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Original Investigation

Endocrinological Outcomes of Intraoperative MRI-Guided Endoscopic Transsphenoidal Surgery for Non-Functioning Pituitary Adenoma

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ABSTRACT

AIM: To assess the endocrinological outcomes of high-field (1.5-T) intraoperative magnetic resonance imaging (iMRI)-guided endoscopic transsphenoidal surgery (TSS) for non-functioning pituitary adenomas (NFPAs).

MATERIAL and METHODS: Radiological and endocrinological data were retrospectively collected and analyzed for 133 consecutive patients who underwent iMRI-guided endoscopic TSS for NFPA.

RESULTS: Between the first and final scans, the gross total resection (GTR) rate increased from 42.9% to 63.9%. Preoperatively, 105 patients were deficient in at least 1 pituitary hormone axis (corticotroph axis: 51 patients, gonadotrope axis: 89 patients, thyrotrope axis: 51 patients, growth hormone axis: 19 patients). After surgery, varying rates of improvement were observed in patients with deficiencies in the growth hormone (89.5%), corticotroph (78.4%), gonadotrope (49.4%), and thyrotrope axes (33.3%). Pituitary function deteriorated in 75 patients (corticotroph axis: 23 patients, gonadotrope axis: 30, thyrotrope axis: 56 patients). Univariate logistic regression analyses revealed that, among patients with hypopituitarism of the gonadotrope axis, women were more likely than men to experience recovery (odds ratio [OR]: 0.417, 95% confidence interval [CI]: 0.191–0.913; p=0.029) and not experience deterioration (OR: 2.539, 95% CI: 1.057–6.098; p=0.037). The increased GTR rate, based on the iMRI findings, was not associated with an increased incidence of postoperative hypopituitarism or lower recovery rates in the pituitary axes (both p>0.05).

CONCLUSION: The GTR rate for NFPAs was increased using iMRI, although this increase was not associated with improvement or deterioration of hypopituitarism.

KEYWORDS: Intraoperative MRI, Endoscope, Pituitary, NFPAs, Hypopituitarism, Surgery

INTRODUCTION

Non-functioning pituitary adenomas (NFPAs) are the most common pituitary adenomas (approximately one-third of all cases) (19,22). Because hormonal hypersecretion syndromes are often absent in cases of NFPA, these cases are usually diagnosed when the adjacent anatomical structures are compressed and the patient experiences related events, such as headache, visual disturbances, and/or impaired pituitary function (23). Hormonal deficiencies gradually evolve and eventually become the leading signs and symptoms at presentation in these cases (16). Postoperative adenoma remnants are a risk factor for adenoma recurrence and postoperative hypopituitarism (14), which highlights the importance of regular follow-up examinations and medication. Thus, in patients with NFPA and hypopituitarism, gross total resection (GTR) and restoration of pituitary function are

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recommended. However, surgical treatment of NFPA remains challenging, given the incidence of suprasellar and cavernous sinus extension (38), and the high rate of unsuspected tumor remnants (4,30).

Endoscopic transsphenoidal surgery (TSS) has become a popular procedure in hospitals throughout the world (35,39). Its advantages include better illumination, which provides the neurosurgeon with a better view of the sellar, parasellar, and suprasellar regions. However, morphological assessment of resection radicality remains necessary. Several intraoperative procedures have been devised to achieve better postoperative results. In this context, modern intraoperative magnetic resonance imaging (iMRI) is a remarkable technique that was revolutionized by the pioneering efforts of Black et al. in the 1990s (7). This technique provides real-time feedback during the procedure and continuously updates the archived images for most widely used neuronavigation systems (11), which helps improve the GTR rate (12). Therefore, iMRI-guided procedures may help improve pituitary function recovery by eliminating the need to probe for tumor remnants, which can harm the pituitary gland and affect its function. Although Nimsky et al. reported a series of iMRI-guided operations for hormonally inactive pituitary macro-adenomas in 2006 (27), few subsequent studies have evaluated the effects of iMRI on the GTR rate and the endocrinological changes after TSS for NFPAs. This retrospective study evaluated consecutive patients to determine whether high-field iMRI influenced the success of resection and endocrinological outcomes after endoscopic TSS for NFPAs.

