Endoscopic Versus Microscopic Transsphenoidal Surgery in the Treatment of Pituitary Adenoma: A Systematic Review and Meta-Analysis

Aijun Li, Weisheng Liu, Peicheng Cao, Yuehua Zheng, Zhenfu Bu, Tao Zhou

■ BACKGROUND: **Inconsistent findings have been reported regarding the efficacy and safety of endoscopic and microscopic transsphenoidal surgery for pituitary adenoma. This study aimed to assess the benefits and shortcomings of these surgical methods in patients with pituitary adenoma.**

■ METHODS: **The electronic databases PubMed, Embase, and the Cochrane Library were systematically searched, as well as proceedings of major meetings. Eligible studies with a retrospective or prospective design that evaluated endoscopic versus microscopic methods in patients with pituitary adenoma were included. Primary outcomes included gross tumor removal, cerebrospinal fluid leak, diabetes insipidus, and other complications.**

■ RESULTS: **Overall, 23 studies (4 prospective and 19 retrospective) assessing 2272 patients with pituitary adenoma were included in the final analysis. Endoscopic transsphenoidal surgery was associated with a higher incidence of gross tumor removal (odds ratio, 1.52; 95% confidence interval, 1.11–2.08; $P = 0.009$) than those with microscopic transsphenoidal surgery. In addition, endoscopic transsphenoidal surgery had no significant effect on the risk of cerebrospinal fluid leak, compared with microscopic transsphenoidal surgery. Furthermore, endoscopic transsphenoidal surgery was associated with a 22% reduction in risk of diabetes insipidus compared with microscopic transsphenoidal surgery, but the difference was not statistically significant. Endoscopic transsphenoidal surgery significantly reduced the risk of septal perforation (odds ratio, 0.29; 95% confidence interval, 0.11–0.78; $P = 0.014$) and was not associated with the risk of meningitis, epistaxis, hematoma, hypopituitarism, hypothyroidism, hypocortisolism, total mortality, and recurrence.**

■ CONCLUSIONS: **Endoscopic transsphenoidal surgery is associated with higher gross tumor removal and lower incidence of septal perforation in patients with pituitary adenoma. Future large-scale prospective randomized controlled trials are needed to verify these findings.**

INTRODUCTION

Pituitary adenomas account for approximately 10% of all primary intracranial tumors.[1] They are classified based on hormonal activity: nonsecreting, prolactinoma, and adrenocorticotropic hormone, growth hormone, and thyroid-stimulating hormone producing, respectively.[2] Because medication usually yields unacceptable side effects in patients with pituitary adenoma, transsphenoidal surgery is a well-established choice in the treatment of this tumor and has continuously improved in the past decade.[3] Microsurgery via a transsphenoidal approach is widely used for pituitary surgery and has become the gold standard, merging microscopy and intraoperative fluoroscopy.[4,5] Over the past decade, endoscopic transsphenoidal surgery has been increasingly used to remove pituitary tumors and other lesions of the sella.[6-8] However, how these 2 surgical methods compare remains controversial.

Ammirati et al.[9] performed a meta-analysis to evaluate the short-term effects of endoscopic and microscopic pituitary adenoma surgeries and found that endoscopic removal of pituitary

Key words
- Endoscopic
- Meta-analysis
- Microscopic
- Pituitary adenoma

Abbreviations and Acronyms
CI: Confidence interval
CSF: Cerebrospinal fluid
DI: Diabetes insipidus
GTR: Gross tumor removal
OR: Odds ratio

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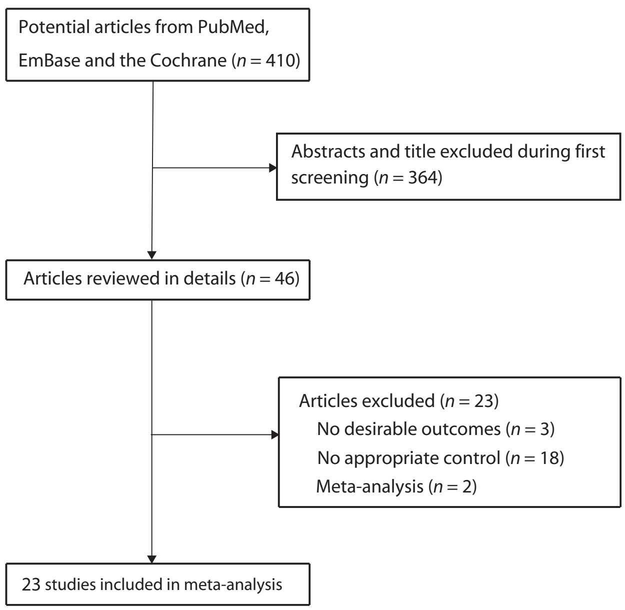

Figure 1. Flow diagram showing the study selection process.

adenomas does not seem to confer any advantages over the microscopic technique; in addition, vascular complications were significantly more common in the endoscopy group compared with the microscopy group. However, Gao et al.[10] indicated that endoscopic surgery is associated with higher gross tumor removal (GTR), with a lower risk of septal perforation, yielding inconsistent results from the 2 interventions. Recently, several studies investigating endoscopic versus microscopic surgeries have been reported. To evaluate the potential benefits and complications of the 2 transsphenoidal surgery types, a comprehensive systematic review and meta-analysis of pooled data were performed, including the latest efficacy and safety findings of endoscopic versus microscopic methods in the treatment of pituitary adenomas.

