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LITERATURE REVIEW

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Benefits of stereotactic radiosurgical anterior capsulotomy for obsessive-compulsive disorder: a meta-analysis

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OBJECTIVE Anterior capsulotomy (AC) is a therapeutic option for patients with severe, treatment-resistant obsessive-compulsive disorder (OCD). The procedure can be performed via multiple techniques, with stereotactic radiosurgery (SRS) gaining popularity because of its minimally invasive nature. The risk-benefit profile of AC performed specifically with SRS has not been well characterized. Therefore, the primary objective of this study was to characterize outcomes following stereotactic radiosurgical AC in OCD patients.

METHODS Studies assessing mean Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores before and after stereotactic radiosurgical AC for OCD were included in this analysis. Inverse-variance fixed-effect modeling was used for pooling, and random-effects estimate of the ratio of means and standard mean differences were calculated at 6 months, 12 months, and the last follow-up for Y-BOCS scores, as well as the last follow-up for the Beck Depression Inventory (BDI)/BDI-II scores. A generalized linear mixed model was used to generate fixed- and random-effects models for categorical outcomes. Univariate random-effects meta-regression was used to evaluate associations between postoperative Y-BOCS scores and study covariates. Adverse events were summed across studies. Publication bias was assessed with Begg's test.

RESULTS Eleven studies with 180 patients were eligible for inclusion. The mean Y-BOCS score decreased from 33.28 to 17.45 at the last-follow up ($p < 0.001$). Sixty percent of patients were classified as responders and 10% as partial responders, 18% experienced remission, and 4% had worsened Y-BOCS scores. The degree of improvement in the Y-BOCS score correlated with time since surgery ($p = 0.046$). In the random-effects model, the mean BDI at the last follow-up was not significantly different from that preoperatively. However, in an analysis performed with available paired pre- and postoperative BDI/BDI-II scores, there was significant improvement in the BDI/BDI-II scores postoperatively. Adverse events numbered 235, with headaches, weight change, mood changes, worsened depression/anxiety, and apathy occurring most commonly.

CONCLUSIONS Stereotactic radiosurgical AC is an effective technique for treating OCD. Its efficacy is similar to that of AC performed via other lesioning techniques.

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KEYWORDS stereotactic radiosurgery; anterior capsulotomy; obsessive-compulsive disorder; functional neurosurgery

Obsessive-compulsive disorder (OCD) is characterized by obsessions, recurring intrusive thoughts, and compulsions, which are defined as repetitive behaviors aimed at neutralizing obsessions. OCD is common, with a lifetime prevalence of approximately 2.5% of the population.[1] A growing array of treatment options including medications, psychotherapy, and transcranial magnetic stimulation have been used to assist patients with OCD;[2] however, an estimated 40%–60% of patients have a suboptimal response to standard therapies.[3] Patients with treatment-refractory severe OCD are candidates for neurosurgical interventions including neuroablative procedures.

Anterior capsulotomy (AC) is a neuroablative procedure that has been used to treat OCD. AC lesions disrupt

ABBREVIATIONS AC = anterior capsulotomy; ALIC = anterior limb of the internal capsule; BDI = Beck Depression Inventory; DBS = deep brain stimulation; NOS = Newcastle-Ottawa Scale; OCD = obsessive-compulsive disorder; PI = prediction interval; RCT = randomized controlled trial; ROB 2 = Cochrane Risk of Bias 2 tool; RoM = ratio of means; SMD = standard mean difference; SRS = stereotactic radiosurgery; Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

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the white matter tract in the anterior limb of the internal capsule (ALIC) connecting the prefrontal cortex and mediodorsal thalamus, thereby reducing the hyperactivity of corticostriatal circuitry involving the orbitofrontal cortex, anterior cingulate cortex, and caudate that has been implicated in OCD.[4–6] Reported response rates following AC have ranged from 47% to 79%, with 11%–24% of patients experiencing remission.[7–12] In addition to OCD, AC has also been used to treat depression. Several studies and meta-analyses have indicated response rates of 25%–60% for depression.[13–19] Studies of OCD patients with comorbid depression have found that 25%–70% of patients who undergo AC will have a depression response.[20–23]

AC lesions can be performed using multiple techniques including stereotactic radiosurgery (SRS), radiofrequency ablation, mechanical lesioning, laser ablation, and focused ultrasound.[9] SRS has grown in popularity as a method for performing AC because of its minimally invasive nature and ability to be performed in the outpatient setting without the need for an incision or general anesthesia. That said, despite the unique risk profile that radiation use may have on both complication rates and efficacy, there has been limited evidence demonstrating the extent of benefits that patients receive from stereotactic radiosurgical AC exclusively. While several meta-analyses of AC exist, patients undergoing SRS make up a minority of cases.[7–12,24–26] Additionally, although a randomized controlled trial (RCT) has demonstrated the efficacy of stereotactic radiosurgical capsulotomy, it and other nonrandomized studies have had sample sizes in the single digits, making it difficult to provide patients with accurate percentages on the efficacy and complication rates specific to stereotactic radiosurgical AC. Thus, the goal of the present study was to perform a meta-analysis to quantify outcomes following stereotactic radiosurgical AC for OCD.

Methods

Search Strategy

PubMed, World of Science, and Embase databases were searched from inception to May 15, 2022. The search terms included "OCD", "Gamma Knife", "radiosurgery", and "capsulotomy." One author (R.G.) conducted the literature search and screened studies for eligibility using article titles and abstracts. Two authors (R.G., J.W.C.) screened the full text of eligible papers. The present study was not prospectively registered in a database.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: human studies, RCTs or observational studies, a primary diagnosis of OCD, use of SRS to perform AC, and use of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) to quantify OCD symptoms before and/or after stereotactic radiosurgical AC. Exclusion criteria were as follows: Y-BOCS scores not provided, lesioning other than AC performed, technique other than SRS used to perform AC, case reports, non–English language articles, letters, reviews, meta-analyses, or abstracts. In cases of overlap in patient populations between multiple studies, the study with the larger sample size was included in the final analysis.

