REVIEW

Outcome of endoscopic vs microsurgical transsphenoidal resection for Cushing's disease

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Abstract

Introduction: It is unclear whether the proportions of remission and the recurrence rates differ between endoscopic transsphenoidal surgery (TS) and microscopic TS in Cushing's disease (CD); thus, we conducted a systematic review and meta-analysis to evaluate studies of endoscopic TS and microscopic TS.

Methods: We conducted a comprehensive search of PubMed to identify relevant studies. Remission and recurrence were used as outcome measures following surgical treatment of CD.

Results: A total of 24 cohort studies involving 1670 adult patients were included in the comparison. Among these studies, 702 patients across 9 studies underwent endoscopic TS, and 968 patients across 15 studies underwent microscopic TS. Similar baseline characteristics were observed in both groups. There was no significant difference in remission between the two groups: 79.7% (95% CI: 73.1–85.0%) in the endoscopic group and 76.9% (95% CI: 71.3–81.6%) in the microscopic group ($P = 0.485$). It appears that patients who underwent endoscopic surgery experience recurrence less often than patients who underwent microscopic surgery, with recurrence proportions of 11.0% and 15.9%, respectively ($P = 0.134$). However, if follow-up time is taken into account, both groups had a recurrence rate of approximately 4% per person per year (95% CI: 3.1–5.4% and 3.6–5.1%, $P = 0.651$).

Conclusions: We found that remission proportion and recurrence rate were the same in patients who underwent endoscopic TS as in patients who underwent microscopic TS. The definition of diagnosis, remission and recurrence should always be considered in the studies assessing therapeutic efficacy in CD.

Introduction

Cushing's disease (CD) is a subtype of pituitary adenoma with hypercortisolism and presents a particular challenge to neurosurgeons. Transsphenoidal surgery (TS) has long been the standard of care for patients with CD (1, 2, 3, 4). However, even under the most favorable circumstances, previous reports have found recurrence proportions of up to 10–20% after the first TS (5, 6, 7). Recurrent or residual CD is associated with a threefold to fivefold increase in mortality rate (8, 9, 10).

In recent decades, the application of endoscopes in the approach for treating pituitary adenomas has gained considerable popularity (11, 55, 56). The endoscopic technique provides a panoramic surgical view with increased illumination of the anatomic structures and allows for a close-up visual examination of the suspected tumor. Different optical angles can be used to make it possible to reach the suprasellar region as well as lateral extensions (12, 13). Owing to these advantages, increasing

numbers of neurosurgeons have started to adopt the endoscopic technique in recent years. Compared with microscopic surgery, endoscopic transsphenoidal tumor resection seems to lead to improved patient outcomes, especially in those patients with cavernous sinus invasion (14, 15, 16, 17, 18, 19, 20). In patients with CD, though a few studies do indicate a lower recurrence rate (15, 21, 22), it is still unclear whether the endoscopic technique has any advantages. Indeed, follow-up time in these studies was relatively short. It is unclear whether the proportions of remission and recurrence rates differ between endoscopic TS and microscopic TS.

The best way to compare clinical outcomes between endoscopic TS and microscopic TS is to execute a clinical trial (23), which is neither feasible nor practical due to limited sample size, variation in surgeons' experience, institutional differences and ethical considerations. Thus, to gain more insight into the potential advantages of endoscopic TS for patients with CD, especially with respect to endocrine outcomes, we conducted a systematic review and meta-analysis to evaluate studies of endoscopic TS and microscopic TS.

Method

Study search strategy

We conducted a comprehensive search ('Pituitary ACTH Hypersecretion/surgery' (Mesh) or 'CD surgery') using PubMed to identify relevant studies without limitation on language. Reference lists from studies and systematic reviews identified electronically were manually searched to identify additional eligible studies. When more than one publication shared the same patient population, we included only the most recent report in the meta-analysis.

Inclusion and exclusion criteria

We identified eligible articles based on the following inclusion criteria: (1) publication date (later than 2005); (2) study design (cohort studies); (3) target adult population (microscopic TS or endoscopic TS of CD) and (4) sufficient published data to allow for the estimation of a rate with a 95% confidence interval (CI).

To compare the differences between patients with endoscopic surgery and patients with microscopic surgery, several exclusion criteria were employed as follows: (1) studies without endocrinology outcome or follow-up data; (2) studies with a specific focus on a particular kind of tumor (e.g., macroadenomas or MRI-negative tumors); (3) studies that included children and/or teenagers; (4) studies with fewer than 20 CD patients and (5) studies that included both procedures or did not mention which procedure was used.

Studies with patients treated prior to 1990 were considered separately because the follow-up period was longer in these studies. We included these studies in this meta-analysis to examine the effect of long-term follow-up on recurrence.

Data extraction

The decision about whether a study should be included was made by the author (N Q). The results were reviewed by two senior physicians (M S and X S). The data extracted included the first author's name and publication date, as well as patient age, gender composition, MRI feature, endocrine remission, follow-up time and recurrence.

The diagnosis of CD was established by Cushingoid symptoms; endogenous hypercortisolism; dynamic test, inferior petrosal sinus sampling and pituitary MRI in most studies. Positron emission tomography with 18-fluorodeoxyglucose to localize a hypermetabolic focus within the sella was used in one study (22). The term 'remission' is defined by hypocortisolism with low serum cortisol ($<5\,\mu g/dL$) and/or low urinary free cortisol ($<20\,mg$ per $24\,h$), and/or low cortisol ($<1.8\,mg/dL$) level after $1\,mg$ dexamethasone. Most of the studies also defined eucortisolism as remission (15, 17, 18, 25, 28, 29, 30, 31, 32, 33, 34, 36, 37). Several studies also include the need for corticosteroid replacement and significant changes in clinical features as remission criteria (14, 25, 30, 34, 35). The proportion of remission was calculated by dividing the number of patients with remission following surgery by the total number of patients. Half of the publications defined 'recurrence' as elevated cortisol serum level and/or elevated midnight salivary cortisol levels and/or elevated 24-h UFC levels associated with clinical symptoms of CD (16, 20, 26, 28, 29, 30, 33, 38). The proportion of recurrence following surgery was calculated by dividing the number of patients with recurrence by the number of patients with remission. We also estimated the recurrence rate, which was the number of patients with recurrence following surgery divided by the follow-up time (in patient-years) for patients with remission.