METHODS

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of Weifang People's Hospital research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Data Sources and Search Strategy

This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement issued in 2009 (Checklist S1).[11] Data were collected from studies to assess the efficacy and safety of endoscopic versus microscopic surgeries in the treatment of pituitary adenomas. To be consistent with previous meta-analysis protocols, any studies comparing endoscopic with microscopic methods needed to follow up the patients in both groups identically, to avoid systematic errors and resultant bias, ensuring the reliability of this study.

Studies comparing endoscopic and microscopic surgeries published in English were eligible regardless of publication status. The databases PubMed, Embase, and the Cochrane Library were systematically searched, ending in August 2016, with the terms "transsphenoidal" AND "surgery" OR "endoscopic" OR "endoscopy" OR "microscopic" OR "microsurgery" AND "pituitary". In addition, the authors were contacted to obtain any possible additional unpublished results, and bibliographies of the included publications were reviewed for potentially relevant studies. Proceedings of major meetings were also searched to identify additional studies. Medical subject heading, disease status, intervention and control, and outcomes investigated were used to identify relevant studies.

Study Selection and Data Abstraction

The literature search was independently performed by 2 authors, using a standardized approach. Any inconsistencies between them were settled by group discussion until a consensus was reached. A study was eligible for inclusion if meeting the following criteria: 1) efficacy or safety comparison of endoscopic with microscopic surgeries; 2) all included patients had pituitary adenomas, with the study reporting at least 1 of the most relevant outcomes, including GTR, cerebrospinal fluid (CSF) leak, diabetes insipidus (DI), septal perforation, meningitis, epistaxis, hematoma, hypopituitarism, hypothyroidism, hypocortisolism, total mortality, and recurrence. Data from eligible trials were independently abstracted, in duplicate, by 2 independent investigators, using a standard protocol, and were reviewed by a third investigator. Any discrepancies were resolved by group discussion, and the primary authors made the final decision. Extracted data included first author's name, publication year, country, study design, sample size, mean patient age, number of males, and number of GTR cases. The numbers of GTR, CSF leak, DI, septal perforation, meningitis, epistaxis, hematoma, hypopituitarism, hypothyroidism, hypocortisolism, total mortality, and recurrence cases were abstracted in each group. Then, the data extracted were entered into a dedicated Excel spreadsheet with a standardized flow step. Data were retrieved according to the intention-to-treat principle, and the principal investigators of all studies were contacted directly to obtain additional information and solve discrepancies until a consensus was reached.

Statistical Analysis

The results of each study were presented as dichotomous frequency data, and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from the numbers of outcomes and patients in each group, extracted from each study before data pooling. Both the fixed and random effects models were used to

Table 1. Baseline Characteristic of Studies Included in the Systematic Review and Meta-Analysis

Study	Publication Year	Country	Study Design	Sample Size	Mean Age	Number of Male	Cases of Gross Tumor Removal	Intervention
Sheehan et al.[20]	1999	USA	Retrospective	70	58.3	49	22	Endoscopic transnasal; sublabial transseptal approach
Cappabianca et al.[21]	1999	USA	Retrospective	30	NA	NA	23	Endoscopic endonasal transsphenoidal surgery; traditional transnasal transsphenoidal approach
Koren et al.[22]	1999	Israel	Retrospective	40	NA	NA	NA	Endoscopic transnasal transsphenoidal microsurgery; sublabial approach
White et al.[23]	2004	USA	Retrospective	100	42.3	57	NA	Endoscopic, minimally invasive pituitary surgery; sublabial transseptal procedures
Casler et al.[24]	2005	USA	Retrospective	30	46.1	16	22	Endoscopic approach; trans-sphenoidal surgery
Neal et al.[25]	2007	USA	Retrospective	29	41.9	13	8	Sublabial transsphenoidal approach; transnasal transsphenoidal approach; endoscopic transnasal approach
Jain et al.[26]	2007	India	Prospective	20	35.9	9	10	Endoscopic endonasal transsphenoidal using 4-mm diameter sinonasal rigid endoscopes: 0° and 3°; microscopic endonasal transsphenoidal surgery
Atkinson et al.[27]	2008	USA	Retrospective	42	44.4	9	36	Endoscopic transsphenoidal microsurgery; sublabial transseptal transsphenoidal microsurgery
Duz et al.[28]	2008	Turkey	Retrospective	68	NA	NA	35	Transsphenoidal surgery; sublabial approach to endoscopic surgery
O'Maley et al.[29]	2008	USA	Retrospective	50	49.4	31	31	Endoscopic resection; microscopic resection
Choe et al.[30]	2008	Korea	Retrospective	23	47.5	7	18	Endoscopic endonasal transsphenoidal approach; sublabial microscopic transsphenoidal approach
Higgins et al.[31]	2008	UK	Retrospective	48	53.4	25	34	Endoscopic transnasal transsphenoidal approach; microscopic resection with either sublabial or transnasal transseptal approach.
D'Haens et al.[32]	2009	Belgium	Retrospective	120	36.0	63	68	Fully endonasal endoscopic surgery using a rigid endoscope 300 mm in length and 4 mm in diameter (Olympus, Hamburg, Germany) with angled lenses of 0°, 30°, and 70°; raditional sublabial transseptal transsphenoidal approach or an endonasal microsurgical approach.
Messerer et al.[33]	2011	France	Retrospective	164	56.8	98	102	Endonasal endoscopic transsphenoidal surgery with a 4-mm rigid endoscope (Karl Storz) and an intraoperative MR imaging neuronavigation system (Medtronic); traditional sublabial transeptal transsphenoidal surgery
Cheng et al.[34]	2011	China	Retrospective	127	35.6	51	77	Endoscopic transsphenoidal surgery; traditional trans-sphenoidal microsurgery
Razak et al.[35]	2013	UK	Retrospective	80	48.4	41	23	Endoscopic trans-sphenoidal surgery; microscopic trans-septal approach
Kahilogullari et al.[36]	2013	Austria	Prospective	50	43.7	10	NA	Endoscopic transsphenoidal; microscopic transsphenoidal
Halvorsen et al.[37]	2014	Norway	Retrospective	506	57.0	291	NA	Endoscopic endonasal transsphenoidal approach using standard Storz endoscopes (180/4 mm) with 0°, 30° and 45° angulations (attached to cameras); microscopic transseptal approach
Dallapiazza et al.[38]	2014	USA	Retrospective	99	56.4	51	94	Endoscopic transsphenoidal; microscopic transsphenoidal
Lenzi et al.[39]	2015	Italy	Retrospective	37	42.0	19	21	Endoscopic; microsurgical
Karppinen et al.[40]	2015	Finland	Retrospective	185	58.4	118	87	Endoscopic transsphenoidal; microscopic transsphenoidal
Little et al.[41]	2015	USA	Prospective	218	51.9	104	NA	Endoscopic transsphenoidal; microscopic transsphenoidal
Zaidi et al.[42]	2016	USA	Prospective	135	57.8	85	98	Fully endoscopic binostril transsphenoidal surgery; uninostril microscopic surgery

