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Extracapsular Resection of Pituitary Adenomas: A Systematic Review

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Abstract

There is considerable variation in the surgical techniques for transsphenoidal excision of pituitary tumors. Recently, an extracapsular method has been developed that involves using the tumor pseudocapsule as a dissection plane to increase the extent of resection. This review assessed the outcomes of this new approach as compared with standard transsphenoidal surgery. We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE/PubMed, the US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov), the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch), and LILACS databases for relevant literature and checked reference lists of relevant articles. Randomized controlled trials and prospective and retrospective cohort studies comparing extracapsular and intracapsular resection of pituitary tumors were included in the review. Five cohort studies with 1,588 participants were included. Extracapsular resection was associated with a higher likelihood of complete excision (relative risk [RR] 1.31, 95% confidence interval [CI] 1.01–1.70, $p = 0.04$) and endocrinologic remission (RR 1.26, 95% CI 1.03–1.54, $p = 0.02$). Because there was a significant risk of bias and substantial heterogeneity, the estimates of effect may not be robust. In patients with pituitary adenomas undergoing transsphenoidal excision, extracapsular resection may be associated with higher rates of complete excision and endocrinologic remission, but the evidence is not strong. Hence, randomized controlled trials to determine the magnitude of benefit and identify an improvement in progression-free or overall survival are warranted.

Keywords
- pituitary adenoma
- transsphenoidal excision
- extracapsular resection

Introduction

Pituitary tumors are a common primary brain tumor, accounting for up to 15% of cases in the US, eclipsed only by meningiomas and glioblastomas.[1] These tumors may present with signs of mass effect, such as compression of the optic chiasm, hypersecretion of hormones, pituitary insufficiency, or pituitary apoplexy. They may also be asymptomatic

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lesions discovered on cranial imaging for other indications; in this scenario, they are described as incedentalomas. The latest World Health Organization (WHO) grading system lists adenomas based on the cell of origin (e.g., somatotroph adenoma, etc.), and also includes pituitary carcinomas and pituitary blastomas.[2] Currently, surgery is the recommended primary treatment of symptomatic patients with nonfunctioning pituitary adenomas,[3] Cushing's disease,[4] acromegaly,[5] and thyrotropin-secreting adenomas,[6] and is a second-line treatment for patients with prolactinomas who fail medical management with dopamine agonists.[7]

The first transcranial surgery for a pituitary tumor was performed by Sir Victor Horsley in 1889, and this was followed by the first transsphenoidal surgery by Hermann Schloffer in 1907.[8] A century of advances in technology and surgical techniques have allowed safe and efficient removal of pituitary tumors, with most presently being removed through a transsphenoidal route. In a recent systematic review comparing microscopic against endoscopic transsphenoidal excision of pituitary tumors, the latter was found to have a higher likelihood of achieving a gross total excision (odds ratio [OR] 1.52, 95% confidence interval [CI] 1.11–2.08, $p = 0.009$).[9]

Because of the desire to improve outcomes, new approaches are being developed. One such method is extracapsular dissection, which takes advantage of the pseudocapsule that develops around pituitary adenomas. This pseudocapsule was discovered in 1936 to be composed of compressed pituitary cells surrounding these tumors.[10] Interest in the use of this pseudocapsule as a surgical capsule to aid in the total excision of pituitary tumors has recently increased, but most studies are case reports or limited case series that have focused on surgical techniques.[11–14] Because the benefits of this new approach have not yet been clearly defined, we sought to provide evidence that in patients undergoing transsphenoidal surgery for pituitary adenomas, extracapsular resection improved the extent of resection compared with standard resection. We also determined whether it afforded higher rates of endocrinologic remission or increased the risk of postoperative complications such as cerebrospinal fluid (CSF) rhinorrhea and hypopituitarism.

Methodology

The preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines[15] were used to guide the review.

Criteria for Considering Studies for This Review

Types of Studies

To increase the sensitivity of the literature search, we included randomized controlled trials (RCTs) as well as prospective and retrospective cohort studies. Case reports and case series without comparison between the two interventions were not eligible.

Types of Participants

People of either sex, aged 18 years or above with a radiologically definite pituitary adenoma, with any type of clinical presentation (hemorrhage, vision impairment, endocrinopathies) were allowed. We excluded studies involving patients with other types of sellar or suprasellar tumors such as craniopharyngiomas or meningiomas.

