Original Article

Neuronavigation-assisted pituitary neuroendocrine tumor resection: a systematic review and meta-analysis

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Background: The advancement of pituitary surgery has rendered it a secure and efficient treatment method; nevertheless, the potential for incomplete tumor removal and cerebrospinal fluid (CSF) leak remains. Neuronavigation-assisted pituitary neuroendocrine tumor (PitNET) resections have been driving a rising number of attentions in recent years. However, there is currently a lack of comprehensive quantitative evaluation of the effectiveness of neuronavigation-assisted pituitary tumor resection. We aimed to assess the curative effects and complications with or without the use of an image-based neuronavigation in PitNET resection.

Methods: A systematic review and meta-analysis was performed by searching PubMed, EMBASE, Cochrane Library, Web of Science, and Scopus from inception until May 1, 2024 in English to identify any studies reporting gross total resection (GTR) or postoperative complications in patients who underwent neuronavigation-assisted PitNET resection, excluding conference abstracts and studies with fewer than five subjects. We also searched the reference lists of previous systematic reviews and other relevant publications in databases. We reviewed and analyzed the studies that investigated the operative effects and complications of neuronavigation in PitNET resection. Study quality was assessed by the Newcastle-Ottawa scale, and publication bias was evaluated by funnel plot. Review manager 5.3 was employed for meta-analysis. The results were expressed as odds ratio (OR) with 95% confidence interval (CI) of image-assisted techniques for the incidence of GTR and complications.

Results: A total of 42 publications that fulfilled the established searching criteria were obtained from the above-mentioned databases, all of which with the Newcastle-Ottawa Scale scores ≥ six ★. Among the included publications, 37 studies indicated that the OR of image-based neuronavigation was 2.29 (95% CI: 2.02–2.60, P<0.00001, I^2=24%) for GTR. The other five studies compared the neuronavigation group (experimental group) and non-neuronavigation group (control group), exhibiting high heterogeneity (I^2=91%). After sensitivity analysis, the results showed that the rate of the CSF leak of the neuronavigation group was slightly lower than that of the non-neuronavigation group (OR: 0.84, 95% CI: 0.73–0.97, P=0.01, I^2=43%).

Conclusions: According to the existing data, neuronavigation-assisted PitNET resection can increase the rates of GTR and reduce the incidence of postoperative complications. Our results provide a reference for the selection of surgical methods for PitNET resection in future clinical practice.

Keywords: Pituitary neuroendocrine tumor (PitNET); neuronavigation; magnetic resonance imaging; meta-analysis

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Introduction

Pituitary tumor represents a common intracranial pathology and pituitary neuroendocrine tumor (PitNET) is the most common type of pituitary tumor, in which usually hormones are abnormally secreted and systematic upwards compression of optic structures occurs, resulting in a wide variety of clinical sequelae (1,2). Transsphenoidal surgery (TSS), known for its simplicity and minimal invasiveness, is widely embraced as the primary treatment for most PitNET cases, with both the endoscope and microscope yielding satisfactory clinical outcomes (3,4). For PitNET, gross total resection (GTR) has been found to significantly reduce the chances of recurrence is the surgical ideal target (3,5). In recent years, intraoperative neuronavigation for intracranial surgery, especially intraoperative magnetic resonance imaging (iMRI) system, has become increasingly popular and has significantly facilitated pituitary and other skull base surgeries (6). The combined technique has shown promising results in the enhancement of the therapeutic effects of surgeries and in the preservation of the hypophysis (7). Furthermore, its implementation reduces the associated complications, including cerebrospinal fluid (CSF) leak, intraoperative hemorrhage, hypopituitarism, headache, nasal septal perforation, and postoperative pain and discomfort (8). Nevertheless, controversies exist in the publications on the impact of intraoperative neuronavigation in TSS, regarding the various types of surgical mirrors and imaging systems (8,9).

Currently, a large number of studies have been performed to explore the operative effects of neuronavigation-assisted PitNET resections (9-16), but no comprehensive and consistent evaluation and quantitative analysis of research results have been conducted. Therefore, we conducted a systematic review and meta-analysis to assess the curative effects and complications of PitNET resection with or without the use of an image-based neuronavigation, as well as the clinical values of the image-assisted techniques. We present this article in accordance with the PRISMA reporting checklist (17) (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1570/rc).

Methods

This systematic review and meta-analysis was registered with PROSPERO (CRD42022332705) (https://www.crd.york.ac.uk/PROSPERO/).

Search strategies

We searched publications in the following databases: PubMed, Cochrane Library, EMBASE, Web of Science, and Scopus, which were completed by May 1, 2024. During the literature search phase, there were no restrictions on date and type of publication. Our search strategy included the use of combinations of the following terms: Pituitary Neoplasm; Pituitary Neoplasms; Pituitary Tumor; Pituitary Tumors; Pituitary Adenoma; Pituitary Adenomas; Pituitary Carcinoma; Pituitary Carcinomas; Cancer of the Pituitary; Cancer of Pituitary; Pituitary Cancer; Pituitary Cancers; Frameless Stereotaxy; Stereotaxy, Frameless; Image-guidance; Intraoperative Magnetic; Resonance Imaging; Intraoperative MRI (iMRI); Stereotaxy Neuronavigation (SNN); MR Imaging Neuronavigation (INN); iMRI; SNN; INN; Stereotaxy-guided Operative Neurosurgery; Frame Stereotactic Neurosurgery; Frameless Stereotactic Neurosurgery; MR Image-guided; Neuro-navigation; CT-guided; MRI-guided; Gross Total Resection; GTR; Extent of Resection. We searched for word variations as far as possible. Furthermore, reference lists for previous systematic reviews and other relevant publications were manually searched to complement the database. The last comprehensive search was conducted by May 3, 2024.