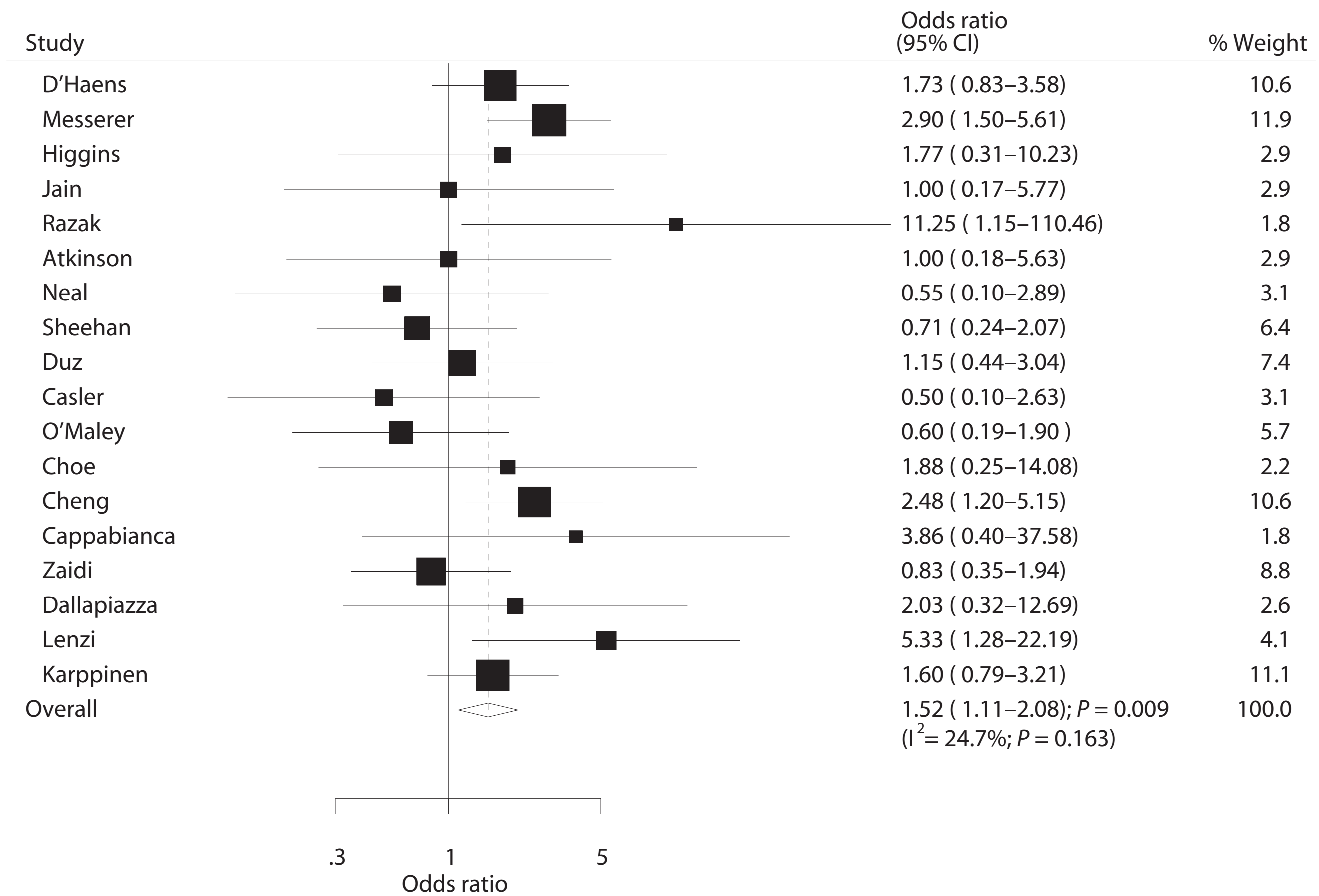

Figure 2. Effect of endoscopic transsphenoidal surgery on gross tumor removal, compared with microscopic surgery. CI, confidence interval.