Types of Interventions

Studies comparing intracapsular or extracapsular resection through a transsphenoidal route, whether with the use of an endoscope or microscope, were included. Individual variations in operative techniques and the use of neuronavigation and ultrasonic aspirators were permitted.

Types of Outcome Measures

The primary outcome was the extent of resection on postoperative imaging, whether computed tomography (CT) or magnetic resonance imaging (MRI), at any time after surgery. Endocrinologic remission, occurrence of postoperative CSF leak, or hypopituitarism were the secondary outcomes.

Search Methods for Identification of Studies

The following databases were searched: the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE/PubMed, the US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov), the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch), and LILACS. The following search terms were combined: "pituitary," "adenoma or microadenoma or macroadenoma," "extracapsular or pseudocapsule," and "resection or excision." We also checked bibliographies of relevant articles to identify further published, ongoing, and unpublished studies.

Data Collection and Analysis

Study Selection and Data Extraction

We screened the abstracts of the updated search results for potentially eligible studies for this review, and obtained the full published articles for studies likely to be relevant. We then used a data extraction form to obtain data on risk of bias and other study characteristics, participants, imaging, interventions, results, and outcomes during follow-up. If the required data were not available in a publication, we contacted the corresponding author for further information.

Assessment of Risk of Bias in Included Studies

The risk of bias was planned to be assessed using the Revised Cochrane Risk of Bias tool for randomized trials (RoB 2)[16] for randomized studies and the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool[17] for nonrandomized studies. The quality of evidence for each outcome was determined using the GRADE approach.[18]

Measures of Treatment Effect

Statistical analysis was performed using the RevMan program (Version 5.4. The Cochrane Collaboration, 2020).[19] Risk ratios (RRs) and their corresponding CIs were calculated for different outcomes, and forest plots were created. For comparable studies, it was planned to calculate a weighted

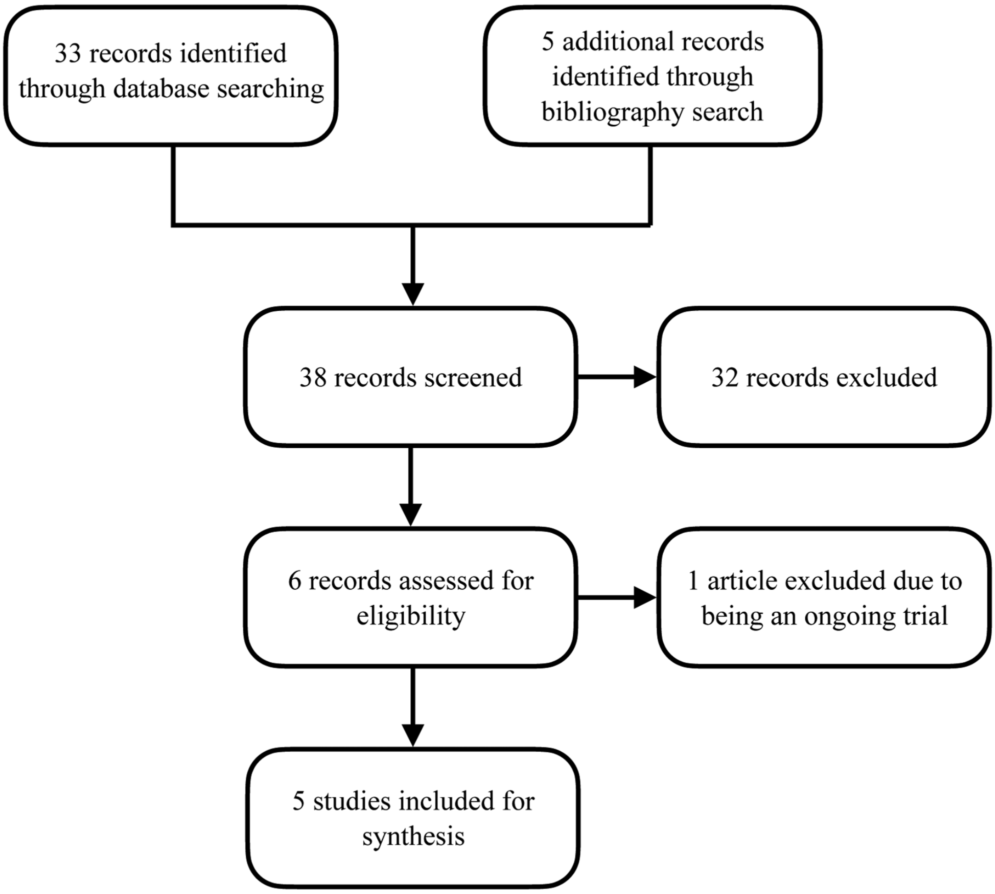

Fig. 1 Flow chart of the systematic process used for the review ($n = 5$)