Study selection

Only *in vivo* studies enrolling humans of all age groups in English were considered, regardless of the age and nationality of the subjects. Considering the limited number of the expected randomized controlled trials (RCTs), we also intended to include eligible case-control trials and cohort studies. Conference abstracts and studies with fewer than five subjects were excluded. Studies would be eligible if they fulfilled all of the following criteria: (I) studies reporting pituitary tumor resection without restrictions on the surgical area, surgical personnel, and specific surgical approach; (II) RCTs, case control trials, prospective cohort studies or retrospective cohort studies, including an experimental group with iMRI and a control group without iMRI, or an experimental group with other neuronavigation system, and a control group without any neuronavigation; (III) the enrolled studies included appropriate outcome indicators, such as GTR, operative time, surgery cost, and postoperative complications containing CSF leak, headache, hypopituitarism, diabetes insipidus, vision decreasing, rhinoliquorrhea, epistaxis, and CNS infection; (IV) patients included in the studies underwent either endoscopic or microscopic transsphenoidal resection for PitNET with neuronavigation. In addition, to avoid interference from pituitary tumors of different pathological types on the effectiveness of neuronavigation, cases in the publications reporting Rathke cleft cysts, craniopharyngiomas, gliomas, meningiomas, or other irrelevant lesions without classification, were excluded. Moreover, studies primarily addressing patients for whom the surgical target was solely decompression were excluded. The following consecutive steps of the literature screening process were performed. First, we used Review Manager 5.3 to remove duplicate publications and then manually removed residual duplicates. Second, we analyzed the titles and abstracts, which were performed by two independent investigators (Y.H. and H.L.) based on the pre-set inclusion and exclusion criteria. If disagreements occurred, a third investigator with more than ten-year experience of neurologic radiology (Y.L.) would make the final determination. Third, publications whose titles and abstracts could not provide sufficient information to make the decision on their inclusion or exclusion were subsequently re-analyzed by full-text screening. Finally, to avoid the double counting of data derived from multiple studies from the same group of researchers, we assessed the sample size, recruitment period, and baseline sample characteristics of each article to identify and exclude duplicate data across different publications. While exact cohort duplicates were excluded, we did include updated versions of previously published cohorts with a sample size increase of at least 50%.

Risk of bias assessment

The above-mentioned two investigators also independently evaluated the quality of the included publications. If there was a difference, they would consult with a 3rd reviewer. The quality evaluation and cross-checking were carried out according to the evaluation criteria of the Newcastle-Ottawa Scale (NOS) (5), mainly considering the selection methods of the case groups and the control groups, the comparability of the case groups and the control groups, and the exposure assessment methods.

Data analysis

Review manager 5.3 was employed for meta-analysis. The odds ratio (OR) along with 95% confidence interval (CI) were used as the effect indexes of image-based neuronavigation for the incidence of GTR and postoperative CSF leak. Low, moderate and high have been provisionally assigned to I^2 values of 25%, 50% and 75%, respectively (based on the Cochrane Handbook guidelines) (18). I^2<50%, indicated that the heterogeneity among studies was acceptable, and a fixed-effect model was used; I^2 ≥50% indicated high heterogeneity among the groups, and thus a random-effect model was used (19). After analysis, we found that there was small heterogeneity in GTR-relevant publications, so a fixed effects meta-analysis was decided upon. To explore the source of heterogeneity, the subgroup analysis was performed. The patients were divided into three subgroups based on the MRI field strength: low-field iMRI subgroup (<1.5T), high-field iMRI subgroup (≥1.5T, <3T), and ultra-high-field iMRI subgroup (≥3T) (20). The patients were also divided into a microscopic group and an endoscopic group according to the types of surgical mirrors. However, there was great heterogeneity in postoperative CSF leak-relevant publications, so a random-effect meta-analysis was decided to be implemented. Subgroup analysis could not be performed due to insufficient data. Sensitivity analysis was performed by removing single literature in sequence and then obtaining new statistical results from the remaining articles in Review Manager 5.3. The meta-analysis results were illustrated with forest plots, and the publication bias was analyzed with funnel plots.

Results

Study selection

Through searching electronic databases, we retrieved 2,500 potentially eligible publications (Table S1). After the evaluation of the titles and abstracts, 452 potentially eligible publications were selected for full-text screening.

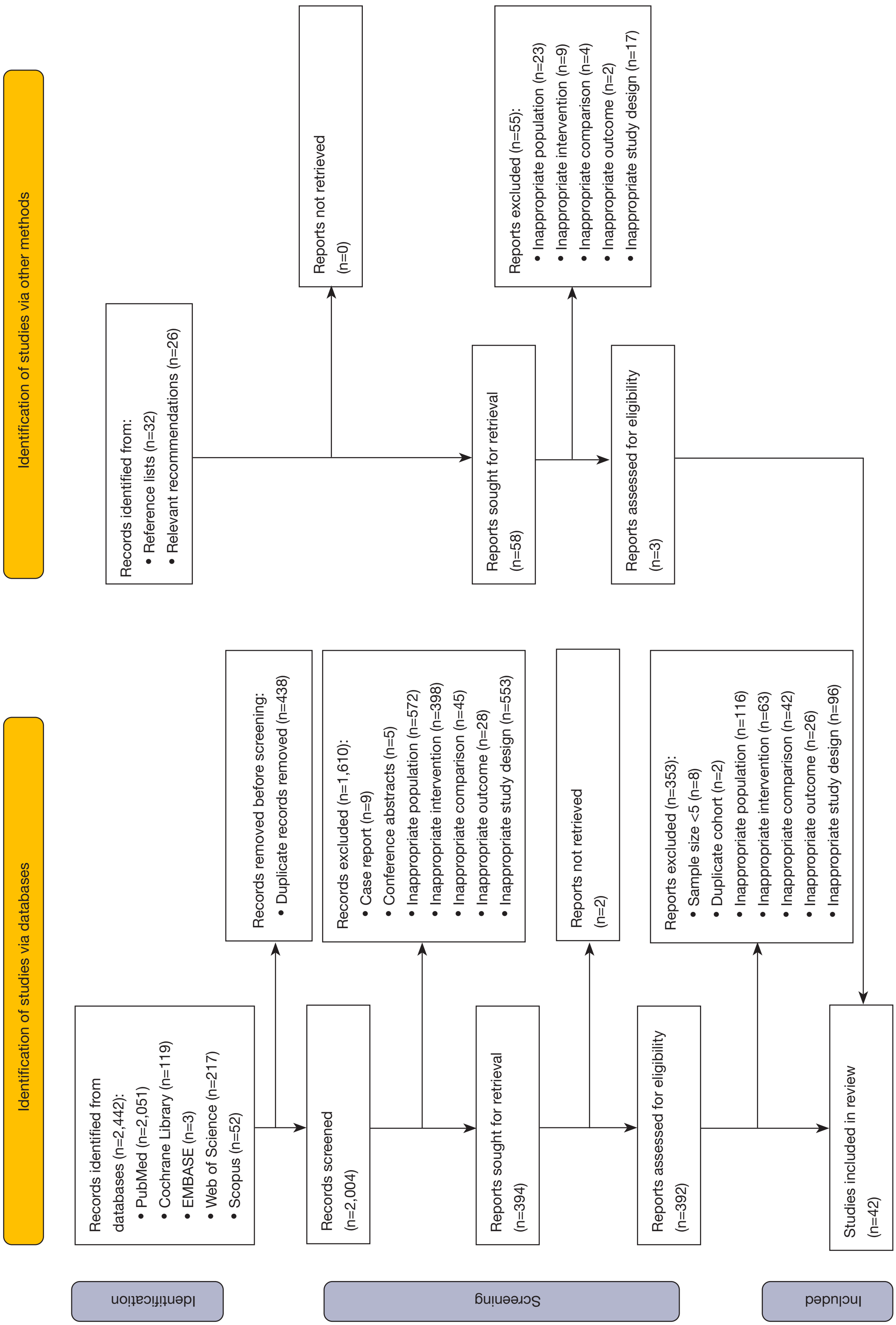

Figure 1 Flow diagram of publications inclusion and exclusion for the systematic review and meta-analysis.

