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Meta-analysis on the effect of pituitary adenoma resection on pituitary function

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ABSTRACT

Objective. A meta-analysis was conducted on the effect of pituitary adenoma resection on pituitary function.

Methods. The Cochrane Library, Ovid, PubMed, the Excerpta Medica Database (EMBASE), and the Chinese Biomedical Literature Databases (CBM) were searched to find trials about the evaluation of pituitary target glands before and after pituitary adenoma resection. The databases were searched from the earliest available trials until the end of September 2019. Based on the inclusion and exclusion criteria, two researchers independently selected literature, extracted data, and evaluated the quality of the studies, and then used Revman 5.2 software to conduct a meta-analysis.

Results. Eleven clinical trials were included, with a total of 3,237 subjects. Meta-analysis showed that the number of patients with hypofunction of the thyroid and gonadal axes substantially decreased after pituitary tumour resection, and that the difference was statistically significant: odds ratio (OR) = 1.72 [95% confidence interval (CI), 1.18–2.52; P = 0.005] and OR = 2.06 (95% CI, 1.42–3.00; P = 0.0002). The number of patients with a poor total suprarenal gland axis after pituitary tumour resection did not change significantly compared to the number found before the operation; the difference was not statistically significant: OR = 1.04 (95% CI, 0.72–1.48; P = 0.85). However, the number of patients who had adrenal axis dysfunction both before and after the operation was significantly reduced, and the difference was statistically significant: OR = 1.46 (95% CI, 1.21–1.78; P = 0.0001).

Conclusion. The function of the thyroid and gonadal axes of pituitary gland tumour patients can be improved, to some extent, after pituitary tumour resection. Patients with pituitary tumours who have hypofunction of the adrenal axis can recover effectively after tumour resection.

Key words: pituitary tumour, pituitary function, adrenal glands, thyroid gland, meta-analysis

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Introduction

Pituitary adenoma, one of the pituitary tumours, is the third most common primary intracranial tumour, after meningioma and glioma. Some tumours can secrete excessive pituitary hormones to cause metabolic disorders and damage to corresponding target organs. The tumours also compress normal pituitary tissue and blood vessels to cause secondary hypofunction of the pituitary and lead to the involvement of the corresponding target glands. In the 1930s, the transcranial approach was widely used to remove tumours. In recent decades, with improved transsphenoidal surgery techniques, it has been noticed that the suprasellar extension of a tumour is often non-invasive growth, most of which is brittle and soft, and some of which is haemorrhagic, necrotic and cystic, making it easy to remove under a microscope. Therefore, the transsphenoidal approach is also used for large adenomas, and even giant adenomas, with visual pathway compression. Due to the continuous improvement and rapid development of surgical methods, transsphenoidal surgery is mainly used today. The tumour is selectively removed under the microscope. For the expansion of suprasellar growth and the development of large

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adenomas in the parasellar and cavernous sinus, combined subfrontal pterional and orbital subfrontal approaches further improve the removal of large giant adenomas.

Surgical treatment can relieve tumour compression, which is helpful for the recovery of the pituitary function and the improvement of the preoperative high hormone level. However, all surgical methods cause irritation and damage to the pituitary tissue, which leads to hypo-functioning of the pituitary. To counteract this damage, long-term hormone replacement therapy and long-term follow-up are needed, but both of these can affect a patient's quality of life.

The treatment of pituitary adenomas requires a multidisciplinary approach, and pituitary function must be fully evaluated before and after the operation. To date, there has been no large-scale study on the recovery of pituitary function after pituitary adenoma surgery.

Therefore, the purpose of this study was to evaluate the function of the target glands of the pituitary before and after pituitary adenoma resection, and to provide evidence-based medical findings for the treatment of pituitary adenoma.

Material and methods

This meta-analysis was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISM) guidelines. Author's statement: all supporting data is included in the article and its supplementary materials. This study did not require ethical approval because analyses were based on previously published studies.

Literature retrieval, literature screening, data extraction, quality evaluation

Two researchers searched the Cochrane Controlled Trials Register, Ovid, PubMed/Excerpta Medica Database (EMBASE), and the Chinese Biomedical Literature Databases (CBM) from the earliest available trials through until the end of September 2019. References and related reviews that were found in the literature were also retrieved. The primary retrieval words were (1) pituitary adenomas, acromegaly, Cushing's Disease, growth hormone (GH)-producing pituitary adenoma, and prolactin (PRL)-secreting adenoma, and prolactinoma; (2) pituitary surgery, pituitary microsurgery, transnasal surgery, preoperative, and postoperative; and (3) surgical complication, anterior pituitary function, pituitary insufficiency, endocrine deficit, thyroid insufficiency, hypothyroidism, adrenal insufficiency, hypoadrenalism, hypocortisolism, and hypogonadism.