evaluate summary ORs for beneficial and harmful effects of endoscopic versus microscopic surgeries in the treatment of patients with pituitary adenomas. Although the 2 models yielded similar findings, results from the random effects model were presented because it assumed that true underlying effects vary among the included studies.[12,13] Heterogeneity of intervention effects among the included studies was evaluated statistically by the Q statistic; $P < 0.10$ was considered to represent significant heterogeneity.[14,15] Then, subgroup analyses were performed for GTR, CSF leak, and DI, based on publication year, country, study design, and mean patient age. P values for heterogeneity between subgroups were calculated by χ^2 test and meta-regression.[16] Sensitivity analysis was performed by removing each individual study from the overall analysis.[17] Visual inspection of funnel plots for GTR, CSF leak, and DI was conducted; Egger[18] and Begg[19] tests were used to statistically and quantitatively evaluate publication bias. Two-sided $P < 0.05$ was considered as statistically significant. Statistical analyses were conducted with the STATA software (StataCorp LP, College Station, Texas, USA).

RESULTS

The study selection process is presented in Figure 1. A total of 410 articles were identified in the initial electronic search; of these, 364 were excluded after removal of duplicates and irrelevant studies during an initial review based on titles and abstracts. Then, full texts were retrieved for the remaining 46 studies. After detailed evaluation, 23 studies met the inclusion criteria and were selected for final analysis.[20-42] The studies included in this meta-analysis compared endoscopic with microscopic surgeries in GTR, CSF leak, DI, septal perforation, meningitis, epistaxis, hematoma, hypopituitarism, hypothyroidism, hypocortisolism, total mortality, and recurrence rates in patients with pituitary adenomas. A manual search of the reference lists in these reports yielded no new eligible studies. Table 1 summarizes the characteristics of included studies as well as important baseline data of the 2272 patients. Four studies had a prospective design,[26,36,41,42] whereas the remaining 19 were retrospective.[20-25,27-35,37-40] Sample sizes ranged from 20 to 506, and mean patient age was 35.6–58.4 years.

Table 2. Sensitivity Analysis for Gross Total Resection

Excluding Study	Odds Ratio and 95% Confidence Interval	*P* Value	Heterogeneity (%)	*P* Value for Heterogeneity
D'Haens et al.[32]	1.49 (1.05—2.11)	0.026	29.0	0.127
Messerer et al.[33]	1.40 (1.02—1.91)	0.036	14.5	0.284
Higgins et al.[31]	1.51 (1.08—2.10)	0.015	29.1	0.126
Jain et al.[26]	1.54 (1.11—2.13)	0.010	28.3	0.133
Razak et al.[35]	1.48 (1.10—2.00)	0.010	18.8	0.234
Atkinson et al.[27]	1.54 (1.11—2.13)	0.010	28.3	0.133
Neal et al.[25]	1.57 (1.15—2.16)	0.005	23.8	0.179
Sheehan et al.[20]	1.61 (1.17—2.21)	0.003	21.3	0.206
Duz et al.[28]	1.55 (1.11—2.17)	0.011	27.8	0.138
Casler et al.[24]	1.58 (1.16—2.16)	0.004	22.7	0.190
O'Maley et al.[29]	1.62 (1.19—2.20)	0.002	18.9	0.232
Choe et al.[30]	1.51 (1.09—2.09)	0.014	29.1	0.126
Cheng et al.[34]	1.43 (1.03—2.00)	0.034	23.5	0.182
Cappabianca et al.[21]	1.49 (1.08—2.06)	0.015	27.2	0.144
Zaidi et al.[42]	1.62 (1.18—2.23)	0.003	20.6	0.213
Dallapiazza et al.[38]	1.50 (1.08—2.09)	0.015	28.9	0.127
Lenzi et al.[39]	1.46 (1.07—1.98)	0.015	18.8	0.234
Karppinen et al.[40]	1.50 (1.06—2.13)	0.024	29.2	0.125

Data comparing the effects of endoscopic versus microscopic surgeries on GTR were available in 18 studies, which included 1307 patients with pituitary adenomas, reporting 826 GTR cases. Overall, summary OR showed a 52% increase in GTR (OR, 1.52; 95% CI, 1.11—2.08; P = 0.009; **Figure 2**), and a nonsignificant heterogeneity was observed (I^2 = 24.7%; P = 0.163). Sensitivity analysis was performed, and the conclusion was not affected after sequentially excluding individual studies (**Table 2**). Subgroup analysis suggested that endoscopic surgery was associated with increased incidence of GTR for studies conducted in 2010 or later, not in the United States, with a retrospective design (**Table 3**). Furthermore, there was significant heterogeneity between subgroups for GTR based on publication year (P = 0.014) and country (P = 0.001).

Data comparing the effects of endoscopic versus microscopic surgeries on CSF leak were available in 21 studies, which included 1698 patients with pituitary adenomas; 164 cases of CSF leak were reported. There was no significant difference between endoscopic and microscopic surgeries for CSF leak (OR, 0.98; 95% CI, 0.71—1.36; **Figure 3**), and no evidence of heterogeneity was found (I^2 = 0.0%; P = 0.972). Sensitivity analysis indicated that the results were not affected by sequential exclusion of any particular trial from all pooled analysis (**Table 4**). In addition, conclusions based on publication year, country, study design, and mean age were similar with those obtained in the overall analysis (**Table 3**). There was no significant heterogeneity between subgroups for CSF leak (**Table 3**).