Ultimately, 42 eligible publications were selected for the analysis by synthesis in this study (*Figure 1*). Moreover, two publications registered in Web of Science that may meet the criteria were not chosen for full-text screen because we did not have access to the full text or the results (the data were not available even after contacting the authors).

Quality assessment of the included publications

Based on the NOS, the 42 included publications were subjected to a systematic quality evaluation. Eight items were contained in the NOS, categorizing into three dimensions: subject selection containing (I) is the case definition adequate? (II) Representativeness of the cases; (III) selection of controls; (IV) definition of controls, comparability containing (I) comparability of cases and controls on the bases of the design or analysis and exposure containing (I) admission of exposure; (II) same method of admission for cases and controls; (III) non-response rate in case control study. A succession of response options were provided for each item. The star system was used for semi-quantitative assessment of research quality. A maximum of one star was awarded for each item, except for item related to comparability which were awarded two stars. The NOS scores range from zero ★ to nine ★ (21). A higher score indicated a better quality. Generally, studies with at least 4 points were included in the meta-analysis (22). Among all the publications included in this study, 33 publications clearly grouped the patients by "age" and "sex", indicating that the most important confounding factors were controlled, and the total score was eight points (Tables S2,S3); two publications did not clearly group the patients by "age" or "gender", which received a total score of seven points (23,24); seven did not clearly group the patients by "age" and "gender", and received a total score of six points (12,25-30). In addition, the quality of the exposure assessment methods of the 42 publications was high, and thus was given three ★, whereas the quality of the selection assessment methods of the 42 publications was good and awarded two ★.

Characteristics of the included studies

We included a total number of 42 studies, 37 of which assessed intraoperative and postoperative GTR rates and the other five publications were associated with postoperative CSF leak. An overview of the characteristics of the included publications was presented in *Tables 1,2*. In terms of field

Table 1 An overview of the characteristics of the included literatures relevant to GTR

Author	Year	Total number of patients	Age (years), mean (± SD) or mean (range) or n [%]	Male, n [%]	Microscopic/ endoscopic, n	Field strength	NFPT, n [%]
Low-field							
Ahn *et al.* (31)	2008	51	NA	NA	51/0	0.15 T Polestar N20	NA
Berkmann *et al.* (6)	2011	32	57 (±17.9)	23 [72]	NA	0.15 T PoleStar N20	26 [81]
Berkmann *et al.* (32)	2012	92	NA	NA	92/0	0.15 T Polestar N20	79 [86]
Bohinski *et al.* (8)	2001	29	51 (24–74)	18 [62]	29/0	0.3 T AIRIS II	22 [76]
Fahlbusch *et al.* (33)	2001	44	53 (±14.9)	29 [66]	44/0	0.2 T Magnetom Open	39 [89]
García *et al.* (34)	2017	30	55	13 [43]	0/30	0.15 T Polestar N30	15 [50]
Hlavica *et al.* (13)	2013	104	59 (22–86)	57 [55]	104/0	0.15 T Polestar N20	104 [100]
Jiménez *et al.* (35)	2016	18	NA	NA	0/18	0.15 T Polestar N20	10 [56]
Martin *et al.* (36)	1999	5	36.2 (28–42)	2 [40]	5/0	0.5 T	0 [0]
Ramm-Pettersen *et al.* (37)	2011	20	54 (23–71)	13 [65]	20/0	0.5 T Signa SP	16 [80]
Schwartz *et al.* (38)	2006	15	49 (29–67)	9 [60]	0/15	0.12 T Polestar N10	11 [73]
Strange *et al.* (39)	2020	231	55.5 (18–88)	127 [55]	0/231	0.15 T Polestar N20	160 [69]
Wu *et al.* (40)	2009	55	45.9 (±12.6)	36 [65]	55/0	0.15 T Polestar N20	29 [53]

Table 1 (*continued*)

Table 1 (*continued*)

Author	Year	Total number of patients	Age (years), mean (± SD) or mean (range) or n [%]	Male, n [%]	Microscopic/ endoscopic, n	Field strength	NFPT, n [%]
High-field							
Berkmann *et al.* (41)	2014	85	55 (±14)	57 [67]	85/0	1.5 T Magnetom	85 [100]
Chen *et al.* (23)	2012	13	NA	NA	13/0	1.5 T Magnetom	NA
Dort *et al.* (42)	2001	15	50 (15–80)	8 [53]	15/0	1.5 T	NA
Gohla *et al.* (43)	2020	42	52 (17–79)	23 [55]	42/0	1.5 T Espree	35 [83]
Hlaváč *et al.* (44)	2019	111	57.3 (22–78)	75 [68]	66/45	1.5 T Espree	91 [82]
Kuge *et al.* (45)	2013	35	54.3 (±15.5)	18 [51]	0/35	1.5 T	27 [77]
Li *et al.* (46)	2015	30	36 (21–65)	13 [43]	30/0	1.5 T Espree	9 [30]
Nimsky *et al.* (25)	2004	48	NA	NA	48/0	1.5 T	NA
Nimsky *et al.* (12)	2006	85	NA	NA	85/0	1.5 T Magnetom	85 [100]
Pal'a *et al.* (9)	2017	96	54 (7–78)	71 [74]	68/28	1.5 T Espree	64 [67]
Paľa *et al.* (47)	2022	59	57	42 [71]	0/59	1.5 T	42 [71]
Pala *et al.* (48)	2022	190	55	106 [56]	88/102	1.5 T	NA
Paterno' *et al.* (29)	2014	49	NA	NA	0/49	1.5 T Espree	49 [100]
Sylvester *et al.* (30)	2015	156	NA	NA	115/41	1.5 T Espree	NA
Szerlip *et al.* (49)	2011	53	49 (1.8 SEM)	25 [47]	53/0	1.5 T Espree	39 [74]
Tanei *et al.* (50)	2013	14	37.4 (±11.8)	2 [14]	0/14	1.5 T Magnetom	0 [0]
Zhang *et al.* (51)	2017	137	7–82	73 [53]	0/137	1.5 T Espree	103 [75]
Zhang *et al.* (52)	2019	133	50 (±12)	61 [46]	0/133	1.5 T Espree	133 [100]
Ultra-high-field							
Fomekong *et al.* (53)	2014	73	NA	46 [63]	73/0	3 T Intera	NA
Netuka *et al.* (26)	2011	49	NA	NA	NA	3 T	NA
Qiu *et al.* (27)	2012	49	NA	NA	NA	3 T Mangetom	NA
Serra *et al.* (11)	2016	51	33 [65]	27 [53]	0/51	3 T Mangetom	33 [65]
Staartjes *et al.* (10)	2019	95	65 [68]	53 [56]	0/95	3 T Mangetom	65 [68]
Zaidi *et al.* (14)	2016	20	14 [70]	9 [45]	0/20	3 T Verio	14 [70]