Data Extraction

Extracted variables included sample size, patient age and gender, targeting details, follow-up time points, mean pre- and postoperative Y-BOCS scores at all available time points, responder status at the last follow-up (remission, response, partial response, worsened), disease duration, mean pre- and postoperative Beck Depression Inventory (BDI) or BDI-II scores, and adverse events. In addition to group level data, individual patient data for both Y-BOCS and BDI/BDI-II scores were extracted when available. Remission was defined as a Y-BOCS score ≤ 8; response, at least 35% improvement in the score; partial response, 25%–34% improvement in the score; nonresponse, 0%–24% improvement in the score; and worsening, an increased postoperative score. The BDI/BDI-II was chosen because it was the scale most used to measure depression in the included studies.

Reported adverse events were included in our analysis only if they were new symptoms after AC. One study detailed adverse events specifically attributed to psychiatric medications; however, these were not included in order to focus our analysis on the effects of stereotactic radiosurgical AC.[20] Adverse events were categorized as procedure related, neuropsychiatric, neurological, or other. Neuropsychiatric adverse events were further divided into cognitive and psychiatric categories. Two authors (R.G., J.W.C.) conducted data extraction.

Quality Assessment

The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of observational studies.[27] This scale assigns a rating from 0 to 9: 0–2, poor quality; 3–5, fair quality; and 6–9, good/high quality. The Cochrane Risk of Bias 2 tool (ROB 2) was used to evaluate the quality of RCTs.[28] This scale assigns an either "low" or "high" risk of bias to studies. Two authors (R.G., N.C.H.) independently rated each study included in our analysis. Any discrepancies were resolved by the lead author (S.K.B.).

Statistical Analysis

For continuous outcomes, the random-effects estimate of the ratio of means (RoM), or response ratio, as well as the standard mean difference (SMD), was calculated for each study at 6 months, 12 months, and the last known follow-up for mean Y-BOCS scores. These measures were only calculated at the last known follow-up for mean BDI/BDI-II scores due to data availability. An inverse-variance fixed-effect model was used for pooling. For cohorts with available individual patient data, additional paired analysis of pre- and postoperative Y-BOCS and BDI/BDI-II scores was performed using dependent-samples t-tests. For categorical outcomes, namely patient response category, a generalized linear mixed model was used to generate fixed- and random-effects models.[29,30] Forest plots were generated with study-level estimates of outcomes, pooled estimates across studies with accompanying 95% confidence intervals, and the relative weighted contribution per study. For binomial outcomes, specifically responder status, 95% prediction intervals (PIs) were reported to assess heterogeneity.[31] The Q statistic and I^2 index were used to

assess for heterogeneity. A $p < 0.1$ for the Q statistic was deemed indicative of between-study heterogeneity. An $I^2 <$ 50% was considered low heterogeneity; 51%–75%, moderate heterogeneity; and > 75%, substantial heterogeneity.[32] Univariate random-effects meta-regression using aggregate-level data was used to evaluate associations between postoperative Y-BOCS scores and study covariates (mean age at surgery, gender, duration of symptoms, time to follow-up). Adverse events were summed across studies. The percent frequency of adverse events was calculated by dividing the number of adverse events by the combined sample size of the studies reporting adverse events. Publication bias was assessed quantitatively with Begg's test.

Results

Study Characteristics

The literature search yielded 850 articles, 245 of which were unique. Titles and abstracts were screened for eligibility. The full text of 17 articles was assessed. Eleven met the inclusion criteria, one of which was an RCT, and the rest were observational studies.[20–23,33–38] A PRISMA flowchart is presented in Fig. 1. One observational study was divided into two cohorts on the basis of whether one or two isocenters had been used bilaterally.[33] The included RCT was also divided into two cohorts: patients receiving active treatment or patients initially receiving sham treatment and later opting for active treatment.[22] The 11 studies comprised 13 cohorts yielding 180 patients with baseline data.[20–23,33–39] One of these studies, by Gupta et al., was not included in the analysis of change in postoperative Y-BOCS scores because it provided median rather than mean scores; however, it was included in determining responder status and adverse events, as these factors do not rely on measures of central tendency.[39] All observational studies met the NOS criteria for good/high quality. The RCT received a rating of low risk of bias, per the ROB 2. The mean age was 34.61 ± 2.25 years. Eighty-seven of the 171 patients (50.9%) with known sex data were female. The mean disease duration was 15.77 ± 2.80 years. All studies used bilateral lesioning, and the number of isocenters ranged from 1 to 5. In general, lesions targeted the ventral third of the anterior internal capsule and were 8–21 mm rostral to the posterior border of the anterior commissure. Radiation doses ranged from 120 to 200 Gy. Characteristics of the included studies are summarized in Table 1.

OCD Symptoms

Among 12 cohorts comprising 140 patients with preoperative Y-BOCS scores and 129 patients with postoperative scores, the pooled mean preoperative score was 33.28 (95% CI 32.38–34.17) and the pooled mean last follow-up score was 17.45 (95% CI 15.79–19.11) at a mean follow-up of 54.80 ± 28.53 months. The RoM was 0.54 (95% CI 0.48–0.61, $p < 0.001$) and the SMD was –1.93 (95% CI –2.35 to –1.50, $p < 0.001$) for the preoperative to last follow-up Y-BOCS score change (Fig. 2). There was minimal study heterogeneity ($I^2 = 37.0\%$, $p = 0.095$). No significant publication bias was present by Begg's test ($p = 0.41$). We also examined the change in the mean Y-BOCS score from preoperatively to the fixed postoperative time points of 6 and 12 months. Among 6 cohorts comprising 90 preoperative patients and 87 patients at 6 months, the pooled mean preoperative Y-BOCS score was 34.22 (95% CI 33.08–35.36) and pooled mean 6-month postoperative score was 26.45 (95% CI 21.70–31.20).[21,23,33,35,36] The RoM was 0.78 (95% CI 0.60–1.02, $p = 0.060$) and the SMD was –1.23 (95% CI –2.17 to –0.29, $p = 0.025$; Supplemental Fig. 1) for the preoperative to 6-month postoperative Y-BOCS score change. Among 7 cohorts comprising 98 preoperative patients and 91 postoperative patients, the pooled mean preoperative Y-BOCS score was 33.78 (95% CI 32.65–34.91) and the pooled mean 12-month postoperative score was 22.92 (95% CI 18.61–27.24).[22,33,36–38] The RoM was 0.67 (95% CI 0.54–0.84, $p < 0.01$) and the SMD was –1.49 (95% CI –2.34 to –0.63, $p < 0.01$) for the preoperative to 12-month follow-up Y-BOCS score change (Supplemental Fig. 2).

