Thesis

Prediction of recovery of postoperative pituitary function by position and volume of the gland on preoperative MRI

submitted by

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Graz, 17.03.2026

Statement of Originality

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Zusammenfassung

Ziel dieser Diplomarbeit war es zu untersuchen, ob präoperative MRT-Parameter der Hypophyse, insbesondere das Volumen der normalen Residualhypophyse sowie deren Lage relativ zum Adenom, mit der postoperativen Veränderung der Hypophysenfunktion assoziiert sind. Im Mittelpunkt stand die Frage, ob sich anhand morphologischer Merkmale im präoperativen MRT eine postoperative endokrine Erholung oder Verschlechterung vorhersagen lässt.

In diese retrospektive monozentrische Studie wurden 255 Patientinnen und Patienten mit Hypophysenmakroadenomen eingeschlossen, die zwischen 2013 und 2022 an der Medizinischen Universität Graz operiert wurden. Erfasst wurden präoperative und postoperative endokrinologische Daten sowie präoperative MRT-Untersuchungen. Die postoperative Hypophysenfunktion wurde anhand der Veränderung der Anzahl insuffizienter Hypophysenachsen nach 12 Monaten als „better“, „unchanged“ oder „worse“ klassifiziert. Im MRT wurden das Tumorvolumen, die maximale Tumorgröße, das Volumen der normalen Residualhypophyse sowie deren Lage nach der modifizierten Di-Maio-Klassifikation als superior oder lateral bestimmt.

Die Auswertung zeigte, dass ein größeres präoperatives Residualhypophysenvolumen mit einer höheren Wahrscheinlichkeit für eine postoperative Verbesserung der Hypophysenfunktion assoziiert war. Patientinnen und Patienten mit verbessertem postoperativem Outcome wiesen im Mittel ein höheres Residualvolumen auf als jene ohne Verbesserung. Auch in der Analyse nach Volumen-Tertilen nahm der Anteil an Verbesserungen mit steigendem Residualvolumen zu. In den logistischen Regressionsmodellen blieb dieser Zusammenhang auch nach Adjustierung für Alter, Geschlecht, Tumorgröße, präoperative Achseninsuffizienz, Lage der Residualhypophyse und postoperative Radiotherapie bestehen.

Hingegen zeigte sich kein stabiler unabhängiger Zusammenhang zwischen Residualvolumen und postoperativer Verschlechterung der Hypophysenfunktion.

Für die Lage der Residualhypophyse relativ zum Tumor ergab sich kein signifikanter Zusammenhang mit dem postoperativen endokrinen Outcome. Weder in der deskriptiven Analyse noch in den Regressionsmodellen zeigte die dichotome Einteilung in superior versus lateral eine unabhängige prognostische Aussagekraft.

Zusammenfassend sprechen die Ergebnisse dieser Studie dafür, dass das präoperative Volumen der normalen Residualhypophyse als bildmorphologischer Marker für das Potenzial einer postoperativen funktionellen Erholung relevant sein kann. Die topographische Lage der Drüse allein scheint hingegen keinen eigenständigen prädiktiven Wert zu besitzen. Die Ergebnisse unterstützen damit eine integrierte präoperative Risikostratifizierung unter Berücksichtigung von Residualvolumen, Tumorausdehnung und präoperativem endokrinem Status.

Abstract

The aim of this diploma thesis was to investigate whether preoperative MRI characteristics of the pituitary gland, particularly residual gland volume and gland position relative to the adenoma, are associated with postoperative changes in pituitary function. The main objective was to assess whether morphological imaging parameters can help predict endocrine recovery or deterioration after surgery.

This retrospective single-center study included 255 patients with pituitary macroadenomas who underwent surgery at the Medical University of Graz between 2013 and 2022. Preoperative and postoperative endocrine data as well as preoperative MRI scans were analyzed. Postoperative pituitary outcome was defined according to the change in the number of insufficient pituitary axes at 12 months and categorized as better, unchanged, or worse. MRI assessment included tumor volume, maximum tumor diameter, preoperative residual gland volume, and residual gland position classified as superior or lateral according to a the modified Di Maio approach.

The analysis demonstrated that a larger preoperative residual pituitary gland volume was associated with a higher likelihood of postoperative improvement in pituitary function. Patients with improved endocrine outcome had, on average, a larger residual gland volume than those without improvement. Likewise, the proportion of patients showing improvement increased across residual gland volume tertiles. In logistic regression analyses, this association remained present after adjustment for age, sex, tumor size, preoperative axis insufficiency, gland position, and postoperative radiotherapy. In contrast, no stable independent association was found between residual gland volume and postoperative worsening of pituitary function.

Residual gland position relative to the adenoma was not significantly associated with postoperative endocrine outcome. Neither descriptive analyses nor

regression models showed an independent prognostic value for the simplified distinction between superior and lateral gland position.

In conclusion, this study suggests that preoperative residual pituitary gland volume may serve as a relevant imaging marker for postoperative endocrine recovery, whereas gland position alone does not appear to provide independent prognostic information. These findings support an integrated preoperative risk assessment that combines residual gland volume, tumor burden, and preoperative endocrine status.

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List of abbreviations

ACTH	adrenocorticotropic hormone
ADH	antidiuretic hormone
CI	confidence interval
CISS	constructive interference in steady state
CRH	corticotropin-releasing hormone
FSH	follicle-stimulating hormone
GH	growth hormone
GHD	growth hormone deficiency
GHRH	growth hormone–releasing hormone
GnRH	gonadotropin-releasing hormone
IGF-1	insulin-like growth factor 1
III	oculomotor nerve
IV	trochlear nerve
LH	luteinizing hormone
MPRAGE	magnetization-prepared rapid acquisition gradient echo
MR	magnetic resonance
MRI	magnetic resonance imaging
NFPA	non-functional pituitary adenomas
NRPG	normal residual pituitary gland
OR	odds ratio
OT	oxytocin
PIT1	pituitary-specific transcription factor 1
PitNET	pituitary neuroendocrine tumor(s)
PRL	prolactin
SD	standard deviation
SF1	steroidogenic factor 1
TPIT	T-box transcription factor
TRH	thyrotropin-releasing hormone
TSH	thyroid-stimulating hormone
V1	ophthalmic nerve
V2	maxillary nerve
VIBE	volumetric interpolated breath-hold examination
VI	abducens nerve
WHO	World Health Organization

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1. Introduction

1.1. The pituitary gland

The pituitary gland (glandula pituitaria) is a central endocrine gland and plays a key role in maintaining homeostasis via several hormonal regulatory circuits (hypothalamic–pituitary–thyroid, adrenal, gonadal and somatotropic axes). It is therefore often referred to as the “master gland” (1-3).

It is located in the sella turcica, a saddle-shaped depression in the sphenoid bone (os sphenoidale) and is connected to the hypothalamus via the pituitary stalk (infundibulum) (1,4). The diaphragma sellae, a duplication of the dura mater with a central opening for the stalk, spans the glandular body (5). Histologically and functionally, the pituitary gland is divided into the adenohypophysis (anterior lobe) and the neurohypophysis (posterior lobe). The adenohypophysis arises from ectodermal tissue of Rathke's pouch and is a classic endocrine gland, while the neurohypophysis, as an extension of the diencephalon, represents neurosecretory tissue (1–3).

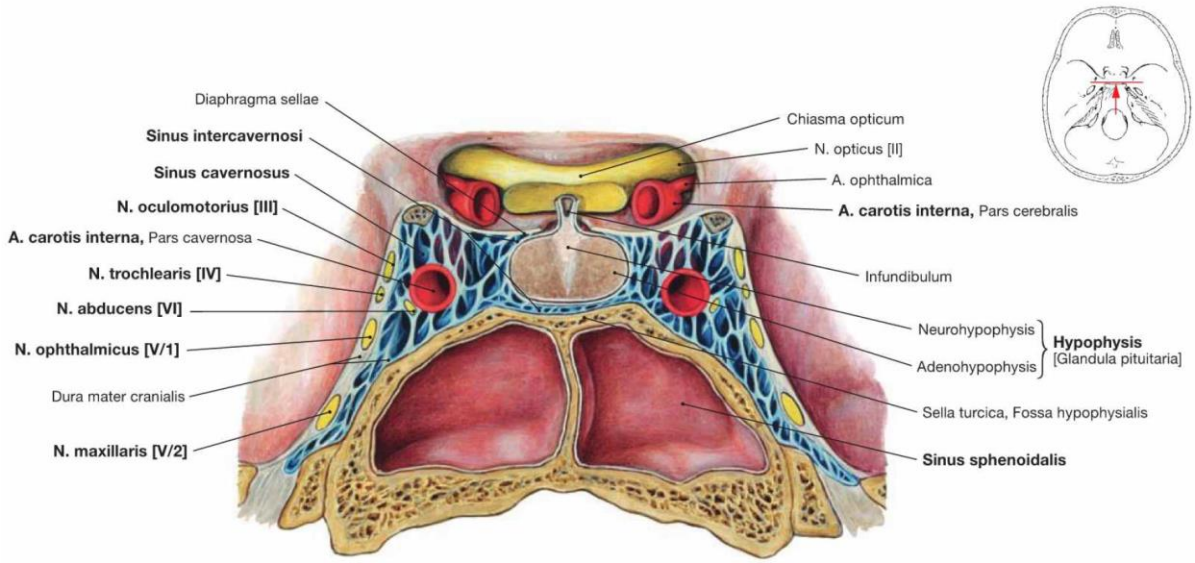

Figure 1. Pituitary gland and cavernous sinus, frontal section, posterior view. Reproduced from (4), p. 223.

The pituitary gland is exceptionally well vascularized. The adenohypophysis is mainly supplied by the paired superior hypophyseal arteries, which originate from the internal carotid artery and the anterior cerebral artery or the posterior communicating artery (4–6). These vessels initially form a primary capillary bed in the median eminence and proximal pituitary stalk, into which the hypothalamic releasing and inhibiting hormones (including TRH, CRH, GHRH, GnRH, somatostatin and dopamine) are secreted (1,2,6).

From there, long portal veins extend to the adenohypophysis and form a secondary capillary network, called the hypothalamic-pituitary portal system, through which the hypothalamic control hormones act in high concentrations on the endocrine anterior lobe cells (1–3,6). It is estimated that 60–70% of the blood supply to the adenohypophysis is mediated via these portal vessels (6).

The neurohypophysis, the distal pituitary stalk and parts of the pars tuberalis are mainly supplied by the inferior pituitary arteries, which emerge from the intracavernous segment of the internal carotid artery (4,5). Venous drainage occurs via pituitary veins into the cavernous sinuses and from there into the dural venous sinuses (5). This special vascular architecture explains the close functional coupling between the hypothalamus and pituitary gland, as well as the vulnerability of the organ in the event of hemodynamic disturbances (e.g., shock, postpartum hemorrhage, pituitary apoplexy) (1,6,7).

The adenohypophysis consists of several specific endocrine cell populations:

- Somatotropic cells: Production of growth hormone (GH) → Regulation of height growth, protein and fat metabolism and stimulation of IGF-1 synthesis in the liver (2,3).
- Lactotrope cells: Production of prolactin (PRL) → lactation, mammary gland development, and modulating effects on reproduction and metabolism (2,3).
- Thyrotropic cells: Production of thyroid-stimulating hormone (TSH) → Regulation of thyroid hormone secretion and basal metabolic rate (2,6).

- Corticotropic cells: Production of adrenocorticotropic hormone (ACTH) → Stimulation of glucocorticoid production in the adrenal cortex, central role in the stress response (2,3).
- Gonadotropic cells: Production of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) → Control of gametogenesis and sex hormone production in the ovaries and testes, respectively (2,3).

The neurohypophysis stores and secretes two peptide hormones synthesized in the hypothalamus (supraoptic and paraventricular nuclei):

- Arginine vasopressin (ADH) → Regulation of water balance and plasma osmolality via Vasopressin 2 receptors in the kidneys and influence on vascular tone (Vasopressin 1 receptors) (1–3).
- Oxytocin (OT) → uterine contraction, labor induction, milk ejection, and effects on social and emotional behavior (1–3).

The pituitary gland thus represents a central point of integration between the nervous system (hypothalamus) and peripheral endocrine target organs (1–3).