Statistical methods

Demographic characteristics (age, gender, tumor volume and cavernous sinus invasion) and outcome (remission proportion, recurrence proportion and recurrence rate) between endoscopic and microsurgical approaches were compared using 'metaprop' function in R. Whether random-effects or fixed-effects should be used was decided by the I^2 tests. 'Forest' function in R was used for the forest plot with subgroup analysis. The presence of heterogeneity across trials was evaluated, and a P value ≤0.05 was considered to be significant. Meta-regressions were performed with potential modifiers. The sensitivity analysis was also performed by removing a single study to determine the influence of that individual data set on the pooled proportions or rates. Funnel plots were also constructed to estimate the publication bias of the literature. All the statistical analyses were performed with R Studio, version 1.0.143.

Results

Study characteristics

A total of 1104 citations were identified by our search strategy. After a detailed evaluation of these articles, 80 studies remained for assessment. After applying the selection criteria, 36 cohort studies involving 4326 patients were identified and included in the meta-analysis (14, 15, 16, 17, 18, 19, 20, 21, 22, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50). In these 36 studies, 2656 patients were included in 12 studies (39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50) with treatments prior to 1990 and long-term follow-up. Among the remaining 24 studies, 702 patients across nine studies underwent endoscopic TS (14, 15, 16, 17, 18, 19, 20, 21, 22), and 968 patients across 15 studies underwent microscopic TS (24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38). Baseline patient characteristics are summarized in Table 1.

Demographic characteristics

No study directly compared endoscopic and microsurgical approaches. Similar baseline characteristics were observed in both groups. The average patient age in the endoscopic group and the microscopic group was 41.3 years and 41.4 years, respectively (P=0.981). Females accounted for 79.5% (95% CI: 72.5–85.1%) of 702 patients who underwent endoscopic surgery and 81.4% (95% CI: 78.2–84.1%) of 968 patients who underwent microsurgery (P=0.583).

Table 1 Characteristic of 24 studies of endoscopic or microscopic trans-sphenoidal ACTH-secreting adenoma resection.

Study	Year	Place	Method	Cases	Age	Female (%)	MRI- PAs (%)	Micro PAs (%)	Macro PAs (%)	CS invasion (%)
Frank et al. (14)	1998–2004	Bologna, Italy	Endoscopy	56	41	32 (57.1%)	0 (0.0%)	25 (44.6%)	31 (55.4%)	3 (5.4%)
Derdashti (15)	2004–2007	Toronto, Canada	Endoscopy	25	42	19 (76.0%)	5 (20.0%)	15 (60.0%)	5 (20.0%)	7 (28.0%)
Wagenmakers et al. (16)	1998–2011	Nijmegen, Netherland	Endoscopy	86	42.3	62 (72.1%)	20 (23.3%)	35 (40.7%)	31 (36.0%)	15 (17.4%)
Starke et al. (17)	2004–2011	Virginia, USA	Endoscopy	61	49	52 (85.2%)	16 (26.2%)	30 (49.2%)	15 (24.6%)	6 (9.8%)
Berker et al. (21)	2006–2012	Ankara, Turkey	Endoscopy	90	38.7	79 (87.8%)	4 (4.4%)	57 (63.3%)	29 (32.2%)	NA
Kuo et al. (18)	2000–2014	Taipei, China	Endoscopy	40	41	38 (95.0%)	0 (0.0%)	22 (55.0%)	18 (45.0%)	9 (22.5%)
Sarkar et al. (22)	2009–2014	Vellore, India	Endoscopy	64	31.9	51 (79.7%)	8 (12.5%)	45 (70.3%)	11 (17.2%)	NA
Shin et al. (19)	2002–2013	Pittsburgh, USA	Endoscopy	50	44	39 (78.0%)	10 (20.0%)	27 (54.0%)	13 (26.0%)	6 (12.0%)
Cebula et al. (20)	2008–2013	Suresnes, France	Endoscopy	230	42	188 (81.7%)	70 (30.4%)	106 (46.1%)	54 (23.5%)	59 (25.7%)
Esposito et al. (24)	1998–2005	Los Angeles, USA	Microscopy	40	39	37 (93.0%)	8 (20.0%)	23 (57.5%)	9 (22.5%)	NA
Acebes et al. (25)	1997–2004	Barcelona, Spain	Microscopy	44	41.5	39 (88.6%)	7 (15.9%)	27 (61.4%)	10 (22.7%)	4 (9.1%)
Santoro et al. (26)	1995–2004	Roma, Italy	Microscopy	36	44	28 (77.8%)	0 (0.0%)	22 (61.1%)	14 (38.9%)	NA
Patil et al. (27)	1992–2006	Virginia, USA	Microscopy	36	40.3	26 (72.2%)	10 (27.8%)	23 (63.9%)	3 (8.3%)	0 (0.0%)
Patil et al. (28)	1992–2006	Virginia, USA	Microscopy	215	39.6	166 (77.2%)	84 (39.1%)	131 (60.9%)	0 (0.0%)	NA
Carrasco et al. (29)	1996–2006	Paris, France	Microscopy	68	36	59 (86.8%)	0 (0.0%)	58 (85.3%)	10 (14.7%)	10 (14.7%)
Fomekong et al. (30)	1996–2007	Brussels, Belgium	Microscopy	40	43	37 (92.5%)	3 (7.5%)	25 (62.5%)	12 (30.0%)	6 (15.0%)
Alwani et al. (31)	1991–2006	Rotterdam, Netherland	Microscopy	79	40.8	63 (79.7%)	14 (17.7%)	44 (55.7%)	21 (26.6%)	NA
Witek and Zieliński (32)	2005–2009	Warsaw, Poland	Microscopy	36	36.3	30 (83.3%)	8 (22.2%)	22 (61.1%)	6 (16.7%)	NA
Dimopoulou et al. (33)	1990–2012	Tuebingen, Germany	Microscopy	120	50	96 (80.0%)	30 (25.0%)	58 (48.3%)	32 (26.7%)	13 (10.8%)
Hameed et al. (34)	2001–2009	Oregon, USA	Microscopy	52	45	38 (73.1%)	15 (26.9%)	28 (53.8%)	16 (30.8%)	NA
Barbot et al. (35)	2001–2009	Padova, Italy	Microscopy	57	38	48 (84.2%)	15 (26.3%)	34 (59.6%)	8 (14.0%)	NA
Lampropoulos et al. (36)	2004–2011	Crete, Greece	Microscopy	23	46.6	21 (91.3%)	5 (21.7%)	9 (39.1%)	9 (39.1%)	NA
Solak et al. (37)	2007–2014	Zagreb, Croatia	Microscopy	33	38	27 (81.8%)	0 (0.0%)	23 (69.7%)	10 (30.3%)	4 (12.1%)
Amlashi et al. (38)	2005–2014	Boston, USA	Microscopy	89	42.4	74 (83.1%)	0 (0.0%)	79 (88.8%)	10 (11.2%)	NA

NA, not available; PAs, pituitary adenomas.