The two researchers (Ju and Cui) independently conducted literature screening, data extraction, and quality evaluation. They cross-checked their results and mediated any disagreements via discussion or with the assistance of a third researcher. All literature was screened sequentially for the inclusion and exclusion criteria. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method was adopted for quality evaluation, and the evaluation contents included the type of literature, the length of follow-up after the procedure, the percentage of patients lost to follow-up, and the presentation of the results.

Inclusion and exclusion criteria

Inclusion criteria: (1) a case-control study reporting pituitary function of pituitary tumour patients before and after tumour resection; (2) the diagnostic criteria of a pituitary tumour; (3) the judgment standard that the function of all pituitary target-gland axes were in line with the diagnostic criteria of internationally recognised guidelines; and (4) the included literature reported the functional changes of the thyroid, gonadal, and adrenal axes before and after the operation.

Exclusion criteria: (1) duplicate publication; (2) when one of the three target glands was excluded or when the functions of the three target glands were not evaluated completely; and (3) trials that did not include outcome indicators or reported data that could not be analysed.

Statistical analysis

Revman 5.2 software as recommended by the Cochrane Collaboration Network was used for meta-analysis. According to the follow-up time, subgroup analysis was conducted. For classification data, odds ratios (OR) were used for effect-size consolidation. All effect sizes were expressed as a 95% confidence interval (CI). A chi-square test was used to test the heterogeneity of all included tests. The significance level was set as $P = 0.10$. When $P > 0.10$ and $I^2 < 50\%$, the results were not heterogenous, and a fixed-effects model was used for combined analysis; When $P < 0.10$ and $I^2 > 50\%$, the results were heterogenous, and a random-effects model was used for combined analysis.

Results

Literature retrieval results

The preliminary inspection found 416 articles. After reading the title, abstract, and full text, any literature that did not meet the inclusion criteria was excluded. The final study group included 11 clinically controlled trials, with a total of 3,237 subjects.

The surgical methods were consistent, with most of the studies using microsurgery or neuroendoscopy through the sphenoidal sinus; only a small number of patients in two studies were treated with craniotomy. Flow charts and the results of literature screening are set out in Figure 1; basic characteristics of the trials included in this study are set out in Table 1; and baseline data of the trials included in this study is set out in Table 2.

Evaluation of adrenal axis function

The 11 studies in our meta-analysis included complete evaluation data of the pituitary-adrenal axis function before and after the operation: 2,663 cases evaluated before, and

2,660 cases evaluated after, the operation. Patients with adrenocortical dysfunction included those presenting either with such dysfunction as a unique factor or in combination with multiple target-gland dysfunctions; the latter group included 418 cases before, and 366 cases after, the operation.

Heterogeneity analysis revealed that there was statistical homogeneity among the 11 studies, and a random-effects model (D-L) was used for effect-size consolidation. Analysis showed that follow-ups ranged from 16.3 days to 60.1 months. The percentage of patients with adrenal axis dysfunction after the operation was similar to the percentage before the procedure, and the difference was not statistically significant: OR = 1.04 (95% CI, 0.72–1.48; P = 0.85) (Fig. 2).

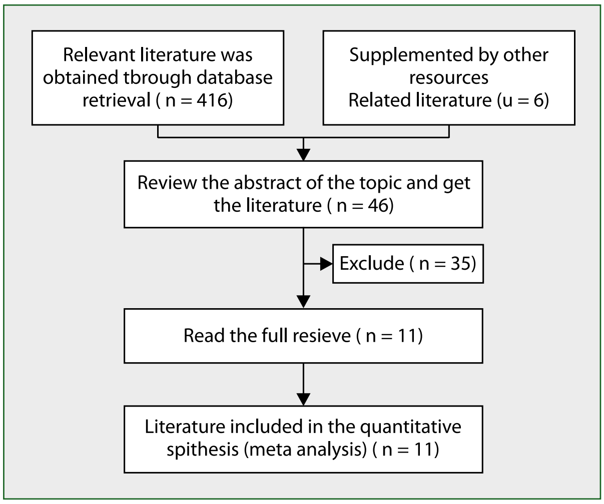

Figure 1. Literature selection process and results

Evaluation of thyroid gland axis function

The 11 studies included complete evaluation data of the pituitary-thyroid axis function before and after the operation: 2,999 cases evaluated before, and 2,983 cases evaluated after, the operation. Patients with thyroid dysfunction included those presenting either with the dysfunction as a unique factor or in combination with multiple target-gland dysfunctions, which was based on the results of TSH, FT3 and FT4; the latter group included 595 cases before, and 407 cases after, the operation.

