

Original Article

Effect of repeated transsphenoidal surgery in recurrent or residual pituitary adenomas: A systematic review and meta-analysis

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Abstract

Background: Recurrent or residual pituitary adenomas previously treated by transsphenoidal surgery are not uncommon. There are no strongly established guidelines to perform treatment of such cases. The objective of this study is to elucidate the effect of transsphenoidal reoperation in residual or recurrent pituitary adenomas.

Methods: We made a systematic review of the literature to elucidate this effect through electronic search in MEDLINE/PubMed and Cochrane Central database. PRISMA statement was used as a basis for this systematic review and analysis of the risk of bias was made according to the Grading of Recommendations, Assessment, Development and Evaluation recommendations.

Results: In this review, fifteen studies were finally pooled analyzed. Although remission rates (RRs) and follow-up periods varied widely, from 149 patients with growth hormone-secreting tumors the mean RR was 44.5%, from 273 patients with adrenocorticotrophic hormone-secreting tumors the mean RR was 55.5% and among 173 patients with nonsecreting tumors, RR was 76.1%. There was significant higher RR in nonsecreting tumors. Mean follow-up was 32.1 months. No difference was found between microscopic and endoscopic techniques.

Conclusions: A second transsphenoidal surgery is accompanied by a chance of remission in approximately half of cases with secreting tumors. In nonsecreting ones, success is higher.

Key Words: Endoscopy, microsurgery, pituitary adenoma, transsphenoidal, treatment

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INTRODUCTION

Treatment of pituitary adenomas is often surgical, especially in hormone-secreting tumors or those with a mass effect on surrounding structures, such as the optic chiasm.^[1-5] The presence of residual tumor and tumor recurrence in the postoperative period are not uncommon. Treatment of both conditions remains subject to individual selection since no established

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guidelines on the type of treatment option for these cases is currently available.^[1,6-9]

In addition, it is well known that risks are higher in patients subjected to repeated transsphenoidal surgery than in patients without prior therapy.^[4-8] Thus, it is important to conduct a critical analysis of the effect of repeated surgery.

The objective of this study is to elucidate the effects of transsphenoidal reoperation for pituitary adenomas.

METHODS

A systematic review of the literature on the effects of repeated transsphenoidal surgery was performed using the MEDLINE (via PubMed) database and the Cochrane Central Register of Controlled Trials. The PRISMA statement and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) recommendations were followed.

Structure of the search strategy

The literature search was based on structured questions, which defined the criteria for inclusion of papers, based on types of participants (patients), intervention and control, follow-up, and types of studies, following the PICOT strategy.

Types of participants: Adult patients, of both genders, with pituitary adenoma, who experienced tumor recurrence or residual tumor after primary surgery and underwent revision surgery. Prolactinomas were excluded from evaluation due to the established concept of its treatment with dopaminergic agonists.

We excluded patients who either underwent radiotherapy (RT)/radiosurgery or who were receiving medical therapy to attain remission previously to the second transsphenoidal surgery.

Types of intervention/exposure: Transsphenoidal reoperation of pituitary adenomas.

Outcomes: The outcome selected for the study was the remission rate (RR) after second operation (reoperation).

Follow-up time or extraction of outcomes: We included all studies that reported follow-up time.

Types of study: We aimed to include clinical trials; if not possible, we accepted all cohorts. Case reports and studies evaluating <10 cases were excluded.

Language: Articles published in English, Portuguese, French, and Spanish from 1964 to 2014 were considered for analysis.

Analysis of risk of bias: The risk of bias was analyzed in accordance with the GRADE criteria.

Search strategies

The search strategy used is detailed below:

“Pituitary neoplasms” [MeSH Terms] OR “pituitary” [All Fields] AND “recurrence” [MeSH Terms] AND Transsphenoidal [All Fields] AND “surgery” [Subheading] OR “surgery” [All Fields] OR “surgical procedures, operative” [MeSH Terms] OR “surgical” [All Fields] AND “procedures” [All Fields] AND “operative” [All Fields] OR “operative surgical procedures” [All Fields] OR “surgery” [All Fields].

Searches were performed by two authors independently, and disagreements were resolved by discussion.

