FACULTY OF MEDICINE
AND HEALTH SCIENCES

4 YEARS 4-HANDS SURGERY

SURGICAL RESULTS AFTER ENDOSCOPIC PITUITARY SURGERY

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WORD OF GRATITUDE

A great number of individuals contributed to this masterthesis and we would like to express our sincere gratitude towards them.

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ABSTRACT

4 years 4-hands surgery: surgical results after endoscopic pituitary surgery

Introduction: The aim of this study is to investigate the outcome of endoscopic transsphenoidal surgery (ETSS) for pituitary adenomas (PAs), performed by a duo of surgeons. Complication rates, as well as postoperative outcomes, were compared with results in literature. Prognostic factors for postoperative outcomes were studied. Parameters indicating cure were compared between patients with a microadenoma and patients with a macro- or giant adenoma. Learning curves were plotted, exploring the number of patients needed to be treated in order to reach a proficiency level.

Materials and method: Retrospective analysis of surgical outcomes in 82 patients with PAs, operated at the Ghent University Hospital between January 2012 and July 2018, was performed. Patient files were consulted in order to collect data.

Results: Postoperative complications (transient and permanent) were observed in 17 cases (20.7%). Postoperative haemorrhage, perioperative internal carotid artery (ICA) injury, severe epistaxis, transient coma and postoperative decreased visual acuity were not observed in this patient population. Also, death did not occur. Meningitis, permanent diabetes insipidus (PDI), hyposmia and panhypopituitarism were each present in 1.2% of the cases. Seven patients (8.5%) experienced transient diabetes insipidus (TDI). Syndrome of inappropriate antidiuretic hormone secretion (SIADH) was seen in two patients (2.4%). A postoperative cerebrospinal fluid (CSF) leak was diagnosed in four cases (4.9%). Hormonal dysfunction was newly induced in ten cases (12.2%). In 87.1% of patients, who suffered from preoperative visual deficit and/or diplopia, a postoperative improvement was observed. 91.2% of patients with preoperative hormonal deficiency, had a partial or total recovery. In cases where a FA was diagnosed, 39.9% of these patients achieved complete hormonal remission. Complete removal was achieved in 55.1% and gross total removal (GTR) in 74.4%.

The preoperative size of the adenoma was related to the postoperative presence of a remnant, hormonal control and a newly induced hormonal dysfunction. A significant association between cavernous sinus invasion and incomplete adenoma resection was found. Also, previous surgery seems to affect the presence of a remnant.

Conclusion: The performance of the surgeons in this study was comparable to literature, even though the patient population was challenging. Higher rates were found for hormonal recovery and ophthalmologic outcomes. Results regarding hormonal remission and remnant were slightly lower than in literature. Adenoma size, Knosp grade, previous surgery and invasion of the cavernous sinus were prognostic factors for specific postoperative outcomes.

4 jaar 4-handen chirurgie: resultaten na endoscopische hypofyseheelkunde

Introductie: In dit onderzoeksproject worden de resultaten na endoscopische transsfenoïdale hypofyseheelkunde onderzocht. Alle operaties werden uitgevoerd door hetzelfde duo chirurgen. Zowel complicatiecijfers als resultaten na chirurgie werden vergeleken met deze uit de literatuur. Prognostische factoren voor de inschatting van postoperatieve uitkomsten werden onderzocht. Leercurves werden opgesteld en geïnterpreteerd.

Materialen en methodologie: In deze studie zijn 82 patiënten met een hypofyseadenoom opgenomen. Hiervoor ondergingen deze patiënten een operatie tussen januari 2012 en juli 2016 in het Universitair Ziekenhuis Gent. Patiënten eigenschappen en hun postoperatieve resultaten werden retrospectief opgezocht in het elektronisch patiëntendossier.

Resultaten: Postoperatieve complicaties waren aanwezig bij 17 patiënten (20,7%). Postoperatieve bloeding, perioperatieve beschadiging van de a. carotis interna, ernstige epistaxis, postoperatieve vermindering van het zicht, transiënt coma en overlijden kwamen niet voor. Meningitis, permanente diabetes insipidus, hyposmie en panhypopituarisme werden elk vastgesteld bij 1,2% van de gevallen. Een transiënte episode van diabetes insipidus werd geobserveerd bij zeven patiënten (8,5 %). SIADH werd bij twee patiënten (2,4%) vastgesteld. Een postoperatief CSF lek werd gediagnosticeerd in vier gevallen (4,9%). Nieuw geïnduceerde hormonale dysfunctie werd gezien in tien gevallen (12,2%). 87,1% van de patiënten die preoperatief visuele klachten en/of diplopie meldden, ervaarden een verbetering postoperatief. 91,2% van de patiënten met preoperatieve hormonale uitval herstelden partieel of volledig. Van alle patiënten gediagnosticeerd met een functionerend adenoom, herstelde 39,9% naar normale hormoonwaarden. Volledige resectie werd bekomen in 55,1%. *Gross total removal* werd vastgesteld in 74,4%.

De preoperatieve grootte van het adenoom was gecorreleerd met het postoperatief achterblijven van een rest, hormonale controle en een nieuw geïnduceerde hormonale disfunctie. Een significant verband werd gevonden tussen invasie van de sinus cavernosus en incomplete resectie. Ook voorafgaande hypofyse chirurgie beïnvloedde de aanwezigheid van restweefsel.