Paired analysis was conducted for the studies that provided patient-level data. In 9 cohorts containing 63 patients with both preoperative and postoperative individual Y-BOCS scores, the paired t-test analysis indicated a statistically significant difference between the mean preoperative (32.56, 95% CI 31.48–33.63) and mean postoperative (18.00, 95% CI 15.35–20.65) Y-BOCS scores at a mean last follow-up of 45.5 ± 44.1 months ($p < 0.001$; Supplemental Fig. 3).

Regression analysis indicated that there was a significant relationship between follow-up Y-BOCS score and follow-up length, with the Y-BOCS score decreasing as the follow-up increased ($p = 0.046$; Fig. 3). Age ($p = 0.430$), gender ($p = 0.266$), and disease duration ($p = 0.106$) were not significantly associated with the change in the Y-BOCS score.

We additionally examined responder status. Studies varied in their reporting of different types of responder status; thus, the number of patients included in each analysis of responder status also varied. As detailed previously, the study by Gupta et al. was not included in the above analysis of change in postoperative Y-BOCS scores but was included in the following analyses of responder status.[39] A pooled analysis of all 13 cohorts composed of 176 patients with available data revealed that the estimated proportion of responders was 0.60 (95% PI 0.30–0.83; Fig. 4A).[20–23,33–39] A pooled analysis of 12 cohorts comprising 136 patients revealed that the estimated proportion of partial responders was 0.10 (95% PI 0.03–0.27; Fig. 4B).[20–23,33–38] Across 10 cohorts including 83 patients, the estimated proportion of patients experiencing remission was 0.18 (95% PI 0.04–0.55; Fig. 5A).[20–23,34–38] Across 11 cohorts with 123 patients, the estimated proportion of patients who worsened postoperatively was 0.04 (95% PI 0.01–0.11; Fig. 5B).[20–23,34–39]

Depression Symptoms

We also examined the impact of stereotactic radiosurgical AC on depression scores in these OCD cohorts. Four cohorts with 27 patients had pre- and postoperative BDI/BDI-II scores.[20–22] The pooled mean preoperative BDI/BDI-II score was 23.93 (95% CI 19.79–28.08), and the pooled mean postoperative BDI/BDI-II score was 15.13

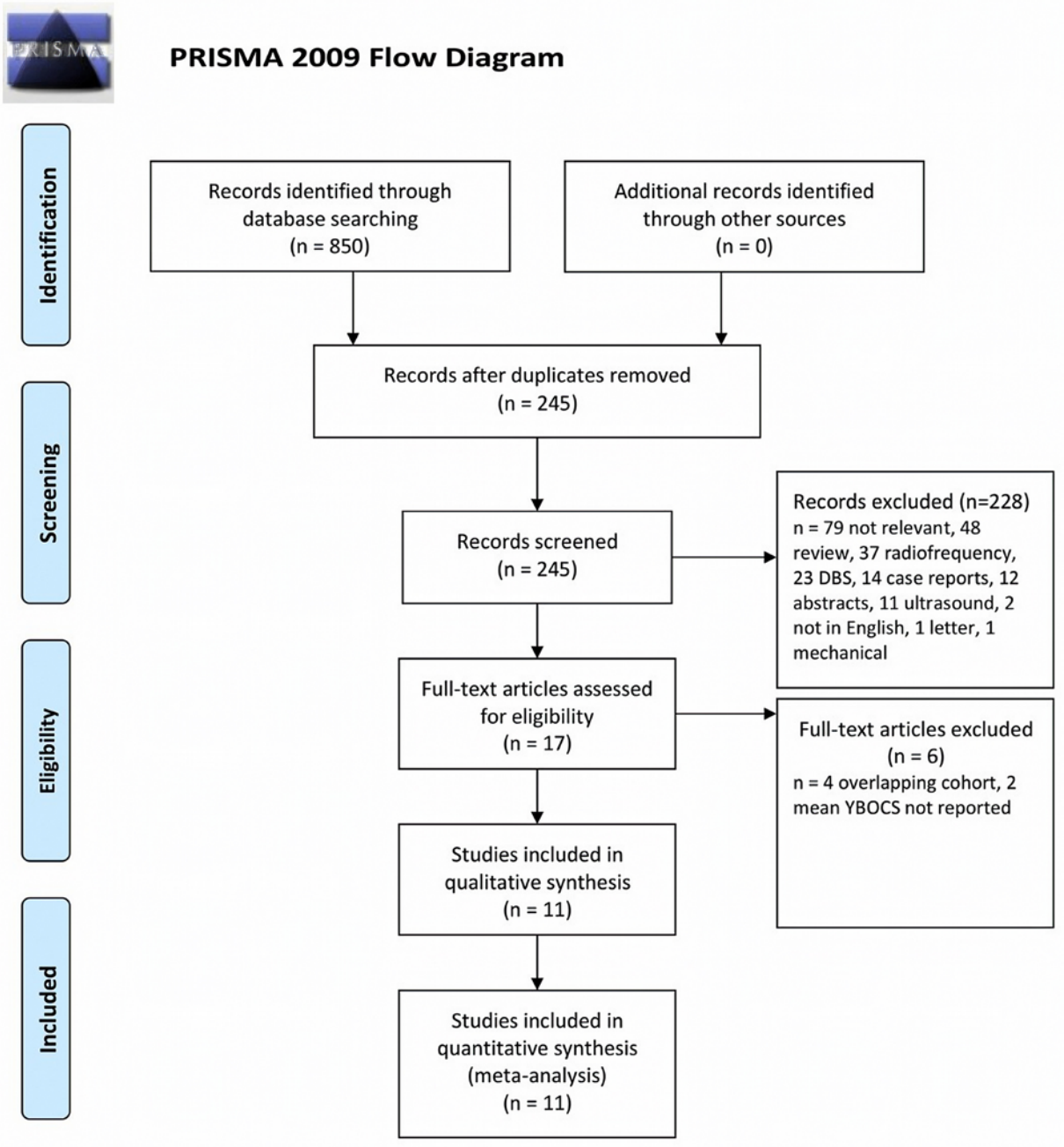

FIG. 1. PRISMA flow diagram of included and excluded studies. Data added to the PRISMA template (from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med.* 2009;6[7]:e1000097) under the terms of the Creative Commons Attribution (CC BY-NC 2.0) License (https://creativecommons.org/licenses/by/2.0). Figure is available in color online only.