Statistics

RR was described as a percentage, mean, standard deviation, range, and confidence intervals. Follow-up time was described as mean, standard deviation, and range.

A meta-analysis of pooled data was made according to the type of tumor. The RRs of the surgical operated pituitary adenomas were compared across pituitary tumors types according to the method proposed by Neyeloff *et al.*^[20] for observational data.

A comparison between secreting and nonsecreting tumors was performed with Chi-square test.

RESULTS

Search

The search strategy retrieved 410 articles [Figure 1]. Twenty-two papers were initially selected by their titles alone. Eight articles were initially selected by the electronic search. One other study known to the authors was added, and six additional studies were included after cross-referencing of selected papers. The final sample included 15 publications for analysis.

Data extraction [Table 1]

Laws *et al.*^[16] analyzed 158 patients with pituitary tumors who underwent secondary transsphenoidal surgery, of whom 127 had adenomas. Thirteen were growth hormone (GH)-secreting, 47 were prolactin (PRL)-secreting, 4 were adrenocorticotrophic hormone (ACTH)-secreting, and 34 were nonsecreting. Mean follow-up time was 37 months. RRs were 42% for GH tumors, 29% for PRL tumors, and 25% for ACTH tumors; no data were available for remission in nonsecreting tumors.^[16]

Friedman *et al.*^[13] reported the outcomes of 31 patients with Cushing’s disease after second transsphenoidal surgery. Over 11 months of follow-up, 22 patients (70.96%) achieved remission.^[13]

Long *et al.*^[17] described the results of secondary transsphenoidal surgery in 16 patients with GH-secreting

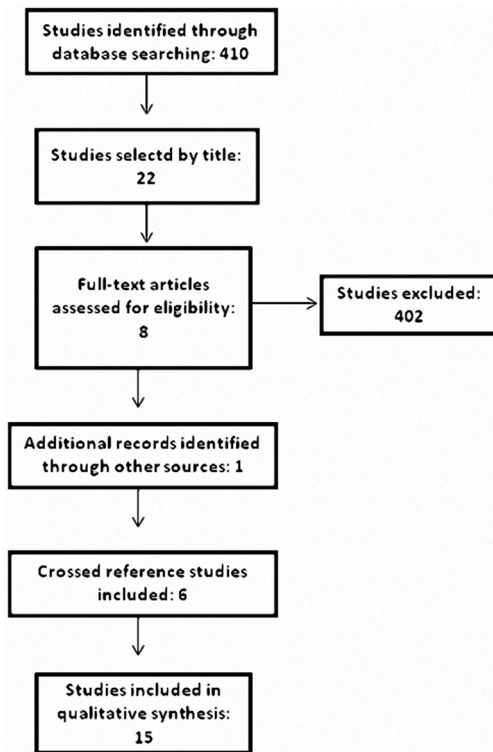


Figure 1: Search strategy and results

adenomas. After an average follow-up of 8.2 years, the authors reported normalization of GH levels in 19% of patients and a >50% reduction in GH levels in 69% of patients. For pooled analysis, we considered 19% as the RR.^[13]

Abe and Lüdecke^[1] analyzed 270 patients with GH-secreting adenomas, of whom 28 experienced recurrence and underwent secondary surgery. Of the 28 recurrent tumors, 18 could be resected and 10 could not. Among the 18 patients operated, 16 achieved remission (57.14%). The follow-up time was 17.5 ± 2.7 months.^[1]

Kurosaki *et al.*^[15] analyzed 22 patients with GH-secreting tumors. The RR was 59% with a follow-up of more than 4 years.^[15]

Benveniste *et al.*^[4] studied 96 patients undergoing reoperation for residual tumor or recurrence of pituitary adenomas without RT. Mean follow-up was 31 months. Overall, 37 patients had nonsecreting tumors, whereas 7 had GH-secreting and 44 had ACTH-secreting tumors. Surgery for recurrent or residual mass was associated with gross resection rates of 93% in nonsecreting tumors and remission in 57% in secreting tumors.^[4]