Heterogeneity analysis revealed that there was statistical homogeneity among these 11 studies, and a random-effects model was used for effect-size consolidation. The analysis showed that the percentage of patients with hypofunction of the thyroid axis after pituitary tumour resection was marginally lower than the percentage before the operation, but the difference was not statistically significant: OR = 1.45 (95% CI, 0.95–2.21; P = 0.08). The percentage of patients with hypofunction of the thyroid axis at more than 12 months after pituitary tumour resection was substantially lower than the percentage

Table 1. Basic information of published literature

Study ID	Journal	Publication year	Published level	Research design and methodology	Dates when cases collected
Andrew, 2019 [1]	J Neurosurg	2019	full text	Prospective multicentre control study of before and after treatment	2015–2017
David, 2012 [2]	Swiss Medical Weekly	2012	full text	Retrospective control study of before and after treatment	2005–2009
Pietro, 2018 [3]	Endocrine	2018	full text	Retrospective control study of before and after treatment	1990–2016
Rayees, 2019 [4]	Indian J Endocr Metab	2019	full text	Retrospective control study of before and after treatment	2015–2017
Ruopeng, 2019 [5]	World Neurosurg	2019	full text	Retrospective control study of before and after treatment	2016
Arman, 2015 [6]	J Neurosurg	2015	full text	Retrospective control study of before and after treatment	U
Garg, 2001 [7]	JAPI	2001	full text	Retrospective control study of before and after treatment	1982–1995
Bryan, 1997 [8]	J Neurosurg	1997	full text	Retrospective control study of before and after treatment	U
Song, 2019 [9]	J Clin Neurosurg	2019	full text	Retrospective control study of before and after treatment	2016–2017
Masamichi, 2000 [10]	Neurosurgery	2000	full text	Retrospective control study of before and after treatment	1991–1999
He, 2005 [11]	CMINS	2005	full text	Retrospective control study of before and after treatment	2002–2004

U — unclear

Table 2. Baseline data of included study

Author	Nationality	Tumour types	Tumour sizes	Operation type	Numbers (men/women)	Average age [years]	Mean follow-up
Andrew, 2019 [1]	America	n NF	Mean 2.5 cm	Neuroendoscopic surgery	169 (99/77)	57.6	6 months
David, 2012 [2]	Swiss	NF 109 GH 39	Mean 2.3 cm	Endonasal transsphenoidal adenoma removal	148 (83/65)	55	32 months
Pietro, 2018 [3]	Italian	NF 795 GH 595 ACTH 496 TSH 51	Mean 1.8cm	Endonasal transsphenoidal adenoma removal	2,145 (927/1,218)	46.3	60.1 months
Rayees, 2019 [4]	Indian	GH	Microadenoma 10 Macroadenoma 41	93% Endonasal transsphenoidal adenoma removal 7% Craniotomy	51 (U)	42.3	3 months
Ruopeng, 2019 [5]	Chinese	NF	Macroadenoma 121 Giant adenoma 43	Endonasal transsphenoidal adenoma removal	164 (76/88)	50.6	21.1 months
Arman, 2015 [6]	American	NF	Mean 2.2 cm	Endonasal transsphenoidal adenoma removal	305 (170/135)	57 (16–93)	6 months
Garg, 2001 [7]	Indian	NF 25 GH 25	Mean 3.5 cm	Endonasal transsphenoidal adenoma removal	50 (33/17)	39.4 (19–75)	3 months
Bryan, 1997 [8]	America	n ACTH	Microadenoma 4 Macroadenoma 6	Endonasal transsphenoidal adenoma removal	10 (6/4)	14–60	42 months
Song, 2019 [9]	Chinese	NF 118 ACTH 2 LH 3 PR 4 GH 11	U	Endonasal Transsphenoidal adenoma removal 130 Craniotomy 8	138 (70/68)	50 (5–75)	17.6 months
Masamichi, 2000 [10]	German	NF	Mean 3.36 cm	Endonasal transsphenoidal adenoma removal	32 (17/15)	73.9 (70–84)	16.3 days
He, 2005 [11]	Chinese	GH 2 PRL 6 NF 17	Macroadenoma 15 Giant adenoma 10	Endonasal transsphenoidal adenoma removal	25 (9/16)	46 (15–63)	3 months

NF — nonfunctioning adrenal adenoma; GH — GH-secreting adenoma; ACTH — ACTH-secreting adenoma; LH — luteinising adenoma; PRL — prolactinoma; U — unclear

before the operation, and the difference was statistically significant: OR = 1.72 (95% CI, 1.18–2.52; P = 0.005) (Fig. 3).

Evaluation of gonad axis function

The 11 studies in the meta-analysis included complete evaluation data of the pituitary-gonad axis function before and after the operation: 3,136 cases evaluated before, and 3,155 cases evaluated after, the operation. Patients with gonad axis dysfunction included those solely with gonad axis dysfunction as well as patients with multiple target-gland dysfunctions, including gonad axis dysfunction; the latter group included 1,540 patients before, and 934 patients after, surgery.