Data comparing the effects of endoscopic versus microscopic surgeries on DI were available in 17 studies, which included 1350 patients with pituitary adenomas; 125 DI cases were reported. Overall, summary OR showed a 22% reduction in the risk of DI, but no statistically significant correlation was found (OR, 0.78; 95% CI, 0.53—1.14; P = 0.198; **Figure 4**). In addition, there was no evidence of heterogeneity (I^2 = 0.0%; P = 0.517). Sensitivity analysis indicated that the conclusions were not affected by sequentially excluding individual studies (**Table 5**). Furthermore, heterogeneity between subgroups was not statistically significant, and conclusions of subgroup analyses were consistent with overall findings (**Table 3**).

Summary results for other complications are presented in **Table 6**. Overall, endoscopic surgery was associated with lower risk of septal perforation (OR, 0.29; 95% CI, 0.11—0.78; P = 0.014) compared with microscopic surgery. Meanwhile, meningitis (OR, 1.28; 95% CI, 0.58—2.81; P = 0.545), epistaxis (OR, 0.69; 95% CI, 0.28—1.73; P = 0.428), hematoma (OR, 0.66; 95% CI, 0.21—2.06; P = 0.477), hypopituitarism (OR, 0.54; 95% CI, 0.27—1.12; P = 0.097), hypothyroidism (OR, 0.71; 95% CI, 0.41—1.22; P = 0.217), hypocortisolism (OR, 1.14; 95% CI, 0.73—1.78; P = 0.558), total mortality (OR, 1.41; 95% CI, 0.29—6.95; P = 0.673), and recurrence (OR, 0.69; 95% CI, 0.17—2.74; P = 0.595) rates were unaffected.

The funnel plots could not rule out potential publication bias for GTR, CSF leak, and DI. Egger and Begg test results indicated that there was no evidence of publication bias for GTR (P values in Egger and Begg tests, 0.669 and 0.325, respectively; **Figure 5A**), CSF leak (P values in Egger and Begg tests, 0.992 and 0.740, respectively; **Figure 5B**), and DI (P values in Egger and Begg tests, 0.665 and 0.592, respectively; **Figure 5C**).

Table 3. Subgroup Analyses for Gross Total Resection, Cerebrospinal Fluid Leak, and Diabetes Insipidus

Outcomes	Subgroup	Odds Ratio and 95% Confidence Interval	*P* Value	Heterogeneity (%)	Between-Subgroup Heterogeneity
Gross total resection	Publication year				
	2010 or after	2.17 (1.34–3.50)	0.002	40.3	0.014
	2010 previous	1.10 (0.75–1.61)	0.635	0.0	
	Country				
	United States	0.81 (0.51–1.30)	0.385	0.0	0.001
	Other	2.09 (1.54–2.84)	<0.001	0.0	
	Study design				
	Prospective	0.86 (0.40–1.84)	0.694	0.0	0.097
	Retrospective	1.64 (1.17–2.29)	0.004	24.3	
	Mean age (years)				
	≥50	1.48 (0.90–2.44)	0.119	35.4	0.952
	<50	1.53 (0.91–2.58)	0.112	34.9	
Cerebrospinal fluid leak	Publication year				
	2010 or after	0.94 (0.60–1.46)	0.767	0.0	0.778
	2010 previous	1.04 (0.65–1.68)	0.860	0.0	
	Country				
	United States	0.78 (0.45–1.36)	0.379	0.0	0.313
	Other	1.11 (0.74–1.66)	0.608	0.0	
	Study design				
	Prospective	0.72 (0.29–1.82)	0.490	0.0	0.490
	Retrospective	1.03 (0.73–1.45)	0.878	0.0	
	Mean age (years)				
	≥50	0.96 (0.59–1.58)	0.875	0.0	1.000
	<50	1.00 (0.61–1.63)	0.988	0.0	
Diabetes insipidus	Publication year				
	2010 or after	0.62 (0.37–1.04)	0.069	0.0	0.199
	2010 previous	1.01 (0.58–1.78)	0.963	2.7	
	Country				
	United States	0.88 (0.48–1.62)	0.678	23.0	0.386
	Other	0.64 (0.36–1.14)	0.129	0.0	
	Study design				
	Prospective	0.37 (0.11–1.20)	0.097	0.0	0.185
	Retrospective	0.85 (0.57–1.27)	0.423	0.0	
	Mean age (years)				
	≥50	0.84 (0.49–1.44)	0.525	0.0	0.079
	<50	0.61 (0.35–1.06)	0.081	0.0	