Hofmann *et al.*^[14] studied 16 patients with a previously operated pituitary tumor who presented with recurrent Cushing's disease. Of these 16 patients, 13 underwent selective adenectomy and 3 underwent hemihypophysectomy. Six patients had remission of Cushing's disease while seven remained affected (three of

whom had tumors with cavernous sinus invasion). One of these underwent bilateral adrenalectomy and improved, and another underwent RT and adrenalectomy. The follow-up period was 23 months.^[14]

Rudnik *et al.*^[22] evaluated 20 patients who underwent endoscopic surgery of recurrent adenomas or residual tumor not completely removed during the first surgical procedure. The analyzed group had 14 nonsecreting adenomas, 4 GH-secreting adenomas, 1 PRL-secreting adenoma, and 1 ACTH-secreting adenoma. Of these, 19 were macroadenomas, while 1 was a microadenoma. The follow-up period after surgery was between 12 and 42 months (mean, 24.2 months). The gross resection rate was 42.8% in nonsecreting tumors, and RR was 33.3% in secreting tumors. While ACTH and PRL-secreting tumors were associated with 100% remission, GH tumors had 0%.^[22]

Patil *et al.*^[21] reviewed the medical records of 455 patients who underwent surgery for Cushing's disease between 1992 and 2006. Mean follow-up was 36 months. Of these patients, 40 underwent repeat surgery, and 36 patients with clinical and biochemical evidence of recurrent Cushing's disease after the first surgery who had endocrine follow-up were included. Overall, 22 patients (61.1%) achieved remission after the second surgery.^[21]

Wagenmakers *et al.*^[24] described 24 patients treated for persistent Cushing's disease over 24 months of follow-up. Remission after the second surgery was achieved in 10 of 14 patients who underwent repeated surgery.^[24]

Yamada *et al.*^[25] studied 53 cases of the recurrent GH-secreting tumor with a follow-up period of 55.9 months. Patients were divided into groups (A, B, C) according to their endocrine profile in the early postoperative period: Group A, success, in 26 of 53 (49%); Group B, insufficient, in 9 of 53 (16.98%); and Group C, unsuccessful, in 18 of 53 (33.9%).^[25]

Chang *et al.*^[8] studied 81 patients in two groups: Gross resection versus subtotal resection and RT. The mean follow-up was 3.6 years. Gross resection could be reached in 92.4%.^[8]

Dimopoulou *et al.*^[11] evaluated 120 patients with Cushing's disease, of whom 36 underwent a second surgery. The RR was 42%. Follow-up time was 62 ± 54 months.^[11]

Cavallo *et al.*^[7] performed transsphenoidal endoscopic surgery for residual or recurrent pituitary adenomas in 59 patients. Of these, 31 had previously undergone surgery via a microsurgical transsphenoidal approach, 22 by means of an endoscopic transsphenoidal route, and 6 through a transcranial route. Forty-one patients presented with nonsecreting tumors, while 18 were hormone-secreting (8 ACTH, 6 GH, 3 GH + PRL, and 1 PRL). Follow-up ranged from 2 to 149 months.^[7]