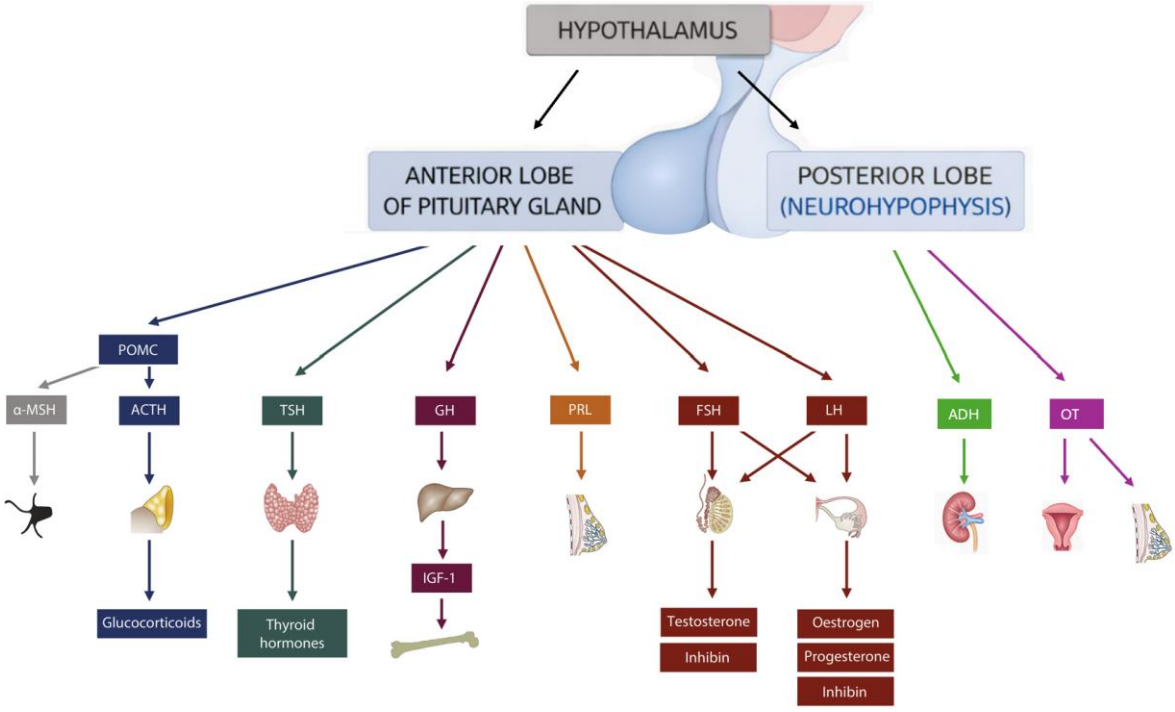

Figure 2. Schematic overview of anterior and posterior pituitary hormones and their target organs. Adapted from (6).

Anatomy of the Pituitary Gland

The pituitary gland is embedded in a narrow, anatomically complex compartment. The sella turcica is bounded ventrally and superiorly by the tuberculum sellae, dorsally by the dorsum sellae and the posterior clinoid processes, and laterally by the medial wall of the cavernous sinus (4,5).

Cranially, the optic chiasm is located in the suprasellar cistern. Its position can be prefixed, normal, or postfixed and influences the tumor size at which visual symptoms occur (4,5,7). Posteriorly, the hypothalamus and the floor of the third ventricle are adjacent. Laterally, the pituitary gland is bordered by the cavernous sinuses with the intracavernous internal carotid artery and cranial nerves III, IV, V1, V2, and VI (4,5). Caudally, the sella borders the sphenoid sinus (clivus, upper part), whose pneumatization and bone thickness are decisive factors for transsphenoidal access (4,5).

The microanatomical studies by Renn and Rhoton demonstrated numerous variations in sella geometry, carotid artery course, and bone thickness in the area of the sella, sphenoid sinus, and cavernous sinus. This results in a significant individual risk profile for surgical procedures (4,5). Even moderate increases in volume in this confined space can stretch the pituitary stalk, displace residual pituitary tissue, and compress optical and oculomotor structures, causing both endocrine and neurological deficits (4,5,7).

1.2. Pituitary Adenoma/Pituitary Neuroendocrine Tumor

Pituitary adenomas, referred to as pituitary neuroendocrine tumors (PitNETs) in the current WHO nomenclature (2022), are benign, mostly monoclonal neoplasms of the adenohypophysis (8, 12-14). They account for approximately 10–15% of all primary intracranial tumors (9,11,16). Epidemiological studies report an incidence of approximately 3.9–7.4 cases per 100,000 person-years and a prevalence of clinically manifest adenomas of 76–116 cases per 100,000 inhabitants (≈ 1:1000) (9,16). Autopsy and imaging-based series show that small, clinically silent adenomas are significantly more common: in the meta-analysis by Ezzat et al., the overall prevalence of pituitary adenomas was approximately 16.7% (14.4% in autopsy studies, 22.5% in imaging-based studies) (16).

Clinically, pituitary adenomas are traditionally classified according to size and hormonal activity (2,8,14,15):

Size:

- Microadenomas: diameter < 10 mm
- Macroadenomas: diameter ≥ 10 mm
- Giant Adenomas: diameter > 40 mm

Hormonal Activity:

- Functional (hormone-secreting)
- Non-functional adenomas (non-hormone-secreting)

Functional adenomas lead to hypersecretion syndromes: prolactinomas (hyperprolactinemia, hypogonadism), GH-producing tumors (acromegaly/gigantism), ACTH-producing adenomas (Cushing's syndrome), and more rarely TSH-producing or plurihormonal tumors (14). Non-functional adenomas (NFPA) do not show any clinically relevant hypersecretion syndrome and often become symptomatic due to mass effect (headaches, visual acuity and visual field defects) or secondary hypopituitarism (14,15).

The 4th edition of the WHO classification (2017) and the updated 5th edition (2022) have significantly refined the classification of pituitary tumors: Adenohypophyseal tumors are classified according to hormonal cell line (somatotropic, lactotrophic, corticotropic, thyrotrophic, gonadotropic, plurihormonal) and according to the expression of specific transcription factors (PIT1, TPIT, SF1) (12,13). The term pituitary neuroendocrine tumor (PitNET) is intended to emphasize the neuroendocrine nature and spectrum of indolent to potentially aggressive tumors (12-14). Aggressiveness has been assessed on the basis of invasiveness, proliferation index (e.g. Ki-67), mitotic rate, and clinical behavior (tendency to recur, resistance to therapy), among other factors (12-14). However, in the updated WHO classification, no clear criteria for aggressiveness have been defined. Pituitary carcinomas, which are defined by their metastatic status are extremely rare (< 0.2% of all tumors) (12,13).

Adenomas can grow beyond the boundaries of the sella turcica: suprasellar (compression of the optic chiasm), parasellar (invasion of the cavernous sinus), retrosellar (towards the clivus/brain stem), or infrasellar (erosion of the sella floor, invasion of the sphenoid sinus) (4,5,15).
Invasion into the cavernous sinus is graded using the Knosp classification and is relevant both surgically (complete resection is more difficult) and prognostically (higher recurrence rate) (15,17). Suprasellar expanding tumors can elevate and flatten the optic chiasm; radiological parameters such as the degree of chiasm compression, contact with optical structures, and displacement of the pituitary stalk have been established as important predictors of visual and possibly endocrine risks (15,21).

The clinical presentation can be roughly divided into three main groups (2,14,15):

1. Hormonal hypersecretion

   Acromegaly, Cushing's syndrome, hyperprolactinemia, etc. can lead to metabolic, cardiovascular, and skeletal complications over years (14).

2. Hypopituitarism

   Displacement or compression of the residual pituitary tissue leads to isolated or multiple axis deficits, including panhypopituitarism. Clinically, symptoms range from nonspecific fatigue, loss of libido, and weight gain to life-threatening secondary adrenal insufficiency (2,3,14,15).

3. Mass effect

   Larger macroadenomas can cause headaches, visual impairment, bitemporal hemianopsia, and oculomotor paresis in cases of parasellar extension (4,5,14).

Pituitary apoplexy is a special emergency in which acute haemorrhage or ischemia occurs in an adenoma, typically with sudden onset of headache, loss of vision, neurological deficits as well as secondary adrenal insufficiency (7).

With the widespread availability of MRI diagnostics, increasingly more incidental pituitary lesions ("pituitary incidentalomas") are being described. In such cases, systematic investigation for hormone excess, hypopituitarism, and visual deficits is recommended, as well as risk-adapted imaging follow-up (17,18).

Transsphenoidal resection is the standard treatment for most symptomatic pituitary adenomas (except for prolactin secreting tumors) — especially in cases of visual impairment, space-occupying symptoms, or hormonal overproduction that cannot be adequately controlled with medication (14,15,17,18).

Risk factors for new or persistent postoperative hypopituitarism discussed in the literature include tumor size, preoperative functional deficits, invasiveness, intraoperative cerebrospinal fluid fistula, reoperations, and adjuvant radiotherapy (17-20). However, individual prediction remains difficult.

1.3. Pituitary dysfunction

Hypopituitarism is defined as a deficiency of one or more pituitary hormones resulting from structural or functional damage to the pituitary gland or hypothalamus. It can affect any axis (GH, gonadotropins, TSH, ACTH, prolactin, ADH) and is often multi-axial. In adults in industrialized countries, pituitary adenomas are among the most common acquired causes (22,23).

Typically, patients with non-functional macroadenomas initially show deficits in the gonadotropic and somatotropic axes, followed by TSH and ACTH insufficiency. In the large Swedish registry study of 838 NFPA patients, preoperative LH/FSH, TSH, GH, and ACTH deficits were present in 51%, 39%, 28%, and 31% of cases, respectively (24). In the monocentric study by Mavromati et al., 67% of 137 patients had at least one axis insufficiency (hypogonadism 62%, central hypothyroidism 41%, secondary adrenal insufficiency 31%, GHD 30%) (25). Clinically, this results in secondary hypogonadism (loss of libido, menstrual disorders, infertility), central hypothyroidism (fatigue, weight gain, bradycardia), secondary adrenal insufficiency (orthostatic symptoms, hyponatremia, risk of

adrenal crisis), and GH deficiency (reduced quality of life, altered body composition, dyslipidemia) (22,23). The posterior portions (ADH secretion) are less frequently affected in NFPA; manifest diabetes insipidus occurs more frequently postoperatively or in cases of very large/invasive tumors or apoplexy (23).

Untreated or inadequately treated hypopituitarism is associated with a significantly reduced quality of life and increased mortality (22–24,26). Those affected report pronounced fatigue, lack of motivation, cognitive impairments, sleep disorders, and depressive symptoms, which are clearly reflected in validated quality of life instruments (e.g. Adult Hypopituitarism Questionnaire, AHQ) (26,27). Meta-analyses and registry data show that adult patients with hypopituitarism have a 1.2 to 4.5 times higher risk of premature mortality, primarily due to cardiovascular events, cerebrovascular disease, and infections (23,24,28).

ACTH insufficiency and inadequate glucocorticoid replacement are particularly unfavourable: in cohort studies, ACTH deficiency in NFPA was associated with an increased risk of mortality and deaths due to adrenal crises (24,29). At the same time, metabolic comorbidities (obesity, hypertension, dyslipidemia, impaired glucose tolerance) lead to additional morbidity and risk of hospitalization (22,30).

In patients with pituitary adenomas, preexisting hormonal deficiencies not only impair symptoms and activities of daily living but also significantly affect long-term prognosis and perioperative risk. Accordingly, meticulous preoperative and postoperative endocrine evaluation is essential (22).

Transsphenoidal resection of a pituitary adenoma can either improve pituitary function (decompression of residual tissue) or worsen it (iatrogenic damage to the gland or stalk). Earlier series in the 1980s and 1990s already showed that hypopituitarism can at least partially regress after resection of large NFPA: Arafah reported reversible hypopituitarism after removal of large non-functional adenomas, and Webb et al. found in a cohort of 234 patients that 48% of preoperatively insufficient patients showed restoration of 1–3 hormones after surgery, with simultaneous rates of new deficits between approximately 10–17%

depending on the axis (31,32). Nomikos et al. examined 721 patients with NFPA and were able to show that transsphenoidal surgery in experienced centers is relevant on pituitary function: preoperative deficits improved in a higher proportion of patients, while new insufficiencies occurred less frequently and were seen significantly more often after transcranial than after transsphenoidal surgery (12).

Fatemi et al. reported in a series of 272 adenoma patients that at least one axis recovered in about half of the patients after transsphenoidal removal, while new deficits mainly affected the HPA axis (34). In the prospective, multicenter study by Little et al. on completely endoscopic surgery, pituitary function improved in a minority of patients; the highest recovery rate was seen in the ACTH axis, while permanent diabetes insipidus rates remained low (35). Mavromati et al. found that among 137 patients with NF macroadenomas, 46% of patients with at least one preoperative axis insufficiency showed postoperative recovery of ≥1 axis, while 10% developed new deficits. Axis-specific recovery rates were 35.7% (LH/FSH), 30.4% (TSH), 15.4% (ACTH), and 45.5% (GH); new deficits occurred in 8.3%, 1.6%, 9.2%, and 5.1%, respectively. Overall, 24.6% of patients improved globally, while only 7% experienced a deterioration in overall function (25).