(95% CI 8.76–21.50) at a mean last follow-up of 46.3 ± 28.4 months. A random-effects model demonstrated an RoM of 0.62 (95% CI 0.3–1.16, p = 0.09) and an SMD of –0.77 (95% CI –1.84 to 0.30, p = 0.106; Fig. 6). There was minimal study heterogeneity (I^2 = 36.6%, p = 0.194). Begg's test did not demonstrate any significant publication bias (p = 0.359). In the 4 cohorts containing 27 patients with both preoperative and postoperative patient-level BDI/BDI-II data, paired t-test analysis revealed a statistically significant difference between the mean preoperative BDI/BDI-II score (23.89, 95% CI 19.63–28.14) and mean postoperative last follow-up score (14.56, 95% CI 9.77–19.34, p < 0.001; Supplemental Fig. 4).

Adverse Events

Ten cohorts with 149 patients reported information on adverse events.[20–22,33–37,39] There were 235 adverse events

TABLE 1. Summary of studies assessing mean Y-BOCS scores before and after stereotactic radiosurgical AC for OCD

Authors & Year	No. of Subjects	Mean Age, yrs (SD)	No. of Females (%)	Targeting Details	FU, mos	Mean Disease Duration, yrs (SD)	Mean Y-BOCS (SD)		Mean BDI (SD)		Total NOS/ ROB 2 Ratings
							Baseline	FU	Baseline	FU	
Ertek et al., 2021[23]	12	30.8 (4.9)	7 (58.3)	2 4-mm isocenters at midputaminal point of ALIC bilat, max dose 140–180 Gy	1, 3, 6	13.83 (6.02)	32.33 (5.33)	20.83 (10.36)	NA	NA	7 (NOS)
Gupta et al., 2019[39]	40	42.5 (13.3)*	16 (40.0)	1–2 4-mm isocenters bilat, at ant ventral limb of internal capsule, max dose 120–180 Gy	6, 12, 36, 60	24.0 (13.5)*	35.0 (3.6)*	27.5 (10.8)*	NA	NA	8 (NOS)
Kondziolka et al., 2011[34]	3	43.7 (9.9)	2 (66.7)	2 4-mm isocenters at midputaminal point of ALIC bilat, max dose 140–150 Gy	41.7	29.0 (5.66)	37.33 (2.89)	16.33 (8.62)	NA	NA	8 (NOS)
Lopes et al., 2014[22] (ATa)	8	32.1 (10.6)	3 (37.5)	2 isocenters bilat, 7–10 mm rostral to pst border of AntCom, max dose 180 Gy	55.2	16.4 (11.6)	32.50 (0.70)	17.80 (10.00)	23.90 (12.10)	18.60 (11.90)	Low (ROB 2)
Lopes et al. 2014[22] (ATb)	4	37.5 (11.7)	3 (75.0)	2 isocenters bilat, 7–10 mm rostral to pst border of AntCom, max dose 180 Gy	56.5	21.25 (14.64)	34.30 (4.30)	16.30 (19.70)	23.50 (15.00)	21.50 (11.60)	Low (ROB 2)
Lopes et al., 2009[20]	5	35 (11.1)	3 (60.0)	2 isocenters bilat, 100 mm rostral to AntCom, max dose 180 Gy	48	17.4 (9.40)	32.20 (1.48)	20.60 (12.28)	25.20 (9.98)	16.60 (13.15)	8 (NOS)
Pattankar et al., 2022[38]	8	30.1 (9.4)	1 (12.5)	2–5 isocenters bilat, targeting midputaminal point, max dose 120–180 Gy	32.6	10.75 (6.32)	29.98 (5.25)	23.62 (8.70)	NA	NA	8 (NOS)
Peker et al., 2020[36]	21 (20 LFU)	32.8 (7.6)	10 (47.6)	For 1 isocenter bilat, 8–10 mm ant to pst border of AntCom; for 2 isocenters bilat, central capsule at most ventral margin of ALIC & touching shell of nucleus accumbens; max dose 140–150 Gy	6, 12, 24, 60	11.9 (5.23)	35.70 (3.99)	15.30 (11.30)	NA	NA	8 (NOS)
Rasmussen et al., 2018[33] (DS)	40 (32 LFU)	32.8 (11.1)	25 (62.5)	2 isocenters bilat, 8–10 mm ant to pst border of AntCom	6, 12, 24, 36	14.2	34.18 (3.15)	16.78 (8.30)	NA	NA	8 (NOS)
Rasmussen et al., 2018[33] (SSR)	15 (14 LFU)	35.9 (8.7)	10 (66.7)	1 target bilat, centrally in capsule, 1/3 distance dorsally from capsule's most ventral extension; repeat isocenter placed immediately ventral of 1st stage isocenter	6, 12, 24, 36	14.34	33.27 (4.82)	19.29 (11.25)	NA	NA	8 (NOS)

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TABLE 1. Summary of studies assessing mean Y-BOCS scores before and after stereotactic radiosurgical AC for OCD

Authors & Year	No. of Subjects	Mean Age, yrs (SD)	No. of Females (%)	Targeting Details	FU, mos	Mean Disease Duration, yrs (SD)	Mean Y-BOCS (SD)		Mean BDI (SD)		Total NOS/ ROB 2 Ratings
							Baseline	FU	Baseline	FU	
Rück et al., 2008[37]	9 (8 LFU)	41 (11)	NA	1 or 3 isocenters bilat, max dose 160–200 Gy	12, ≈139	NA	33.40 (4.20)	14.20 (12.10)	NA	NA	8 (NOS)
Sheehan et al., 2013[35]	5	36.8 (8.8)	2 (40.0)	1 4-mm isocenter bilat, at midputaminal point of ALIC, max dose 140–160 Gy	22.2	20.0 (8.15)	32.20 (1.30)	16.20 (8.29)	NA	NA	8 (NOS)
Spatola et al., 2018[21]	10	41.2 (10.7)	5 (50.0)	2 4-mm isocenters at midputaminal point of ALIC bilat at most ventral portion, max dose 120 Gy	41	15.3 (6.8)	32.70 (4.80)	14.70 (8.80)	23.40 (9.90)	9.00 (6.50)	8 (NOS)

ant = anterior; AntCom = anterior commissure; ATa = active treatment; ATb = sham treatment then active treatment; DS = double shot; FU = follow-up; LFU = last FU; NA = not available; pst = posterior; SSR = single shot repeated.
* Median (standard deviation).