estimate of the RR across reports using the Mantel–Haenszel method using a random effects model. For missing data, an effort was made to contact study authors. An assessment of heterogeneity was planned using the I^2 statistics, with values greater than 75% being substantial. A table summarizing the findings of the following outcomes was created: compete resection, endocrinologic remission, postoperative CSF leak, and postoperative hypopituitarism.

Results

Identified Studies

Our database search identified 33 completed studies, and an additional 5 studies were identified using bibliography search (►**Fig. 1**). Thirty-two (32) studies did not meet the inclusion criteria. The only RCT that was found was still ongoing (Registration number: ChiCTR-TRC-09000595), and we were left with 5 cohort studies for analysis.

Included Studies

A brief description of the included studies is presented below, and a summary of their characteristics is presented in ►**Table 1**.

Kim et al performed a single-institution, single-neurosurgeon prospective cohort study on patients who underwent pituitary surgery from January 1992 to December 2011 in Yonsei University College of Medicine, Korea.[20] A total of 1,372 cases were done, but 283 were excluded due to cavernous sinus invasion or revision surgery, and 1,089 were included in the study. Their patients had a mean age of 43.4 years, with 537 (49.3%) harboring functional tumors. Surgery was performed using a conventional microscopic transsphenoidal approach, and an attempt was made at identifying a pseudocapsule in all patients. An extracapsular en bloc resection was tried where feasible. Postoperative MRI was done within 48 hours to assess the extent of resection. Preoperative and postoperative pituitary function tests were performed to assess endocrinologic remission in functional tumors or development of a new hypopituitarism. Other outcomes such as a CSF leak, DI, or visual deterioration were also measured.

Li et al performed a single-institution, prospective cohort study on patients who underwent surgery for noninvasive functioning pituitary adenomas from October 2008 to November 2014 in The First Affiliated Hospital of Anhui Medical University, China.[21] A total of 206 cases were done, with a mean age of 38.9 years. Surgery was performed using a microscopic or endoscopic transsphenoidal approach. Postoperative MRI was done at 3 months to assess the extent of resection. Preoperative and postoperative pituitary function tests were performed to assess endocrinologic remission. Other outcomes measured included CSF rhinorrhea and DI.

Table 1 Summary of included studies

	Kim et al	Li et al	Qu et al	Taylor et al	Xie et al
Design	Prospective cohort Patients assigned to intervention based on intraoperative findings	Prospective cohort Method of patient assignment unclear	Prospective cohort Method of patient assignment unclear	Prospective cohort Patients in the first 2 years assigned to control, second 5 years to extracapsular	Retrospective cohort Patients were grouped based on the actual surgery done
Population	$N = 1,089$, both sexes, all ages	$N = 206$, both sexes, all ages	$N = 142$, both sexes, all ages	$N = 108$, both sexes, all ages	$N = 43$, both sexes, all ages
Tumor invasiveness	Noninvasive	Noninvasive	Noninvasive	Both	Both
Tumor function	Both	Functional	Both	Both	Functional (GH-secreting)
Approach	Microscopic	Both	Both	Microscopic	Endoscopic
Postop imaging	MRI < 48 h	MRI at 3 mo	MRI at 3 mo	MRI at 2 mo	MRI at 3 mo
Outcomes measured	Extent of resection, recurrence, endocrinologic remission, DI, CSF rhinorrhea, hypopituitarism	Extent of resection, endocrinologic remission, DI, CSF rhinorrhea, hypopituitarism	Extent of resection, endocrinologic remission, DI, CSF rhinorrhea, hypopituitarism, hemorrhage, visual deterioration	Extent of resection, rate of endocrinologic deficits, rate of recovery of prior deficits, DI, CSF rhinorrhea	Extent of resection, endocrinologic remission, DI, CSF rhinorrhea, hypopituitarism, infection, GH, IGF-1, OGTT-GH levels

Qu et al performed a single-institution, single-neurosurgeon prospective cohort study on 142 consecutive patients who underwent pituitary surgery from January 2004 to October 2007 in Provincial Hospital, which is affiliated with Shandong University, Jinan, China.[22] Patients with medical therapy, radiotherapy, prior surgery, or with tumors extending into the cavernous sinus were excluded from this series. Their patients had a mean age of 37.0 years, with 86 (60.6%) harboring functional tumors. Surgery was performed using a conventional microscopic transsphenoidal approach. Postoperative MRI was done at 3 months to assess the extent of resection. Preoperative and postoperative pituitary function tests were performed to assess endocrinologic remission in functional tumors or development of new hypopituitarism. The development of DI, CSF rhinorrhea, and visual deterioration was also monitored.