The Swedish registry study by Al-Shamkhi et al. showed a more complex picture in 838 NFPA patients: one year postoperatively, the proportion of ACTH insufficiency increased from 29% to 38%. At the same time, there were both recoveries and new deficits in all axes, and further dynamic changes occurred between year 1 and year 5. The authors therefore emphasize the need for long-term, repeated endocrine re-evaluation (24).

In addition, recent studies indicate that tumor-related factors influence the postoperative endocrine outcome: De Alcubierre et al. showed that fibrotic ("hard") adenomas with larger volumes and higher Ki-67 more frequently lead to new postoperative hormone deficits (odds ratio ≈ 8.6) and are more difficult to resect (36).

1.4. Diagnostics and the role of MRI

The diagnosis of pituitary adenomas is based on a combination of clinical examination, systematic endocrinological laboratory diagnostics, and high-resolution imaging (2,18,21). Magnetic resonance imaging (MRI) with thin-slice T1-weighted sequences before and after contrast agent administration is considered the gold standard for morphological assessment of the pituitary gland and the sellar region (4,18,24).

MRI can be used to assess tumor size (height, width, depth), volume, direction of spread (suprasellar, parasellar, retrosellar, infrasellar), invasion into the cavernous sinus, and the course of the pituitary stalk (4,18,24). In addition, the location and thickness of the residual pituitary tissue (e.g. dorsal or lateral cap) can be identified (24,29).

In addition to conventional morphological parameters, recent studies have also examined signal intensities, contrast agent uptake, texture features, and radiomic parameters in order to obtain additional prognostic information (18,29,30).

1.5. Position of the gland relative to the Adenoma

In analogy to the classification proposed by Di Maio et al., the position of the normal residual pituitary gland (NRPG) was defined relative to the macroadenoma on contrast-enhanced coronal T1-weighted MRI. In their original work, the displacement of the NRPG (and the neurohypophyseal bright spot) was categorized as superior, superolateral or lateral (37).

Superior displacement describes a predominantly symmetric upward draping of the gland over the tumour dome, usually located above the diaphragma sellae in the suprasellar space. Lateral displacement refers to a crescent or rim of pituitary tissue situated along one lateral border of the macroadenoma, often extending from the intrasellar compartment into the suprasellar region (37).

For the purposes of the present study, this concept was adopted and simplified: we differentiated between superior and lateral displacement patterns of the pituitary gland. Cases with a superolateral configuration according to Di Maio et al. were allocated to the superior group if the main component of the NRPG was located above the tumour, and to the lateral group if the predominant residual tissue was along the lateral tumour margin (37).

2. Materials and Methods

2.1. Study Population

This retrospective, monocentric study included 273 patients who underwent surgery for pituitary adenomas at the Medical University of Graz between 2013 and 2022. Their age at time of surgery ranged from 18 to 80 years. Re-operations were excluded from the study cohort.

Data was collected using the hospital information system of the Styrian Hospital Association (KAGes, openMEDOCS). All personal data was pseudonymized to comply with applicable data protection regulations. The electronic medical records and surgical reports from the Department of Pathology, the Clinical Department of Endocrinology and Diabetology, and the Department of Neurosurgery at the Medical University of Graz were evaluated.

Inclusion criteria for further analysis was the availability of the pre- and postoperative clinical and endocrinological data, as well as a preoperative pituitary MRI (isovoxel), which was used to assess the location and volume of the pituitary gland in relation to the tumor.

This study was approved by the ethics committee of the Medical University of Graz (EK number: 36-064 ex 23/24).

2.2. Data collection

2.2.1. Medocs

The clinical and perioperative data were retrospectively collected from the hospital information system of the Styrian Hospital Association (KAGes, openMEDOCS). The evaluation was based exclusively on pseudonymized data sets. Electronic medical records, including doctor's letters, findings, and progress documentation, as well as surgical reports from the Clinical Department of Neurosurgery, endocrinological doctor's letters from the Clinical Department of Endocrinology and Diabetology, and histopathological findings from the Department of Pathology at the Medical University of Graz were considered. Data extraction was performed using a predefined collection scheme.

The last documented endocrinological status prior to surgery was defined as the preoperative reference point. The postoperative reference point was the endocrinological follow-up after 12 months, with a time window of 9–15 months being accepted. The functional status of the pituitary gland was assessed for the corticotropic, thyrotropic, gonadotropic, and somatotropic axes. Axis insufficiency was present if either corresponding replacement therapy was documented in the endocrinological records or axis insufficiency was explicitly diagnosed in the endocrinological report, even if no substitution therapy had (yet) been documented. To prevent misclassification, potential pre-existing diagnoses or comorbidities that could necessitate hormone substitution independent of pituitary pathology (e.g., primary thyroid disease treated with levothyroxine) were reviewed. In such cases, an endocrine axis was classified as pituitary-related insufficiency only if the endocrinological assessment explicitly documented a central (pituitary) etiology. A composite variable was constructed by summing the number of insufficient endocrine axes per patient; patients were then categorized preoperatively into groups with 0, 1, 2, or >2 insufficient axes. The clinical outcome was defined as a change between preoperatively and the 12-month follow-up and was classified as “better” (reduction), “unchanged”, and “worse” (increase).

Data collected/derived from openMEDOCS:

- Age (at the time of surgery) and gender
- Clinical diagnosis of pituitary adenoma and the histopathological subtype of the adenoma
- Date of surgery
- Surgical report
- Preoperative hormone status (last status before surgery): insufficiency yes/no; based on replacement therapy and/or explicit endocrinological diagnosis
- Review of relevant previous diagnoses/comorbidities to rule out non-pituitary substitution (e.g., thyroid disease)
- Endocrinology: Number of insufficient axes preoperatively (0 / 1 / 2 / >2)
- Change of status of insufficiency after surgery (better / unchanged / worse)

2.2.2. MRI

Preoperative imaging was performed using magnetic resonance imaging (MRI) of the sella/parasellar region (1.5 or 3.0 Tesla). Contrast-enhanced T1-weighted sequences (MPRAGE protocols) were used to assess the soft tissue structures; in addition, MR angiography time-of-flight sequences were included in the analysis to visualize vascular structures, where available. In 2022, VIBE and CISS protocols were included into the MRI protocol (38).

The sellar and parasellar structures were evaluated using the Medtronic S8 Navigation System (Medtronic, Colorado, USA) by creating a model from the available preoperative image data sets.

Volumetric analysis of the normal, intact pituitary tissue (normal residual pituitary gland, NRPG) and the adenoma was primarily performed on preoperative contrast-enhanced T1-weighted MPRAGE sequences. The NRPG was identified, analog to the description by Di Maio et al., as a thin, contrast-enhanced tissue rim that can be distinguished from the adenoma, which usually shows less enhancement. In

cases of pronounced deformation, the neurohypophyseal “bright spot” and the contrast-enhancing infundibulum were used as additional landmarks for orientation (37).

Segmentation was performed in the Medtronic S8 system by manually marking the contours of the NRPG and tumor, starting in the coronal plane on all layers where reliable delineation was possible. The segmentation was then checked in the two orthogonal planes to identify and supplement any missing parts. The software automatically calculated the volumes from the segmented areas, considering the layer thickness; the volumes were output in cm^3.

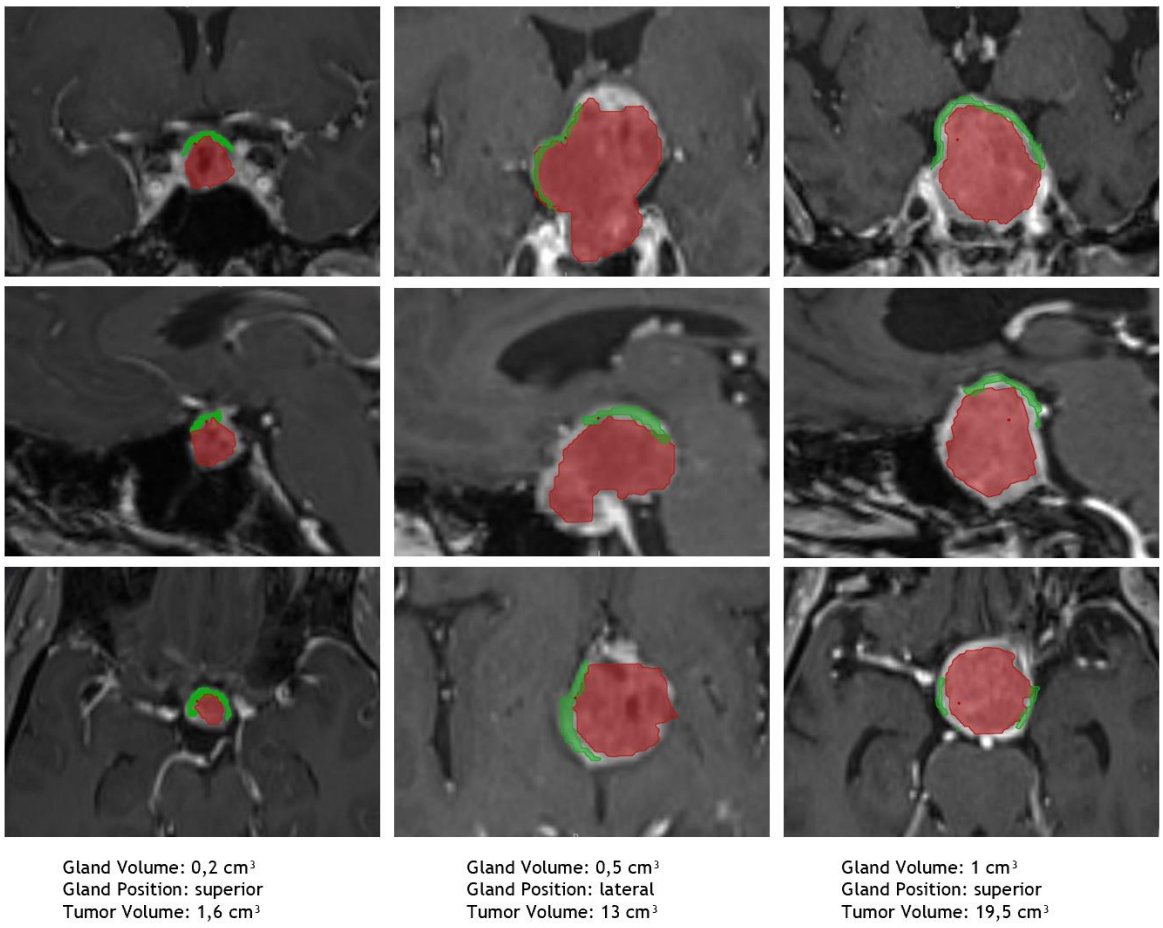

Figure 3. Representative MRI images used for Stealth-based segmentation and measurement of pituitary adenoma and residual pituitary gland. The adenoma is highlighted in red and the residual pituitary gland in green. The examples shown illustrate different preoperative residual gland volumes.

For size categorization, the maximum tumor diameter was determined: adenomas <10 mm were classified as microadenomas, adenomas ≥10 mm as macroadenomas. The location of the NRPG relative to the tumor was categorized based on the predominant direction of displacement using preoperative MRI. For the present study, the position of the pituitary tissue was documented as superior or lateral (modified Di Maio classification) (37).

Data collected from MRI:

- Maximum tumor diameter; micro/macro classification
- Tumor volume (cm^3; segmentation in Medtronic S8)
- Position of NRPG relative to tumor (superior/lateral)
- NRPG volume (cm^3; segmentation in Medtronic S8)

2.3. Data preparation

Only cases with a preoperative MRI suitable for the planned measurements, a preoperative endocrinological status, and a postoperative endocrinological follow-up were included in the analysis. The postoperative follow-up was defined as a 12-month check-up, with a time window of 9–15 months being accepted.

Seven patients were excluded due to missing/unevaluable imaging and two were excluded due to missing follow-up. Microadenomas (<10 mm) were excluded (n=11) due to a missing compression-related changes in NRPG morphology (displacement/volumetry). In prospective observations of micro-incidentalomas, no changes in pituitary function have been reported (39). In addition, patients were excluded if preoperative imaging was missing or could not be evaluated and/or no endocrinological follow-up was documented within the defined time window.

After applying all exclusion criteria, a final study cohort of 255 patients was obtained.

2.4. Statistical Analysis

Statistical analysis was performed using SPSS version 29.0 (SPSS Inc., IBM, Armonk, New York, USA). Continuous variables were assessed for normality using visual inspection of histograms and Q–Q plots. Normally distributed data are presented as mean ± standard deviation (SD), while categorical variables are reported as absolute numbers and percentages.