■ MATERIAL and METHODS

Between January 2011 and December 2013, 133 patients with NFPAs were treated by a single neurosurgeon (XHM) at our department. All procedures were performed with the assistance of an endoscope and high-field (1.5-T) iMRI. Patients were excluded if they had a history of previous therapies, such as irradiation or dopamine agonist treatment.

Preoperative and Postoperative Endocrinological Assessments

Preoperative and postoperative blood tests were performed for all patients to detect changes in their anterior pituitary hormone levels. In all cases, an endocrinologist identified any endocrinological changes based on pre-defined assessment criteria. Hypothalamic-pituitary-adrenal axis deficiency was defined as morning (09:00) serum cortisol levels below the normal range (198.7–797.5 nmol/L) or peak cortisol levels of <450nmol/L after an insulin tolerance test. Thyrotrope axis deficiency was defined as levels below the normal range for serum-free T4 (normal range: 10.42–24.32pmol/L) and/or T4 (normal range: 55.34–160.88 nmol/L). For male patients, gonadotrope axis deficiency was defined as serum testosterone levels below the normal range (8.4–28.7 nmol/L) with low or normal levels of luteinizing hormone (normal range for 19–70 years old: 1.5–9.3 IU/L; >70 years old: 3.1–34.6 IU/L) or follicle-stimulating hormone (1.4–18.1 IU/L). For premenopausal female patients, gonadotropin axis deficiency was defined as gonadotropin levels below the normal range (luteinizing hormone: 0.5–76.3 mIU/mL; follicle-stimulating hormone: 1.5–33.4 IU/L) plus estradiol levels that were persistently below the normal range (48.2–1,531.9 pmol/L). For postmenopausal female patients, the normal ranges were defined as 15.9–54.0 mIU/mL for luteinizing hormone and 23–116.3 IU/L for follicle-stimulating hormone. A gonadotropin-releasing hormone test (100 μg intravenously) was performed for unclear cases, with growth hormone deficiency defined as a peak of <5μg/L after a glucose/insulin tolerance test.

Radiological Assessments

All patients underwent preoperative, intraoperative, and postoperative contrast-enhanced MRI. Tumor volumes and diameters were assessed using software (iPlan 3.0; BrainLAB, Feldkirchen, Germany). Patients were classified according to Hardy's system as having a grade I tumor (diameter: <10 mm), a grade II tumor (diameter: 10–20 mm and suprasellar extension within 10 mm of the sphenoidal plane), a grade III tumor (diameter: 20–40 mm and suprasellar extension up to 30 mm), or agrade IV tumor (diameter: >40 mm and extension far beyond the sellar space) (3,15). Because most tumors were large or had invaded the surrounding structures, the cohort was divided into two groups: planned GTR and planned subtotal resection. Successful GTR was defined as no visible tumor during the intraoperative assessment and at the 3-month postoperative MRI evaluation.

iMRI and Surgical Procedures

While the patient remained still, ceiling-mounted rails were used to move the 1.5-T MRI device (Espree TM, Siemens, Germany) approximately 8 m between the operating room and the MRI diagnostic room, which were separated by a screening door with an air lock. After maximum tumor resection, surgical instruments and other ferromagnetic objects were moved outside the 5-gauss line. The iMRI device was then moved into the diagnostic room and the iMRI sequences were obtained.

Figure 1 shows the work flow of iMRI-guided surgery for NFPAs. Standard endoscopic TSS was performed by a single surgeon. All patients underwent preoperative MRI and the results were uploaded into the iPlan software. After the neurosurgeon declared that the resection was complete or that further resection could not safely be performed, the surgery was interrupted and iMRI was performed. When the iMRI confirmed GTR, the surgery was completed with sellar reconstruction. When the results revealed safely accessible residual tumor tissue, further endoscopic inspection was performed after the iMRI scans were integrated into the navigation system. Figure 2A-F shows an example of how the iMRI was used to help treat NFPAs.