Table 1: Data extraction of 15 studies enrolled

Author	Design	Disease	Remission criteria	Number of patients with residual or recurrent tumor	Surgical approach	Remission rate	Follow-up (months)
Laws (1985)	Retrospective cohort	Several	GH <5 µg/mL ACTH <150 ng/mL Gross resection for nonfunctioning	127 (total) 13 GH 47 PRL 4 ACTH 24 Nelson syndrome 5 LH/FSH 34 nonfunctioning	Microscopic	GH - 42% PRL - 29% ACTH - 25% Nelson - 21% Do not describe nonfunctioning	37
Friedman (1989)	Retrospective cohort	ACTH	Cortisol level <6.0 ug/dL and 24-h UFC <90 ug/day	31	Microscopic	70.9%	11
Long (1996)	Retrospective cohort	GH	GH <2 µg/L in OGTT Basal GH <5 mg/L	16	Microscopic	19%	98
Abe (1998)	Retrospective cohort	GH	GH <2 µg/L in OGTT Basal GH <4.5 µg/L	28	Microscopic	57.1%	17.5±2.7
Kurosaki (2003)	Retrospective cohort	GH	GH <2 µg/L in OGTT Basal GH <5 mg/L	22	Microscopic	59%	More than 48
Benveniste (2005)	Retrospective cohort	Several	Not defined	96 (total) 37 nonsecreting 44 ACTH 7 GH 4 PRL 3 GH and PL 1 FSH and LH	Microscopic	93% in nonsecreting 57% in ACTH 57% in non-ACTH	31
Hofmann (2006)	Retrospective cohort	ACTH	Cortisol levels below 2 µg/dL was considered a normal response to 2 mg of dexamethasone Serum basal fasting cortisol levels between 10 and 21 g/dL and plasma ACTH levels were considered normal below 51 pg/mL	16	Microscopic	46%	23
Rudnik (2006)	Retrospective cohort	Several	GH <1 µg/L in OGTT and IGF-1 <450 µg/L	20 (total) 14 nonsecreting 4 GH 1 ACTH 1 PRL	Endoscopic	42.8% in nonsecreting 0% in GH 100% in PRL 100% in ACTH	24.2
Patil (2008)	Retrospective cohort	ACTH	Normal postoperative 24-h UFC or continued need for glucocorticoid replacement after TS surgery Recurrence was defined as an elevated 24-h UFC with clinical signs and symptoms consistent with Cushing's disease	36	Microscopic	61.1%	36
Wagenmakers (2009)	Retrospective cohort	ACTH	Cortisol level ≤50 nmol/L 24-48 h after glucocorticoid withdrawal and/or suppression of plasma cortisol level ≤50 nmol/L after 1 mg dexamethasone overnight within the first 3 months after transsphenoidal surgery	14	Endoscopic	64.28%	24
Yamada (2010)	Retrospective cohort	GH	GH <1 µg/mL in OGTT and normal IGF-1 level	53	Microscopic	58.4%	55.9
Chang (2010)	Retrospective cohort	Nonsecreting tumors	Gross resection	81	Microscopic	92.4%	42

Contd...

Table 1: Contd...

Author	Design	Disease	Remission criteria	Number of patients with residual or recurrent tumor	Surgical approach	Remission rate	Follow-up (months)
Dimopoulou (2013)	Retrospective cohort	ACTH	UFC >5 mg/dL after LDDST, and late-night salivary cortisol >145 ng/dL	36	Microscopic	42%	62±54
Cavallo (2013)	Retrospective cohort	Several	Secreting: Not defined Not secreting: Gross total resection	59 (total) 41 nonsecreting 8 ACTH 6 GH 3 GH + PRL 1 PRL	Endoscopic	62.7% (total) 68.3% nonsecreting 50% in secreting (do not describe different subtypes)	2-149
Bodaghabadi (2014)	Clinical trial	ACTH	Not defined	26	Microscopic	65.3%	36

ACTH:Adrenocorticotrophic hormone, GH:Growth hormone, OGTT:Oral glucose tolerance test, IGF-I:Insulin growth factor-I, UFC:Urinary free cortisol, LH:Luteinizing hormone, FSH:Follicle-stimulating hormone, PRL:Prolactin, LDDST:Low-dose dexamethasone suppression test

Gross total resection was achieved in 37 cases (62.7%). On average, 38.4% of gross total resections left residual lesions which regrew (60.8% in nonsecreting adenomas, 15 of 24; 14.3% in secreting adenomas, 1 of 7); the recurrence rate was 74.6% (76.5% in nonsecreting adenomas, 13 of 17; 72.7% in secreting adenomas, 8 of 11).^[7]

Bodaghabadi *et al.*^[5] evaluated 52 patients with relapse of Cushing's disease after initial surgical therapy who were treated with further surgery versus stereotactic radiosurgery (gamma knife). Patients were divided into two balanced groups ($n = 26$ each). The mean follow-up was 3 years, and the outcome measure was a disease-free interval. The groups were homogeneous before treatment of relapse, with no differences in age, gender, type of adenoma (micro or macro), and hormone levels. The time to recurrence was 38 months among patients undergoing radiosurgery and 30 months in the surgery group ($P = 0.36$). Nine patients in the surgery group experienced recurrence, versus 10 patients in the gamma knife group.^[5]

Analysis of data pooled by tumor type

Growth hormone-secreting

Yamada, Kurosaki, Rudnik, Cavallo, Benveniste, Abe, Laws, and Long included a total of 149 patients with residual or recurrent GH-secreting tumors. Data from Benveniste and Cavallo were not pooled due to a low number of studied patients.