(Table 2); the most common were headache (15.4%), weight change (14.1%), mood changes (9.4%), worsened depression/anxiety (8.1%), and apathy (8.1%). Most reported headaches were transient. One-third of the worsened depression/anxiety cases were transient.

Discussion

In this meta-analysis, we quantitatively examined the outcomes of OCD patients following stereotactic radiosurgical AC. We report that the mean Y-BOCS score decreased 47.5% from 33.28 to 17.48 postoperatively. Ten percent of patients were partial responders, 60% were responders, and 18% experienced remission at the last follow-up. Adverse event rates were relatively low. Our results support the efficacy of SRS for performing AC for medically refractory OCD and provide a quantitative estimate of its efficacy from the available literature.

Impact on OCD Symptoms

While previous analyses have reported the efficacy of AC to treat OCD symptoms, they have generally not differentiated outcomes by the technique used to perform capsulotomy. Our study quantifies outcomes following AC performed via SRS specifically. Prior meta-analyses combining multiple techniques for performing AC, including SRS, radiofrequency lesioning, mechanical lesioning, and laser ablation, have similarly noted a 46%–57% reduction in Y-BOCS scores following AC.[7,8,10–12,25,26] One prior meta-analysis of stereotactic radiosurgical AC demonstrated a 67% response rate and an 18.9% remission rate, but it did not include additional outcome measures such as the mean improvement in Y-BOCS scores as our study does.[9] Other meta-analyses including multiple AC techniques have found response rates of 47%–79%,[7–12] partial response rate of 18%,[8] and remission rate of 11%–24%.[8,9,11] Our results suggest that SRS has an efficacy similar to that of other techniques for performing AC; however, head-to-head studies are necessary to definitively determine this. One prior meta-analysis found no difference between radiofrequency and SRS lesion outcomes; however, only 33 SRS patients were included, and the radiofrequency group included cingulotomy patients.[26] Another meta-analysis noted that 79% of radiofrequency patients, 67% of SRS patients, 36.9% of mechanical patients, and 54.5% of focused ultrasound patients responded; however, statistical comparisons were not done, and Y-BOCS scores for these subgroups were not reported.[9] To understand the relative outcomes of SRS versus radiofrequency capsulotomy, it is important to also quantify outcome following radiofrequency capsulotomy specifically. Another meta-analysis focusing on the cost-effectiveness of focused ultrasound compared to radiofrequency capsulotomy found Y-BOCS score reductions of 56.6% following radiofrequency capsulotomy but did include pre- or postoperative Y-BOCS scores or responder status.[25] Further studies are needed to allow direct comparisons of different capsulotomy techniques.

We performed meta-regression to determine whether demographic and clinical variables were associated with the postoperative Y-BOCS score. Age, gender, and disease

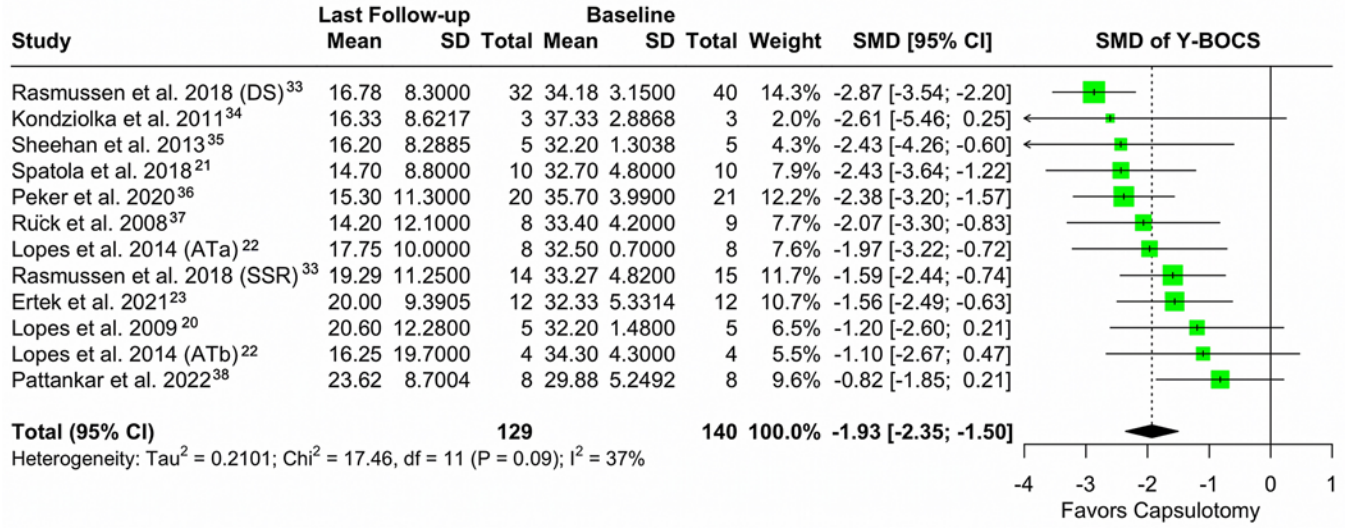

FIG. 2. Forest plot of SMDs between preoperative and last available follow-up Y-BOCS scores. ATa = active treatment; ATb = sham treatment then active treatment; DS = double shot; SSR = single shot repeated. Figure is available in color online only.

duration were not associated with the postoperative score; however, we found that the Y-BOCS score improved with an increased follow-up duration. Several previous studies have examined Y-BOCS scores over time following radiosurgical AC. One study found that it took 2–3 years for patients to attain a maximal response following SRS capsulotomy, depending on the lesioning strategy.[33] Another SRS and radiofrequency study demonstrated a significant decrease in Y-BOCS scores between baseline and 1-year follow-up testing but not between the 1-year and long-term follow-up at a mean 10.9 years, suggesting a stabilization of scores. While the response following all AC techniques is generally understood to take months, it is possible that SRS has an even slower time course, as the lesions created with SRS can require weeks or months to become visible.[40] Another factor that may be related to outcome following SRS is lesion location and size. Studies have suggested that patients treated with two bilateral lesions initially have a better and more rapid response than those treated with a single bilateral lesion initially.[33] Differences in targeting techniques likely explain some of the heterogeneity in outcomes of the included studies in the present analysis. Additionally, it is important to note that optimal responses following capsulotomy are most likely to occur in the setting of ongoing comprehensive OCD treatment including pharmacological and psychotherapeutic therapies. Research has suggested that OCD outcomes following deep brain stimulation (DBS) are optimized by concurrent exposure and response prevention therapy.[41] It is likely that a similar effect is present for capsulotomy, and future research should examine the interaction that concurrent, nonsurgical interventions have on the capsulotomy treatment effect.