GTR, gross total resection; SD, standard deviation; NFPT, nonfunctioning pituitary tumor; NA, not applicable; SEM, standard error of mean.

strength selection, low-field, high-field, and ultra-high-field iMRI was used in 13, 18, and 6 of the published studies, respectively. Regarding the surgical technique employed, microscopic and endoscopic resection were performed in 17 and 13 of the studies, respectively.

Statistical analysis of the GTR and postoperative CSF leak results

The fixed-effect model indicated that, in the 37 included publications (2,271 subjects), the OR of image-based neuronavigation was 2.29 (95% CI: 2.02–2.60, P<0.00001)

Table 2 An overview of the characteristics of the included literatures relevant to postoperative CSF leak

Author	Year	Sample capacity		Intervening measure	
		Experimental group	Control group	Experimental group	Control group
Achey *et al.* (54)	2019	175	444	Stereotactic CT-assisted endoscope	Endoscope
Alshareef *et al.* (55)	2021	34	104	IOUS	Without IOUS
Chung *et al.* (24)	2015	2,996	45,446	CT/MRI-assisted endoscope	Endoscope
Eboli *et al.* (28)	2011	208	65	iCT/EM-assisted TSA	Fluoroscope-assisted TSA
Tosaka *et al.* (56)	2015	30	30	iCT-assisted endoscopic TSA	Conventional endoscopic TSA

CSF leak, cerebrospinal fluid leak; CT, computed tomography; IOUS, intraoperative ultrasonography; MRI, magnetic resonance imaging; iCT, intraoperative computed tomography; EM, frameless electromagnetic; TSA, transsphenoidal approach.

for GTR (*Figure 2*). The I^2 statistic was 24% representing smaller heterogeneity. Therefore, a fixed-effect model was selected for meta-analysis.

The fixed-effect model indicated that, in the five included publications (49,532 subjects), the OR of image-based neuronavigation was 0.77 (95% CI: 0.67–0.88, P<0.01) for postoperative CSF leak. Heterogeneity, as measured by I^2 statistic, reached up to 91%, so a random effect model was selected for meta-analysis.

Factors affecting GTR

To explore the source of heterogeneity, the subgroup analysis was performed in GTR-related publications based on the magnetic field strength and the type of surgical mirror as mentioned before. The statistical analysis results are presented in *Figure 3* and *Figure 4*.

Low-field iMRI publications (n=13), containing a total of 726 objects, indicated that using low-field iMRI was significantly associated with the incidence of GTR (OR: 2.01, 95% CI: 1.60–2.53, P<0.00001, I^2=33%) (6,8,13,31-40). High-field iMRI publications (n=18), containing a total number of 1,351 objects, revealed that the high-field iMRI has a higher correlation with the incidence of GTR (OR: 2.36, 95% CI: 2.00–2.79, P<0.00001, I^2=30%) (9,12,23,25,29,41-49). In the ultra-high-field iMRI group (n=6) including 337 objects, we found that the ultra-high-field iMRI had the highest correlation with the incidence of GTR (OR: 2.72, 95% CI: 1.94–3.83, P<0.00001, I^2=0%) (10,11,14,26,27,53). However, the differences among the three subgroups were not statistically significant (P=0.31, I^2=14.9%) (*Figure 3*).

The microscopic group (n=17), containing a total of 844 objects, indicated that the rate of GTR was 2.85 times higher in patients with iMRI than in patients without iMRI (95% CI: 2.29–3.55, P<0.00001, I^2=0%) (8,12,13,23,25,31-33,36,37,40-43,46,53,57). In the endoscopic group (n=13), containing a total of 887 objects, indicated that the rate of GTR was 2.18 times higher in patients with iMRI than in patients without iMRI (95% CI: 1.80–2.65, P<0.00001, I^2=51%) (10,11,14,29,34,35,38,39,45,48,50-52). Our results showed that there was no statistically significant difference between the two groups (P=0.07, I^2=68.9%) (*Figure 4*).

However, due to the insufficient literature data, we were unable to perform other subgroup analyses.

Sensitivity analysis

Five publications were subjected to sensitivity analysis. After removing any single literature, a new meta-analysis was carried out respectively. We found that heterogeneity was significantly reduced (91% to 43%) when the literature of Eboli *et al.* (28) was removed, indicating that the heterogeneity was most likely to be derived from this article. We decided to exclude it and established that the postoperative CSF leak incidence slightly decreased after the utilization of neuronavigation (OR: 0.84, 95% CI: 0.73–0.97, P=0.01, I^2=43%).