Postoperative Assessment and Follow-up

The first postoperative MR scan to detect tumor remnants in the sellar region was routinely performed at 3 months after surgery. The patients were asked to report any changes in their eyesight, field of vision, or any post-nasal drip (which might suggest a CSF leak). Postoperative neuro-ophthalmologic examinations were performed before the patient left the

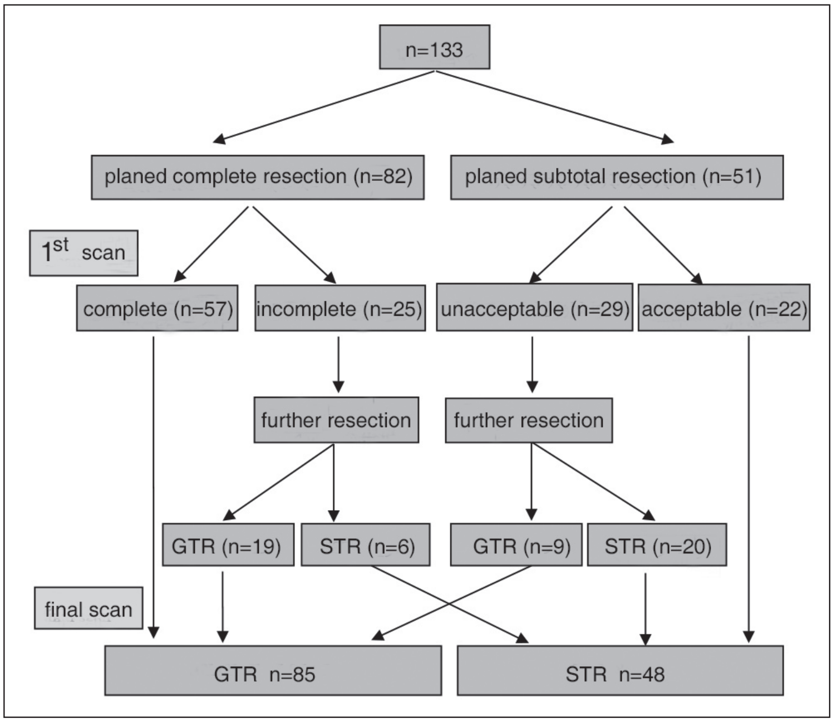

Figure 1: Work flow based on the intraoperative magnetic resonance imaging.