Impact on Comorbid Depression Symptoms

Group-level analysis did not demonstrate a significant decrease in depression scores following stereotactic radiosurgical AC; however, an analysis of available patient-level data with a paired comparison of pre- and postoperative scores did reveal a significant decrease in postoperative BDI/BDI-II scores. All 8 cohorts that reported any depression scores had decreased depression scores postoperatively, with 4 reaching statistical significance.[20–23,33,37] Prior meta-analyses examining OCD patients who had undergone AC via any neuroablative technique have also found a significant decline in depression symptoms postoperatively.[7,10,24] Additionally, observational studies and meta-analyses that examined AC for primary major depression have shown the procedure's efficacy for this disorder.[13–19] Future SRS studies with larger sample sizes tracking depression outcomes will help to determine if these results extend to stereotactic radiosurgical AC.

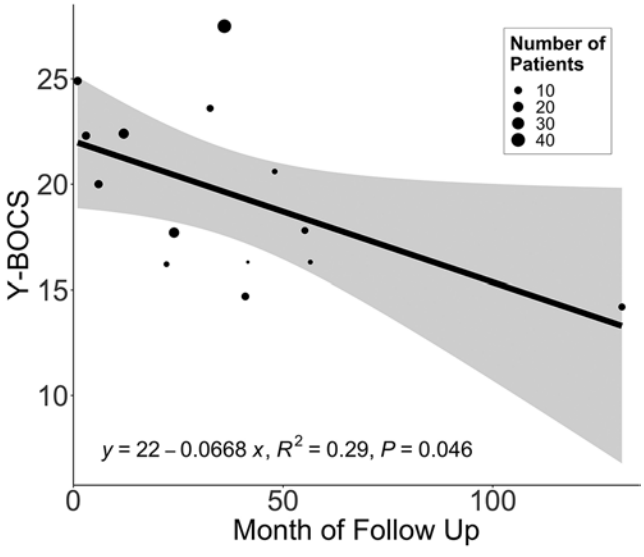

FIG. 3. Regression analysis demonstrating the relationship between Y-BOCS score and months of follow-up.

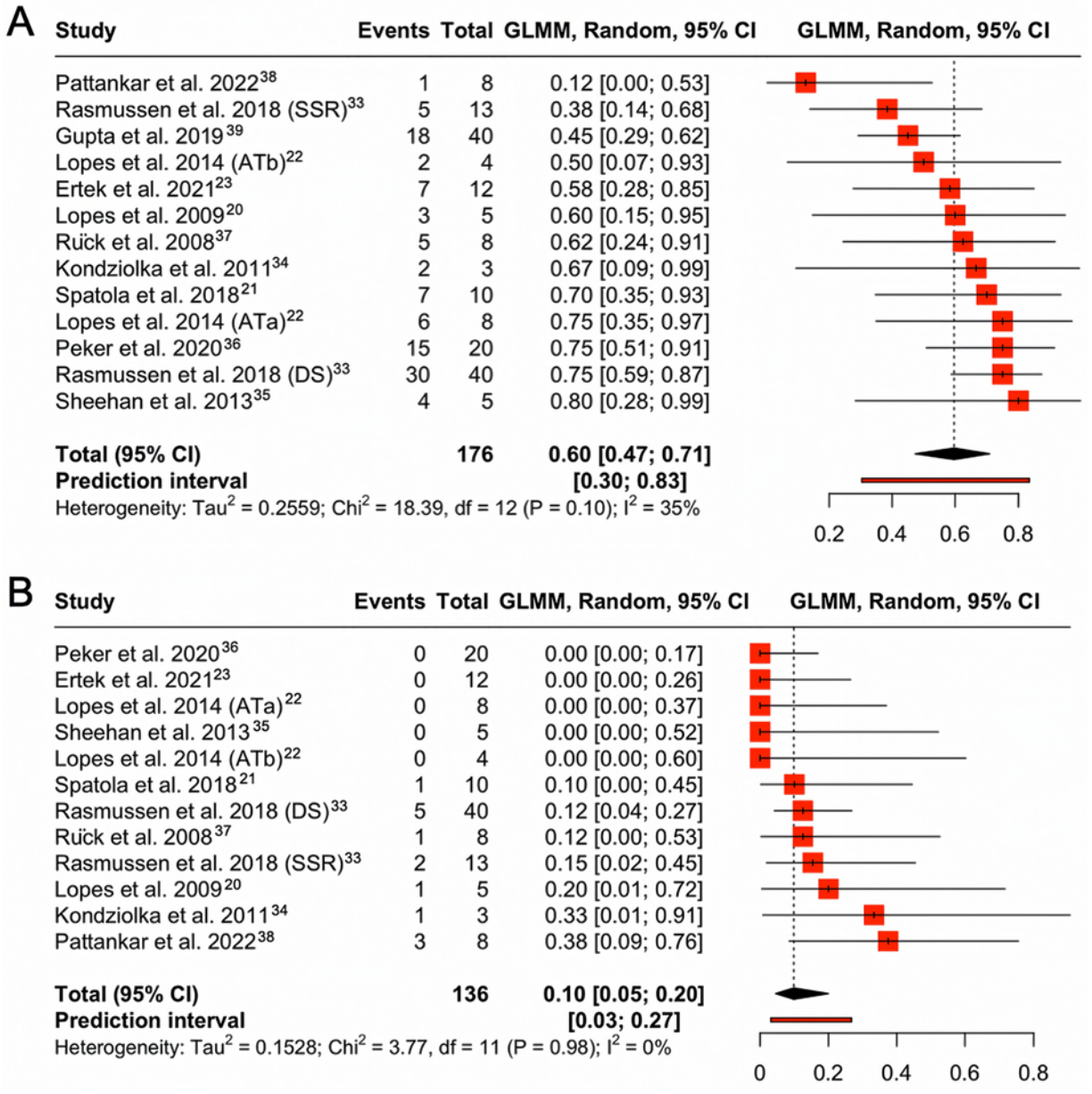

FIG. 4. Pooled analysis of the proportion of patients who responded (**A**) or partially responded (**B**) at the last available follow-up. GLMM = generalized linear mixed model. Figure is available in color online only.