More patients in the microscopic group (62.8%) had micro-adenomas than did patients in the endoscopic group (53.1%, 95% CI: 56.1–69.1% and 46.4–59.7% respectively, $P=0.043$). Conversely, more patients in the endoscopic group (30.6%) had macroadenomas than did patients in the microscopic group (22.0%, 95% CI: 23.5–38.7% and 17.0–27.9% respectively, $P=0.066$). The proportion of MRI-negative tumors was nearly the same in both groups with 16.2% and 17.6% (95% CI: 10.3–24.4% and 12.3–24.5%, $P=0.769$), respectively. We determined that 17.0% of patients treated endoscopically had cavernous sinus invasion compared with 11.9% of patients treated microsurgically (95% CI: 11.6–24.2% and 8.8–16.0%, $P=0.149$), though most of the studies did not supply these data.

Outcome assessment

There was no significant difference in remission proportion between the two groups, as shown in Fig. 1: 79.7% (95% CI: 73.1–85.0%) of the patients who underwent endoscopic TS were in remission compared to 76.9% (95% CI: 71.3–81.6%) in the microscopic TS group ($P=0.485$) (Table 2). There was no difference in the remission of magnetic resonance image (MRI)-negative tumors or of macroadenomas (Figs 2 and 3, $P=0.229$ and $P=0.809$, respectively); however, the proportion of remission in micro-adenomas was significantly higher in the endoscopic group (87.3%, 95% CI: 83.2–90.5%) than in the microscopic group (79.3%, 95% CI: 75.1–82.9%, $P=0.004$, Fig. 4).

It seems that fewer patients who underwent endoscopic surgery recurred than did patients who underwent microscopic surgery (Fig. 5), with recurrence proportions of 11.0% and 15.9% (95% CI: 7.6–15.7% and 11.5–21.7%, respectively; $P=0.134$), respectively. However, if follow-up time is taken into account (36 months in endoscopic group and 53 months in microscopic group, $P=0.057$), both groups had a recurrence rate of approximately 4% per person per year (Fig. 6, 95% CI: 3.1–5.4% and 3.6–5.1%, respectively; $P=0.651$).
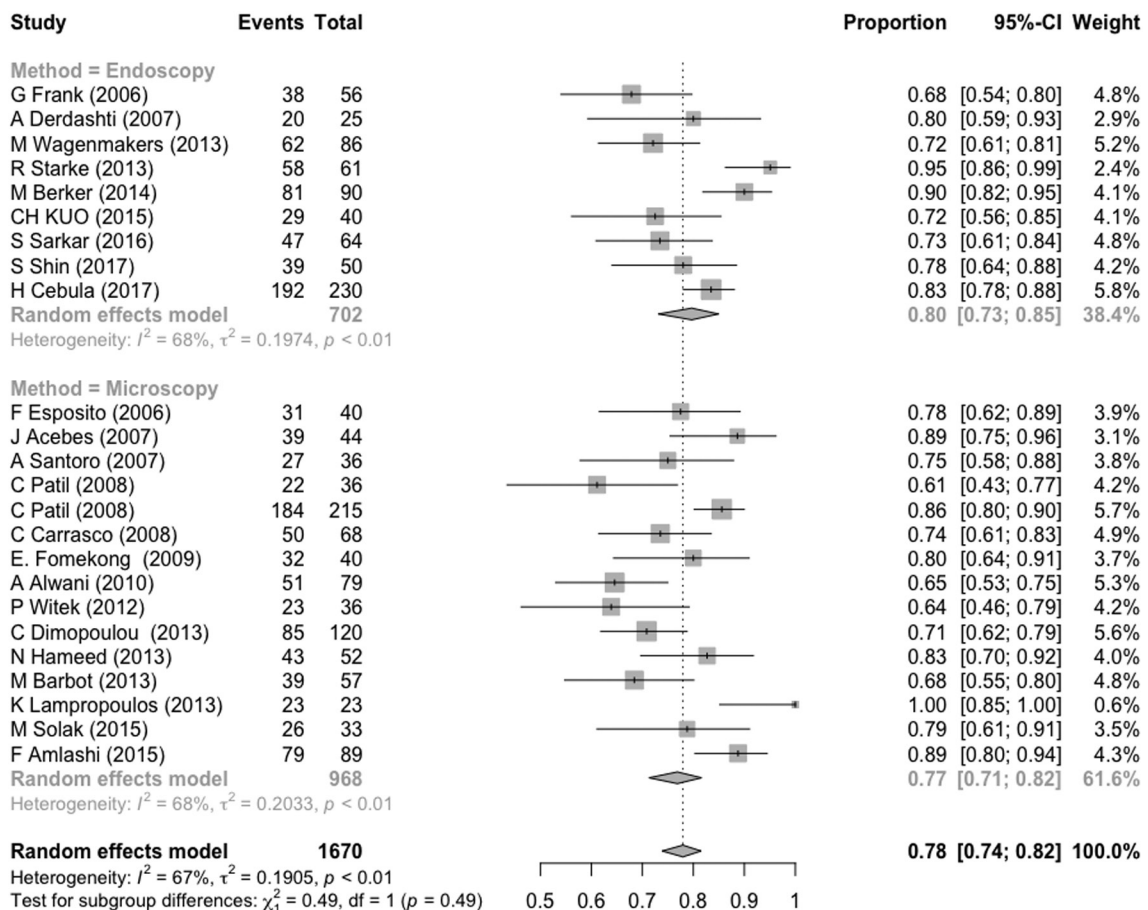
Figure 1
Forest plot of remission proportion in the two groups.

Table 2 Outcomes in endoscopic or microscopic trans-sphenoidal ACTH-secreting adenoma resection.