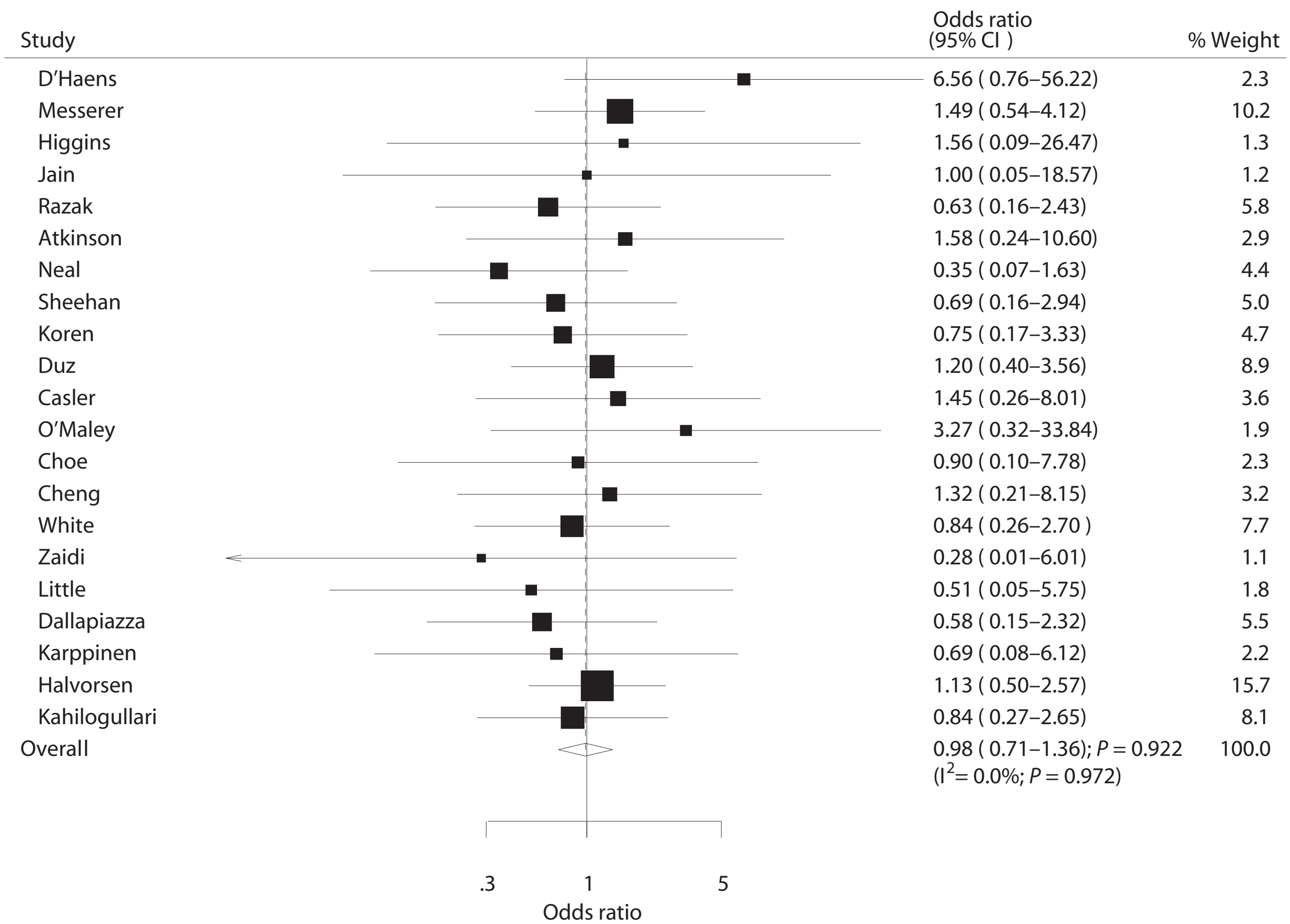

Figure 3. Effect of endoscopic transsphenoidal surgery on cerebrospinal fluid leak, compared with microscopic surgery. CI, confidence interval.

DISCUSSION

The current standard interventions for pituitary adenomas are transsphenoidal surgery by endoscopic or microscopic approaches. However, the efficacy and safety of the 2 surgical procedures remain controversial. Previous meta-analyses do not provide certain evidence for intervention effects. An increasing number of trials have evaluated endoscopic and microscopic surgeries for efficacy and safety in the treatment of pituitary adenomas and acquired varying data, and doctors have few evidence-based intervention guidelines. We therefore performed a comprehensive meta-analysis to explore the potential differences between endoscopic and microscopic surgeries in patients with pituitary adenomas. This quantitative study included 2272 patients with pituitary adenoma assessed in 23 studies; compared with microscopic surgery, the endoscopic approach showed beneficial effects on GTR and reduced the risk of septal perforation. For other complications, no significant differences between endoscopic and microscopic methods were found. These findings were reliable, and sensitivity and subgroup analyses were consistent with the overall conclusions for GTR, CSF leak, and DI.

A previous meta-analysis included direct and indirect evidence and showed that patients who undergo endoscopic surgery have no significant advantages but instead show an increased risk of vascular complications.[9] This study could be criticized because it was based on a variety of sources, and only 8 of the included studies directly compared endoscopic and microscopic methods. However, the findings corroborate a meta-analysis published in 2014.[10] However, that study encountered criticism because of the lack of stratified analyses. In addition, the data abstracted from the included studies were not consistent with the original articles. The present study suggested a higher GTR incidence in endoscopic surgery compared with the microscopic approach. Several studies included reported similar results. Messerer et al.[33] concluded that quality of resection is significantly improved after 1 year, in patients who underwent endoscopic surgery (GTR, 74% vs. 50%; $P = 0.002$). Razak et al.[35] suggested that endoscopic transsphenoidal surgery provides favorable results in both tumor resection and control compared with microscopic surgery. Cheng et al.[34] found that the rate of disease control is higher in endoscopic surgery compared with