Adverse Events

We reviewed the adverse events in the studies included in our meta-analysis. Headaches were the most common adverse event, reported in 15.4% of patients, though the headaches were transient in many of these patients. Weight change was reported in 14.1% of patients. Indeed, AC has been reported to have a higher incidence of postoperative weight gain than DBS of the ventral capsule/ventral striatum or nucleus accumbens performed for OCD, with one review finding that 29% of AC patients gained more than 10% of their body weight postoperatively while only 3% of DBS patients did.[26] However, some authors have suggested that weight gain after this procedure may be related to an improvement in symptoms and the reversal of OCD-related weight loss.[10] Others have posited that AC may be associated with some degree of decreased inhibitory control, which could contribute to increased food intake.[26] Stereotactic radiosurgical and radiofrequency AC have been associated with similar rates of weight gain.[37] Increased anxiety or depression was observed in 8.1% of stereotactic radiosurgical AC cases in our analysis, although it was transient in one-third of the cases. Potential worsening of psychiatric symptoms is an important adverse event for clinicians to monitor for in a vulnerable patient population with an elevated baseline suicide risk.[42] Adverse events specific to radiation included cerebral edema/radiation

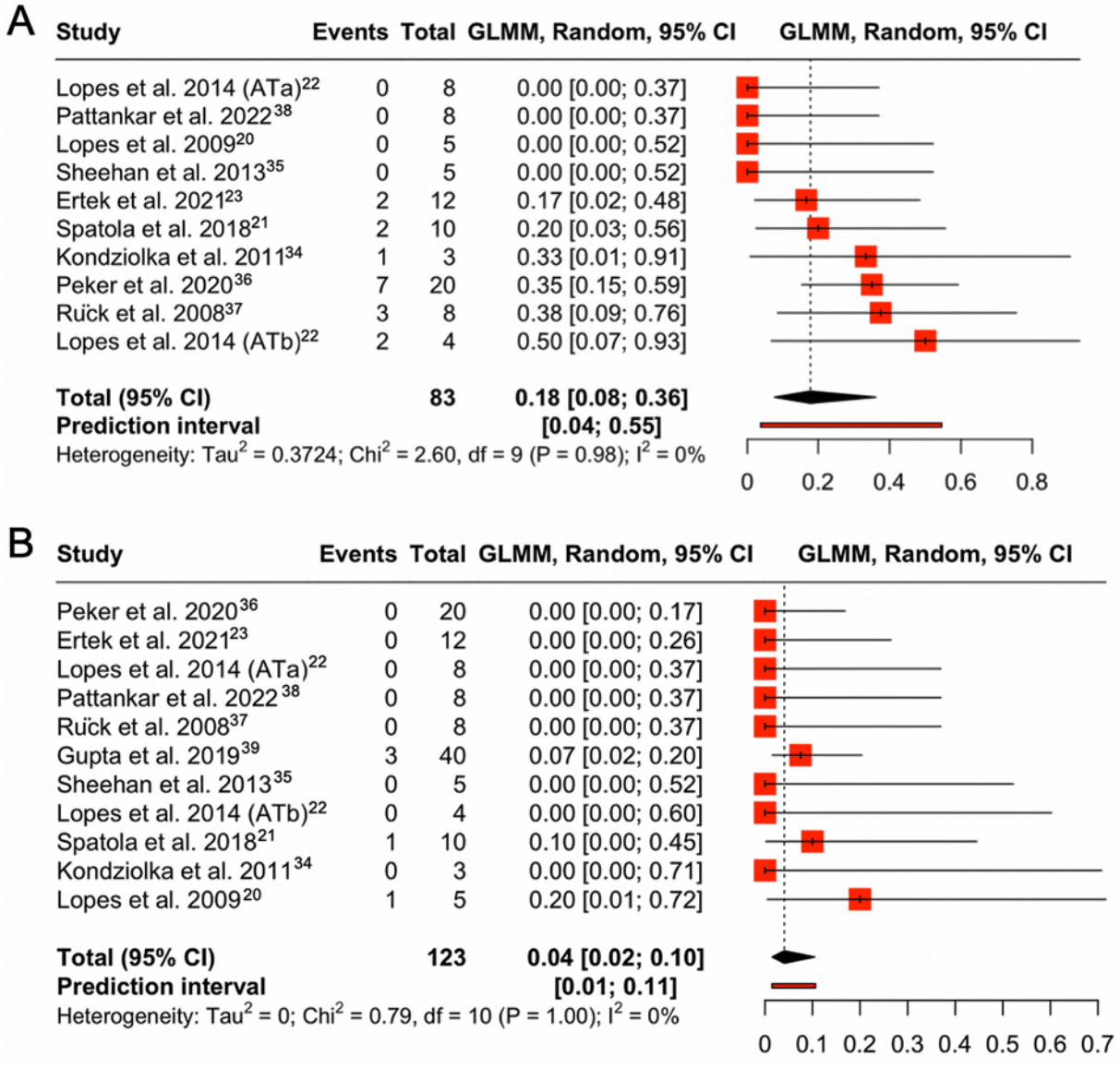

FIG. 5. Pooled analysis of the proportion of patients who had remission (**A**) or worsened (**B**) at the last available follow-up. Figure is available in color online only.