Evaluation of the publication bias

An assessment of the risk of bias in the publications describing GTR and postoperative CSF leak was performed. The funnel plot analysis showed that the distribution of studies on both sides of the funnel plot was not completely symmetrical, suggesting that publication bias might exist.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Ahn 2008	48	51	38	51	0.7%	5.47 [1.45, 20.60]
Berkmann 2011	21	32	17	32	1.8%	1.68 [0.62, 4.61]
Berkmann 2012	51	60	22	32	1.3%	2.58 [0.92, 7.21]
Berkmann 2014	56	85	37	85	3.9%	2.51 [1.35, 4.66]
Bohinski 2001	16	29	7	29	1.0%	3.87 [1.26, 11.88]
Chen 2012	10	13	5	13	0.4%	5.33 [0.97, 29.39]
Dort 2001	14	15	11	15	0.2%	5.09 [0.50, 52.29]
Fahlbusch 2001	31	44	19	44	1.7%	3.14 [1.30, 7.57]
Fomekong 2014	53	73	43	73	3.6%	1.85 [0.92, 3.70]
García 2017	25	30	18	30	0.9%	3.33 [1.00, 11.14]
Gohla 2020	18	42	12	42	2.1%	1.88 [0.76, 4.64]
Hlaváč 2019	43	111	33	111	6.2%	1.49 [0.86, 2.61]
Hlavica 2013	70	104	48	104	4.8%	2.40 [1.37, 4.22]
Jimenéz 2016	14	18	8	18	0.5%	4.38 [1.03, 18.63]
Kuge 2013	25	35	23	35	2.0%	1.30 [0.47, 3.59]
Li 2015	24	30	18	30	1.1%	2.67 [0.84, 8.46]
Martin 1999	4	5	2	5	0.1%	6.00 [0.35, 101.57]
Netuka 2011	45	49	34	49	0.8%	4.96 [1.51, 16.31]
Nimsky 2004	42	48	27	48	1.0%	5.44 [1.95, 15.22]
Nimsky 2006	70	85	49	85	2.6%	3.43 [1.70, 6.93]
Pala 2022 (190 pts)	178	190	152	190	2.9%	3.71 [1.87, 7.35]
Pala 2022 (59 pts)	29	59	20	59	3.1%	1.89 [0.90, 3.96]
Pal' a 2017	58	96	46	96	5.6%	1.66 [0.94, 2.94]
Paterno 2014	49	49	23	49	0.1%	111.64 [6.52, 1911.90]
Qiu 2012	42	49	38	49	1.7%	1.74 [0.61, 4.94]
Ramm-Pettersen 2011	12	20	8	20	1.0%	2.25 [0.63, 7.97]
Schwartz 2006	13	15	12	15	0.5%	1.63 [0.23, 11.46]
Serra 2016	31	51	16	51	1.9%	3.39 [1.50, 7.67]
Staartjes 2019	68	95	42	95	3.7%	3.18 [1.74, 5.80]
Strange 2020	120	231	111	231	16.3%	1.17 [0.81, 1.68]
Sylvester 2015	56	156	44	156	8.6%	1.43 [0.88, 2.30]
Szerlip 2011	33	53	20	53	2.3%	2.72 [1.24, 5.97]
Tanei 2013	11	14	7	14	0.5%	3.67 [0.70, 19.12]
Wu 2009	46	55	32	55	1.6%	3.67 [1.50, 8.97]
Zaidi 2016	16	20	12	20	0.7%	2.67 [0.65, 10.97]
Zhang 2017	88	137	59	137	6.5%	2.37 [1.46, 3.86]
Zhang 2019	85	133	57	133	6.3%	2.36 [1.44, 3.87]
Total (95% CI)		**2382**		**2354**	**100.0%**	**2.29 [2.02, 2.60]**
Total events	1615		1170			

Heterogeneity: Chi² = 47.64, df = 36 (P = 0.09); I² = 24%
Test for overall effect: Z = 12.99 (P < 0.00001)

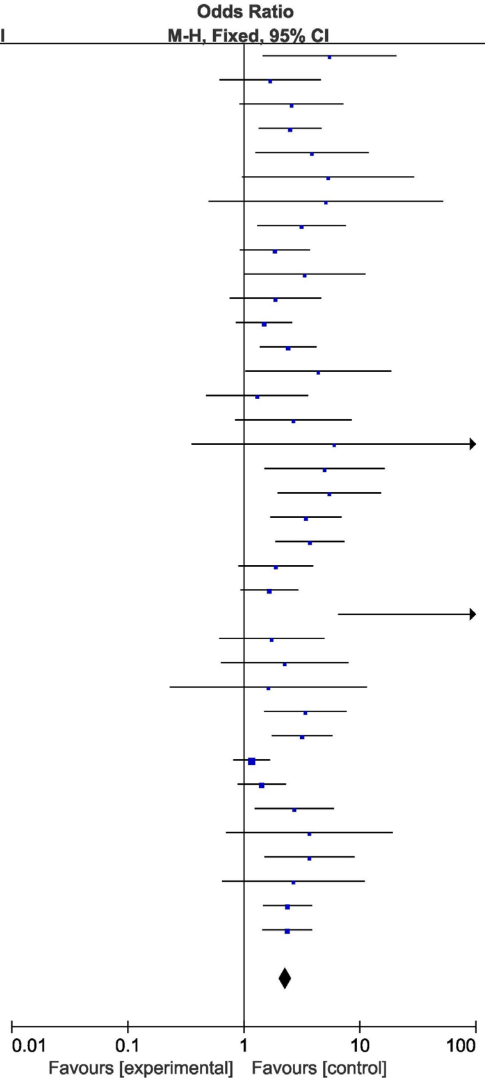

Figure 2 Forest graph demonstrating the results of the change in GTR from intraoperative MRI to postoperative MRI. M-H, Metropolis-Hastings; CI, confidence interval; pts, patients; GTR, gross total resection; MRI, magnetic resonance imaging.

Discussion

Our systematic review and meta-analysis summarized the efficacy of the neuronavigation, especially the magnetic resonance imaging neuronavigation, in PitNET resection. To comprehensively evaluate the operative effect, we selected the most commonly used GTR as an evaluation indicator and included postoperative CSF leak as an evaluation indicator for complications. The results of the meta-analysis of previous research achievements showed that the use of neuronavigation systems increased the rate of GTR. In addition, postoperative CSF leak incidence slightly decreased after the utilization of neuronavigation, revealing that intraoperative neuronavigation can improve the surgical outcomes. It is noteworthy that moderate heterogeneity existed among different articles. We speculated that this heterogeneity might be to some extent due to the differences in factors among different centers, such as demographics, surgical techniques, and imaging systems. To explore the specific sources of heterogeneity, we performed subgroup analyses of statistics to address variables such as field strength and surgical instrument. Our results showed that the benefits of iMRI surgical mirror exerted a moderate influence on GTR, whereas the field