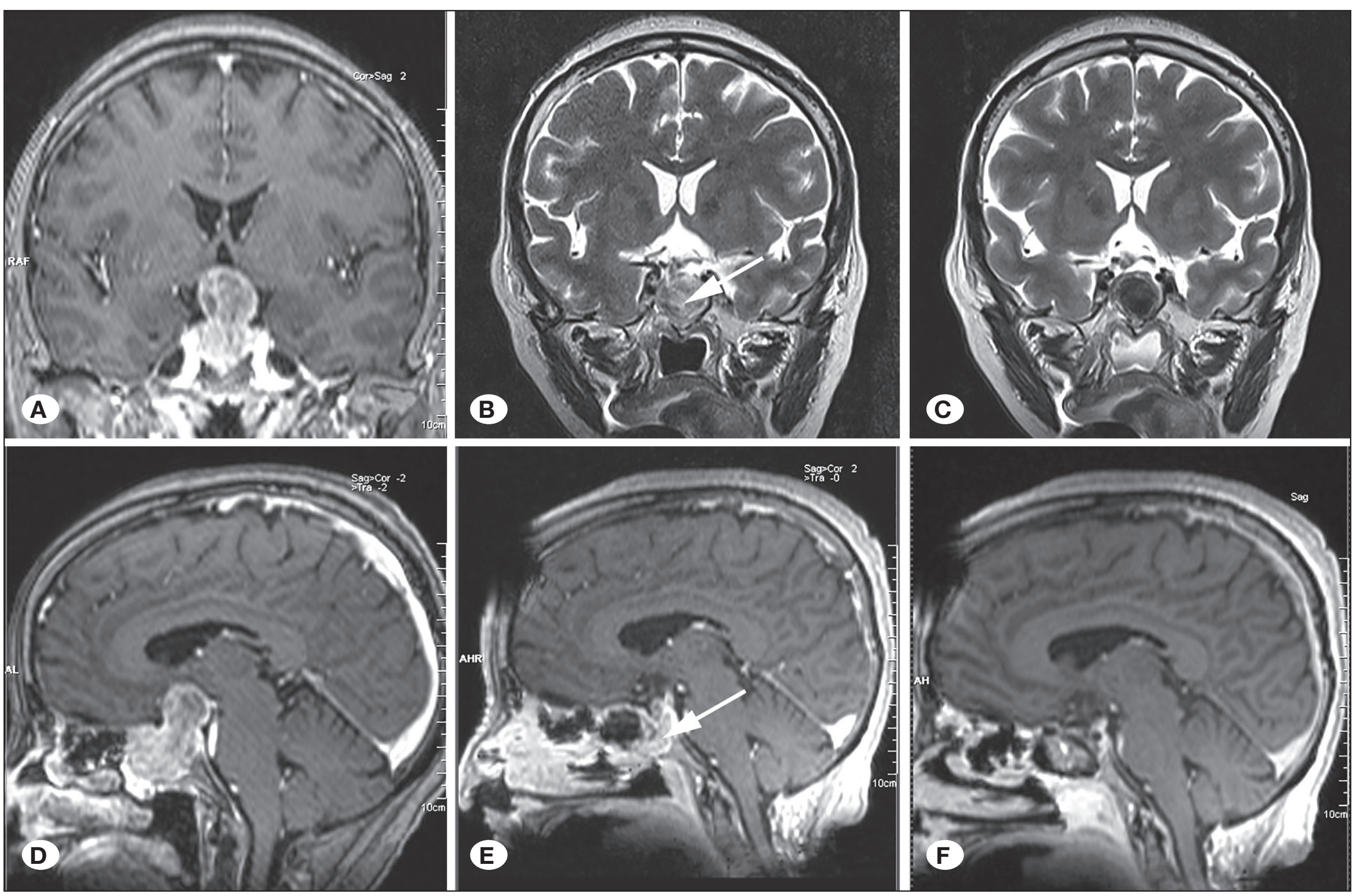

Figure 2: The intraoperative magnetic resonance imaging-guided endoscopic transsphenoidal surgery for a large nonfunctioning pituitary adenoma **(**the preoperative images, **A and D)**. The intraoperative images showed tumor remnants after the primary resection (**B and E,** arrows). The intraoperative images after extended resection showed gross tumor resection **(C and F)**.

hospital and during the follow-up period. Postoperative endocrinological examinations were performed at 1 week after surgery. Clinical, endocrinological, and neuroradiological outcomes were assessed at 3–6 months postoperatively and then annually thereafter.

Statistical Analysis

Microsoft Excel (version 2007) and SPSS software (version 17.0; SPSS Inc., Chicago, IL) were used to perform all statistical analyses. Quantitative variables were reported as mean±standard deviation. Univariate logistic regression analyses were performed to identify variables to predicted changes in pituitary function, and the results were reported as odds ratiosand 95% confidence intervals. A two-tailed p-value of <0.05 was considered statistically significant.

■ RESULTS

The iMRI quality was sufficient to show the extent of resection and all surrounding anatomical structures (i.e., the normal pituitary gland, internal carotid artery, optic apparatus, and pituitary stalk). The total number of scans ranged from 1 to 4 (mean:1.3 ± 0.5), excluding the initial scan that was performed before the resection. The average time for each iMRI scan was 12.0 ± 1.9 min, which included the time required to prepare for intraoperative imaging and update the neuronavigation system. No adverse events or unanticipated side effects were observed. The extents of resection were identical in all cases based on the intraoperative and 3-month postoperative iMRI findings.

Patient Characteristics and Preoperative Assessment

The 133 consecutive patients included 61 men and 72 women (Table I). The mean age was 50 ± 12 years (range:18–80 years). Fifty-six patients reported experiencing dizziness and headaches. Ophthalmological examinations revealed that 100 patients had visual field defects and/or decreased visual acuity. Preoperative hypopituitarism was detected in 105 patients (78.9%). Thirty-eight patients had prior surgical treatment. The average adenoma diameter was 3.4 ± 0.9 cm (range: 1.3–5.8 cm) and giant adenomas were found in 91 patients (68.4%).

Intraoperative Findings and Extent of Resection

Figure 1 provides an overview of the outcomes after the iMRI. Eighty-two patients underwent planned GTR based on their clinicalor radiographic features. Fifty-seven patients (42.9%) had no visible tumor remnants on their first high-field iMRI scans, while 54 patients (40.6%) underwent further resection based on the first iMRI scan. The GTR rate increased from 42.9% (57/133) to 63.9% (85/133) when iMRI was used. Most remnant tumors were found in a suprasellar space attached to the optic apparatus and the third ventricle floor, invaded the cavernous sinus and surrounded the internal carotid artery, or located at the fold of the sellar diaphragm.

