduction of indirect social costs, since most of the patients, in the case in which the treatment is effective, are able to go back to a normal social life and are able to be employed; radiosurgery also avoids the expense and morbidity (lead breakage, infection and stroke) associated with a surgical intervention (DBS).

Thanks to the several advantages listed above, several groups started to test the effect of the different dosages of radiation in GKRS. Rück et al., analysing his series, reported that, using a dosage of 200 Gy, there were 10 complications like apathy, decline in executive function and disinhibition [12]. The good results presented by Rück et al., in terms of functional outcome, were later confirmed in the series presented by Kondziolka et al. in their series [5]. In their series, however, they did not report any main complication [11].

Another problem considered, together with the proper dosage to use, was the volume appropriate for a GK capsulotomy, which is still a topic of discussion. In Rück et al.'s study, radiofrequency thermos-lesion or radiosurgical lesioning in each capsule was performed [18]. Meanwhile, Kondziolka et al. tried a double-isocenter lesion, which has been proposed more than a decade before, observing a clinical improvement of at least 35% in the Y-BOCS score, defined as the least to define an improvement, in 59% of patients 1 year and in 69% of patients 2 years after GKRS [5]. Kondziolka et al.'s approach was recalled by Lopes et al., reporting a similar rate of success (60%) [8]. In a recent study, Spatola et al. began with a lower dose of 140 Gy given the concerns linked to side effects [19]. After, they adopted a dose of 160 Gy with the single-isocenter approach to produce a sufficient lesioning effect. The therapeutic value in lesioning the superior portion of the capsule seems less certain, showing a clinical improvement in 80% of the patients. No side effects were noted.

GKC Outcomes and Complications

Kihlström et al., in their preliminary study [4], reported the presence of several complications in 5 out of the 9 patients (55.56%); the main complications reported included headache, apathy, fatigue, loss of initiative and disinhibition. On the last control (at 33–41 months after the procedure), three (33%) remained symptomatic.

In the later Karolinska cohort, published by Rück et al. [18], in addition to the complication described before, they noted other important complications, like a general weight gain (from a mean weight of 69.8 to 76.0 kg), and also sexual disinhibition (8%), urinary incontinence (4%), radiation necrosis (4%) and brain oedema (4%). In this series, it has been also hypothesised a correlation between radiation dose and the complications, since they noticed that there was a higher frequency of complications in patients receiving a higher dose (considered to be 200 Gy).

In a recent retrospective series, presented by Rasmussen et al. [17], several complications have been outlined. Most patients complained of a postoperative headache that resolved between the second and fifth day. More worrying complications, however, occurred. Five patients (9%) developed oedema with headache. Six patients developed asymptomatic lacunar infarcts in the first year of follow-up, presumably because of the lesioning of small vessels. Manic episodes developed in 3 patients (5.45%) which had previous stories of manic episodes, which have been easily controlled with mood stabilisers. Also brain cysts have developed after treatment in 3 patients (5.45%). Two of the cysts were clinically asymptomatic. The third one presented with headache, dizziness and visual changes 10 months after GKRS.

In the next year, Lopes et al. published the first double-blind clinical randomised trial, involving 16 patients [9].

Eight patients were randomised to active gamma ventral capsulotomy (GVC), and the other eight to a sham procedure, which includes a sham attachment on the GK device. At the end of the active phase of the study, which happens 1 year later, 2 patients (25%) randomised to the GVC arm achieved a response, and no one achieved a satisfactory response in the sham arm [9].

Even though there was no statistical difference in terms of primary outcome, median Y-BOCS scores at 12 months were 23.5 for the GVC arm vs. 31 for the sham arm ($p = 0.01$). The patients were still followed even after the end of the trial; during a following control (54-month open-label follow-up), 3 non-responder patients in the GVC arm showed satisfactory results at months 14, 18 and 24, respectively [9].

After the first 12 months, all the patients in the sham group were offered open-label active treatment and four accepted. Of those who accepted, two achieved a complete response, at months 6 and 36. Therefore, a total of 7 out of 12 patients (58%) showed a good result.

Sheehan et al. studied 5 patients who underwent GVC with a single ventral shot [19]. The median pre-GVC Y-BOCS score was 32 (range, 31–34). Four of the five patients (80%) were considered to have achieved marked clinical improvement, with an important reduction in Y-BOCS scores (up to 59–62%).

The most recent study about radiosurgical treatment of OCD was performed by Spatola et al., where they reported their series of 10 patients treated with anterior GKRS capsulotomy. In their study, seven patients showed a complete response, one a partial response and two were defined as non-responders. The complications were minimal: one patient gained weight and two had memory deficits.

Use of GKRS in the Treatment of Medical Refractory OCD: Which Evidence Do We Have?

The available evidence regarding GKC for severe, refractory OCD demonstrates a complex interplay between several variables, which includes patient selection (difficulty in diagnosing correctly OCD) and radiation dose planning. Thanks to the technological advancement and the awareness of lethal effects of high radiation doses, centres all around the world have started to decrease it [17]. Even though the results of the Karolinska group were promising, with 50% of the patients showing satisfactory improvements, several important complications have been reported (like radiation necrosis–induced cysts and oedema) [18]. Because of these risks, they lowered the total dose, limiting the distribution to a single 4-mm isocenter at 180 Gy near the dorsoventral mid-point of the ALIC, which, however, gave a poor response in the patients [17]. In order to obtain a higher response, avoiding the main complications, they used a two-shot GVC procedure, which allowed a larger lesion with a larger resulting lesion volume. The hypothesis was, indeed, correct; in fact, the first GVC cohort showed a 38% full and 15% partial response rate at 12 months with insignificant complications and a second cohort with a 55% full response rate at 12 months, but non-negligible rate of adverse events.

In the randomised clinical trial performed by Lopes et al., they used 180-Gy two-shot GVC with a GK model B. The data they presented highlighted the importance of considering a long interval between treatment and the potential response, before declaring the failure of the therapy. Although some have reported improvement in the first 3 months after the procedure [19], most have reported changes in the 6–12-month range, although some do not improve until 24 or even 36 months [9]. Most probably, decreasing the radiation dose-volume delivery may have an effect on time to response, but there is no evidence about this theory. The reduction in the number and the dose of the isocenters most probably contributed in the reduction of adverse events.

Conclusions

Up to now, the general management of patients affected by OCD is still complex and presents several difficulties. In a selected group of patients affected by OCD refractory to medical and cognitive behavioural therapy, neurosurgical (deep brain stimulation) and radiosurgical (gamma knife surgery) interventions are seen to be a valid solution. The review of the literature presented shows that GKRS is a valid alternative in the treatment of refractory OCD. There is also a weak evidence that GKRS capsulotomy is effective not only in reducing obsession and compulsion symptoms but also in improving quality of life and reducing depression and anxiety.

Compliance with Ethical Standards

Ethical Statement The present study does not need any approval from the ethical committee nor a signed informed consent from patients.

Conflict of Interest The authors declare that they have no conflict of interest.

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