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.2.1 Low-field iMRI						
Ahn 2008	48	51	38	51	0.7%	5.47 [1.45, 20.60]
Berkmann 2011	21	32	17	32	1.8%	1.68 [0.62, 4.61]
Berkmann 2012	51	60	22	32	1.3%	2.58 [0.92, 7.21]
Bohinski 2001	16	29	7	29	1.0%	3.87 [1.26, 11.88]
Fahlbusch 2001	31	44	19	44	1.7%	3.14 [1.30, 7.57]
García 2017	25	30	18	30	0.9%	3.33 [1.00, 11.14]
Hlavica 2013	70	104	48	104	4.8%	2.40 [1.37, 4.22]
Jimenéz 2016	14	18	8	18	0.5%	4.38 [1.03, 18.63]
Martin 1999	4	5	2	5	0.1%	6.00 [0.35, 101.57]
Ramm-Pettersen 2011	12	20	8	20	1.0%	2.25 [0.63, 7.97]
Schwartz 2006	13	15	12	15	0.5%	1.63 [0.23, 11.46]
Strange 2020	120	231	111	231	16.3%	1.17 [0.81, 1.68]
Wu 2009	46	55	32	55	1.6%	3.67 [1.50, 8.97]
Subtotal (95% CI)		**694**		**666**	**32.2%**	**2.01 [1.60, 2.53]**
Total events	471		342			
Heterogeneity: Chi² = 17.87, df = 12 (P = 0.12); I² = 33%						
Test for overall effect: Z = 6.03 (P < 0.00001)						
1.2.2 High-field iMRI						
Berkmann 2014	56	85	37	85	3.9%	2.51 [1.35, 4.66]
Chen 2012	10	13	5	13	0.4%	5.33 [0.97, 29.39]
Dort 2001	14	15	11	15	0.2%	5.09 [0.50, 52.29]
Gohla 2020	18	42	12	42	2.1%	1.88 [0.76, 4.64]
Hlaváč 2019	43	111	33	111	6.2%	1.49 [0.86, 2.61]
Kuge 2013	25	35	23	35	2.0%	1.30 [0.47, 3.59]
Li 2015	24	30	18	30	1.1%	2.67 [0.84, 8.46]
Nimsky 2004	42	48	27	48	1.0%	5.44 [1.95, 15.22]
Nimsky 2006	70	85	49	85	2.6%	3.43 [1.70, 6.93]
Pala 2022 (190 pts)	178	190	152	190	2.9%	3.71 [1.87, 7.35]
Pala 2022 (59 pts)	29	59	20	59	3.1%	1.89 [0.90, 3.96]
Pal'a 2017	58	96	46	96	5.6%	1.66 [0.94, 2.94]
Paterno 2014	49	49	23	49	0.1%	111.64 [6.52, 1911.90]
Sylvester 2015	56	156	44	156	8.6%	1.43 [0.88, 2.30]
Szerlip 2011	33	53	20	53	2.3%	2.72 [1.24, 5.97]
Tanei 2013	11	14	7	14	0.5%	3.67 [0.70, 19.12]
Zhang 2017	88	137	59	137	6.5%	2.37 [1.46, 3.86]
Zhang 2019	85	133	57	133	6.3%	2.36 [1.44, 3.87]
Subtotal (95% CI)		**1351**		**1351**	**55.3%**	**2.36 [2.00, 2.79]**
Total events	889		643			
Heterogeneity: Chi² = 24.37, df = 17 (P = 0.11); I² = 30%						
Test for overall effect: Z = 10.05 (P < 0.00001)						
1.2.3 Ultra-high-filed iMRI						
Fomekong 2014	53	73	43	73	3.6%	1.85 [0.92, 3.70]
Netuka 2011	45	49	34	49	0.8%	4.96 [1.51, 16.31]
Qiu 2012	42	49	38	49	1.7%	1.74 [0.61, 4.94]
Serra 2016	31	51	16	51	1.9%	3.39 [1.50, 7.67]
Staartjes 2019	68	95	42	95	3.7%	3.18 [1.74, 5.80]
Zaidi 2016	16	20	12	20	0.7%	2.67 [0.65, 10.97]
Subtotal (95% CI)		**337**		**337**	**12.4%**	**2.72 [1.94, 3.83]**
Total events	255		185			
Heterogeneity: Chi² = 3.42, df = 5 (P = 0.64); I² = 0%						
Test for overall effect: Z = 5.75 (P < 0.00001)						
Total (95% CI)		**2382**		**2354**	**100.0%**	**2.29 [2.02, 2.60]**
Total events	1615		1170			
Heterogeneity: Chi² = 47.64, df = 36 (P = 0.09); I² = 24%						
Test for overall effect: Z = 12.99 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.35, df = 2 (P = 0.31), I² = 14.9%						

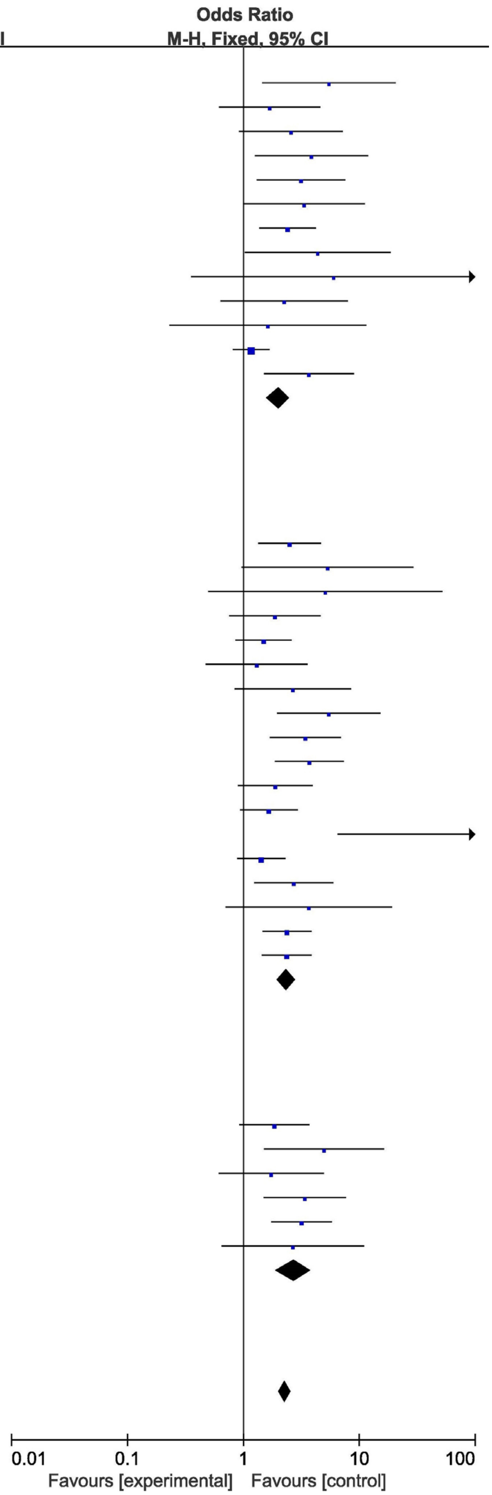

Figure 3 Forest plot of subgroup analysis for GTR with subgrouping by field strength. M-H, Metropolis-Hastings; CI, confidence interval; iMRI, intraoperative magnetic resonance imaging; pts, patients; GTR, gross total resection.