For group-based comparisons involving continuous variables, one-way analysis of variance (ANOVA) was used when comparing more than two groups. In case of statistically significant global tests, post-hoc comparisons were explored descriptively. For categorical variables, Pearson's chi-square (x^2) test was applied; Fisher's exact test was used where expected cell counts were small. Effect sizes for categorical associations were quantified using Cramér's V. The significance level was set at $\alpha = 0.05$ (two-sided).

For descriptive analyses, patients were grouped by the number of preoperative insufficient pituitary axes (0 / 1 / 2 / >2), postoperative change in pituitary function (better / unchanged / worse), and preoperative residual gland volume using tertiles. Tertiles were defined by predefined cut-offs: T1 ≤ 0.30 cm^3, T2 > 0.30 to ≤ 0.50 cm^3, and T3 > 0.50 cm^3. Differences in the distribution of postoperative change categories between groups were tested using the chi-square (x^2) test; Cramér's V was reported as an effect size when appropriate.

To quantify associations, binary logistic regression was used, and results are presented as odds ratios (OR) with 95% confidence intervals (95% CI). Postoperative change was analyzed in two binary contrasts: better vs (unchanged+worse) and worse vs (better+unchanged). Residual gland volume was evaluated both as tertiles and as a continuous variable (reported per +0.1 cm^3). Both unadjusted and adjusted models were fitted. Adjusted models included age, sex, maximum tumor size, preoperative axis insufficiency, DiMaio position, and postoperative radiotherapy. Predicted probabilities with 95% confidence intervals were plotted across the observed volume range.

3. Results

3.1. Descriptive Statistics

The study cohort consisted of 255 macroadenomas, which met the inclusion and exclusion criteria for further analysis. The mean age of patients was 56.4 ± 14.1 years. The maximum tumor diameter was 25.5 ± 10.9 mm on average; the mean tumor volume was 7.00 ± 10.14 cm^3. The preoperative residual gland volume was 0.50 ± 0.29 cm^3 on average.

In terms of gender, there was an almost equal distribution with 131/255 (51.4%) male and 124/255 (48.6%) female patients. In terms of DiMaio position, the residual gland was predominantly located superiorly (201/255; 78.8%), while a lateral position was present in 54/255 (21.2%) cases. Postoperative radiation therapy was performed in a total of 30/255 (11.8%) patients.

Preoperative pituitary insufficiency (number of insufficient pituitary axes) was distributed as follows: 0 axes (normal gland function): 152/255 (59.6%), 1 axis: 50/255 (19.6%), 2 axes: 23/255 (9.0%), and >2 axes: 30/255 (11.8%). The postoperative change in pituitary function was predominantly unchanged (155/255; 60.8%), followed by worse (70/255; 27.5%) and better (30/255; 11.8%).

The distribution of histopathological subtypes showed LH/FSH (gonadotroph, 86/255; 33.7%) and null-cell (68/255; 26.7%) as the most common entities. Other subtypes were ACTH (corticotroph, 36/255; 14.1%), GH (somatotroph, 20/255; 7.8%), PRL (lactotroph, 18/255; 7.1%), and PRL+GH (mammosomatotroph, 13/255; 5.1%); plurihormonal and apoplectic each occurred in 6/255 (2.35%) cases. Rare subtypes such as TSH (thyrotroph) were only observed in isolated cases (1/255 each; 0.39%).

For the subsequent group-based comparisons, the characteristics of the collective are compared according to preoperative axis insufficiency (**Table 1**) and postoperative changes (**Table 2**).

In **Table 1**, four groups were formed according to the preoperative number of insufficient pituitary axes: 0 axes (n=152), 1 axis (n=50), 2 axes (n=23), and >2 axes (n=30). Significant differences in age were observed between these groups (0 axes: 53.6 ± 13.8 years; 1 axis: 60.1 ± 14.8; 2 axes: 62.7 ± 11.2; >2 axes: 59.3 ± 13.7; $p < 0.001$) and in preoperative residual gland volume (0 axes: 0.44 ± 0.24 cm^3; 1 axis: 0.56 ± 0.31; 2 axes: 0.57 ± 0.38; >2 axes: 0.64 ± 0.38; $p = 0.002$). Tumor volume differed significantly between the preoperative axis insufficiency groups and was higher on average in the groups with ≥1 axis than in the 0-axis group ($p < 0.001$). Similarly, the maximum tumor diameter differed significantly between the groups (0 axes: 22.6 ± 9.4 mm; 1 axis: 30.1 ± 11.9; 2 axes: 28.8 ± 12.0; >2 axes: 29.7 ± 11.7; $p < 0.001$).

The gender distribution varied significantly ($p < 0.001$): while in the group with 0 axis insufficiencies, 61/152 (40.1%) were male and 91/152 (59.9%) were female; male patients predominated in the group with >2 axes (24/30 [80.0%]), with a female proportion of 6/30 (20.0%).

In contrast, there were no differences between the preoperative insufficiency groups ($p = 0.927$) for the DiMaio position (superior vs. lateral). The superior position was dominant in all groups (e.g. 0 axes: 120/152 [78.9%]; >2 axes: 24/30 [80.0%]). The rate of postoperative radiotherapy did not differ significantly between groups ($p = 0.653$) and was overall low, occurring in approximately 10%–12% of patients (19/152 [12.5%] in the 0-axis group and 3/30 [10.0%] in the >2-axis group).

In contrast, there was a correlation between postoperative changes in pituitary function (better/unchanged/worse) and preoperative axis insufficiency ($p < 0.001$): In the group with 0 axes the function remained unchanged in the majority of cases (113/152 [74.3%]), and deterioration was observed in 39/152 (25.7%). In contrast, improvement was observed more frequently in the group with >2 axes (12/30 [40.0%]) and deterioration only rarely (3/30 [10.0%]).

The distribution of histopathological subtypes did not differ significantly between the groups (p = 0.140). Overall, LH/FSH tumors and null-cell adenomas were the most common (e.g. 0 axes: LH/FSH 47/152 [30.9%], null-cell 26/152 [17.1%]).

Table 1: Baseline characteristics according to preoperative pituitary axis insufficiency

Variable	0 (n=152)	1 (n=50)	2 (n=23)	>2 (n=30)	p
Age (years), mean ± SD	53.6 ± 13.8	60.1 ± 14.8	62.7 ± 11.2	59.3 ± 13.7	0.002
Preop residual gland volume (cm^3), mean ± SD	0.44 ± 0.24	0.56 ± 0.31	0.57 ± 0.38	0.64 ± 0.38	0.002
Max tumor diameter (mm), mean ± SD	22.6 ± 9.4	30.1 ± 11.9	28.8 ± 12.0	29.7 ± 11.7	<0.001
Tumor volume (cm^3), mean ± SD	4.67 ± 5.26	11.23 ± 16.19	10.97 ± 15.48	8.72 ± 7.58	<0.001
Male, n (%)	61 (40.1%)	29 (58.0%)	17 (73.9%)	24 (80.0%)	<0.001
Female, n (%)	91 (59.9%)	21 (42.0%)	6 (26.1%)	6 (20.0%)	
DiMaio superior, n (%)	120 (78.9%)	38 (76.0%)	19 (82.6%)	24 (80.0%)	0.927
DiMaio lateral, n (%)	32 (21.1%)	12 (24.0%)	4 (17.4%)	6 (20.0%)	
Postop radiotherapy: No, n (%)	133 (87.5%)	43 (86.0%)	22 (95.7%)	27 (90.0%)	0.653
Postop radiotherapy: Yes, n (%)	19 (12.5%)	7 (14.0%)	1 (4.3%)	3 (10.0%)	
Postop change: Better, n (%)	0 (0.0%)	10 (20.0%)	8 (34.8%)	12 (40.0%)	<0.001
Postop change: Unchanged, n (%)	113 (74.3%)	19 (38.0%)	8 (34.8%)	15 (50.0%)	
Postop change: Worse, n (%)	39 (25.7%)	21 (42.0%)	7 (30.4%)	3 (10.0%)	
Histopathology (global)					0.140
ACTH, n (%)	27 (17.8%)	5 (10.0%)	3 (13.0%)	1 (3.3%)	
GH, n (%)	17 (11.2%)	1 (2.0%)	2 (8.7%)	0 (0.0%)	
LH/FSH, n (%)	47 (30.9%)	19 (38.0%)	11 (47.8%)	9 (30.0%)	
PRL, n (%)	13 (8.6%)	4 (8.0%)	0 (0.0%)	1 (3.3%)	
null cell, n (%)	26 (17.1%)	7 (14.0%)	2 (8.7%)	18 (60.0%)	
TSH, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	
PRL+GH, n (%)	4 (2.6%)	6 (12.0%)	0 (0.0%)	3 (10.0%)	
plurihormonal, n (%)	4 (2.6%)	2 (4.0%)	2 (8.7%)	1 (3.3%)	
apoplectic, n (%)	3 (2.0%)	2 (4.0%)	2 (8.7%)	0 (0.0%)	

Three groups were considered for the evaluation of postoperative change (**Table 2**): better (n=30), unchanged (n=155), and worse (n=70). There was no significant difference in age between the groups (better: 55.4 ± 12.2 years; unchanged: 55.5 ± 13.8; worse: 58.8 ± 15.5; p = 0.143). In contrast, there were significant differences in both preoperative residual gland volume (better: 0.68 ± 0.42 cm^3; unchanged: 0.45 ± 0.25; worse: 0.52 ± 0.29; p = 0.002) and in the maximum tumor diameter (better: 28.2 ± 12.1 mm; unchanged: 23.3 ± 10.1; worse: 29.2 ± 11.0; p < 0.001). There was a significant difference in tumor volume between the postoperative change groups, with higher mean volumes in the better and worse groups compared to unchanged (p = 0.048).

The gender distribution did not differ significantly among the postoperative change groups (p = 0.585): male patients comprised 18/30 (60.0%) in the better group, 77/155 (49.7%) in the unchanged group, and 36/70 (51.4%) in the worse group. Likewise, no significant group differences were observed for gland position by the modified Di Maio classification (p = 0.731; superior, 73.3% vs 79.4% vs 80.0%) or for postoperative radiotherapy (p = 0.412; yes, 16.7% vs 9.7% vs 14.3%).

A significant association was observed between preoperative pituitary axis insufficiency and postoperative functional outcome (p < 0.001). In the better outcome group, no patients had normal pituitary function preoperatively (0/30 [0.0%]); instead, insufficiency of more than two axes (12/30 [40.0%]) and single-axis insufficiency (10/30 [33.3%]) were most common. By comparison, patients in the unchanged group most frequently had no preoperative axis insufficiency (113/155 [72.9%]). Similarly, in the worse outcome group, the majority of patients had no preoperative axis insufficiency (39/70 [55.7%]), followed by single-axis insufficiency (21/70 [30.0%]).

The histopathological subtypes did not differ significantly between the postoperative change groups (p = 0.558). For example, in the better group, the proportion of gonadotropic adenomas was relatively high (14/30 [46.7%]), as well as in the unchanged group (52/155 [33.5%]); overall, there was no statistically significant difference between the groups.