Study	Method	Cases	FU (months)	Overall remission (%)	Remission in MRI- PAs (%)	Remission in micro PAs (%)	Remission in macro PAs (%)	Proportion of recurrence (%)	Recur rate (/person year)
Frank et al. (14)	Endoscopy	56	NA	38 (67.9%)	0 (NA)	21 (84.0%)	17 (54.8%)	NA	NA
Dehdashti and Gentili (15)	Endoscopy	25	17	20 (80.0%)	2 (40.0%)	13 (86.7%)	4 (80.0%)	0 (0.0%)	0.0%
Wagenmakers et al. (16)	Endoscopy	86	71	62 (72.1%)	12 (85.7%)	29 (82.9%)	21 (67.7%)	10 (16.1%)	2.7%
Starke et al. (17)	Endoscopy	61	28	58 (95.1%)	16 (100.0%)	29 (96.7%)	13 (86.7%)	6 (12.0%)	5.1%
Berker et al. (21)	Endoscopy	90	32	81 (90.0%)	0 (0.0%)	53 (93.0%)	28 (96.6%)	4 (4.9%)	1.9%
Kuo et al. (18)	Endoscopy	40	40.2	29 (72.5%)	4 (66.7%)	18 (81.8%)	11 (61.1%)	3 (10.3%)	3.1%
Sarkar et al. (22)	Endoscopy	64	29	47 (79.7%)	8 (80.0%)	39 (86.7%)	5 (55.6%)	4 (8.5%)	3.5%
Shin et al. (19)	Endoscopy	50	50	39 (78.0%)	8 (80.0%)	21 (77.8%)	10 (76.9%)	9 (23.1%)	5.5%
Cebula et al. (20)	Endoscopy	230	21	182 (79.1%)	50 (71.4%)	97 (91.5%)	35 (64.8%)	18 (9.9%)	5.7%
Esposito et al. (24)	Microscopy	40	33	31 (77.5%)	4 (50.0%)	21 (91.3%)	6 (66.7%)	1 (3.2%)	1.2%
Acebes et al. (25)	Microscopy	44	49	39 (88.6%)	6 (85.7%)	NA	NA	3 (7.7%)	1.9%
Santoro et al. (26)	Microscopy	36	58.6	27 (75.0%)	0 (NA)	19 (86.4%)	8 (57.1%)	4 (14.8%)	3.0%
Patil et al. (27)	Microscopy	36	36	22 (61.1%)	9 (90.0%)	13 (56.5%)	0 (0.0%)	2 (9.1%)	3.0%
Patil et al. (28)	Microscopy	215	45	184 (85.6%)	NA	NA	NA	37 (20.1%)	5.4%
Carrasco et al. (29)	Microscopy	68	45	50 (73.5%)	0 (NA)	41 (70.7%)	9 (90.0%)	5 (10.0%)	2.7%
Fomekong et al. (30)	Microscopy	40	86	32 (80.0%)	0 (0.0%)	21 (84.0%)	11 (91.7%)	3 (9.4%)	1.3%
Alwani et al. (31)	Microscopy	79	84	51 (64.6%)	8 (57.1%)	37 (84.1%)	9 (42.9%)	10 (19.6%)	2.8%
Witek and Zieliński (32)	Microscopy	36	NA	23 (63.9%)	3 (37.5%)	17 (77.3%)	3 (50.0%)	NA	NA
Dimopoulou et al. (33)	Microscopy	120	79	85 (70.8%)	17 (56.7%)	46 (79.3%)	22 (68.8%)	29 (34.1%)	5.2%
Hameed et al. (34)	Microscopy	52	23.3	43 (82.7%)	6 (75.0%)	25 (89.3%)	12 (75.0%)	6 (14.0%)	7.2%
Barbot et al. (35)	Microscopy	57	83.6	39 (68.4%)	9 (60.0%)	26 (76.5%)	4 (50.0%)	15 (38.5%)	5.5%
Lampropoulos et al. (36)	Microscopy	23	43.2	23 (100.0%)	3 (60.0%)	7 (77.8%)	6 (66.7%)	2 (8.7%)	2.4%
Solak et al. (37)	Microscopy	33	28	26 (78.8%)	0 (NA)	18 (78.3%)	8 (80.0%)	2 (7.7%)	3.3%
Amlashi et al. (38)	Microscopy	89	53.5	79 (88.8%)	0 (NA)	69 (87.3%)	10 (100.0%)	13 (38.2%)	8.6%

FU, Follow-up; NA, not available; Pas, pituitary adenomas.

To investigate the effect of follow-up time on recurrence, we also included studies that reported patients treated prior to 1990 and with long-term follow-up (98 months compared to 53 months, respectively; $P=0.010$) (Table 3). There was no significant difference in remission between patients with long-term follow-up vs patients with relatively short follow-up times: 75.4% (95% CI: 73.1–85.0%) vs 76.9% (95% CI: 71.3–81.6%, $P=0.849$), respectively. Recurrence rate was also comparable between these two groups with 2.7% (95% CI: 2.0–3.8%) and 4.0% (95% CI: 3.2–5.0%) per person per year, respectively.

Quality analysis

Heterogeneity across studies was observed in the proportions of remission ($I^2=67\%$, $P<0.01$) and recurrence ($I^2=67\%$, $P<0.01$). There was no indication of heterogeneity in the recurrence rate ($I^2=17\%$, $P=0.23$). To investigate the source of the heterogeneity, we conducted meta-regressions with several potential modifiers: number of patients, publication year, location in which the study was conducted and remission criteria. Our meta-regression analysis revealed no significant effects on the proportion of remission for publication date ($P=0.362$), study location ($P=0.142$), number of enrolled cases ($P=0.142$) or remission criteria (0.844). Publication date ($P=0.567$), study location ($P=0.135$) and number of enrolled cases ($P=0.440$) did not contribute to the heterogeneity of recurrence proportion.

In the sensitivity analysis, a single study was removed to determine the influence of that individual data set on the pooled proportions or rates; the corresponding proportions and rates were not significantly altered, indicating that our results are statistically robust. Funnel plots were constructed to estimate the publication bias of the literature; the results suggest that any potential publication bias did not substantially influence the results of this meta-analysis.