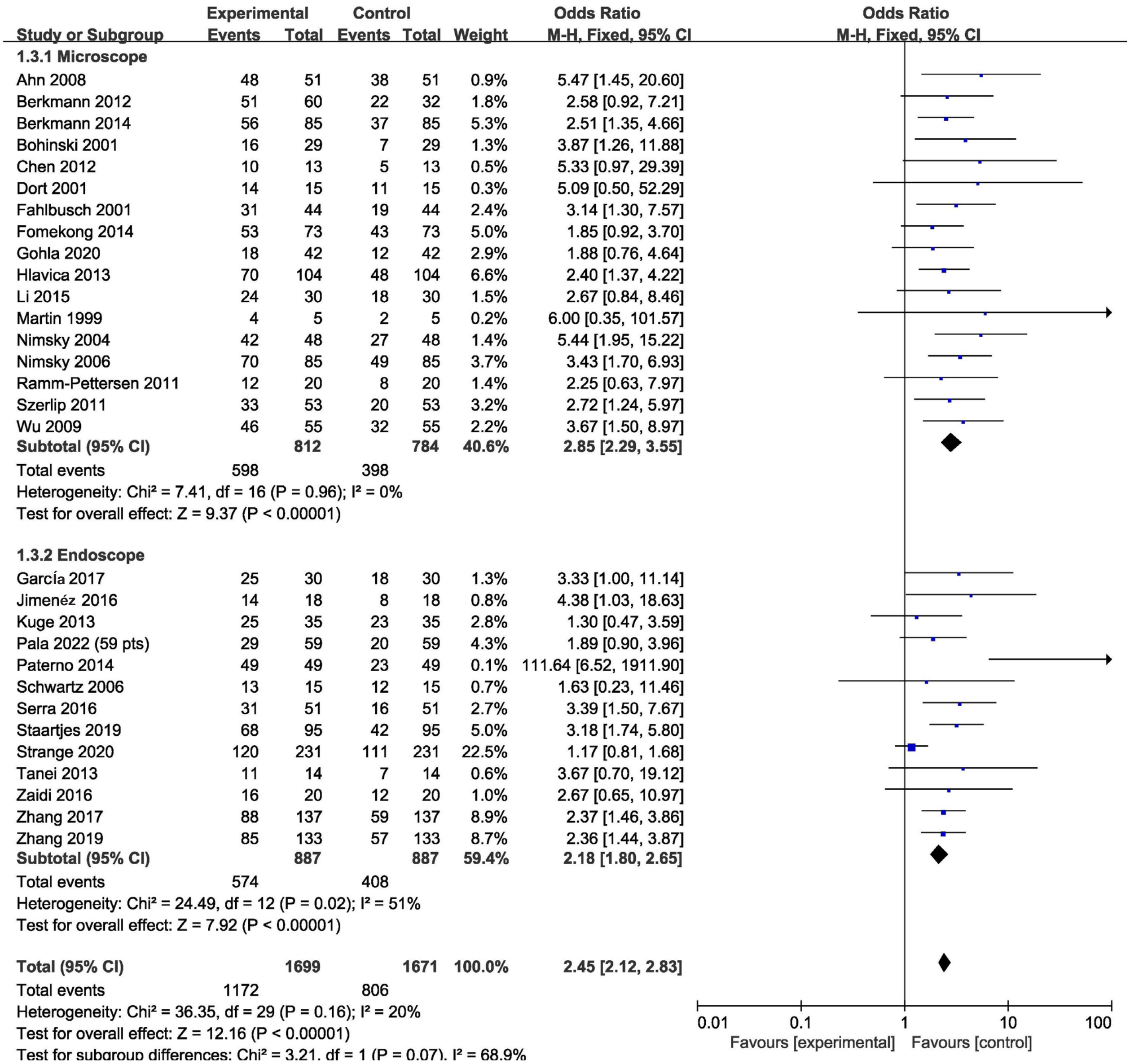

Figure 4 Forest plot of subgroup analysis for GTR with subgrouping by surgical mirror. M-H, Metropolis-Hastings; CI, confidence interval; pts, patients; GTR, gross total resection.

strength had an insignificant impact on GTR. Considering the huge heterogeneity among the included publications concerning the postoperative CSF leak, these results were to be interpreted with caution. Ultimately, we found that the heterogeneity might have been due mainly to one of the publications (Eboli, 2011). Its exclusion significantly reduced the heterogeneity (I^2 from 91% to 43%) (55). Therefore, we assumed that the heterogeneity stemmed from the various quality ratings of the five included articles ranging from six (Eboli, 2011) to eight stars and different imaging equipment, including computed tomography (CT), MRI, and ultrasound. According to the risk of bias analysis in the light of the NOS, all the publications we included were not RCTs, so the "Selection of Controls" item cannot be scored. Among them, nine articles were rated as six and seven points because the confounding factors of age and gender were not adjusted (12,23-30). The statistical results of bias analysis indicated that the funnel plots of GTR-related and postoperative CSF leak-related publications were asymmetric, indicating that potential issues such as publication bias, heterogeneity of studies, and uneven research quality might exist in the studies included. Therefore, caution should be exercised when applying these findings to guide clinical practice.

Previously, few systematic reviews and meta-analyses have evaluated the effects of neuronavigation-assisted PitNET resections (16,58,59). In a systematic review analyzing 85 studies, Soneru *et al.* (16) reported that the GTR rates in 7,124 PitNET patients were determined: in 62 studies, the pooled proportions of GTR were 68.3% and 70.7% for mTSS + iMRI and eTSS + iMRI, respectively. These research results indicated that the final GTR proportions were similar regardless of whether the surgeons used a microscope supplemented with iMRI or an endoscope with or without iMRI. This study focused on comparing the differences between microscopic- and endoscopic-based approaches, whereas our research was focused mainly on comparing the impacts of PitNET surgery with or without iMRI. In 2021, Staartjes *et al.* (58) performed a meta-analysis of 34 studies including 2,130 patients. The researchers evaluated the GTR, extent of resection (EOR), and residual volume (RV). Their results revealed that one fifth of patients undergoing PitNET resection converted from non-GTR to GTR after the use of iMRI. However, no data regarding complications were provided in this study. A meta-analysis conducted by Zhang *et al.* (59) of 33 studies in 2022 and including 2,099 patients analyzed a large number of publications on the evaluation of postoperative CSF leak. Furthermore, these scientists performed subgroup analysis of functioning versus nonfunctioning adenomas, indicating that the use of iMRI significantly increased GTR with comparable benefits for both functioning and nonfunctioning adenomas while decreasing the incidence of postoperative surgical complications. In contrast, more patients were enrolled in our study. According to our evaluation criteria, the included articles in our analysis had a higher level of evidence.