Table 4. Sensitivity Analysis for Cerebrospinal Fluid Leak

Excluding Study	Odds Ratio and 95% Confidence Interval	*P* Value	Heterogeneity (%)	*P* Value for Heterogeneity
D'Haens et al.[32]	0.94 (0.68—1.31)	0.718	0.0	0.996
Messerer et al.[33]	0.94 (0.67—1.32)	0.719	0.0	0.973
Higgins et al.[31]	0.98 (0.71—1.36)	0.894	0.0	0.961
Jain et al.[26]	0.98 (0.71—1.36)	0.922	0.0	0.959
Razak et al.[35]	1.01 (0.72—1.41)	0.947	0.0	0.968
Atkinson et al.[27]	0.97 (0.70—1.35)	0.856	0.0	0.964
Neal et al.[25]	1.03 (0.74—1.44)	0.851	0.0	0.987
Sheehan et al.[20]	1.00 (0.72—1.40)	0.988	0.0	0.964
Koren et al.[22]	1.00 (0.72—1.39)	0.988	0.0	0.962
Duz et al.[28]	0.97 (0.69—1.36)	0.838	0.0	0.962
Casler et al.[24]	0.97 (0.70—1.35)	0.855	0.0	0.963
O'Maley et al.[29]	0.96 (0.69—1.33)	0.812	0.0	0.978
Choe et al.[30]	0.99 (0.71—1.37)	0.933	0.0	0.959
Cheng et al.[34]	0.97 (0.70—1.36)	0.879	0.0	0.961
White et al.[23]	1.00 (0.71—1.40)	0.988	0.0	0.960
Zaidi et al.[42]	1.00 (0.72—1.38)	0.991	0.0	0.971
Little et al.[41]	1.00 (0.72—1.38)	0.980	0.0	0.965
Dallapiazza et al.[38]	1.01 (0.73—1.42)	0.933	0.0	0.970
Karppinen et al.[40]	0.99 (0.71—1.38)	0.961	0.0	0.961
Halvorsen et al.[37]	0.96 (0.67—1.37)	0.814	0.0	0.962
Kahilogullari et al.[36]	1.00 (0.71—1.40)	0.988	0.0	0.960

the microscopic approach. Lenzi et al.[39] indicated that endoscopic surgery is more suitable than the microscopic method in macroadenomas and adenomas with suprasellar extension. A plausible reason is that endoscopy could help gain control over the lateral extension of the tumor. In addition, a previous pituitary or sinus surgery and the flap that might affect the intervention should be stratified in future studies.

Patients who underwent endoscopic transsphenoidal surgery had a lower risk of septal perforation. All included trials reported no significant differences between endoscopic and microscopic surgeries. This finding may be explained by the incidence of septal perforation, which was lower than expected, with broad CIs obtained (i.e., no statistically significant difference). In this study, the large sample size allowed us to quantitatively evaluate the effects on septal perforation of different surgery types; therefore, our findings are potentially more robust than those of any individual study. Furthermore, for the most part, summary results for complications were not significant with surgery type. There are many possible explanations for this lack of significant effects. The tumor type might play an important role in the treatment effect, whereas no stratified results were reported for most included trials; the patients included in this study had different disease statuses, which may also affect intervention outcomes; relatively few complications were reported, which contributed to broad CIs, preventing an intrinsic effect from being obtained; follow-up duration varied in the included studies and might constitute a confounding factor. Therefore, although complications might differ between endoscopic and microscopic surgeries, the differences may be balanced by these factors.

A few limitations of this study should be mentioned. Several of the studies included may not have lasted long enough to adequately determine the efficacy and safety profiles of the 2 surgical approaches. Relatively few events of complications were reported, the sample size of the pooled analysis might not be sufficient, and the acquired results showed no statistically significant associations. Furthermore, information regarding operators, pathologies, follow-up, and the method for GTR evaluation was not available in most studies; although several complications showed no statistically significant associations with surgery type, these findings may be unreliable because of the small number of studies included. Moreover, the unavailability of individual patient data, a limitation inherent to meta-analyses, precluded a more detailed analysis.

This study shows that endoscopic surgery was associated with higher GTR and lower risk of septal perforation, compared with the microscopic approach. Subgroup and sensitivity analyses

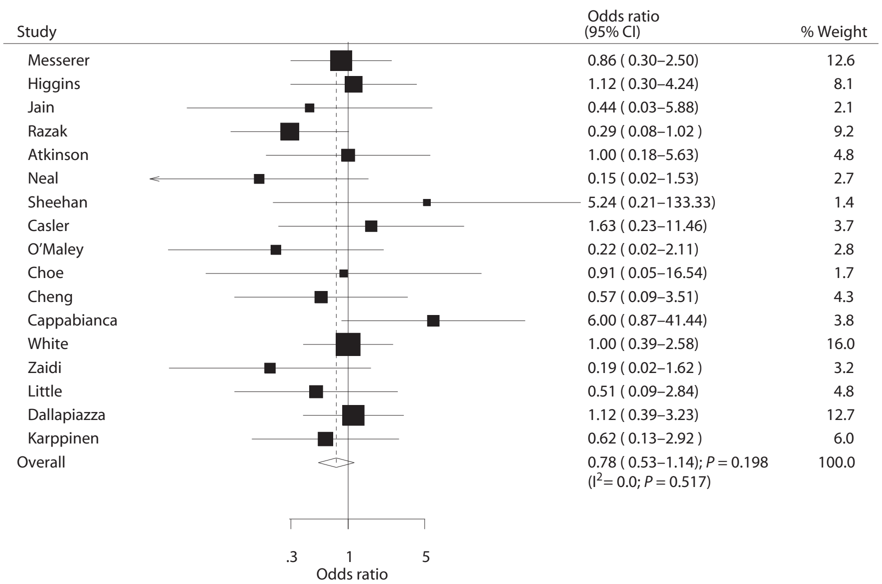

Figure 4. Effect of endoscopic transsphenoidal surgery on diabetes insipidus, compared with microscopic surgery. CI, confidence interval.

yielded results similar to the overall conclusions. However, the main findings of this study are based on retrospective evaluations, and the intervention effects of these 2 surgical approaches remain subject to debate, because no prospective randomized controlled trials are available. Future large-scale randomized controlled trials should be performed to confirm the efficacy and safety profiles of the 2 approaches in the treatment of pituitary adenomas.