Laws used basal GH levels as remission criteria. Long, Abe and Kurosaki used basal GH and GH levels after glucose tolerance test (GTT). Rudnik and Yamada used GH levels after GTT and insulin growth factor-1 levels [Table 1].

The mean RR was $44.5 \pm 23.85\%$ (range, 0–72.8%) with repeated transsphenoidal surgery.^[1,4,7,15-17,22,23] Meta-analysis excluded Rudnik and Cavallo, each with <10 patients evaluated [Figure 2].

Adrenocorticotrophic hormone-secreting

Hofmann, Patil, Bodaghabadi, Wagenmakers, Dimopoulou, Benveniste, Cavallo, Rudnik, Laws, and Friedman included 213 cases of recurrent ACTH-secreting tumors.

Laws used ACTH as remission criteria. Friedman, Hofmann, and Wagenmakers used basal cortisol levels and urinary cortisol levels as remissions criteria. Patil used urinary cortisol levels, and Dimopoulou used urinary and salivary cortisol levels [Table 1]. Cavallo, Bodaghabadi, Benveniste, and Rudnik did not define clear remission criteria for ACTH-secreting tumors.

The mean RR was $55.5 \pm 15.89\%$ (range, 25–72.7%) with repeated transsphenoidal surgery.^[4,5,7,11,13,14,21,22,24] Meta-analysis excluded Laws, Rudnik and Cavallo, each with <10 patients evaluated [Figure 3].

Nonsecreting tumors

Benveniste, Chang, Rudnik, and Cavallo included 173 nonsecreting tumors. Remission was defined as an image criteria revealing gross resection [Table 1].

The gross resection rate was $76.05 \pm 23.52\%$ (ranging from 42.8% to 93%) with repeated transsphenoidal surgery [Figure 4].^[4,7,8,22]

Endoscopic versus microscopic surgery

Yamada, Kurosaki, Benveniste, Abe, Laws, Long, Hofmann, Patil, Bodaghabadi, Dimopoulos, Friedman and Chang reported transsphenoidal surgery using microscopic techniques. The mean RR reported was $56.5 \pm 19.7\%$.^[1,4,5,8,11,13-15,21,25]

Rudnik, Cavallo, and Wagenmakers published surgical series of repeated transsphenoidal surgery using the endoscopic technique.^[7,22,24] The mean RR was $54.9 \pm 14.7\%$. There was no statistical difference in RRs between the two groups.^[7,22,24]

Complications in repeated transsphenoidal surgery

Among 15 studies evaluated, 3 did not even describe complications (Dimopoulou *et al.*; Long *et al.*; Bodaghabadi *et al.*) and 2 described no complications among their patients (Hofmann *et al.*; Kurosaki *et al.*). Finally, 10 studies described complications [Table 2]. There were 121 complications among 586 patients (20.6%). Most frequent complications were diabetes insipidus in 52 patients (8.8%), a cerebrospinal fluid leak in 18 patients (3.0%) and sinusitis in 10 patients (1.7%). There were 6 cases of death, 4 of them being from one single study. Other complications are described in Table 2.

Synthesis of results

The rate of gross resection after repeated transsphenoidal surgery was approximately 76.05% for nonsecreting tumors. In secreting lesions, the average RR was 55.5% in ACTH-secreting and 44.5% in GH-secreting tumors. In short, RRs were higher in nonsecreting tumors than in secreting tumors ($P = 0.001$, Chi-square test).