Table 2: Baseline characteristics according to postoperative change in pituitary function

Variable	Better (n=30)	Unchanged (n=155)	Worse (n=70)	p
Age (years), mean ± SD	55.4 ± 12.2	55.5 ± 13.8	58.8 ± 15.5	0.143
Preop residual gland volume (cm^3), mean ± SD	0.68 ± 0.42	0.45 ± 0.25	0.52 ± 0.29	0.002
Max tumor diameter (mm), mean ± SD	28.2 ± 12.1	23.3 ± 10.1	29.2 ± 11.0	<0.001
Tumor volume (cm^3), mean ± SD	10.0 ± 15.9	5.81 ± 9.95	8.31 ± 6.54	0.048
Male, n (%)	18 (60.0%)	77 (49.7%)	36 (51.4%)	0.585
Female, n (%)	12 (40.0%)	78 (50.3%)	34 (48.6%)	
DiMaio superior, n (%)	22 (73.3%)	123 (79.4%)	56 (80.0%)	0.731
DiMaio lateral, n (%)	8 (26.7%)	32 (20.6%)	14 (20.0%)	
Postop radiotherapy: No, n (%)	25 (83.3%)	140 (90.3%)	60 (85.7%)	0.412
Postop radiotherapy: Yes, n (%)	5 (16.7%)	15 (9.7%)	10 (14.3%)	
Preop axis insufficiency: 0, n (%)	0 (0.0%)	113 (72.9%)	39 (55.7%)	<0.001
Preop axis insufficiency: 1, n (%)	10 (33.3%)	19 (12.3%)	21 (30.0%)	
Preop axis insufficiency: 2, n (%)	8 (26.7%)	8 (5.2%)	7 (10.0%)	
Preop axis insufficiency: >2, n (%)	12 (40.0%)	15 (9.7%)	3 (4.3%)	
Histopathology				0.558
ACTH, n (%)	4 (13.3%)	24 (15.5%)	8 (11.4%)	
GH, n (%)	0 (0.0%)	15 (9.7%)	5 (7.1%)	
LH/FSH, n (%)	14 (46.7%)	52 (33.5%)	20 (28.6%)	
PRL, n (%)	4 (13.3%)	7 (4.5%)	7 (10.0%)	
null cell, n (%)	3 (10.0%)	30 (19.4%)	35 (50.0%)	
TSH, n (%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	
PRL+GH, n (%)	3 (10.0%)	7 (4.5%)	3 (4.3%)	
plurihormonal, n (%)	1 (3.3%)	4 (2.6%)	2 (2.8%)	
apoplectic, n (%)	0 (0.0%)	4 (2.6%)	2 (2.9%)	

3.2. Position and Outcome

The postoperative change in pituitary function (coded as better/unchanged/worse) was analyzed in relation to the DiMaio position of the residual gland (superior vs. lateral). Of a total of 255 macroadenomas, 201/255 (78.8%) had a superior position and 54/255 (21.2%) had a lateral position. The distribution of change categories was comparable between superior and lateral (superior: better 22/201 [10.9%], unchanged 123/201 [61.2%], worse 56/201 [27.9%]; lateral: better 8/54 [14.8%], unchanged 32/54 [59.3%], worse 14/54 [25.9%]) and showed no significant correlation in comparison ($x^2(2)=0.626$; $p=0.731$; **Table 3**; **Figure 4**).

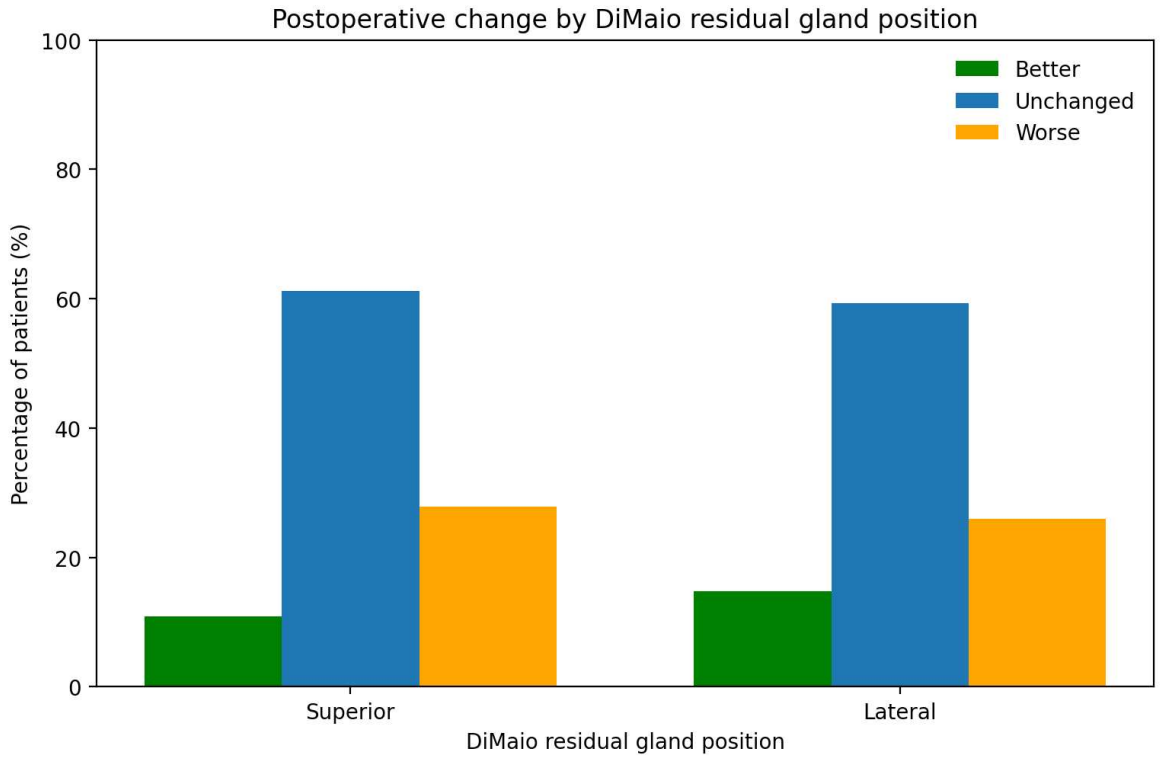

Figure 4. Postoperative change in pituitary function by DiMaio residual gland position (superior vs lateral). Bars show the percentage of patients within each position category classified as Better, Unchanged, or Worse.

Table 3: DiMaio position and postoperative change in pituitary function

DiMaio position	Better n (%)	Unchanged n (%)	Worse n (%)	Total n
Superior	22 (10.9%)	123 (61.2%)	56 (27.9%)	201
Lateral	8 (14.8%)	32 (59.3%)	14 (25.9%)	54

$x^2(2)=0.626$, p=0.731, Cramér's V=0.050

Logistic regression models were calculated for quantitative estimation (**Table 4**). In the analysis of worse vs. (better+unchanged), there was no increase in odds for lateral vs. superior (unadjusted: OR 0.91; 95% CI 0.46–1.79; p=0.777). Even after adjusting for age, sex, tumor size, preoperative residual gland volume, preoperative axis insufficiency, and postoperative radiation, the effect remained absent (OR 0.98; 95% CI 0.48–2.00; p=0.956). Similarly, the analysis of better vs. (unchanged+worse) showed no significant association (unadjusted: OR 1.42; 95% CI 0.59–3.38; p=0.435; adjusted: OR 1.87; 95% CI 0.63–5.59; p=0.260), with wide confidence intervals due to low event numbers in the better group. Overall, there was no evidence of an independent association between the DiMaio position and postoperative improvement or deterioration.

Table 4: Binary logistic regression analysis of the association between DiMaio position and postoperative pituitary function outcome

Outcome contrast	Model	N used	OR (Lateral vs Superior)	95% CI	p
Worse vs (Better+Unchanged)	Unadjusted	255	0.91	0.46-1.79	0.777
Worse vs (Better+Unchanged)	Adjusted*	255	0.98	0.48-2.00	0.956
Better vs (Unchanged+Worse)	Unadjusted	255	1.42	0.59-3.38	0.435
Better vs (Unchanged+Worse)	Adjusted*	255	1.87	0.63-5.59	0.260

*Adjusted for: age, sex, tumor size (mm), preoperative residual gland volume (cm^3), preoperative axis insufficiency (0/1/2/>2), postoperative radiotherapy.

3.3. Volume and Outcome

For further analysis, the preoperative residual gland volume was divided into tertiles: T1 ≤0.30 cm^3 (n=88), T2 >0.30-≤0.50 cm^3 (n=94), and T3 >0.50 cm^3 (n=73). The distribution of all variables across the tertiles is shown in **Table 5**. The volumes of the residual pituitary gland differed significantly (T1: 0.25 ± 0.06 cm^3; T2: 0.45 ± 0.05; T3: 0.86 ± 0.28; $p < 0.001$). However, there was no significant difference in age between the tertiles (T1: 55.4 ± 14.9 years; T2: 55.7 ± 13.6; T3: 58.4 ± 13.8; $p = 0.478$).

Table 5: Baseline characteristics according to tertiles of preoperative residual gland volume

Variable	T1 ≤0.30 (n=88)	T2 0.31-0.50 (n=94)	T3 >0.50 (n=73)	p
Age (years), mean ± SD	55.4 ± 14.9	55.7 ± 13.6	58.4 ± 13.8	0.478
Preop residual gland volume (cm^3), mean ± SD	0.25 ± 0.06	0.45 ± 0.05	0.86 ± 0.28	<0.001
Max tumor diameter (mm), mean ± SD	22.1 ± 9.5	24.7 ± 9.9	30.5 ± 12.0	<0.001
Tumor volume (cm^3), mean ± SD	4.48 ± 5.26	5.89 ± 5.74	11.47 ± 16.04	<0.001
Male, n (%)	48 (54.5%)	44 (46.8%)	39 (53.4%)	0.532
Female, n (%)	40 (45.5%)	50 (53.2%)	34 (46.6%)	
DiMaio superior, n (%)	77 (87.5%)	66 (70.2%)	58 (79.5%)	0.017
DiMaio lateral, n (%)	11 (12.5%)	28 (29.8%)	15 (20.5%)	
Postop radiotherapy: No, n (%)	74 (84.1%)	86 (91.5%)	65 (89.0%)	0.292
Postop radiotherapy: Yes, n (%)	14 (15.9%)	8 (8.5%)	8 (11.0%)	
Preop axis insufficiency: 0, n (%)	61 (69.3%)	61 (64.9%)	30 (41.1%)	0.005
Preop axis insufficiency: 1, n (%)	11 (12.5%)	20 (21.3%)	19 (26.0%)	
Preop axis insufficiency: 2, n (%)	7 (8.0%)	7 (7.4%)	9 (12.3%)	

Preop axis insufficiency: >2, n (%)	9 (10.2%)	6 (6.4%)	15 (20.5%)	
Postop change: Better, n (%)	5 (5.7%)	10 (10.6%)	15 (20.5%)	0.022
Postop change: Unchanged, n (%)	61 (69.3%)	58 (61.7%)	35 (47.9%)	
Postop change: Worse, n (%)	22 (25.0%)	26 (27.7%)	23 (31.5%)	
Histopathology (global)				0.019
ACTH, n (%)	18 (20.5%)	12 (12.8%)	7 (9.6%)	
GH, n (%)	3 (3.4%)	12 (12.8%)	5 (6.8%)	
LH/FSH, n (%)	31 (35.2%)	32 (34.0%)	23 (31.5%)	
PRL, n (%)	8 (9.1%)	4 (4.3%)	6 (8.2%)	
0 cell (NF+NC), n (%)	15 (17.0%)	29 (30.9%)	24 (32.9%)	
TSH, n (%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	
PRL+GH, n (%)	3 (3.4%)	6 (6.4%)	4 (5.5%)	
plurihormonal, n (%)	0 (0.0%)	3 (3.2%)	3 (4.1%)	
apoplectic, n (%)	3 (3.4%)	2 (2.1%)	1 (1.4%)	

Tumor volume increased significantly across the volume tertiles and was largest in the highest residual glandular volume tertile (T3) ($p < 0.001$). Neither the gender distribution ($p = 0.532$) nor the frequency of postoperative radiation ($p = 0.292$) differed between the groups T1, T2 and T3.

In contrast, the DiMaio position showed a significant correlation with the gland volume tertiles ($p = 0.017$): In group T1, the gland was predominantly located superiorly (77/88 [87.5%]), whereas in group T2, the fraction of superior gland position was lower (66/94 [70.2%]).

In addition, the distribution of preoperative pituitary axis insufficiency differed significantly across residual gland volume tertiles ($p = 0.005$). The fraction of patients without preoperative axis insufficiency was 69.3% in group T1 and 41.1% in group T3. Whereas insufficiency of more than two axes was more frequent in group T3 20.5% than in group T1 10.2%.

Histopathological distribution differed across the tertiles (p = 0.009): ACTH adenomas were more frequent in group T1 (18/88 [20.5%]) than in T3 (6/73 [8.2%]), while the remaining subtypes were distributed variably.