Preoperative and Postoperative Pituitary Functions

Preoperative hypopituitarism was detected in 78.9% of the patients (105/133). Fifty-one patients exhibited evidence of biochemical deficiency in the corticotroph axis, 89 patients exhibited deficiency in the gonadotrope axis, 51 patients exhibited deficiency in the thyrotropeaxis, and 19 patients exhibited deficiency in the growth hormoneaxis. Figure 3 shows the preoperative and postoperative prevalence of hypopituitarism in each axis.

The postoperative endocrinological outcomes are summarized in Table II. Varying rates of improvement were observed in patients with deficiencies in the growth hormoneaxis (89.5%), the corticotroph axis (78.4%), the gonadotrope axis (49.4%), and the thyrotrope axis (33.3%). Seventy-five patients exhibited deterioration in their pituitary function (23 patients in the corticotroph axis, 30 patients in the gonadotrope axis, and 56 patients in the thyrotrope axis).

Univariate analyses were performed to examine the predictive values of sex, age, extent of resection, tumor diameter, tumor volume, previous pituitary surgery, and pituitary apoplexy (Table III, IV). The results revealed that, among patients with hypopituitarism of the gonadotrope axis, female patients had higher recovery rates (p=0.029) and lower deterioration rates (p=0.037) than male patients. However, the detection of resection remnants using iMRI was not associated with a higher incidence of postoperative hypopituitarism or with a lower rate of pituitary deficit recovery.

Table I: Patient Characteristics and Preoperative Assessments

Variables	
No. of patients	133
Mean age, years (range)	50 ± 12 (18–80)
Male sex	61 (45.9)
Symptoms and signs	
Visual field and/or visual acuity impairment	100 (75.2)
Dizziness and/or headache	56 (42.1)
Hypopituitarism	105 (78.9)
Others	14 (10.5)
Hardy’s tumor grade	
Grade I	6 (4.5)
Grade II	36 (27.1)
Grade III	60 (45.1)
Grade IV	31 (23.3)
Mean tumor diameter (cm)	3.4 ± 0.9 (1.3–5.8)
Mean tumor volume (cm^3)	15.6 ± 10.6 (2.3–70.5)
Previous pituitary adenoma resection	38 (28.6)
Follow-up, months (range)	62 ± 9.4 (46-80)

Data are shown as number (%) or mean ± standard deviation (range).

Follow-up

All patients were hospitalized for an average of 7.4 ± 5.4 days and had an average follow-uptime of 62 ± 9.4 months. The preoperative headache disappeared in 45 patients (80.4%) within 3 days after surgery and in 50 cases (89.3%) within the next 7 days. Ophthalmological follow-ups revealed improvement in the visual field deficits for 78 of 100 patients (78.0%). One patient experienced worsening of the visual field deficit. Most patients exhibited recovery from their preoperative hypopituitarism. During the procedure, 24 patients had an intraoperatively detected CSF leak, and 15 of these patients were included in the 54 patients who underwent further resection after the first scan. The rate of CSF leak was only 11.4% (9/79) among patients without further resection. One patient experienced from long-term hypocortisolism, 3 patients experienced hypothyroidism, and 3 patients experienced both conditions.

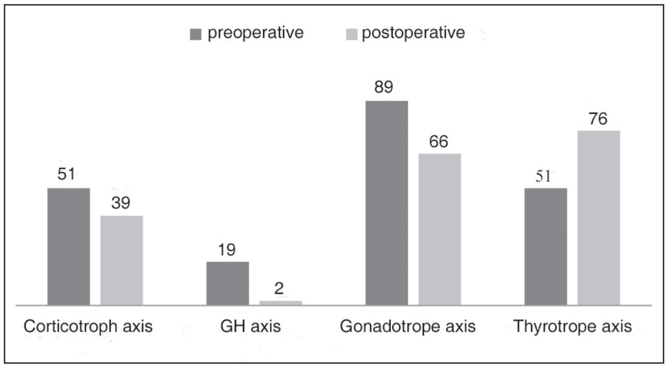

Figure 3: The prevalence of pituitary hormone deficiencies before and after surgery.