Heterogeneity analysis showed that there was statistical homogeneity among these 11 studies, and a random-effects model was used for effect-size consolidation. The analysis showed that the percentage of patients with hypofunction of the gonadal axis at three months or less after pituitary tumour resection was significantly lower than the percentage of patients before the operation, and the difference was statistically significant: OR = 2.23 (95% CI, 1.42–3.49; P = 0.005). The percentage of patients with hypofunction of the gonad axis at more than 12 months after pituitary tumour resection was significantly lower than the percentage before the operation, and the difference was statistically significant: OR = 2.06 (95% CI, 1.42–3.00; P = 0.002) (Fig. 4).

Comparison of percentage of patients with low growth hormone levels before and after operation

Six of the 11 studies [2, 5, 6, 8–10] included complete data on growth hormone levels before and after surgery: 792 patients before, and 784 patients after. Patients with decreased growth hormone levels included those presenting either with

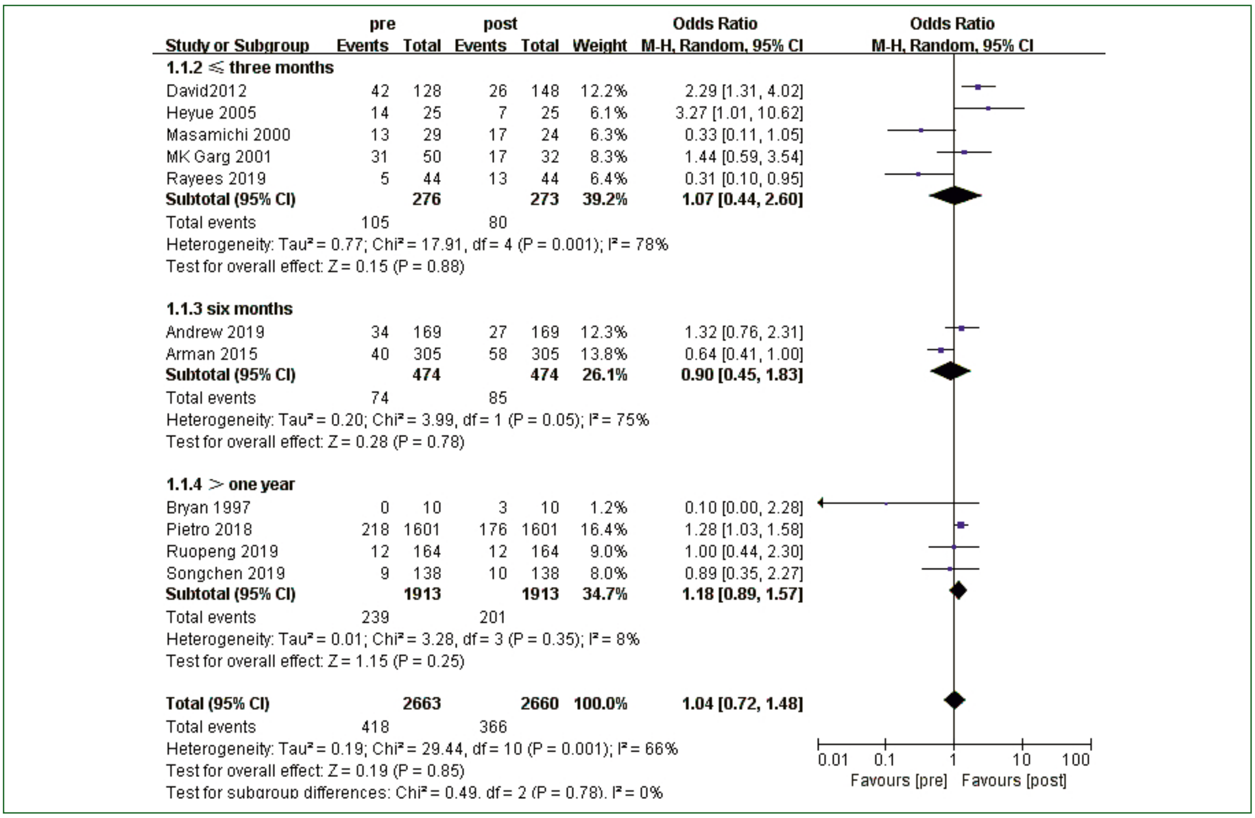

Figure 2. Comparison of adrenal axis dysfunction before and after operation

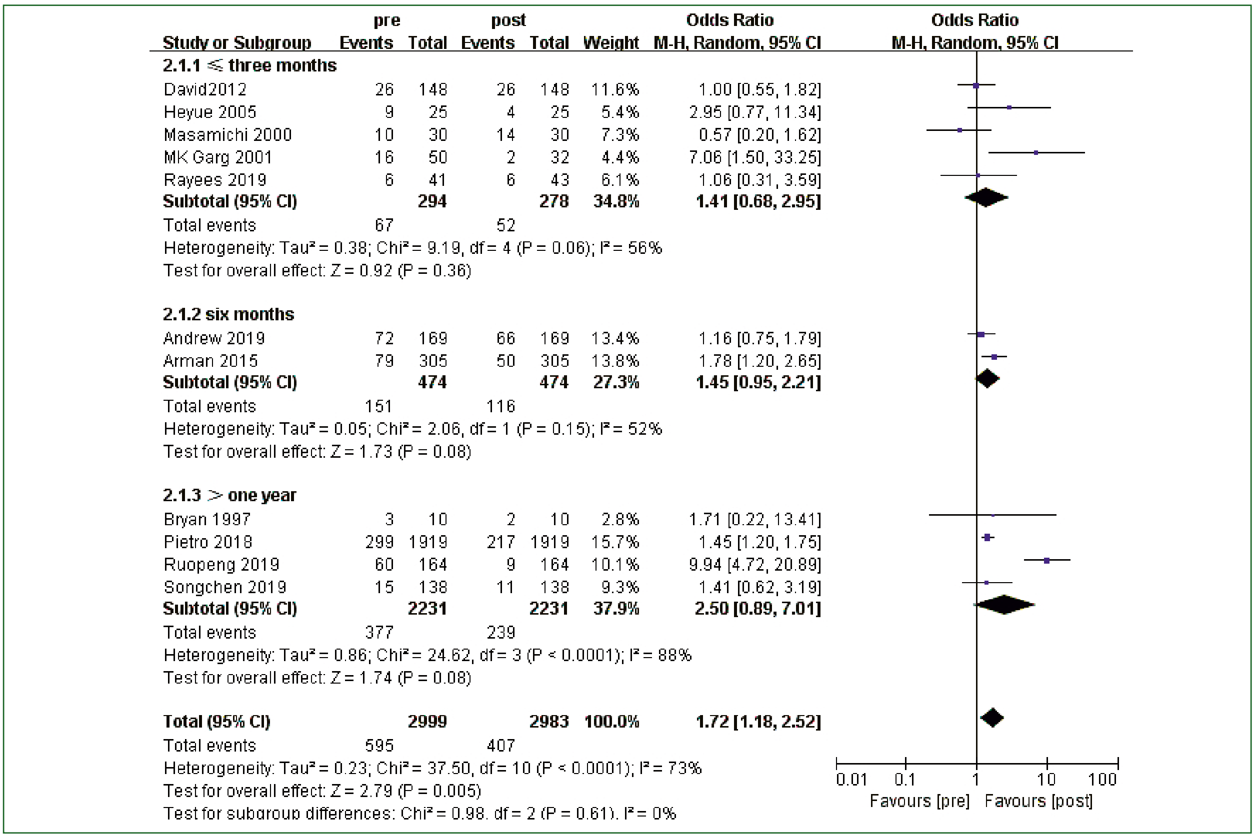

Figure 3. Comparison of thyroid axis dysfunction before and after operation

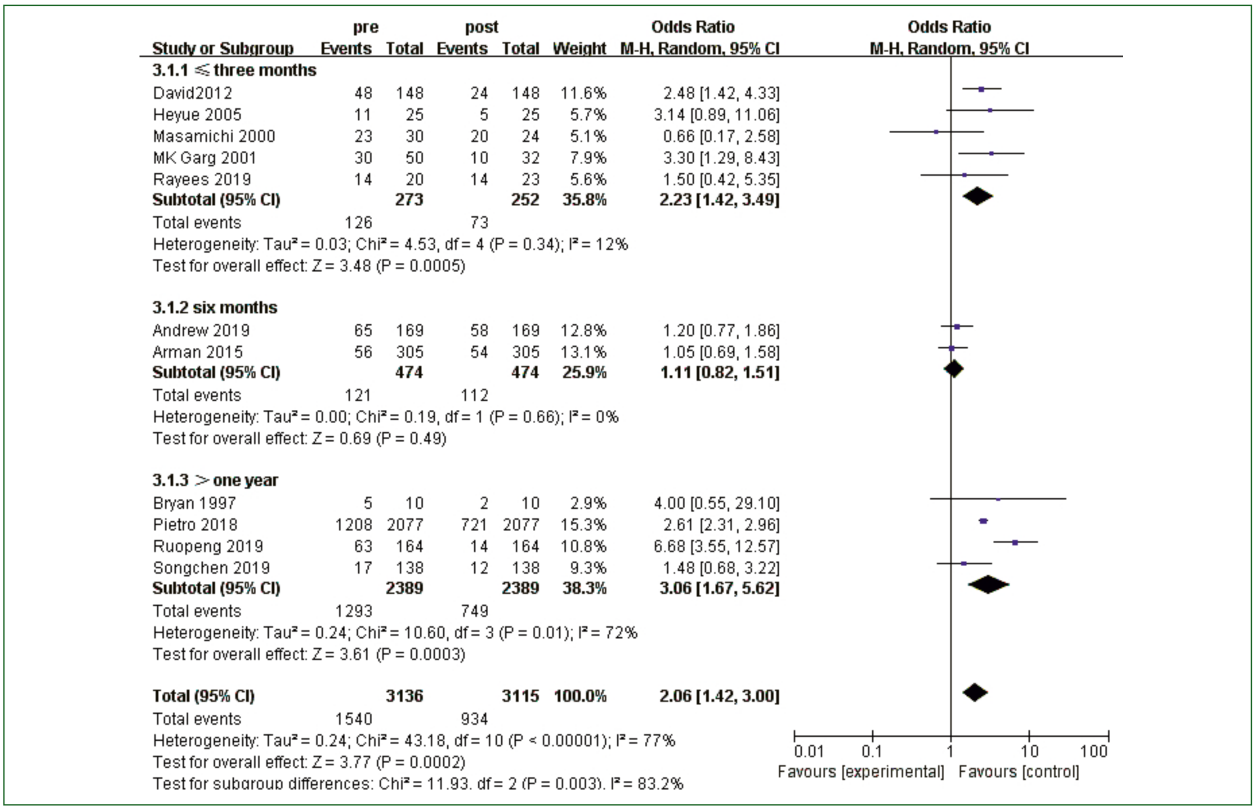

Figure 4. Comparison of gonad axis dysfunction before and after operation

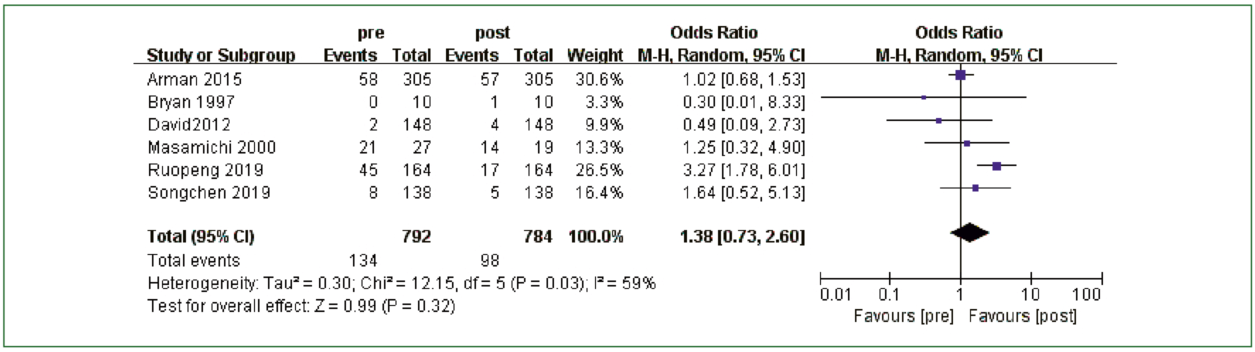

Figure 5. Comparison of GH deficiency before and after operation

the decreased levels as a unique factor or in combination with multiple target-gland dysfunctions; the latter group included 132 patients before, and 98 patients after, surgery. Heterogeneity analysis showed that there was statistical homogeneity among these six studies, and a random-effects model was used for effect-size consolidation. The results showed that after pituitary tumour resection, patients were followed up for 16.3 days to 42 months on average. The percentage of patients with low growth hormone levels was lower than the percentage before the operation, but the difference was not statistically significant: OR = 1.38 (95% CI, 0.73–2.60; P = 0.32) (Fig. 5).

Changes in postoperative function in patients with preoperative pituitary hypofunction

Four of the 11 studies [3, 6, 9, 10] reported patients with new hypofunction of the adrenal, thyroid, and gonadal axes. After eliminating those with new hypofunction from the data set, meta-analysis showed that hypofunction decreased significantly after pituitary tumour resection, and was statistically significant. For the adrenal axis: OR = 1.46 (95% CI, 1.21–1.78; P = 0.0001); for the thyroid axis: OR = 1.78 (95% CI, 1.50–2.12; P < 0.00001); and for the gonad axis: OR = 1.96 (95% CI, 1.23–3.13; P = 0.005) (Fig. 6–8).