Taylor et al performed a single-institution, single-neurosurgeon prospective cohort study on 108 consecutive patients who underwent pituitary surgery from 2008 and 2015 in the University of Virginia Health System, Charlottesville, Virginia, USA.[23] A functional tumor was present in 23 (21.3%) patients. They included patients with invasive tumors and previous pituitary surgery, contrary to the previous studies. Surgery was performed using a conventional microscopic transsphenoidal approach. Postoperative MRI was done at 2 months to assess the extent of resection. Hormonal levels before and after surgery were measured; however, they did not quantify the number of cases that underwent remission.

Finally, Xie et al performed a single-institution, retrospective cohort study on 43 patients with growth-hormone secreting pituitary adenomas who underwent surgery from October 2011 to January 2015 at Zhongshan Hospital, Fudan University, Shanghai, China.[24] An endoscopic endonasal approach was employed in their patients. The extent of resection was assessed with the use of a postoperative MRI at 3 months. Changes in growth hormone levels as well as the development of a postoperative CSF leak were monitored.

Risk of Bias

The ROBINS-I tool was used to assess the risk of bias for each of the individual studies, and the results are presented in ►**Table 2**. All studies were judged to have serious confounding bias, as they did not control for factors that might have determined the intervention used such as tumor size and consistency. The risk of bias in the other domains was low.

Extent of Resection

Data were available for five studies. Extracapsular resection was associated with a significantly increased rate of total resection on postoperative imaging (RR 1.31, 95% confidence interval [CI] 1.01 to 1.70, $p = 0.04$, ►**Fig. 2**).

Endocrinologic Remission

Data were available for four studies. Extracapsular resection was found to be associated with a higher likelihood of achieving endocrinologic remission (RR 1.26, 95% CI 1.03 to 1.54, $p = 0.02$, ►**Fig. 3**).

Postoperative CSF Rhinorrhea

Data were available for five studies. There was no difference between the two groups in terms of permanent postop CSF rhinorrhea (RR 1.21, 95% CI 0.62 to 2.38, $p = 0.58$, ►**Fig. 4**).

Postoperative Hypopituitarism

Data were available for four studies. There was no difference in the likelihood of postoperative hypopituitarism between the two interventions (RR 0.87, 95% CI 0.58 to 1.32, $p = 0.52$, ►**Fig. 5**).

Table 2 Risk of bias analysis for individual studies

Study	Kim et al	Li et al	Qu et al	Taylor et al	Xie et al
Confounding bias	Serious	Serious	Serious	Serious	Serious
Selection bias	Low	Low	Low	Low	Low
Classification of intervention bias	Low	Low	Low	Low	Low
Deviation from intended intervention bias	Low	Low	Low	Low	Low
Missing data bias	Low	Low	Low	Low	Low
Measurement of outcomes bias	Low	Low	Low	Low	Low
Selection of results bias	Low	Low	Low	Low	Low

Study or Subgroup	Extracapsular Events	Extracapsular Total	Intracapsular Events	Intracapsular Total	Weight	Risk Ratio M–H, Random, 95% CI
Xie 2016	18	21	12	22	14.9%	1.57 [1.03, 2.39]
Taylor 2018	61	74	17	34	16.8%	1.65 [1.16, 2.34]
Qu 2011	71	78	44	64	21.8%	1.32 [1.11, 1.58]
Li 2019	97	116	62	90	22.2%	1.21 [1.03, 1.43]
Kim 2014	258	263	773	826	24.2%	1.05 [1.02, 1.07]
Total (95% CI)		**552**		**1036**	**100.0%**	**1.31 [1.01, 1.70]**
Total events	505		908			

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 49.46$, df = 4 ($P < 0.00001$); $I^2 = 92\%$
Test for overall effect: Z = 2.01 (P = 0.04)

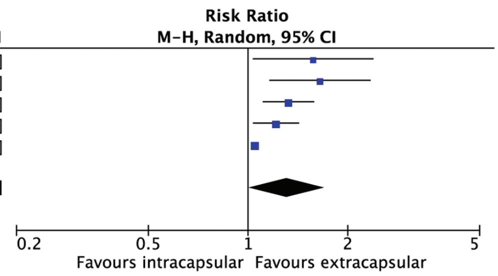

Fig. 2 Forest plot on the effect of extracapsular technique on extent of resection.