Bias

Only one of the publications included was a randomized trial (Bodaghabadi *et al.*),^[5] which compared the results of surgery and radiosurgery. Since the goal of this review was to disclose the effect of surgery, we only used the results of the surgical arm for analysis. All other studies evaluated

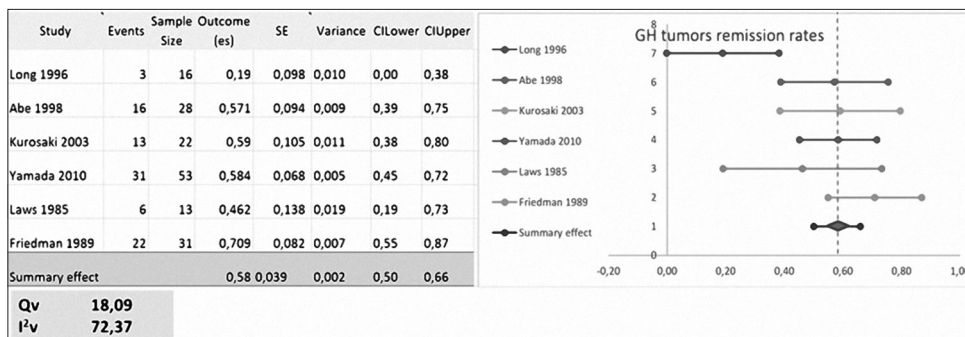


Figure 2: Meta-analysis of growth hormone-secreting tumors remission rates

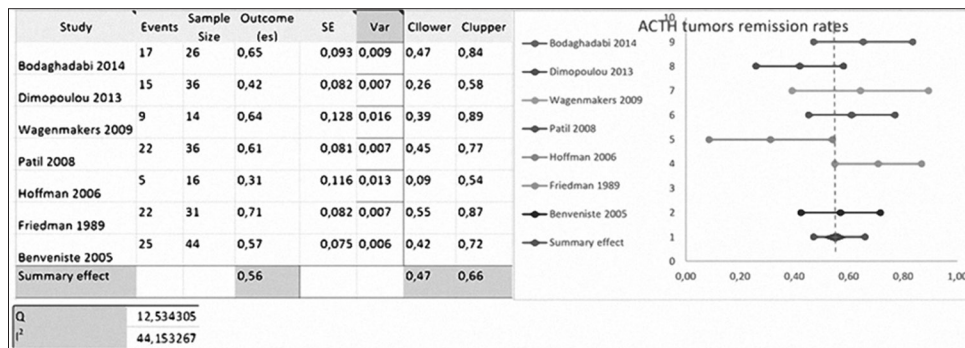


Figure 3: Meta-analysis of adrenocorticotrophic hormone-secreting tumors remission rates

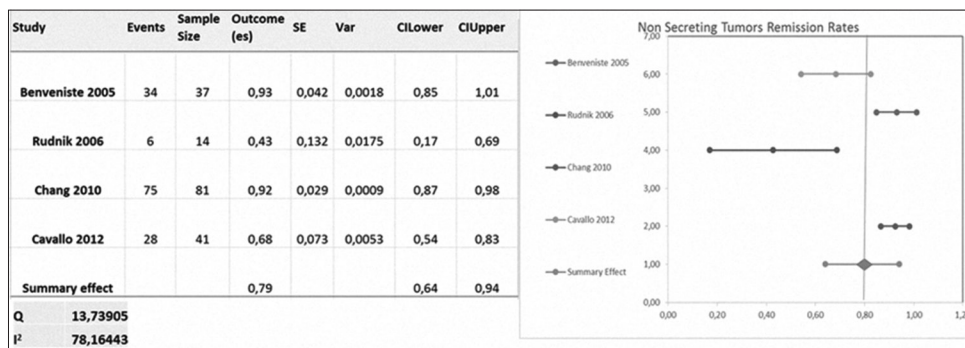


Figure 4: Meta-analysis of nonsecreting tumors remission rates

Table 2: Complications after repeated transsphenoidal surgery

Author	n	Nasal bleeding	DI hematoma	Sellar nerve	VI leak	CSF perforation	Nasal lesion	Vascular lesion	Death	Meningitis	Visual loss	Sinusitis	Graft infection	Pituitary abscess	Hyponatremia
Abe	28	1	4												
Cavallo	59		3	1	2	1									
Laws	158		11	2	1	9	2	2	4	2	4				
Friedman	31					1			1	1					
Rudnik	20		1			1									
Benveniste	96	1	18		1	1						5	1		
Chang	81		1	1		2			1	2		5			3
Patil	36		6												
Yamada	53	1	2		1	1				1				1	2
Wagenmakers	24	2	6			2									
Total	586	5	52	4	5	18	2	2	6	6	4	10	1	1	5