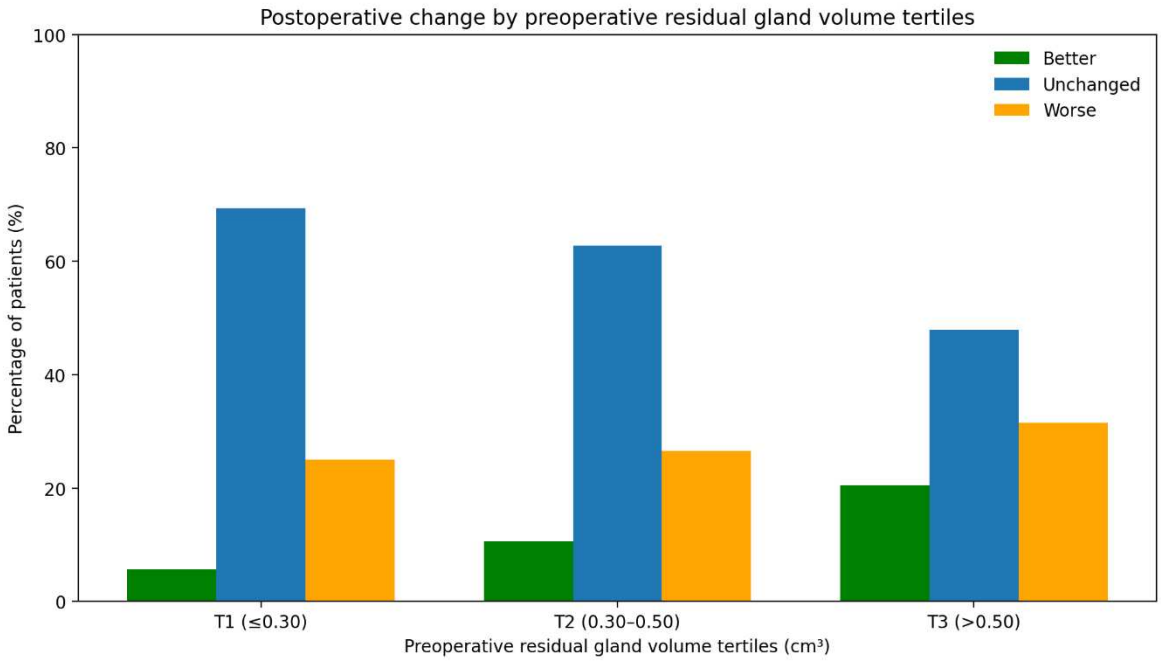

Figure 5. Distribution of postoperative change categories across tertiles of preoperative residual gland volume. Bars represent the percentage of patients within each tertile classified as Better, Unchanged, or Worse.

The three volume tertiles showed a significantly different distribution of the postoperative change categories ($x^2(4)=11.41$; p=0.022; Cramér's V=0.150). **Figure 5** shows the postoperative change for each tertile. The proportion of patients with improvement increased with increasing preoperative residual gland volume from 5/88 (5.7%) in T1 to 10/94 (10.6%) in T2 to 15/73 (20.5%) in T3. At the same time, the proportion of "unchanged" cases decreased from 61/88 (69.3%) in T1 to 35/73 (47.9%) in T3. The proportion of "worse" outcome, on the other hand, was 25% in group T1, 26.6% in group T2 and 31.% in group T3. A "better" outcome occurred more frequently in group T3, than in group T1.

A logistic regression model was calculated to continuously illustrate the relationship between preoperative residual gland volume and postoperative improvement in pituitary function. Preoperative residual gland volume was calculated as the odds ratio (OR) per +0.1 cm^3. In the model better vs. (unchanged + worse), there was a significant unadjusted increase in odds per +0.1 cm^3 (OR 1.21; 95% CI 1.08–1.34; $p < 0.001$)(**Figure 6**).

After adjusting for age, sex, tumor size, preoperative axis insufficiency, DiMaio position, and postoperative radiation, the association remained attenuated (OR 1.17 per +0.1 cm^3; 95% CI 1.00–1.37; $p = 0.045$), suggesting an independent association between higher preoperative residual gland volume and postoperative improvement in pituitary function. Histopathology was compared descriptively between tertiles but was not included as a covariate in the multivariable regression.

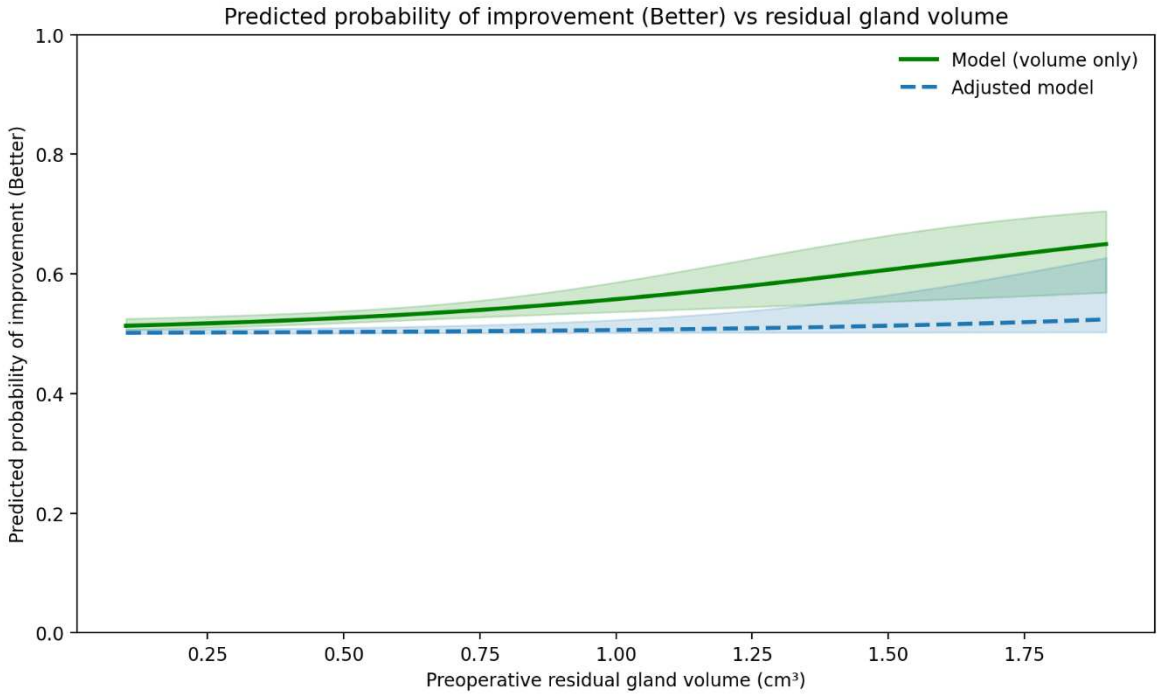

Figure 6. Predicted probability of postoperative improvement (better) across preoperative residual gland volume. Solid line shows the model including volume only; dashed line shows the adjusted model. Shaded areas indicate 95% confidence intervals.

Similarly, the risk of postoperative deterioration was modeled separately as a binary outcome (worse vs. better+unchanged), also interpreted as OR per +0.1 cm^3 and shown in **Figure 7**. Here, no significant correlation between preoperative residual gland volume and deterioration was found in the unadjusted analysis (OR 1.04; 95% CI 0.95–1.14; p = 0.393). Even after adjusting for age, gender, tumor size, preoperative axis insufficiency, DiMaio position, and postoperative radiation, there was no evidence of an independent effect (OR 1.00; 95% CI 0.90–1.11; p = 0.962).

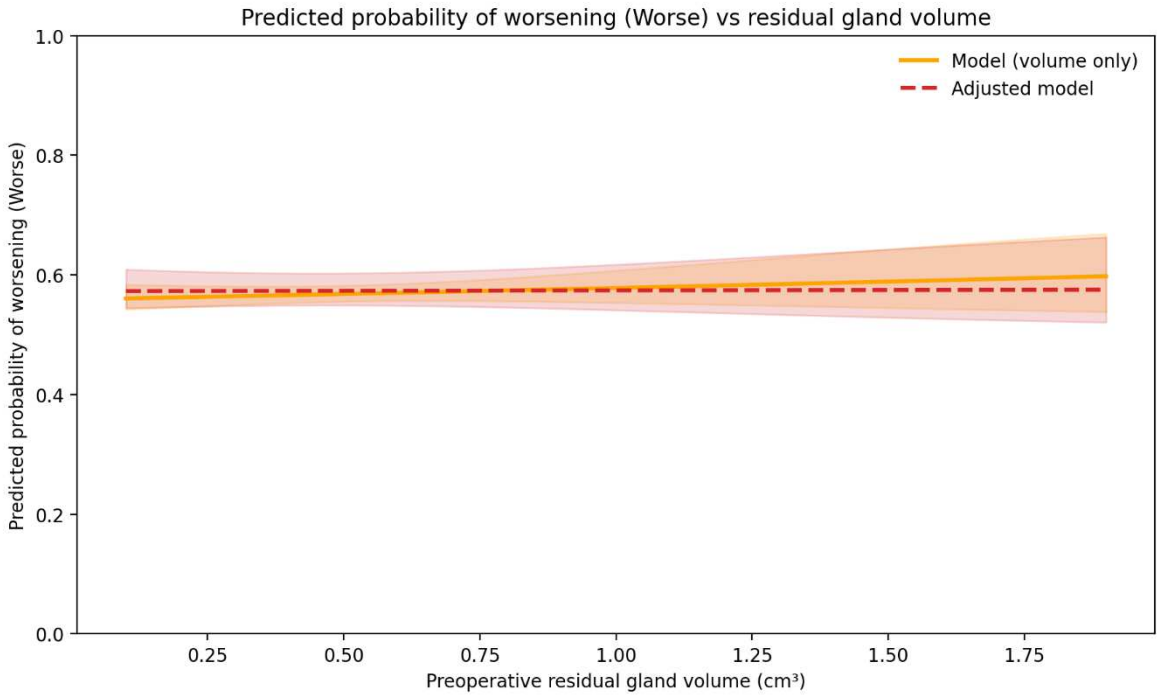

Figure 7. Predicted probability of postoperative worsening (Worse) across preoperative residual gland volume. Solid line shows the model including volume only; dashed line shows the adjusted model. Shaded areas indicate 95% confidence intervals.

4. Discussion

The aim of this thesis was to investigate whether preoperative imaging parameters of the residual pituitary gland, particularly preoperative residual gland volume and the DiMaio position (superior vs. lateral), are associated with postoperative changes in pituitary function (better, unchanged, or worse). Our analysis demonstrated a correlation between preoperative residual gland volume and postoperative functional outcome: patients who showed postoperative improvement had a higher mean preoperative residual gland volume than those without improvement.

Pituitary Gland Volume and Outcome

The established pathophysiological concepts of hypopituitarism in macroadenomas is largely explained by mechanical factors: compression/displacement, stalk/portal vessel compression, increased intrasellar pressure. After surgical decompression, endocrine function may improve in some cases if tissue reserve is preserved (40,41). The fact that postoperative functional outcomes include both improvements and new deficits is also reported in clinical series, making it methodologically sensible to consider “better” and “worse” outcomes separately (35,42).

In our cohort, a significant correlation between preoperative residual gland volume and postoperative change in pituitary function was found. Improvement occurred more frequently with increasing preoperative residual gland volume (tertile trend, > 0.50 cm^3), and in continuous modeling, the probability of improvement was also gradually associated with higher volume (OR per + 0.1 cm^3). Thus, residual gland volume supports the hypothesis that a quantitatively larger preoperative residual gland compartment is associated with a higher chance of functional recovery after decompression (35,40,41).

In contrast, no consistent correlation was found for the deterioration category: neither the tertile analysis nor the continuous modeling revealed a consistent independent volume effect on the risk of deterioration. Therefore, postoperative

deterioration can be explained by several factors: surgical manipulation, pedicle/vascular irritation, already limited reserve, individual vulnerability. On the other hand, preoperative residual gland volume can primarily reflect the recovery capacity postoperatively (25,40,42).

The results are consistent with the reported data in the literature of non-functional macroadenomas, which show similar results of both recovery from preoperative deficits and new disorders after transsphenoidal resection (43). In systematic reviews and cohort studies, preoperative baseline function and tumor burden are repeatedly cited as key influencing factors (25,43). In addition, a correlation was found between higher preoperative residual gland volume and postoperative improvement suggesting that a larger morphologically preserved residual gland compartment can be interpreted as an increased functional reserve. Studies that jointly analyze gland morphology and endocrine outcomes after endoscopic resection also report a relationship between gland volume or postoperative re-expansion and endocrine recovery (44).
In contrast, postoperative deterioration has been found to have multifactorial reasons (associated with surgical and early postoperative factors) in the literature. Accordingly, it is plausible that preoperative residual gland volume primarily reflects the probability of improvement, while it does not necessarily explain the risk of deterioration independently (25,42).

The observed association between greater preoperative residual gland volume and postoperative improvement may be attributable to an interaction between preserved functional reserve and the mechanical effects of the tumor on the pituitary stalk. A larger morphologically recorded residual gland compartment can plausibly represent more potentially functional tissue that regains sufficient perfusion and hypothalamic-pituitary communication after surgical decompression. At the same time, residual gland volume cannot be interpreted independently of tumor burden: larger tumors can displace the gland from the sella and “pull it apart”, resulting in an apparently larger and more extensive residual gland area, without necessarily corresponding to a proportionally higher hormonal reserve. This corresponds to the association between tumor burden and

residual gland volume observed in this study. Reviews describe the mass effect mechanism via pedicle/portal vessels and compression as the central cause of sellar pituitary insufficiency, thus providing a plausible framework in which decompression can enable functional improvement (49).