Study or Subgroup	Extracapsular Events	Extracapsular Total	Intracapsular Events	Intracapsular Total	Weight	Risk Ratio M–H, Random, 95% CI
Kim 2014	129	143	302	354	34.6%	1.06 [0.99, 1.13]
Li 2019	89	116	53	90	26.5%	1.30 [1.07, 1.59]
Qu 2011	42	45	28	41	24.9%	1.37 [1.09, 1.71]
Xie 2016	18	21	12	22	13.9%	1.57 [1.03, 2.39]
Total (95% CI)		**325**		**507**	**100.0%**	**1.26 [1.03, 1.54]**
Total events	278		395			

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 12.73$, df = 3 ($P = 0.005$); $I^2 = 76\%$
Test for overall effect: Z = 2.26 (P = 0.02)

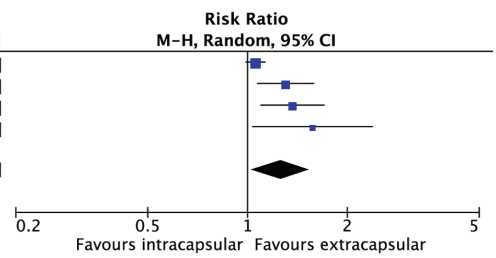

Fig. 3 Forest plot on the effect of extracapsular resection on endocrinologic remission.

Study or Subgroup	Extracapsular Events	Extracapsular Total	Intracapsular Events	Intracapsular Total	Weight	Risk Ratio M–H, Random, 95% CI
Li 2019	2	116	1	90	6.9%	1.55 [0.14, 16.84]
Xie 2016	4	21	2	22	13.2%	2.10 [0.43, 10.26]
Qu 2011	6	78	2	64	13.4%	2.46 [0.51, 11.78]
Kim 2014	11	263	22	826	31.6%	1.57 [0.77, 3.20]
Taylor 2018	16	74	13	34	34.9%	0.57 [0.31, 1.04]
Total (95% CI)		**552**		**1036**	**100.0%**	**1.21 [0.62, 2.38]**
Total events	39		40			

Heterogeneity: $Tau^2 = 0.24$; $Chi^2 = 7.38$, df = 4 ($P = 0.12$); $I^2 = 46\%$
Test for overall effect: Z = 0.56 (P = 0.58)

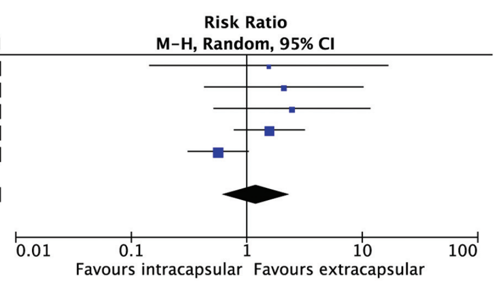

Fig. 4 Forest plot on the effect of extracapsular resection on postoperative CSF rhinorrhea.

Study or Subgroup	Extracapsular Events	Extracapsular Total	Intracapsular Events	Intracapsular Total	Weight	Risk Ratio M–H, Random, 95% CI
Kim 2014	64	235	200	723	69.5%	0.98 [0.77, 1.25]
Qu 2011	7	78	4	64	10.6%	1.44 [0.44, 4.69]
Taylor 2018	8	69	7	28	16.5%	0.46 [0.19, 1.16]
Xie 2016	1	21	3	22	3.4%	0.35 [0.04, 3.10]
Total (95% CI)		**403**		**837**	**100.0%**	**0.87 [0.58, 1.32]**
Total events	80		214			

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 3.72$, df = 3 ($P = 0.29$); $I^2 = 19\%$
Test for overall effect: Z = 0.64 (P = 0.52)

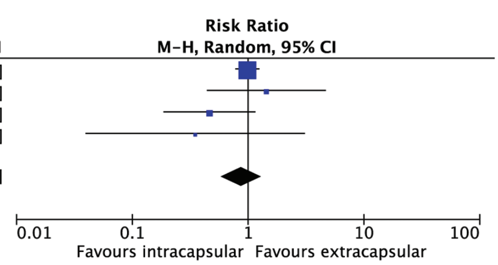

Fig. 5 Forest plot on the effect of extracapsular resection on postoperative hypopituitarism.