Discussion

This systematic review and meta-analysis compares outcomes in endoscopic and microsurgical approaches for the treatment of ACTH-secreting pituitary adenomas. In our study, we found that basic characteristics of patients treated endoscopically were comparable to those of patients treated microscopically, except that more patients treated endoscopically had macroadenomas. Similar remission proportions were found for both endoscopic
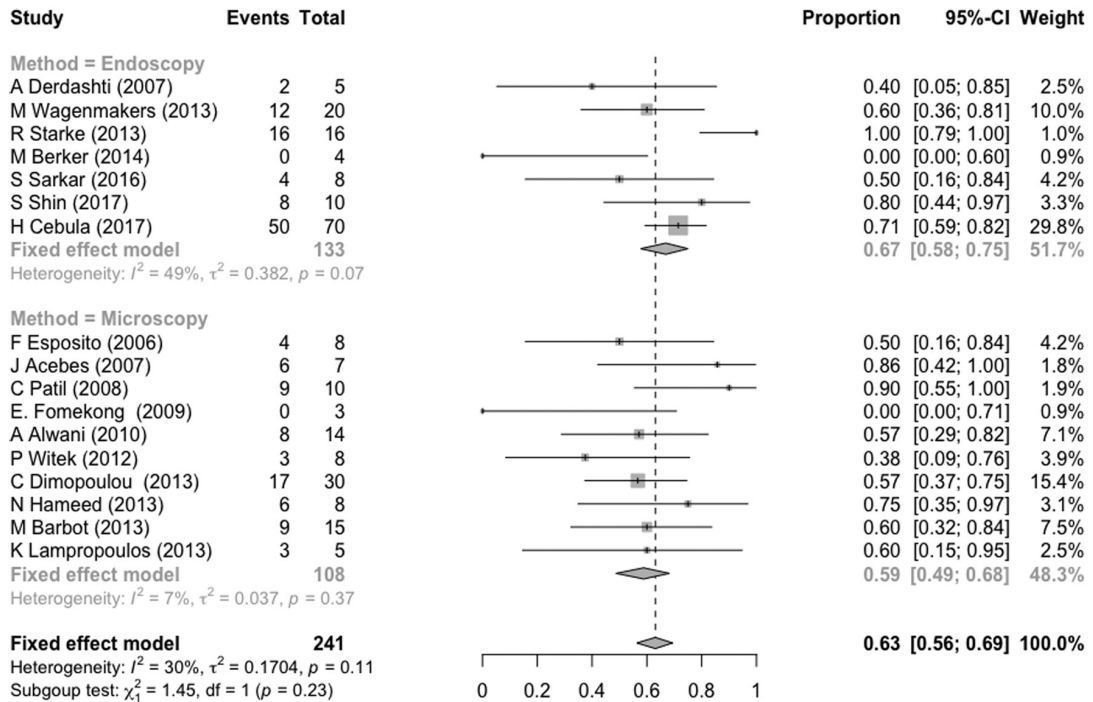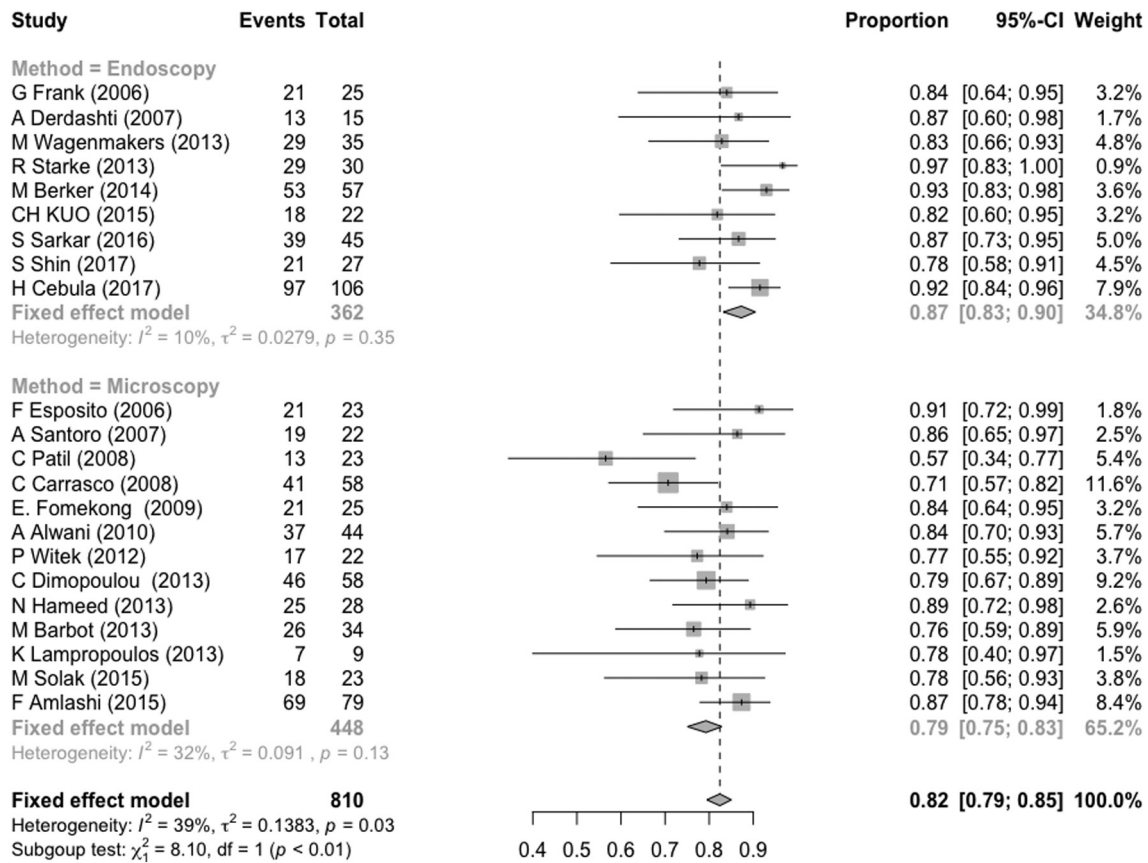
Figure 2