Conversely, a “stretched” sellar system may be more vulnerable to manipulation: intraoperative manipulation of the residual gland and pedicle region is associated with postoperative endocrine morbidity. In a series with video-based assessment of intraoperative gland manipulation, moderate to severe manipulation, firm tumor consistency, and larger tumor size have been found to be associated with an increased risk of iatrogenic gland damage (new axis failure or relevant neuroendocrine complications) (45). Imaging-based stalk parameters also support the relevance of “stretch/stress” of the stalk region: A greater postoperative increase in stalk length (“pituitary stalk stretch”) was an independent predictor of postoperative diabetes insipidus (especially transient), underscoring the sensitivity of the hypothalamic-neurohypophyseal system to mechanical stress and manipulation (46). Although diabetes insipidus primarily affects the neurohypophysis, it is discussed in this context as a sensitive marker for stalk/hypothalamic stress. Further studies report that changes in stalk geometry (e.g. deviation angle) may be associated with the occurrence of diabetes insipidus after transsphenoidal surgery (47), and that intraoperative morphological stalk changes (e.g. enlarged stalk diameter as a sign of possible irritation/edema) may predict new postoperative endocrine deficits, including adrenocortical insufficiency and vasopressin deficiency (48).

Therefore, a dual effect may be present: I) a higher preoperative residual gland volume may indicate a greater reserve or better recovery capacity after decompression; II) the displacement/stretching of the gland and stalk region, which is more common in large tumors, may increase susceptibility to manipulation-related postoperative disorders (45–49).

Despite its plausibility, the observed correlation between preoperative residual gland volume and postoperative improvement is potentially influenced by

confounding factors, as residual gland volume cannot be interpreted independently of tumor burden. Larger tumors are typically associated with greater displacement, stretching, and pedicle/portal vessel impairment and can therefore influence both preoperative function and postoperative recovery dynamics (25,40,41,43,49). Notably, the volume effect in the present analysis was observed not only descriptively but also in adjusted models in the direction of improvement ("better"), whereas no stable independent effect was identified for deterioration. This finding suggests that residual gland volume primarily reflects recovery potential, whereas deterioration is less well explained by preoperative morphology alone (25,42–44).

Another key contextual factor is preoperative axis insufficiency as a marker of already established functional damage. In many series, preoperative hypopituitarism reflects the cumulative effects of tumor-related compression of the gland and stalk and has been associated with both the likelihood of postoperative functional recovery and the risk of new deficits following transsphenoidal resection (40,43,51). Thus, preoperative axis insufficiency can both influence the relationship between morphology and outcome and explain why improvement and deterioration do not behave inversely.

Finally, it should be noted that postoperative deterioration in the literature and also conceptually depends more strongly on surgical and early postoperative factors (e.g. extent of manipulation, pedicle/vascular irritation, tissue handling, perioperative dynamics of individual axes) and can therefore vary despite identical preoperative morphology (25,42,50). This supports the interpretation that preoperative imaging markers such as residual gland volume are particularly suitable for estimating the probability of improvement, while the risk of deterioration is more likely to be determined by a multifactorial interaction of baseline function, tumor characteristics, and surgical influences (25,43–45,49,50). From a clinical perspective, the correlation between higher preoperative residual gland volume and postoperative improvement supports the use of volumetric MRI parameters as part of preoperative risk assessment. Patients with larger preoperative residual gland volume can be advised (under otherwise comparable

conditions) that they have a higher probability of at least partial endocrine recovery after decompression, while also being informed that new deficits can occur even with favorable morphology and are typically influenced by other factors (baseline function, tumor burden, intraoperative influences) (25,50). This is consistence with the literature, which describes postoperative endocrine outcomes after transsphenoidal surgery as bidirectional and considers preoperative baseline function and tumor characteristics to be key determinants of recovery or new deficits (43,51).

In practical terms, this suggests that patients with a larger residual gland volume and a pronounced tumor burden can be considered a group with potentially relevant “decompression gain”, provided that vital residual tissue is present (40,41,49). Conversely, in patients with pronounced preoperative axis insufficiency, expectations of complete functional recovery should be more cautious, as preoperative deficits are associated in many series with a lower probability of recovery and an increased risk of persistent or additional deficits (51). Overall, these findings support a stratified counseling approach in which residual gland volume is not interpreted in isolation but considered together with tumor burden and preoperative endocrine status as part of an integrated risk constellation (25,43,51).

Pituitary Gland Position and Outcome

Analysis of the location of the residual gland according to DiMaio (superior vs. lateral) revealed no evidence of an independent association with postoperative changes in pituitary function in the present cohort. Both the descriptive distribution of the outcome categories and the quantitative modeling (better vs. rest; worse vs. rest) showed no significant effect of the DiMaio proposed identification of the pituitary gland position on preoperative images. Thus, the hypothesis that the rough topographical location category of the residual gland alone has prognostic discriminatory power for the endocrine outcome is not supported in this cohort. The DiMaio classification thus remains primarily an anatomical-descriptive classification of the residual pituitary gland in the context

of macroadenomas, without providing an independent contribution to outcome prediction in the available data (43).

One plausible explanation is that the superior/lateral classification only roughly reflects the actual anatomical and functional situation. Endocrine function is likely to depend more on other quantitative parameters (e.g. residual gland volume) and tumor burden, as well as preoperative functional status, which may mask a potential location effect (25,43,51). In addition, the lateral group is usually smaller, which may limit the precision for small effects. Finally, it is conceivable that the location is primarily relevant for surgical orientation and tissue handling, while the endocrine outcome, especially “worse”, is more strongly influenced by intraoperative factors and early postoperative dynamics (45,50).

The evidence on the prognostic significance of the location of the residual pituitary gland is heterogeneous and dependent on definitions (classification of displacement), endpoints, and imaging times. In the original study by Di Maio et al., preoperative displacement of the normal residual gland was stratified into superior, superolateral, and lateral and correlated with postoperative pituitary function. Postoperative partial or complete loss of function was more common in patients with superior/superolateral displacement than in patients without a superior component ($P = 0.025$); in addition, greater postoperative reconstitution of the residual gland was significantly associated with better hormonal axis function ($P < 0.001$) (37). These findings support the assumption that the spatial configuration of the residual gland, particularly a superior component of displacement, may be associated with a higher risk of endocrine morbidity in certain settings.

In contrast, more recent studies examining preoperative MRI characteristics in relation to postoperative morphological reconstruction and endocrine function often place greater emphasis on quantitative parameters (tumor size/volume, extent of reconstruction) than on the location category alone. In a retrospective cohort, larger preoperative tumor size was associated with a lower probability of normal morphological reconstruction of the residual gland, and postoperative

gland morphology was related to postoperative pituitary function (52). Overall, it can be concluded that although location information may be relevant from a surgical and anatomical perspective, its prognostic significance for endocrine outcome depends on the classification used and the interaction with tumor burden and reconstruction characteristics. Against this background, the simplified dichotomization used in the present study (superior vs lateral) may not reveal an independent effect, given the predominance of stronger determinants such as residual gland volume, tumor burden, and preoperative function.

Several factors may explain why no effect of the DiMaio position was detectable in the present cohort. Dichotomization into superior vs. lateral is methodologically pragmatic, but only roughly reflects anatomical reality. The original DiMaio classification distinguishes between several subtypes (including superolateral), and this finer differentiation may be more prognostically relevant than a simplified dichotomy (37). A potential location effect may be overshadowed by stronger determinants: In the present study, residual gland volume, tumor burden, and preoperative axis insufficiency in particular showed clear relationships with the outcome, so that the location category as an additional predictor provides only limited incremental information (25,43,51). The lateral group is typically smaller, which may limit the precision for small to moderate effects; this is a common problem in clinical subgroup analyses and may explain the lack of significant differences (43,50).

Clinically, it can be concluded that the DiMaio position does not appear to be a suitable sole prognostic marker for endocrine outcome. Its primary benefit lies in the anatomical description of the residual pituitary gland and can be helpful for preoperative planning and intraoperative orientation, without necessarily leading to a clear risk assessment for “better” or “worse” (37,50). For consultation and risk stratification, quantitative parameters (residual gland volume, tumor burden) and preoperative endocrine status therefore appear to be more practical, while positional information should be interpreted more as a contextual variable (25,43,51).

Incidental findings and contextual factors

Preoperative axis insufficiency is a key contextual factor for interpreting imaging markers. Preoperative hypopituitarism reflects the cumulative effect of the tumor on the residual pituitary gland and stalk region and has been repeatedly described in systematic reviews and clinical series as a key determinant of postoperative endocrine development (43,51). More pronounced preoperative axis insufficiency indicates advanced functional damage and can therefore limit the likelihood of complete recovery and increase vulnerability to additional postoperative deficits (25,43,51). At the same time, surgical series show that even in cases of preoperative deficits, axis recovery after decompression is possible, which underscores the importance of preserved functional reserve as well as tumor- and surgery-related factors (25,44).

In context of the present results, this fits with the overarching interpretation that imaging parameters such as residual gland volume and tumor burden should not be understood in isolation but rather structure postoperative dynamics in conjunction with preoperative endocrine function. While residual gland volume was primarily associated with the likelihood of improvement, deterioration appears to be more strongly influenced by baseline function and surgical factors, which is consistent with the literature on new-onset endocrine deficits after transsphenoidal surgery (50).

Tumor size and volume are key structural elements that can significantly influence both preoperative function and postoperative outcomes. Larger tumors are associated with more pronounced mechanical effects (compression/displacement, impairment of portal circulation and pedicle region, increased intrasellar pressure) and are therefore considered key drivers of preoperative axis insufficiency (40,41,49). At the same time, tumor load can shape the morphology of the residual pituitary gland: displacement and stretching can lead to a flattened residual gland area, so that volumetric measurements of the residual gland can reflect both “reserve” and geometric effects (37,44).

In terms of postoperative outcome, tumor burden may confer both favorable and unfavorable effects. Pronounced compression can imply a higher potential for functional improvement after decompression, provided that vital residual tissue is present (40,49). Conversely, greater tumor burden is often associated with increased surgical complexity and intraoperative factors that may contribute to new deficits. Reviews particularly emphasize the role of tissue manipulation and perioperative endocrine dynamics (50). Cohorts with axis-specific evaluation also show that tumor characteristics and baseline function together determine the probability of recovery versus new deficits, underscoring the need for an integrated consideration of tumor burden, residual gland parameters, and preoperative endocrine status (51).

Limitations

The results of this study must be interpreted in the context of several limitations. First, this was a retrospective, single-center analysis, and therefore selection and information bias cannot be excluded. Unmeasured clinical factors, such as the exact duration of symptoms, comorbidities, and details of perioperative management, may influence endocrine outcomes without being fully captured in the dataset (50).

The study design is largely based on imaging measurements. Volumetric parameters (residual gland and tumor volume) depend on image quality, segmentation method, and boundary definition and may contain measurement errors. In addition, a morphologically measured residual gland volume only indirectly reflects the functional reserve, since “visible” tissue is not necessarily vital or hormonally active (37,44). The classification of residual gland location according to DiMaio was also deliberately simplified in the present evaluation (superior vs. lateral); this may lead to an underestimation of a potential location effect, especially if finer subtypes (e.g. superolateral) are more prognostically relevant (37).

Furthermore, the endocrine outcome can be easily communicated clinically as a three-level category (better/unchanged/worse) but remains relatively crude.

Axis-specific differences (e.g. higher recovery rates for individual axes compared to others) and time-dependent effects of recovery can therefore only be represented to a limited extent (43,51). It is also plausible that postoperative deterioration is more strongly influenced by surgical and early postoperative factors; these are often only available in a limited standardized form in retrospective data sets (50).

Summary and outlook

Overall, the results show that preoperative imaging markers of residual pituitary gland and tumor burden are related to postoperative endocrine development. A higher preoperative residual gland volume was consistently associated with a higher probability of postoperative improvement, while no stable independent volume effect was detectable for deterioration. The location of the residual gland according to DiMaio (superior vs. lateral), on the other hand, showed no independent prognostic influence on better or worse outcomes, so that the topographical classification in this simplified form should primarily be interpreted as anatomical context. The findings support integrated risk stratification that evaluates residual gland volume not in isolation but together with tumor burden and preoperative axis insufficiency.

For further studies, it is necessary to validate these results in prospective and, if possible, multicenter cohorts, ideally using standardized volumetry protocols and data on interrater reliability. A more detailed mapping of the residual gland location (including subtypes) as well as axis-specific and time-dependent endpoints could improve selectivity and allow for more differentiated examination of mechanisms.

In addition, models that systematically take surgical variables (e.g. degree of resection, intraoperative manipulation markers) into account would be useful, particularly to better explain the risk of new deficits.