Table 5. Sensitivity Analysis for Diabetes Insipidus

Excluding Study	Odds Ratio and 95% Confidence Interval	*P* Value	Heterogeneity (%)	*P* Value for Heterogeneity
Messerer et al.[33]	0.77 (0.51—1.15)	0.203	0.4	0.447
Higgins et al.[31]	0.76 (0.51—1.12)	0.163	0.0	0.467
Jain et al.[26]	0.79 (0.54—1.16)	0.226	0.0	0.457
Razak et al.[35]	0.86 (0.58—1.28)	0.462	0.0	0.642
Atkinson et al.[27]	0.77 (0.52—1.14)	0.187	0.1	0.450
Neal et al.[25]	0.82 (0.56—1.20)	0.298	0.0	0.593
Sheehan et al.[20]	0.76 (0.52—1.11)	0.157	0.0	0.544
Casler et al.[24]	0.76 (0.52—1.11)	0.159	0.0	0.486
O'Maley et al.[29]	0.81 (0.55—1.19)	0.278	0.0	0.537
Choe et al.[30]	0.78 (0.53—1.14)	0.197	0.6	0.445
Cheng et al.[34]	0.79 (0.54—1.16)	0.235	0.0	0.453
Cappabianca et al.[21]	0.72 (0.49—1.06)	0.094	0.0	0.777
White et al.[23]	0.74 (0.49—1.12)	0.160	0.0	0.467
Zaidi et al.[42]	0.82 (0.56—1.20)	0.301	0.0	0.575
Little et al.[41]	0.80 (0.54—1.17)	0.251	0.0	0.462
Dallapiazza et al.[38]	0.74 (0.49—1.11)	0.145	0.0	0.482
Karppinen et al.[40]	0.79 (0.54—1.17)	0.240	0.1	0.450

Table 6. Summary of the Odds Ratios of Other Complications

Outcomes	Included Studies	Odds Ratio and 95% Confidence Interval	*P* Value	Heterogeneity (%)	*P* Value for Heterogeneity
Septal perforation	6	0.29 (0.11—0.78)	0.014	0.0	0.992
Meningitis	10	1.28 (0.58—2.81)	0.545	0.0	0.642
Epistaxis	10	0.69 (0.28—1.73)	0.428	14.4	0.310
Hematoma	5	0.66 (0.21—2.06)	0.477	0.0	0.831
Hypopituitarism	7	0.54 (0.27—1.12)	0.097	0.0	0.926
Hypothyroidism	4	0.71 (0.41—1.22)	0.217	0.0	0.989
Hypocortisolism	6	1.14 (0.73—1.78)	0.558	0.0	0.782
Total mortality	4	1.41 (0.29—6.95)	0.673	1.6	0.384
Recurrence	4	0.69 (0.17—2.74)	0.595	0.0	0.891

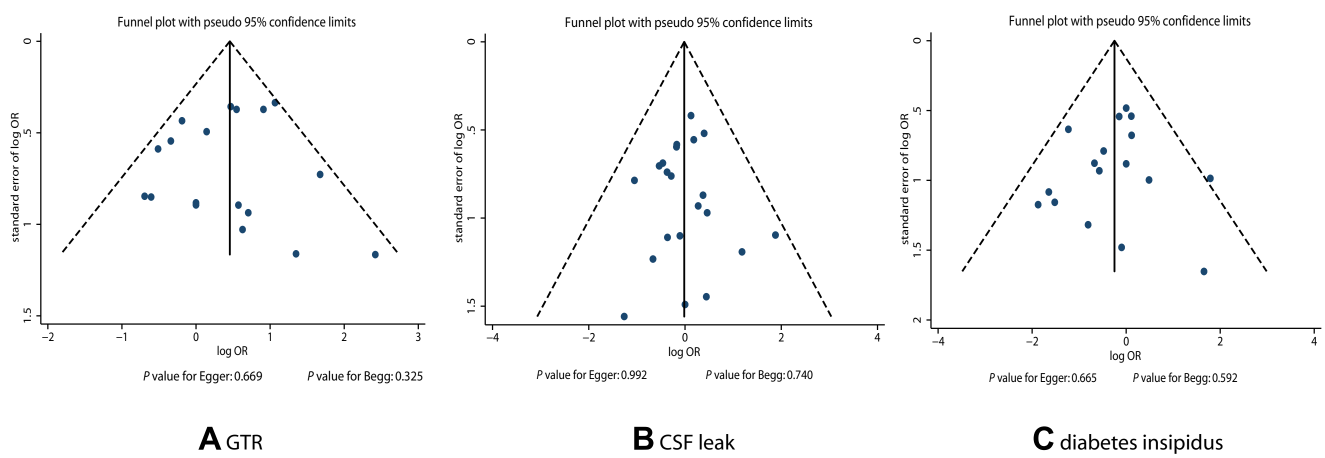

Figure 5. Funnel plots for (**A**) gross tumor removal (GTR), (**B**) cerebrospinal fluid (CSF) leak, and (**C**) diabetes insipidus. OR, odds ratio.

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