Extracapsular resection compared to Intracapsular resection for pituitary adenomas

Patient or population: pituitary adenomas
Setting: Pitutary adenomas
Intervention: Extracapsular resection
Comparison: Intracapsular resection

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Intracapsular resection	Risk difference with Extracapsular resection
Total Resection	1588 (5 observational studies)	⊕⊕◯◯ LOW [a,b]	**RR 1.31** (1.01 to 1.70)	876 per 1,000	**272 more per 1,000** (9 more to 614 more)
CSF leak	1588 (5 observational studies)	⊕⊕⊕◯ MODERATE [a]	**RR 1.21** (0.62 to 2.38)	39 per 1,000	**8 more per 1,000** (15 fewer to 53 more)
Postoperative hypopituitarism	1240 (4 observational studies)	⊕⊕⊕◯ MODERATE [a]	**RR 0.87** (0.58 to 1.32)	256 per 1,000	**33 fewer per 1,000** (107 fewer to 82 more)
Endocrinologic Remission	832 (4 observational studies)	⊕⊕◯◯ LOW [a,b]	**RR 1.26** (1.03 to 1.54)	779 per 1,000	**203 more per 1,000** (23 more to 421 more)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. High baseline confounding bias
b. High heterogeneity (i2>75%)

Fig. 6 Summary of findings.

Finally, the GRADE approach was used to determine the strength of the evidence and create a summary of findings (►**Fig. 6**).

Discussion

This review provides evidence that extracapsular dissection can increase the extent of resection and improve the likelihood of endocrinologic remission in patients undergoing transsphenoidal surgery for pituitary adenomas without increasing the risk for postoperative CSF rhinorrhea or hypopituitarism. More specifically, a total resection is 31% more likely in patients undergoing transsphenoidal surgery using an extracapsular approach compared with standard surgery, and patients with functioning adenomas are 26% more likely to achieve endocrinologic remission with this technique. However, as described in ►**Fig. 6**, the strength of the evidence for this is low. There were no randomized studies included in the review, leading to a high possibility of baseline confounding bias within each study. Across the studies, there was also a substantial level of heterogeneity in the analysis of the results for extent of resection ($I^2 = 92\%$) and endocrinologic remission ($I^2 = 76\%$). Possible sources of heterogeneity include the following: variation in operative techniques, differences in surgeon skill or experience, dissimiliarity in the timing of the postoperative MRI used in assessing completeness of tumor removal, and diversity among patient characteristics between studies. These limitations are inherent in the comparison of uncontrolled studies. Nevertheless, all included studies had point estimates for both extent of resection and endocrinologic remission that favored extracapsular resection, lending strength to the conclusion that the technique is advantageous.

Future research can provide more evidence in support of extracapsular resection through large RCTs with standardized operative techniques (possibly through training of participating surgeons), appropriate randomization and blinding, and consistent methods for measuring outcome. Also, the correlation of extent of resection with recurrence rates and long-term survival can be explored. A review of the factors predicting tumor recurrence in patients undergoing surgery for pituitary adenomas concluded that for nonfunctioning pituitary adenomas, no factor could be identified that increased the risk for recurrence, while for functioning adenomas, postoperative basal hormone levels were the most important factor.[25] The extent of resection was not one of the factors included in their analysis, but any residual tumor could plausibly regrow and cause recurrence of symptoms.

Conclusion

The review provides some evidence that transsphenoidal extracapsular resection of pituitary tumors may be associated with an increased likelihood of complete tumor excision. Furthermore, it may also lead to a higher chance of endocrinologic remission in patients with functional adenomas. The risk of developing a permanent postoperative CSF leak or postoperative hypopituitarism is not significantly different with the new technique.

Ethical Approval

This study complies with and conforms to the World Medical Association Declaration of Helsinki.

Conflict of Interest

None declared.

Author's Contributions

Kenny S. Seng contributed to conception and design of the study; ensuring ethical acceptability, acquisition, analysis, and interpretation of data; manuscript writing; approving and accepting accountability for the study. Oliver Ryan M. Malilay contributed to conception and design of the study; ensuring ethical acceptability, acquisition, analysis, and interpretation of data; manuscript writing; approving and accepting accountability for the study.

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