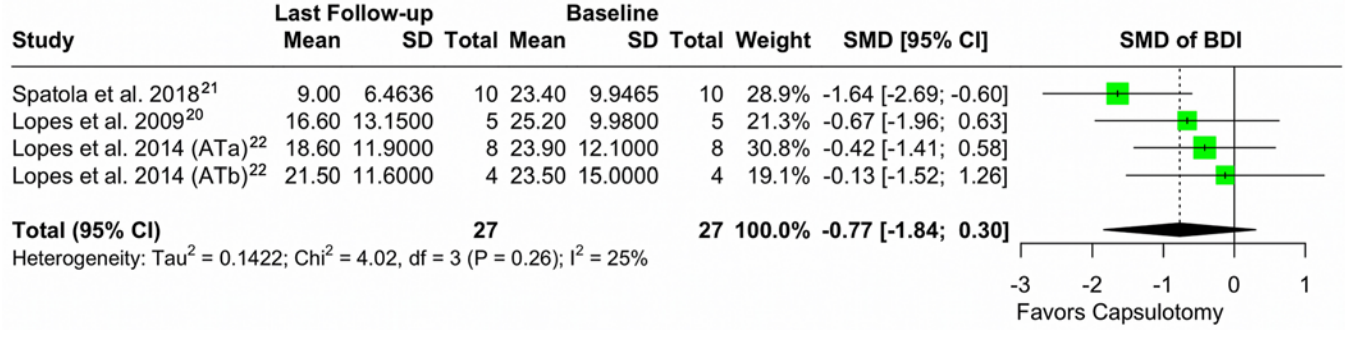

FIG. 6. Random-effects model depicting the SMD of BDI/BDI-II scores at the last available follow-up. Figure is available in color online only.

TABLE 2. Adverse events among 149 patients with available data

Adverse Event	No. (%)
Procedure related	
Skin paresthesia	11 (7.4%)
Cerebral edema/radionecrosis	9 (6.0%)
Dermatitis or pain/edema on skin	8 (5.4%)
Brain cyst	7 (4.7%)
Lacunar infarcts	6 (4.0%)
Neuropsychiatric	
Cognitive	13 (8.7%)
Psychiatric	
Mood changes	14 (9.4%)
Apathy	12 (8.1%)
Worsened anxiety/depression	12 (8.1%)
Worsened OCD	11 (7.3%)
Mania/hypomania	6 (4.0%)
Personality change	5 (3.4%)
Suicidal ideation	3 (2.0%)
Drug dependence	2 (1.3%)
Impulsivity/sexual disinhibition	2 (1.3%)
Visual hallucination	1 (0.7%)
Delirium	1 (0.7%)
Neurological	
Headache	23 (15.4%)
Lightheadedness/vertigo	5 (3.4%)
Sedation	4 (2.7%)
Muscle weakness	3 (2.0%)
Blurred vision/photophobia	2 (1.3%)
Dysarthria	2 (1.3%)
Tremors	2 (1.3%)
Abnormal neurological exam	1 (0.7%)
Dysosmia/dysgeusia	1 (0.7%)
Seizures	1 (0.7%)
Tinnitus	1 (0.7%)
Other	
Weight changes	21 (14.1%)
Appetite changes	11 (7.4%)
Insomnia	10 (6.7%)
Nausea/vomiting	9 (6.0%)
Nightmares	3 (2.0%)
Perspiration/warm hands	2 (1.3%)
Body pain	2 (1.3%)
Abdominal discomfort	1 (0.7%)
Hematuria (due to catheterization)	1 (0.7%)
Hyperventilation	1 (0.7%)
Incontinence	1 (0.7%)
Sialorrhea	1 (0.7%)
Sore throat	1 (0.7%)
Tachycardia	1 (0.7%)
Throat swelling	1 (0.7%)
Urinary infection	1 (0.7%)
Total	235

necrosis, radiation-related skin changes, brain cyst formation, and lacunar infarcts.

We found that 8.7% of patients reported subjective postprocedural cognitive changes including worsened concentration, executive function, and memory. Several studies using formal neuropsychological testing have found no change in neuropsychological functioning after stereotactic radiosurgical AC,[21,33,36] and one study found improvement in some areas of cognitive functioning.[33] Several studies using other lesioning techniques to perform AC and focusing on the cognitive outcomes of these patients via formal neuropsychological evaluation have also reported improved cognition following AC. Taken together, these findings suggest that AC performed with any technique is not likely to worsen cognition.

Study Limitations

The present meta-analysis has several limitations. The number of studies and number of patients within each study were limited because of the available literature. This was particularly true for analyses at common follow-up time points (6 and 12 months) for postoperative Y-BOCS scores. Additionally, limited studies offered patient-level data for the paired analysis as opposed to the group-level, nonpaired analysis. The small sample size may limit the power of our analysis and likely contributes to the large confidence and prediction intervals observed in our study. Future studies with larger sample sizes are required to provide more precise estimates of the benefits associated with this procedure. Only one study was an RCT while the rest were observational studies, and the included studies had variable follow-ups. As discussed above, Y-BOCS scores may change as a function of postoperative time. Additionally, studies included in the meta-analysis had variability in SRS targeting and technique. Differences in precise target location and dose may result in differing outcomes. Thus, future research should attempt to analyze lesion characteristics associated with optimal response. With respect to the analysis of adverse events, there was heterogeneity in the reporting methods. Several studies did not provide exact numbers of adverse events, instead providing more general statements to describe the prevalence of adverse events, which could not be incorporated into our analysis, potentially resulting in an underestimation of the true adverse event rate.

Conclusions

Findings in the present meta-analysis indicate that stereotactic radiosurgical AC results in significant symptom improvement for patients with treatment-resistant OCD. Response rates are similar to those reported for other techniques of performing AC, suggesting that stereotactic radiosurgical AC is a useful minimally invasive therapeutic technique for patients with medically refractory OCD.

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Dr. Bick and Dr. Cmelak reported personal fees from Varian Medical Systems for consulting outside the submitted work.

Author Contributions

Conception and design: Bick. Acquisition of data: Gupta, Chen, Hamo, Cmelak. Analysis and interpretation of data: Bick, Gupta, Hughes, Hamo, Chanbour, Ye, Vadali, Cmelak. Drafting the article: Bick, Gupta, Chen, Hamo, Paulo. Critically revising the article: Bick, Gupta, Hughes, Jean-Baptiste, Paulo, Chanbour, Ye. Reviewed submitted version of manuscript: Bick, Gupta, Chen, Hughes, Jean-Baptiste, Paulo, Chanbour, Fan, Ye, Cmelak. Approved the final version of the manuscript on behalf of all authors: Bick. Statistical analysis: Gupta, Chen, Hughes, Chanbour, Fan, Ye, Vadali. Administrative/technical/material support: Chen. Study supervision: Bick.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

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