5. Conclusion

In summary, this study shows that a higher preoperative residual gland volume is consistently associated with a higher probability of postoperative improvement in pituitary function. In contrast, no stable independent volume effect was found for postoperative deterioration, which underscores the multifactorial genesis of newly occurring deficits and the importance of surgical and early postoperative influences. The DiMaio position (superior vs. lateral) did not show any independent prognostic contribution in this cohort and should therefore be interpreted primarily as anatomical context information.

Overall, the findings support integrated preoperative risk stratification, in which residual gland volume, tumor burden, and preoperative axis insufficiency are used together for consultation.

References

1. Lechan RM, Toni R. Functional anatomy of the hypothalamus and pituitary. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2016–.

2. Melmed S, Auchus RJ, Goldfine AB, Koenig RJ, Rosen CJ, editors. Williams Textbook of Endocrinology. 14th ed. Philadelphia: Elsevier; 2020.

3. Melmed S, editor. The Pituitary. 4th ed. Amsterdam: Academic Press; 2017.

4. Paulsen F, Waschke J. Sobotta atlas of human anatomy. Vol. 3: Head, neck and neuroanatomy. 15th ed. Munich: Elsevier/Urban & Fischer; 2011.

5. Rhoton AL Jr, Harris FS, Renn WH. Microsurgical anatomy of the sellar region and cavernous sinus. Clin Neurosurg. 1977;24:54-85.

6. Feldt-Rasmussen U, Effraimidis G, Klose M. The hypothalamus–pituitary–thyroid (HPT) axis and its role in physiology and pathophysiology of other hypothalamus–pituitary functions. Mol Cell Endocrinol. 2021;525:111173.

7. Briet C, Salenave S, Bonneville JF, Laws ER, Chanson P. Pituitary apoplexy. Endocr Rev. 2015;36(6):622–645.

8. Asa SL, Ezzat S. The pathogenesis of pituitary tumours. Nat Rev Cancer. 2002;2(11):836–849.

9. Daly AF, Beckers A. The epidemiology of pituitary adenomas. Endocrinol Metab Clin North Am. 2020;49(3):347–355.

10. Chin SO, Ku CR, Kim BJ, Kim SW, Park KH, Kim YJ, et al. Epidemiology of functioning pituitary adenomas. Endocrinol Metab (Seoul). 2020;35(2):237–245.

11. Melmed S, Kaiser UB, Lopes MB, Bertherat J, Syro LV, Raverot G, et al. Clinical biology of the pituitary adenoma. Endocr Rev. 2022;43(6):1003–1037.

12. Osamura RY, Lopes MB, Grossman A, Kontogeorgos G, Trouillas J. Pituitary tumors in the 5th WHO classification of endocrine tumors. Endocr Pathol. 2022;33(1):6–26.

13. Casar-Borota O, Burman P, Lopes MB. The 2022 WHO classification of tumors of the pituitary gland: an update on aggressive and metastatic pituitary neuroendocrine tumors. Brain Pathol. 2024;34(1):e13163.

14. Melmed S. Pituitary-tumor endocrinopathies. N Engl J Med. 2020;382(10):937–950.

15. Dekkers OM, Pereira AM, Romijn JA. Treatment and follow-up of clinically nonfunctioning pituitary macroadenomas. J Clin Endocrinol Metab. 2008;93(10):3717–3726.

16. Ezzat S, Asa SL, Couldwell WT, Barr CE, Dodge WE, Vance ML, et al. The prevalence of pituitary adenomas: a systematic review. Cancer. 2004;101(3):613–619.

17. Freda PU, Beckers AM, Katznelson L, Molitch ME, Montori VM, Post KD, et al. Pituitary incidentaloma: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(4):894–904.

18. Molitch ME. Pituitary incidentalomas. Endocrinol Metab Clin North Am. 2020;49(3):375–387.

19. Nomikos P, Ladar C, Fahlbusch R, Buchfelder M. Impact of primary surgery on pituitary function in patients with nonfunctioning pituitary adenomas – a study on 721 patients. Acta Neurochir (Wien). 2004;146(1):27–35.

20. Fatemi N, Dusick JR, Mattozo C, McArthur DL, Cohan P, Boscardin J, et al. Pituitary hormonal loss and recovery after transsphenoidal adenoma removal. Neurosurgery. 2008;63(4):709–719.

21. Zhang Y, Zheng J, Huang Z, Teng Y, Chen C, Xu J. Predicting visual recovery in pituitary adenoma patients post-endoscopic endonasal transsphenoidal surgery: harnessing delta-radiomics of the optic chiasm from MRI. Eur Radiol. 2023;33(11):7482–7493.

22. Iglesias P, Díez JJ. An update on advances in hypopituitarism: etiology, diagnosis, and treatment. J Clin Med. 2024;13(20):6161.

23. Fleseriu M, Hashim IA, Karavitaki N. Hypopituitarism. Lancet. 2024;403(10430):xxx–xxx.

24. Al-Shamkhi N, Berinder K, Borg H, Burman P, Dahlqvist P, Olsson DS, et al. Pituitary function before and after surgery for nonfunctioning pituitary adenomas: data from the Swedish Pituitary Register. Eur J Endocrinol. 2023;189(2):217–224.

25. Mavromati M, Mavrakanas T, Jornayvaz FR, Schaller K, Fitsiori A, Vargas MI, et al. The impact of transsphenoidal surgery on pituitary function in patients with non-functioning macroadenomas. Endocrine. 2023;81(2):340–348.

26. Crespo I, Valassi E, Webb SM. Quality of life in patients with hypopituitarism. Curr Opin Endocrinol Diabetes Obes. 2015;22(4):306–312.

27. Ishii H, Nishikawa T, Kubota N, Wada S, Iwatani Y. The adult hypopituitarism questionnaire (AHQ): reliability and validity for evaluating quality of life in adult patients with hypopituitarism. PLoS One. 2012;7(4):e44304.

28. Pappachan JM, Raskauskiene D, Kutty VR, Clayton RN. Excess mortality associated with hypopituitarism in adults: a meta-analysis of observational studies. J Clin Endocrinol Metab. 2015;100(4):1405–1411.

29. Burman P, Mattsson AF, Johannsson G, Höybye C, Holmer H, Dahlqvist P, et al. Deaths among adult patients with hypopituitarism: hypocortisolism during acute stress, and de novo malignant brain tumours contribute to an increased mortality. J Clin Endocrinol Metab. 2013;98(4):1466–1475.

30. Ebrahimi F, Johannsson G, Ragnarsson O. Excess mortality among hospitalized patients with hypopituitarism. J Clin Endocrinol Metab. 2020;105(11):e3942–e3951.

31. Arafah BM. Reversible hypopituitarism in patients with large nonfunctioning pituitary adenomas. J Clin Endocrinol Metab. 1986;62(6):1173–1179.

32. Webb SM, Rigla M, Wägner A, Oliver B, Bartumeus F. Recovery of hypopituitarism after neurosurgical treatment of pituitary adenomas. J Clin Endocrinol Metab. 1999;84(10):3696–3700.

33. Nomikos P, Ladar C, Fahlbusch R, Buchfelder M. Impact of primary surgery on pituitary function in patients with non-functioning pituitary adenomas – a study on 721 patients. Acta Neurochir (Wien). 2004;146(1):27–35.

34. Fatemi N, Dusick JR, Mattozo C, McArthur DL, Cohan P, Boscardin J, et al. Pituitary hormonal loss and recovery after transsphenoidal adenoma removal. Neurosurgery. 2008;63(4):709–718.

35. Little AS, Gardner PA, Fernandez-Miranda JC, Chicoine MR, Barkhoudarian G, Prevedello DM, et al. Pituitary gland recovery following fully endoscopic transsphenoidal surgery for nonfunctioning pituitary adenoma: results of a prospective multicenter study. J Neurosurg. 2020;133(6):1732–1741.

36. De Alcubierre D, Puliani G, Cozzolino A, Hasenmajer V, Minnetti M, Sada V, et al. Pituitary adenoma consistency affects postoperative hormone function: a retrospective study. BMC Endocr Disord. 2023;23(1):92.

37. Di Maio S, Biswas A, Vézina JL, Hardy J, Mohr G. Pre- and postoperative magnetic resonance imaging appearance of the normal residual pituitary gland following macroadenoma resection: clinical implications. Surg Neurol Int. 2012;3:67.

38. Micko A, Hosmann A, Marik W, Bartsch S, Weber M, Knosp E, et al. Optimizing MR imaging for intraoperative image guidance in sellar pathologies. Pituitary. 2020 Jun;23(3):266–72.

39. Freda PU, Beckers AM, Katznelson L, Molitch ME, Montori VM, Post KD, Vance ML; Endocrine Society. Pituitary incidentaloma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2011 Apr;96(4):894-904. doi: 10.1210/jc.2010-1048. PMID: 21474686; PMCID: PMC5393422.

40. Arafah BM, Prunty D, Ybarra J, Hlavin ML, Selman WR. The dominant role of increased intrasellar pressure in the pathogenesis of hypopituitarism, hyperprolactinemia, and headaches in patients with pituitary adenomas. J Clin Endocrinol Metab. 2000;85(5):1789–1793. doi:10.1210/jcem.85.5.6565.

41. Zayour DH, Selman WR, Arafah BM. Extreme elevation of intrasellar pressure in patients with pituitary tumor apoplexy: relation to pituitary function. J Clin Endocrinol Metab. 2004;89(11):5649–5654. doi:10.1210/jc.2004-0884.

42. Staby I, Krogh J, Klose M, Baekdal J, Feldt-Rasmussen U, Poulsgaard L, Springborg JB, Andreassen M. Pituitary function after transsphenoidal surgery including measurement of basal morning cortisol as predictor of adrenal insufficiency. Endocr Connect. 2021;10(7):750–757. doi:10.1530/EC-21-0155.

43. Pedersen MB, Andreassen M, Springborg J, Krogh J. Endocrine function after transsphenoidal surgery in patients with non-functioning pituitary adenomas: a systematic review and meta-analysis. Neuroendocrinology. 2022;112(9):823–834. doi:10.1159/000522090.

44. Harary M, DiRisio AC, Dawood HY, et al. Endocrine function and gland volume after endoscopic transsphenoidal surgery for nonfunctional pituitary macroadenomas. J Neurosurg. 2019;131(4):1142–1151. doi:10.3171/2018.5.JNS181054.

45. Schur S, Lasry O, Tewfik MA, Di Maio S. Assessing the association of tumor consistency and gland manipulation on hormonal outcomes and delayed hyponatremia in pituitary macroadenoma surgery. Interdiscip Neurosurg. 2020;19:100628. doi:10.1016/j.inat.2019.100628.

46. Hoang AN, McGahan BG, Cua S, et al. Pituitary stalk stretch predicts postoperative diabetes insipidus after pituitary macroadenoma transsphenoidal resection. Oper Neurosurg (Hagerstown). 2023;24(3):248–255. doi:10.1227/ons.0000000000000501.

47. Xue L, Wu J, Chen J, Yang Y. Change in the pituitary stalk deviation angle after transsphenoidal surgery can predict the development of diabetes insipidus for pituitary adenomas. Endocr Connect. 2022;11(11):e220187. doi:10.1530/EC-22-0187.

48. Becker R, Hlavac M, Etzrodt-Walter G, et al. Pituitary stalk morphology as a predictor of new-onset adrenocortical insufficiency and arginine vasopressin deficiency after transsphenoidal resections of pituitary macroadenomas: a retrospective single-center study with a focus on iMRI. Cancers (Basel). 2023;15(15):3929. doi:10.3390/cancers15153929.

49. Jane JA Jr, Catalino MP, Laws ER Jr. Surgical treatment of pituitary adenomas. In: Feingold KR, Adler RA, Ahmed SF, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; updated 2022 Mar 9.

50. Prete A, Corsello SM, Salvatori R. Current best practice in the management of patients after pituitary surgery. Ther Adv Endocrinol Metab. 2017;8(3):33–48. doi:10.1177/2042018816687240.

51. Hwang JY, Aum DJ, Chicoine MR, et al. Axis-specific analysis and predictors of endocrine recovery and deficits for non-functioning pituitary adenomas undergoing endoscopic transsphenoidal surgery. Pituitary. 2020;23(4):389–399. doi:10.1007/s11102-020-01045-z.

52. Hassani B, Hashemi-Madani N, Ataee Kachuee M, Khamseh ME. Magnetic resonance imaging characteristics predict pituitary function in non-functional pituitary macro-adenoma undergoing trans-sphenoidal surgery. BMC Med Imaging. 2022;22(1):60. doi:10.1186/s12880-022-00787-5.

In this work, the following AI-based tools were used solely to optimize the language or wording in accordance with the applicable standards for good scientific practice of the Medical University of Graz:

1. DeepL Write, DeepL SE, https://www.deepl.com/de/write
2. ChatGPT 5.2, OpenAI, https://chatgpt.com