DISCUSSION

The results from this retrospective study indicate that high-field iMRI can affect tumor resection and endocrinological outcomes after endoscopic TSS for NFPA. In this context, a greater extension of resection for NFPAs is associated with low recurrence rates and postoperative hypopituitarism

Table II: Postoperative Endocrinological Outcomes

	Preoperative endocrine deficits	Postoperative endocrine status		
		Improved	Unchanged	Worse
Corticotroph axis (n)	51	40	70	23
Growth hormone axis (n)	19	17	116	0
Gonadotrope axis (n)	89	44	59	30
Thyrotrope axis (n)	51	17	60	56

Table III: Univariate Analyses of Preoperative Pituitary Function Deficiency Improvement according to Demographic and Clinical Characteristics

	Corticotroph axis		GH axis		Gonadotrope axis		Thyrotrope axis	
Variables	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Sex	1.317 (0.597–2.907)	0.495	2.214 (0.770–6.367)	0.140	0.417 (0.191–0.913)	0.029	0.451 (0.141–1.439)	0.179
Age	1.026 (0.992–1.061)	0.138	1.017 (0.972–1.063)	0.466	0.998 (0.967–1.030)	0.907	1.042 (0.993–1.094)	0.094
Extent of resection	0.536 (0.221–1.299)	0.167	1.495 (0.498–4.488)	0.473	1.525 (0.676–3.440)	0.310	1.826 (0.603–5.529)	0.287
Tumor diameter	1.128 (0.618–2.060)	0.694	1.257 (0.541–2.920)	0.594	1.152 (0.630–2.109)	0.646	1.116 (0.476–2.620)	0.801
Tumor volume	1.036 (0.983–1.090)	0.185	0.955 (0.876–1.041)	0.299	0.961 (0.909–1.015)	0.156	0.960 (0.888–1.038)	0.310
Previous pituitary adenoma resection	0.422 (0.174–1.026)	0.057	0.675 (0.210–2.166)	0.509	1.457 (0.594–3.572)	0.411	0.494 (0.151–1.615)	0.244
Pituitary apoplexy	1.102 (0.347–3.507)	0.869	3.202 (0.381–26.905)	0.284	0.930 (0.320–2.704)	0.895	2.609 (0.305–22.319)	0.381

***OR:** Odds ratio, **CI:** Confidence interval.*

Table IV: Univariate Analyses of Features Potentially Associated with Postoperative Worse of Pituitary Function

Variables	Corticotroph axis		Gonadotrope axis		Thyrotrope axis	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Sex	1.197 (0.461–3.110)	0.712	2.539 (1.057–6.098)	0.037	1.411 (0.672–2.964)	0.363
Age	0.995 (0.957–1.034)	0.797	0.995 (0.960–1.032)	0.782	0.973 (0.943–1.004)	0.090
Extent of resection	1.277 (0.474–3.443)	0.629	0.503 (0.180–1.400)	0.188	0.542 (0.240–1.226)	0.141
Tumor diameter	1.164 (0.572–2.368)	0.676	1.405 (0.720–2.742)	0.319	1.423 (0.808–2.506)	0.222
Tumor volume	1.007 (0.951–1.066)	0.809	0.993 (0.936–1.053)	0.807	0.995 (0.949–1.043)	0.847
Previous pituitary adenoma resection	0.449 (0.165–1.220)	0.116	0.683 (0.256–1.819)	0.446	0.437 (0.188–1.013)	0.054
Pituitary apoplexy	0.644 (0.182–2.286)	0.496	1.766 (0.453–6.893)	0.413	1.167 (0.413–3.294)	0.771

(5,9,14,32). In most cases, iMRI can be used to estimate the location, size, and shape of the remnant tumors, as well as identify tumor remnants that cannot be visualized intraoperatively using microscopy or endoscopy, which increases the GTR rate. However, few studies have evaluated the results of iMRI-guided endoscopic TSS for NFPA (3,6,27), and the present study provides the first evidence that high-field iMRI increased the GTR rate for NFPA.

A recent meta-analysis of 5,022 patients with NFPA revealed that the mean postoperative remission rate was 44% (range: 3–92%) (30). We observed a similar GTR rate, with GTR considered present for 57 patients based on their first iMRI and a subsequent 21% increase in the GTR rate (from 42.9% to 63.9%) that was attributable to additional resection, which was performed because the first iMRI identified remnants in 54 of the 133 patients. These results are consistent with those from previous studies regarding TSS aided by high-or low-field iMRI (1,2,6,8,20,26). Never the less, further studies are needed to determine the impact of iMRI on long-term prognoses in patients with NFPAs.