Forest plot of remission proportion of MRI-negative adenomas in the two groups.
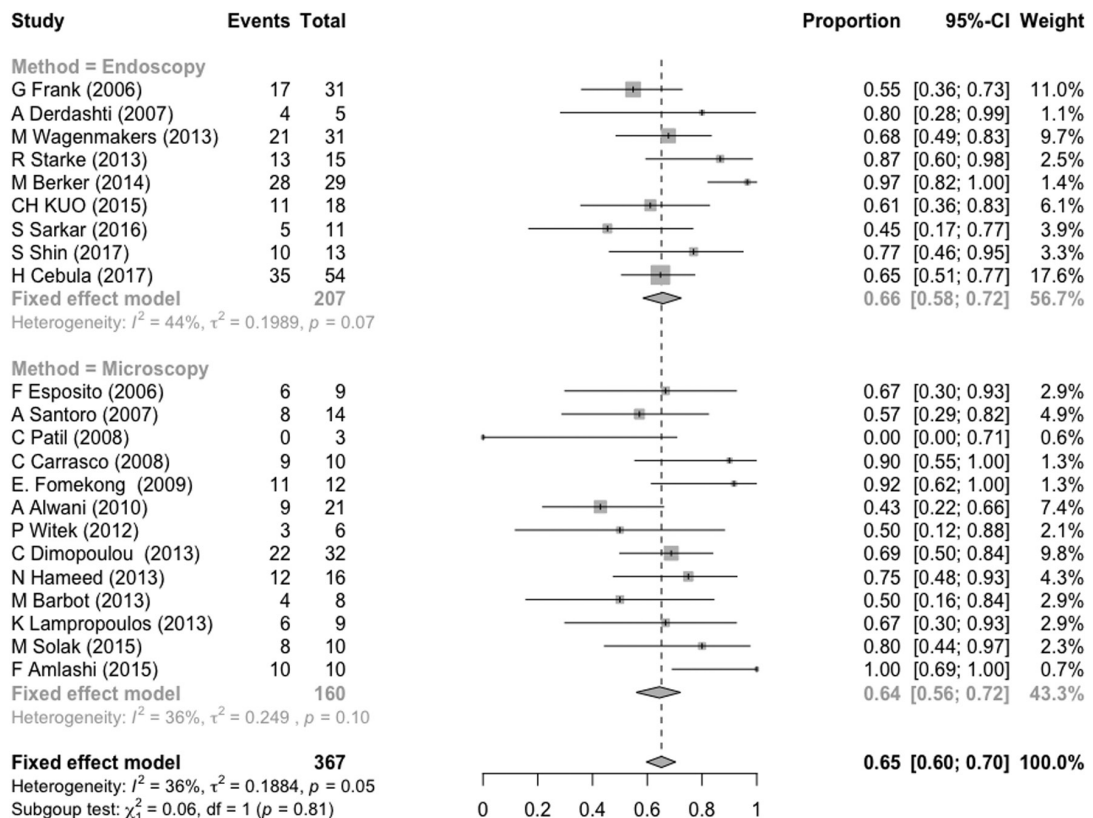
Figure 3

Forest plot of remission proportion of macroadenomas in the two groups.

Figure 4
Forest plot of remission proportion of microadenomas in the two groups.

and microsurgical approaches, though remission criteria differed from study to study. Patients treated with the endoscopic approach for micro-adenomas were more likely to achieve remission than those treated microsurgically. Recurrence seemed to be lower among patients treated endoscopically; however, when follow-up time is taken into account, this advantage disappears.

Because most of the studies with endoscopy were performed in the latest 10–15 years. To eliminate the time as a confounding factor, we only included studies performed after 2005 (the oldest eligible publication on endoscopic TS is 2006). We only included studies with more than 20 patients because we believe surgical outcomes of CD are influenced by doctors' experience. On the other hand, we also performed sensitive analysis, even studies with less 20 patients were included, the result did not change. Studies with patients treated prior to 1990 were considered separately because the follow-up period was longer in these studies.

Endoscopic visualization provides a more panoramic view of the operative field, compared with the microscope, allowing for better viewing of the suprasellar region

(51, 52). It is also possible to use instruments with a variety of angles to access lateral invasions of tumors (12, 13). Endoscopic surgery is an excellent approach for patients with CD, as the typically small size of the tumor requires higher magnification. Intrasellar illumination provided by the endoscope is extremely helpful in the intraoperative identification of abnormal tissue (19, 20, 22, 53). However, continuous adjustment of the endoscope is needed to determine target location within the surgical field, which may compromise maneuverability. Unlike endoscopic visualization, microsurgery offers a continuous view with a stereotactic display, which is familiar to the majority of surgeons and may allow for better control of bleeding in an open field. In recent years, some papers about 3D endoscopy for pituitary adenoma have been published (67, 68). This technique can combine depth perception in microscopy and wide-view in endoscopy. But no studies with 3D endoscopy were reported in patients with CD.

In the early days of endoscopic surgery, a large meta-analysis by Ammirati and coworkers (54) concluded that endoscopic removal of pituitary adenoma does not seem to confer any benefits over microscopic technology in
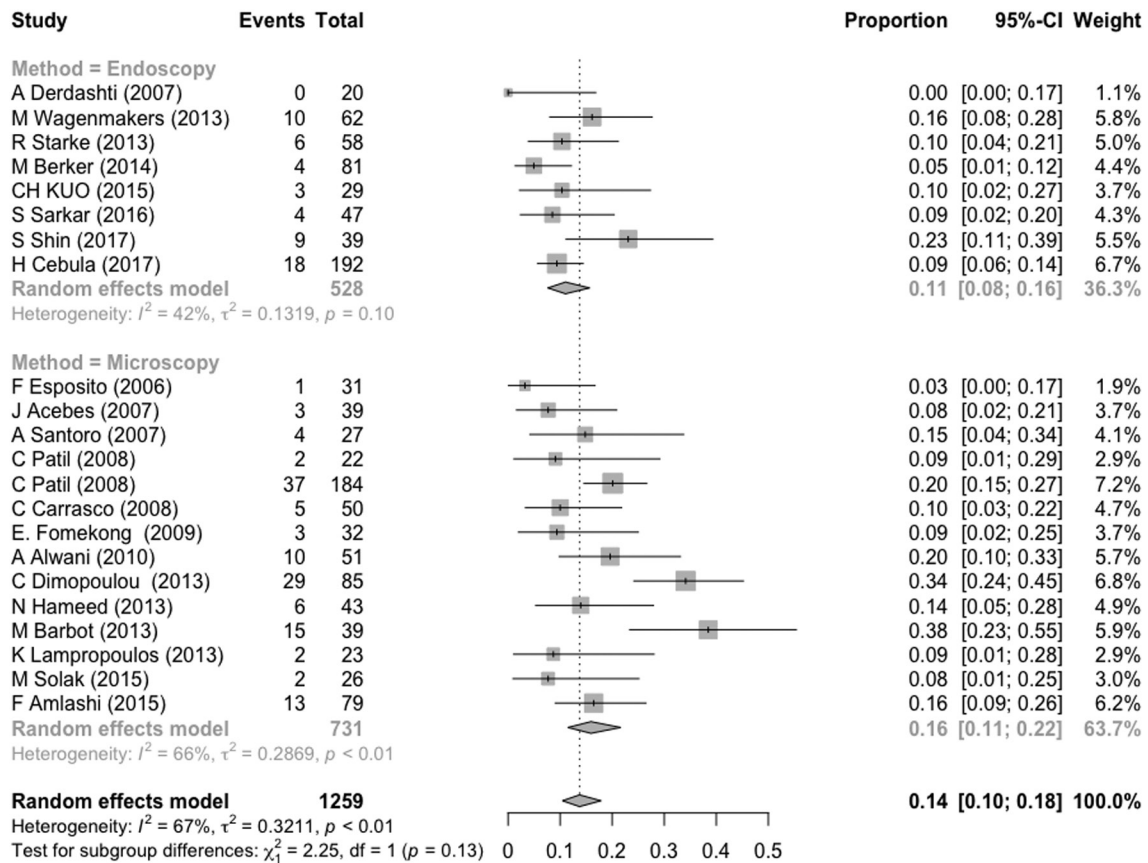
Figure 5
Forest plot of recurrence proportion in the two groups.