Previous studies have suggested that CT/MRI-assisted neuronavigation could grant surgeons with better anatomical information (60). This combined technique can minimize the risks related to the operative approaches and pituitary pathologic therapies. Our research suggests that neuronavigation can improve the transition from non-GTR to GTR. The preponderance of iMRI to the GTR transition mainly comes from the superior identification of intrasellar remnants, which is conducive to enhancing EOR, reducing RV, and preventing injury of the surrounding tissues, which increases the safety of operations (16,61,62). In the light of some authors' viewpoints, low-field iMRI cannot assess parasellar anatomy, cavernous sinus invasion, and small lesions as reliably as high-field iMRI (56). Nonetheless, the results reported in other publications have shown that GTR has been somewhat improved in low-field iMRI (13,14,32,39,63). Although high-field iMRI can likely offer a superior quality of contrast and image resolution to confirm GTR in patients with subtotal resection, low-field iMRI also has relatively high sensitivity (39,64). A potential explanation for this performance is that low-field MRI provides sufficient and precise visualization to identify remnants that need to be further resected. However, those remnants that are unresectable even after ultra-high-field iMRI is not suitable for resection. Neuronavigation utilizes imaging data to enhance the surgeon's orientation, making it a certainly valuable tool to the inexperienced (65). Significantly, the utilization of neuronavigation could not substitute the clinician's solid basic knowledge of anatomy and surgical experiences (16).

In clinical practice, there are controversies about the effect of neuronavigation-assisted PitNET resection. Most authors consider that neuronavigation facilitate PitNET surgery and reduce the incidence of complications (28,54,55). It was claimed that this technique was beneficial for decreasing complications, such as apoplexy, deep venous thrombosis, meningitis, pulmonary embolism, cough variant asthma, wound infection, and arterial injury (28). On the contrary, a few authors have reported that the use of iMRI in a considerable number of patients for the visualization of adenoma remnants might not be able to facilitate further safe resection and can even lead to increased complications, hypopituitarism, or postoperative CSF leak (5,24,30). One possible explanation for these results is that their studies involved relatively complex cases, including such of recurrent disease, advanced age, large suprasellar adenoma extension, and comorbid medical conditions (8). Visualization of the fine structure of the medial cavernous sinus border using neuronavigation may be crucial for preserving its integrity and function (66). Giant PitNETs, defined as tumors with the largest diameter of ≥4 cm, remain a therapeutic challenge due to high invasiveness, irregular growth, and postoperative complications (67,68). Neuronavigation can help to protect the carotid arteries and other lateral structures during the resection of Giant PitNETs (67). As for the awkwardly shaped adenomas, the location of the residual adenoma may be detected, but intra-operative difficulties exist, which can prevent achieving complete resection (5). The extent of resection was significantly limited by the maximum diameter and Knosp grade of giant pituitary adenomas and the increase in PitNET removal rates may be linked to the likelihood of encountering postoperative CSF leak (67). Alshareef *et al.* (55) and Tosaka *et al.* (56) assumed that neuronavigation has no significant effect on postoperative CSF leak. In conclusion, encountering postoperative CSF leaks may be linked to the likelihood of the increase in PitNET removal rates, especially in giant PitNETs, but being irrelevant to whether neuronavigation is applied. In certain scenarios, a concurrent combined approach offers the potential to enhance the removal of adenoma and reduce the risk of residual adenoma swelling and bleeding (4,69). Additionally, some surgeons advocated for a singular transcranial procedure, which is effective in excising suprasellar adenomas and relieving pressure on the optic nerve (70). However, due to the scarcity of literature on PitNET resection based on neuronavigation utilizing either the transcranial or combined approach, these scenarios were not included in our research. Interestingly, we also investigated a small number of articles about CT-based neuronavigation. CT offers advantages such as the provision of more detailed 3D anatomy than that in the conventional setup and the avoidance of repetitive exposure and accumulation of the staff (60). Although the implementation of this technique places patients at an increased risk of radiation exposure, no acute harm has ever been reported (60).

Our results confirm those of previous research and provides reference for the selection of surgical methods for PitNET resection in future clinical practice. Our analysis has shown that the use of iMRI is beneficial for surgery, regardless of the type of mirror and field strength. Additionally, Pojskić *et al.* (3) considered that the two mirrors were complementary and recommended that both mirrors could be used to optimize the minimally invasive surgical technique. Regarding the selection of field strength, we found little difference among different MRI field strength subgroups. Our study has some limitations. First, only postoperative CSF leak was analyzed as an operative complication in our meta-analysis. Other complications such as hypopituitarism and intraoperative blood loss were not considered, hindering the comprehensive evaluation of the value of intraoperative neuronavigation in the reduction of complications. Actually, we collected data of various indicators of complications, but due to the limited amount of individual literature data, we did not include them in the statistical analysis. The second major limitation is that only case-control trials were included, allowing us to describe the improvements in GTR and postoperative CSF leak, without considering the implicit biases described above. Although RCTs are the "gold standard" in the evaluation of the effectiveness and safety of an intervention, there is no such research in the field of neuronavigation-assisted PitNET resection. Third, because of a lack of granularity in the data collected and assessed in our systematic review, we could not perform a comprehensive analysis of the sources of heterogeneity, such as gender, age, and funding, which might have exerted a certain adverse impact on the statistical results. Fourth it was also difficult to determine whether the effects of iMRI would be influenced by the adenoma function and adenoma size. Finally, there is insufficient evaluation of neuronavigation in long-term prognosis nowadays, and it has certain value in evaluating the effectiveness of surgery. Interestingly, there was a scintilla of evidence indicating that long-term operation outcomes were associated with early postoperative imaging rather than the intraoperative neuronavigation (16). Therefore, relevant research should be performed in the future.

In conclusion, this systematic review and meta-analysis showed that the use of neuronavigation is important as it leads to an increase in the rate of GTR and a decrease of postoperative CSF leak in PitNET resection. Our study provides reference points for the selection of neuronavigation-assisted surgeries for PitNET resection in the clinical settings.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-23-1570/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1570/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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