Description of complications in each study, with a number of patients (n) and a number of described complications. DI: Diabetes insipidus, CSF: Cerebrospinal fluid

were observational studies of homogeneous cohorts of patients with recurrent and residual pituitary tumors.^[5]

Several studies evaluated homogeneous samples of recurrent tumors. However, Benveniste, Rudnik, Cavallo, and Laws evaluated a range of tumors but reported remission as an outcome in different subtypes.^[4,7,16,22] Laws *et al.* did not report the RR for nonsecreting tumors.^[16]

All studies described the type of intervention and the outcome measure evaluated in this study, i.e., the average rate of tumor remission.

The length of follow-up varied widely, from 2 to 149 months (mean, 32.1 months), and was significantly different across studies (Chi-square, $P < 0.002$). None of the studies reported the significant loss to follow-up. However, Chang *et al.* found that postoperative images were available for only 74.07% of patients.^[8]

DISCUSSION

The second surgery is a common situation in the treatment of pituitary adenomas, which are lesions especially prone to recurrence or regrowth.^[2,6,9,10,12,18,19,23] Previous studies have already stressed the importance of the first surgery in avoiding reoperation, as it is believed that residual tumor lying within the pituitary gland, dura mater of the sella turcica, or cavernous sinus (by extension from the dura) may be the cause of regrowth.^[10] At repeat surgery, the residual tumor may be found at or immediately contiguous to the site where the lesion was found originally.^[10]

Remission is defined differently in many of the quoted papers. Nevertheless, recurrence of pituitary tumors is a fact and must be addressed.

Currently, there is no guideline for the management of such cases, and treatment protocols are largely based

on individual experience rather than on evidence-based literature. RT and radiosurgery, which are almost always reserved for cases of failed surgical treatment, are being increasingly applied to recurrent tumors, with encouraging results.^[2] However, no studies have adequately addressed the ideal protocol for treatment of recurrent or residual pituitary adenomas. In fact, some tumors, such as acromegaly, would be amenable to perform adjuvant therapy prior to reoperation, and it would be very difficult to evaluate these treatments in a pooled analysis of data. Future trials are encouraged to answer these topics.

In our literature review, we were able to compare the results of reoperation and radiosurgery in only one randomized trial, which included 26 patients in each arm.^[5] All other pooled cohort studies evaluated a total of 509 patients who underwent reoperation without a control group. Thus, we were not able to compare the effects of surgery versus those of other treatment modalities, but we were able to estimate the effect of reoperation.

Stratification of tumors by hormone type revealed striking differences in RRs and prognosis. The average RR was 44.5% in GH-secreting tumors; in ACTH-secreting tumors, 55.5%; and in nonsecreting tumors, 76.05% ($P = 0.001$).

Although the main interest of any intervention with systematic review always will be randomized trials, still now several questions cannot be answered with this type of publications due to the lack of papers until this moment. Then, nonrandomized trials represent the best available evidence. The cohort studies have many potential biases that the data interpretation must be done with caution. As no comparative intervention was selected to be the scope of this review, the main concern in performing a retrospective meta-analysis, i.e. differences in compared populations may be initially disregarded. The data evaluation was done in this study still did not take into consideration that follow-up time

could be an independent factor for lower RRs. This must be considered as a limitation when analyzing the results of this study.

In addition, remission criteria used in literature are distinct and varied among published papers describing tumoral recurrence [Table 1]. The reader must bear in mind that there is not any paper describing long-term follow-up. Some recurrences may be delayed particularly with Cushing's disease.

In summary, the pooled RR in the published literature after transsphenoidal reoperation for residual or recurrent pituitary adenomas was 45.5% in GH-secreting tumors, 55.5% in ACTH-secreting tumors and 76.05% in nonsecreting tumors.

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Conflicts of interest

There are no conflicts of interest.

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