Endocrinological remission is another important goal of endoscopic TSS for NFPAs, as patients with hypopituitarism have a reduced quality of life and life expectancy, even with adequate replacement therapy (10). Furthermore, it takes 3–12 months after surgery to restore anterior pituitary function (33), and GTR significantly influences both tumor control and postoperative recovery from hypopituitarism (5,18,36). However, recent studies have revealed conflicting results regarding the recovery of pituitary function after surgical treatment for NFPAs (2,3,27,37). Moreover, few studies of iMRI have analyzed the association between GTR and postoperative endocrinological changes in each pituitary axis. The present study included 105 patients with preoperative hypopituitarism in one or two pituitary axes, although panhypopituitarism was rare in both the preoperative and postoperative settings. In addition, we identified varying rates of deficiency for the corticotropic axis (38.3%, 51/133), the thyrotropeaxis (38.3%, 51/133), the gonadotropic axis (66.9%, 89/133), and the growth hormone axis (14.3%, 19/133). These rates are higher than the previously reported rates (13,28).

After surgery, most patients exhibited some degree of improvement in their preoperative hypopituitarism for the various axes. However, some patients experienced new-onset deficiency or postoperative deterioration in the various axes, which has been described previously. These cases with new-onset deficiency or deterioration most commonly involved the thyrotrope axis, which conflicts with the findings of previous studies (23,34,36). In addition, the number of patients with a deficiency in the thyrotrope axis increased. Hypopituitarism can be related to compression of the portal circulation rather than destruction of the normal pituitary gland (24). Furthermore, previous studies have indicated that recovery of pituitary function is associated with patient age, preoperative hormonal deficits, tumor size, the absence of hypertension, intraoperative CSF leak, and stalk-effect hyperprolactinemia (28,29,36).

To analyze the association between pituitary function and GTR, we studied the endocrinological and radiological results for all patients and performed univariate logistic regression analyses that included sex, age, extent of resection, tumor diameter, tumor volume, previous pituitary surgery, and pituitary apoplexy (Table III, IV). Among patients with hypopituitarism of the gonadotrope axis, female patients had higher recovery rates (p=0.029) and lower deficiency rates (p=0.037) than male patients, which is consistent with the previously reported results (3). However, the iMRI-detected remnants were not associated with a higher incidence of postoperative hypopituitarism or a lower rate of pituitary axis recovery. These results suggest that relieving pressure on the normal pituitary tissues and portal circulation may accelerate the postoperative recovery of hypopituitarism. However, probing for tumor remnants can damage the pituitary gland and lead to deterioration of its function.

Surgeons attempt to protect pituitary function when performing procedures for patients with NFPA. For example, Linsler et al. (21) recently reported that using an endoscope to intraoperatively distinguish the pituitary gland from the tumor is a feasible method for preserving postoperative pituitary function. In addition, previous studies (25,31) have indicated that the pituitary gland can be easier to detect after administration of a contrast agent because the pituitary rapidly and marked lytakes up the contrast agent. Thus, being able to detect the pituitary gland using iMRI could improve the surgeon's ability to protect its function. However, the pituitary gland drifts during surgery, which can make it difficult to detect. Therefore, further studies are needed to improve our ability to intraoperatively identify normal pituitary glands, which remains a challenge.

The main limitations of iMRI are the extended operation time (12,27) and the false-positive rate (17). The operation time can be minimized to 7–10 min per sequence by obtaining coronal images using T2-weighted turbo spin echo sequences (TE 5,400 ms, TR 98 ms) and contrast-enhanced images using T1-weighted spin echo sequences (TE 1,650 ms, TR 3.02 ms), which can be used as intraoperative comparative controls during the surgery for pituitary adenomas. However, false-positive findings may lead to more aggressive probing for remnants, which can result inan increased rate of complications (i.e., CSF leak, new endocrinological deficits, and hemorrhage). The present study revealed a high rate of CSF leak (24/133) and 27.8% (15/54) of the patients who underwent additional resection after the iMRI scan had a CSF leak. However, these events have not limited the increasing tendency to use iMRI.

■ CONCLUSION

High-field iMRI was useful for increasing the GTR rate after endoscopic TSS for NFPA. However, the increased GTR rate was not associated with improvement or deterioration of hypopituitarism. Gonadotrope axis deficits were more likely to recover or improve in female patients.

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