the short term. However, recent meta-analyses showed that the endoscopic technique is associated with higher gross tumor removal (57) and modest increases of resection rates in residual or recurrent cases (58). In patients with functional pituitary adenomas (growth hormone-secreting adenoma), Phan and coworkers (59) concluded that clinical use of the endoscopic approach conferred potential benefits, including increased remission rates with non-invasive macroadenomas, but that overall endocrine remission is comparable. Chen and coworkers (60) also concluded that both approaches yielded similar rates of remission. However, a meta-analysis comparing outcomes from endoscopic TS and microscopic TS was lacking.
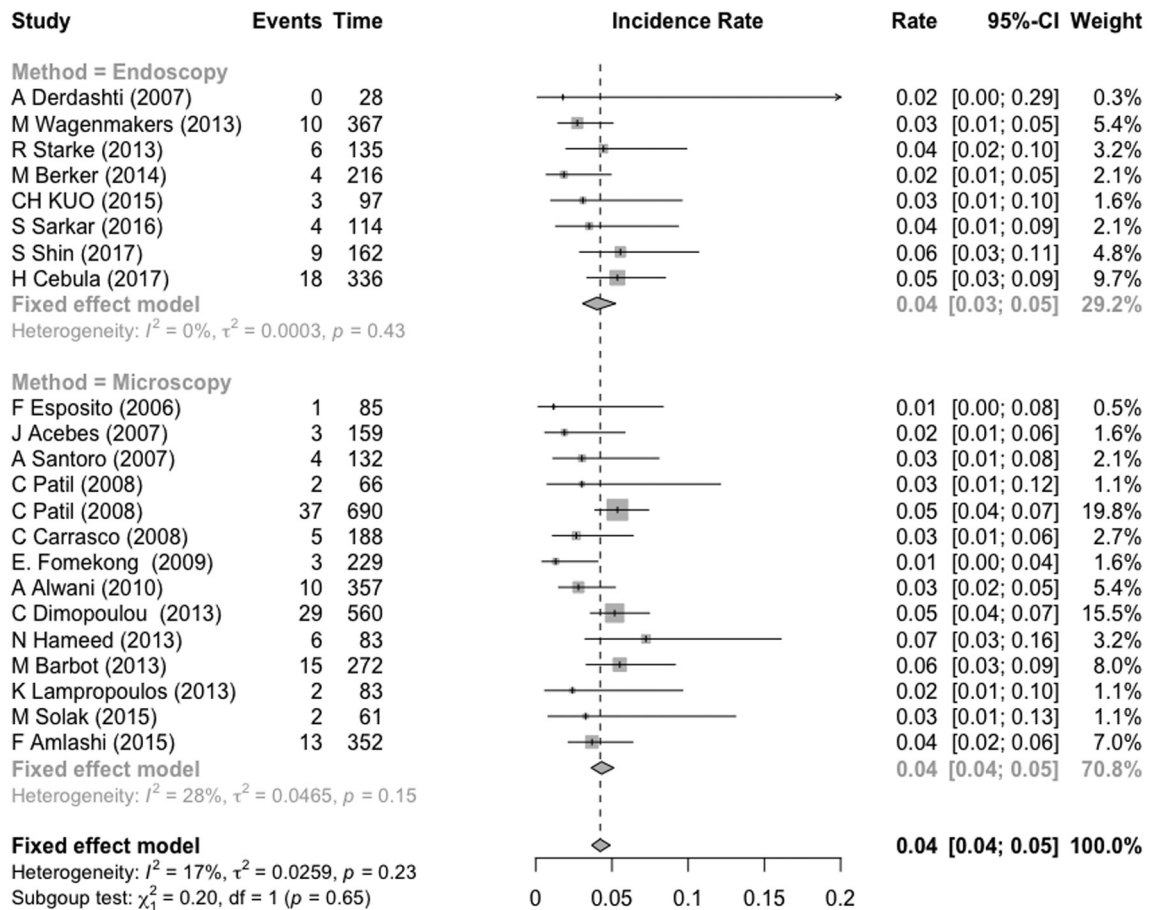
Our results support these findings. Overall remission, remission in macroadenomas, and remission in MRI-negative CD showed no differences between groups. We also found that remission proportions for micro-adenomas were significantly higher in patients treated with the endoscopic approach compared to patients treated with the microsurgical approach. The superior intraoperative

visualization afforded by the endoscopic approach may account for this finding. A much more unobstructed view of the operative field may facilitate resection of much of the tumor, especially the pseudocapsule (61, 62, 63).

Complete surgical resection may be difficult for tumors with cavernous sinus infiltration due to the risks of injury of carotid artery and cranial nerves (69, 70). However, given the low occurrence of tumors with cavernous infiltration in each study, as well as the fact that few studies reported the remission of invasive tumors, the comparison between patients treated with endoscopic TS and microscopic TS was impossible in our analysis.