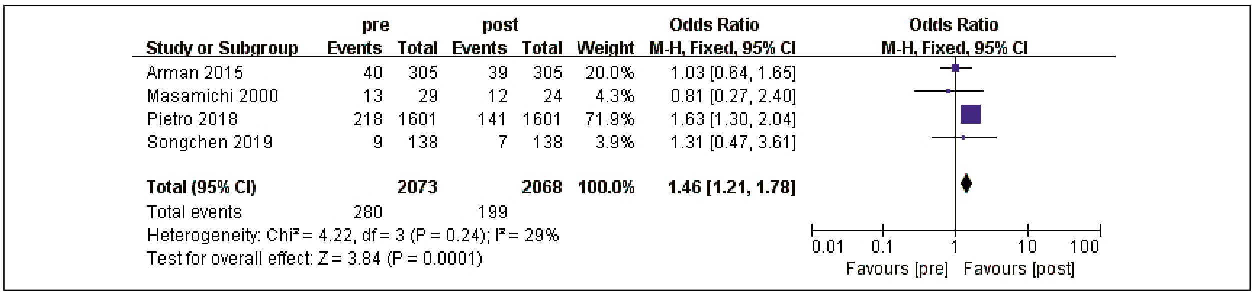

Figure 6. Postoperative functional evaluation of patients with preoperative adrenal axis dysfunction

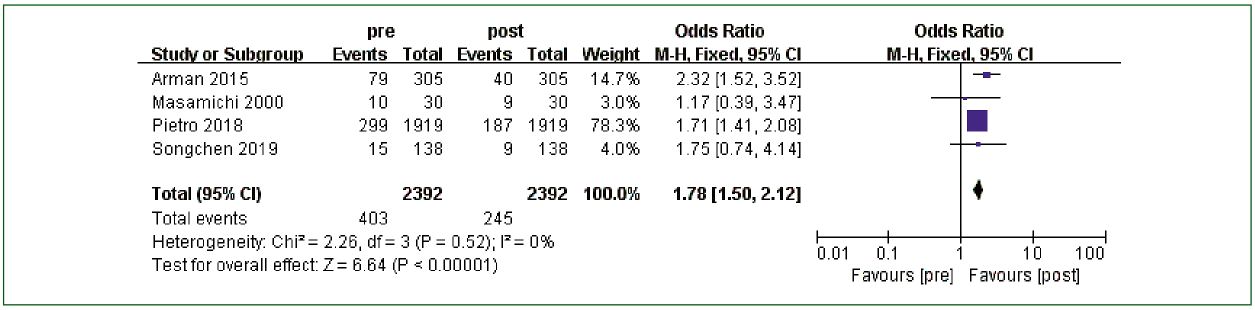

Figure 7. Postoperative functional evaluation of patients with preoperative thyroid axis dysfunction

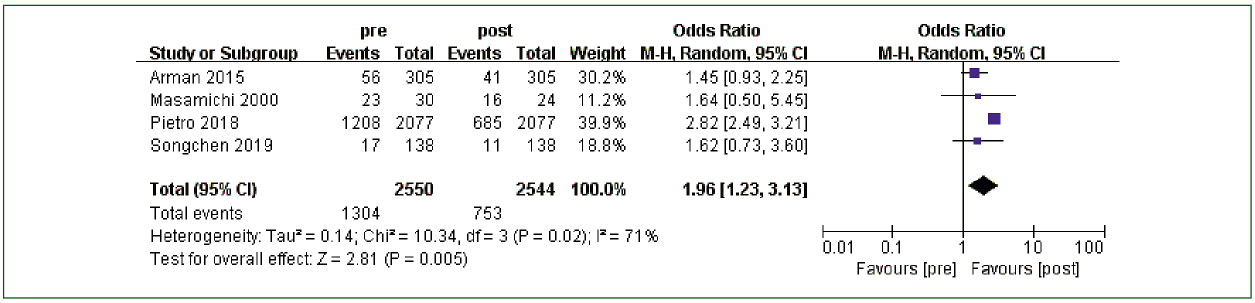

Figure 8. Postoperative functional evaluation of patients with preoperative gonad axis dysfunction

Incidence of new pituitary hypofunction after operation

Four of the 11 studies [3, 6, 9, 10] reported incidence of new hypofunction of the pituitary gland, but only Masamichi reported that the incidence of new hypofunction of the adrenal, thyroid, and gonadal axes was substantially higher; in the other three studies, the incidence of new hypofunction of the three gland axes was 2.5–7.1%, 1.8–4.4%, and 1.0–5.2%.

Publication bias evaluation

A funnel plot was used to evaluate the publication bias of studies included in this meta-analysis. The shape of the funnel plot was symmetrical (Fig. 9); An Egger test showed P > 0.05 for this analysis, so the publication bias of the 11 studies was low.

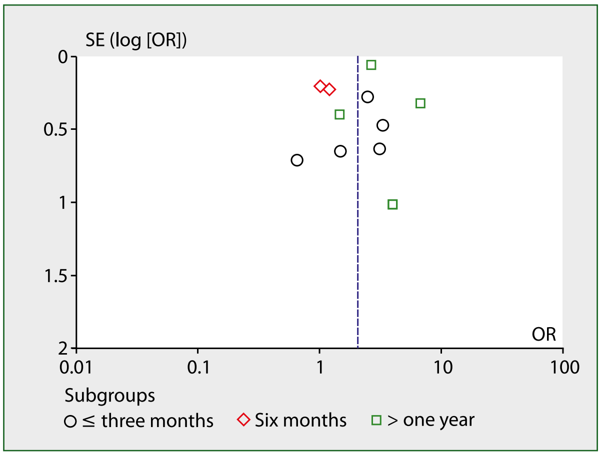

Figure 9. Funnelplot of evaluation of gonad axis function

Discussion

There is presently no consensus as to whether pituitary tumour resection can effectively improve and restore pituitary function because of the high incidence of pituitary damage caused by surgery [12–15]. In our study, meta-analysis was used to systematically evaluate studies from an international cohort.