Regarding postoperative complications, previous studies include thorough descriptions and analyses, most of which demonstrate that patients who underwent endoscopic surgery had comparable proportions of complications, including diabetes insipidus, CSF leakage, hypocortisolemia, hypothyroidism, hypogonadism and visual defects, compared to patients who underwent microscopic surgery (57, 58, 59, 60). In this meta-analysis, we did not include any of these complications. Proportions

Study	Events	Time	Incidence Rate	Rate	95%-CI	Weight
Method = Endoscopy						
A Derdashti (2007)	0	28		0.02	[0.00; 0.29]	0.3%
M Wagenmakers (2013)	10	367		0.03	[0.01; 0.05]	5.4%
R Starke (2013)	6	135		0.04	[0.02; 0.10]	3.2%
M Berker (2014)	4	216		0.02	[0.01; 0.05]	2.1%
CH KUO (2015)	3	97		0.03	[0.01; 0.10]	1.6%
S Sarkar (2016)	4	114		0.04	[0.01; 0.09]	2.1%
S Shin (2017)	9	162		0.06	[0.03; 0.11]	4.8%
H Cebula (2017)	18	336		0.05	[0.03; 0.09]	9.7%
Fixed effect model				0.04	[0.03; 0.05]	29.2%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.0003$, $p = 0.43$						
Method = Microscopy						
F Esposito (2006)	1	85		0.01	[0.00; 0.08]	0.5%
J Acebes (2007)	3	159		0.02	[0.01; 0.06]	1.6%
A Santoro (2007)	4	132		0.03	[0.01; 0.08]	2.1%
C Patil (2008)	2	66		0.03	[0.01; 0.12]	1.1%
C Patil (2008)	37	690		0.05	[0.04; 0.07]	19.8%
C Carrasco (2008)	5	188		0.03	[0.01; 0.06]	2.7%
E. Fomekong (2009)	3	229		0.01	[0.00; 0.04]	1.6%
A Alwani (2010)	10	357		0.03	[0.02; 0.05]	5.4%
C Dimopoulou (2013)	29	560		0.05	[0.04; 0.07]	15.5%
N Hameed (2013)	6	83		0.07	[0.03; 0.16]	3.2%
M Barbot (2013)	15	272		0.06	[0.03; 0.09]	8.0%
K Lampropoulos (2013)	2	83		0.02	[0.01; 0.10]	1.1%
M Solak (2015)	2	61		0.03	[0.01; 0.13]	1.1%
F Amlashi (2015)	13	352		0.04	[0.02; 0.06]	7.0%
Fixed effect model				0.04	[0.04; 0.05]	70.8%
Heterogeneity: $I^2 = 28\%$, $\tau^2 = 0.0465$, $p = 0.15$						
Fixed effect model				**0.04**	**[0.04; 0.05]**	**100.0%**
Heterogeneity: $I^2 = 17\%$, $\tau^2 = 0.0259$, $p = 0.23$						
Subgoup test: $\chi^2_1 = 0.20$, df = 1 ($p = 0.65$)			0 0.05 0.1 0.15 0.2			

Figure 6
Forest plot of recurrence rate in the two groups.

of sinusitis and epistaxis were also comparable in previous reports (59, 64).

The definition of remission for CD varies over time and across studies. The remission of clinical symptoms, the need for glucocorticoid replacement, low or normal cortisol levels, normal 24-h urinary free cortisol levels, late-night salivary cortisol levels and cortisol after the dexamethasone suppression test all have been used in the literature (14, 15, 16, 17, 18, 19, 20, 21, 22, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50). A combination of two or three of the criteria mentioned earlier was used as the remission

Table 3 Studies with patients earlier than 1990 and with long-term follow-up.

Study	Year	Place	Cases	Follow-up (months)	Overall remission (%)	Proportion of recurrence (%)	Recurrence rate (/person year)
Valassi et al. (39)	1982–2007	Boston, USA	620	47.4	477 (76.9%)	62 (13.0%)	3.3%
Lindsay et al. (40)	1982–2004	Bethesda, USA	418	125	331 (79.2%)	40 (12.1%)	1.2%
Kim et al. (41)	1984–2010	Seoul, Korea	54	104.6	38 (70.4%)	18 (47.4%)	5.4%
Ciric et al. (42)	1970–2010	Chicago, Illinois	136	68.4	93 (68.4%)	9 (9.7%)	1.7%
Hassan-Smith et al. (43)	1988–2009	Birmingham, UK	72	55.2	60 (83.3%)	8 (13.3%)	2.9%
Lambert et al. (44)	1980–2011	New York, USA	346	75.6	230 (66.5%)	73 (31.7%)	5.0%
Alexandraki et al. (45)	1969–2001	London, UK	131	180	86 (65.6%)	31 (36.0%)	2.4%
Costenaro et al. (46)	1989–2013	Porto Alegre, Brazil	103	73.2	84 (81.6%)	9 (10.7%)	1.8%
Aranda et al. (47)	1974–2011	Barcelona, Spain	41	168	32 (78.0%)	21 (65.6%)	4.7%
Yamada et al. (48)	1988–2014	Tokyo, Japan	230	72.5	198 (86.1%)	14 (7.1%)	1.2%
Chandler et al. (49)	1980–2012	Michigan, USA	275	80.4	219 (79.6%)	37 (16.9%)	2.5%
Bansal et al. (50)	1987–2015	Maharashtra, India	230	74	151 (65.7%)	48 (31.8%)	5.2%

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criteria in our study. Due to improvements in biochemical assays, a new consensus holds more stringent criteria for remission (65): 'a postoperative cortisol value of <2 mg/dL predicts a higher chance of long-term remission after TS in CD; most patients with postoperative cortisol values of 2–5 mg/dL a few days after TS will also be in remission'. We also performed a subgroup analysis between studies with strict criteria and studies with lenient criteria. It turns out that no difference in remission proportion was observed in the two subgroups.

There was significant heterogeneity in the outcomes. This heterogeneity is likely impacted by differences in surgical technique, surgeon, team and institution experience or outcome criteria. It is also likely that differences in study design and definition of the outcomes influence heterogeneity (66).

A significant weakness of our analysis is that most studies use a relatively short follow-up time in patients with endoscopic TS. To compare recurrence rate between the two surgical groups, we assumed that there was no effect of follow-up time on recurrence rate. Meta-regression showed that the slope of recurrence rate by follow-up time was minus 0.002 ($P = 0.529$), a trend suggesting that as follow-up time increases, recurrence rate may decrease. We found no studies that directly compared endoscopic and microsurgical approaches. Randomized trials with experienced surgeons and trials with long-term follow-up are required to help bridge the current gaps in the literature.

Conclusion

We found that overall remission proportion was the same in CD patients who underwent endoscopic TS compared to patients who underwent microscopic TS. However, patients treated with the endoscopic approach for micro-adenomas were more likely to achieve remission than those treated microsurgically. Patients treated endoscopically were less likely to experience recurrence; however, when follow-up time is taken into account, this advantage disappears. The definition of diagnosis, remission and recurrence is very challenging and variable, which has always to be considered in the interpretation of results of studies assessing therapeutic efficacy in CD.

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