The results revealed that the number of patients with a poor total suprarenal gland axis after pituitary tumour resection was not significantly changed compared to the number of patients before the operation; however, hypothyroidism and hypofunction of the gonad could be restored significantly. In the present study, the percentage of patients with hypofunction of the adrenal cortex, thyroid, and gonad glands was 15.7%, 19.8%, and 49.1%, respectively, before the operation and 13.8%, 13.6%, and 30.0%, respectively, after the operation.

The study showed that patients who had hypofunction of the adrenal axis before the operation saw normal function return after pituitary adenoma resection (excluding those patients who had normal function prior to surgery but who developed adrenal hypofunction after surgery).

Most of the literature only reports the percentage of patients with a complete recovery of pituitary function after the operation but does not report those patients who at least had some improvement in recovery; these patients were able to reduce the dose of their hormone replacement therapy even if they could not cease it altogether. It cannot be said that pituitary adenoma resection surgery had no beneficial effects on improving adrenal function since the incidence of new adrenal hypofunction is low.

The results of the Mortini study, which had the longest mean follow-up time and the largest sample size [3], showed that when patients were followed up for 60 months on average after the operation, the percentage of patients with normal adrenal axis function was significantly higher than the percentage before the operation, even if the patients with new hypofunction of the adrenal axis were included. This suggests that recovery and a return to normal function for the damaged pituitary-adrenal axis is a lengthy process, and that some patients need to undergo glucocorticoid replacement therapy for a long time after the operation. Improvements in the pituitary-thyroid and pituitary-gonad axes are much faster. An explanation for this difference in the recovery rate of the different gland axes needs to be found.

Results of the meta-analysis involving six studies [2, 5, 6, 8–10] showed that the percentage of patients with decreased growth hormone levels was 16.9% before the operation and 12.5% after the operation; this condition improved but not to an extent that was statistically significant. These six studies included 728 patients with nonfunctional pituitary tumours and 50 patients with growth hormone tumours. One study concluded that the hormone recovery rate of patients with a growth hormone tumour was high, and that this may be related to tumour size and age at onset [16]. The reliability of the results was affected by the small number of studies and small sample sizes.

Postoperative diabetes insipidus was reported in four studies [1–3, 8]. Of the 148 patients in the study by Bellut [2], four had diabetes insipidus before surgery and five after surgery, but the number of new diabetes insipidus cases was not explained. Little et al. [1] mentioned that diabetes insipidus occurred in 2.4% of their study patients after the operation; 3.3% of patients in Mason's study [8] had diabetes insipidus after the operation, one for longer than 20 months. However, Mortini [3] had a 0.9% incidence of permanent diabetes insipidus. The findings of these four studies are consistent with results reported elsewhere: the incidence of permanent diabetes insipidus after surgery can be 0.4–15%, but is usually less than 3% [17].

There were four studies reporting new hypofunction of the pituitary gland after surgery, and the incidence was 1.0–7.1% in three of them. The high incidence of new cases reported in Kurosaki [10] may be attributed to the earlier time range for the study (1991–1999) and the limited follow-up (16.3 days on average). Other articles have reported new incidence of pituitary hypofunction (5–13.7%) after pituitary tumour resection [18,19]. The incidence of pituitary hypofunction increases after surgery in nonfunctional adenomas, with an occurrence of 1.5–40% [2, 21, 22].

Fatemi et al. [19] performed multivariate analysis in their study. The results revealed that the strongest predictors for a positive recovery of pituitary function were a younger age and the absence of hypertension. Intraoperative cerebrospinal leakage and tumour size were independent predictors of new pituitary hypofunction. Other studies indicated that patient age was a key factor affecting whether the pituitary was injured during surgery, with older patients more likely to have hypofunction of the pituitary after the procedure [6, 23]. Nomikos et al. [21] showed that smaller nonfunctional tumours were most likely to result in eventual normal hormone levels.

From all of these findings in the literature it can be seen that a wide range of variables can predict new hypofunction of the pituitary, including patient age, tumour size, tumour type, surgical strategy, intraoperative complications, and surgeon experience.

Conclusion

The function of the thyroid and gonadal axes of patients with a pituitary gland tumour can be improved, to some extent, after pituitary tumour resection. For patients with pituitary adenoma who already had hypofunction of the adrenal axis before the operation the function can be improved, to some extent, after pituitary adenoma resection.

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