Conclusie: De prestaties van de chirurgen aangehaald in deze studie waren vergelijkbaar met die in de literatuur, hoewel de moeilijkheidsgraad van de aandoeningen bij de patiëntenpopulatie hoog was. Betere resultaten konden waargenomen worden voor hormonaal en oftalmologisch herstel. De resultaten voor hormonale remissie en restweefsels waren iets lager dan deze in literatuur. Adenoomgrootte, Knosp graad, eerdere operaties en invasie van de sinus cavernosus waren prognostische factoren voor specifieke postoperatieve resultaten.

1 INTRODUCTION

1.1 Anatomy of the pituitary gland

The pituitary gland, also known as the hypophysis, is located at the inferior side of the brain near the optic chiasm. It can be subdivided into two main parts: the anterior pituitary or adenohypophysis and the posterior pituitary or neurohypophysis. The intermediate lobe is small in humans. Embryologically, the adenohypophysis originates from an invagination of Rathke's pouch (oral ectoderm), while the neurohypophysis arises from a bulge of the third ventricular floor (neural ectoderm) (1,2). A small stalk called the infundibulum connects the hypothalamus to the hypophysis, containing the portal blood supply. This unpaired gland is caudally entirely enclosed by the sella turcica, a basket shaped depression of the sphenoid bone (1,3). In transsphenoidal surgery (TSS), the pituitary gland can be accessed by opening the sphenoid sinus which is located anteriorly and caudally of this gland. The basilar artery and the pons are located posteriorly and the chiasma opticum superiorly to this gland. Lateral of the sella turcica, the cavernous sinus and ICA can be found (1) (see Figure 1).

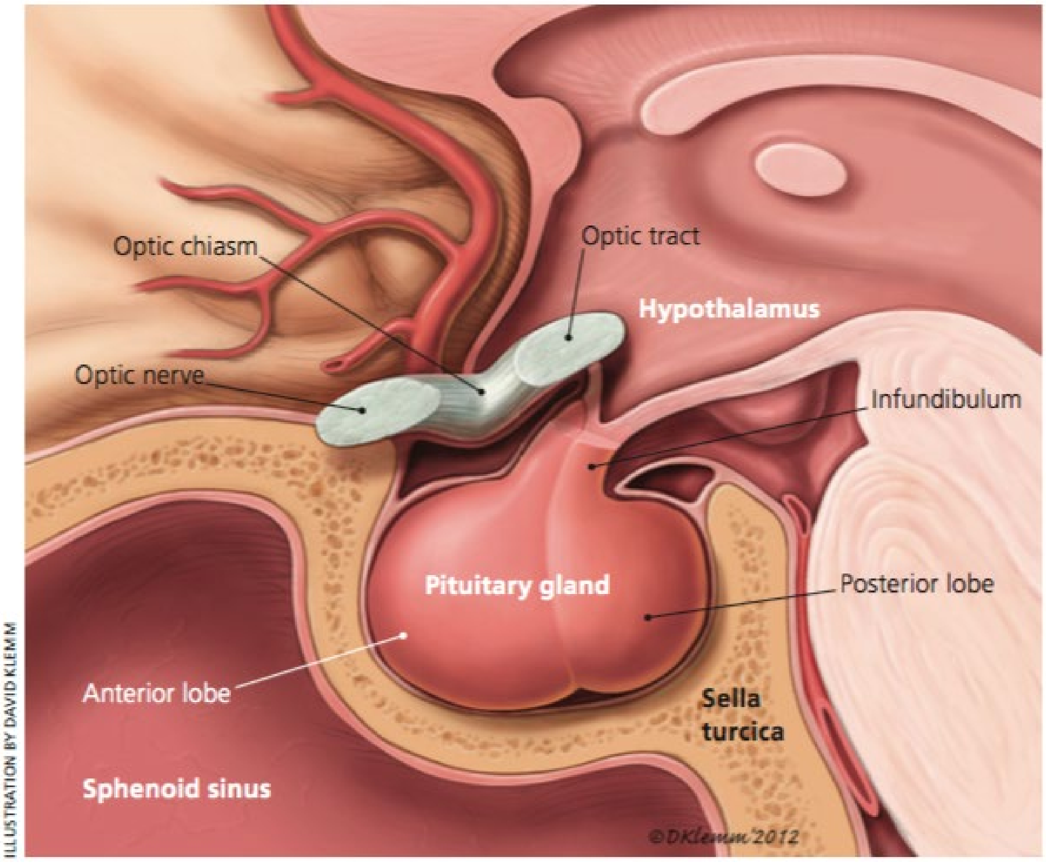

Figure 1. Anatomy of the pituitary gland (3)

1.2 Physiology of the pituitary gland

1.2.1 Hormones

The hypothalamus controls the pituitary gland by releasing inhibitory or trophic hormones in the pituitary portal blood: dopamin, somatostatin, growth hormone releasing factor, corticotropin releasing hormone (CRH), thyrotropin releasing hormone (TRH) and gonadotropin releasing hormone (GnRH). In response to these hormones, the anterior pituitary gland secretes respectively: prolactin, growth hormone (GH), adrenocorticotropic hormone (ACTH), thyroid stimulating hormone (TSH), luteinizing hormone (LH) and follicle stimulating hormone (FSH).
The posterior pituitary stores and releases oxytocin and anti-diuretic hormone (ADH) (2).

1.2.2 Feedback system

Negative feedback guarantees the strict regulation of most hormone systems in the human body. For example, TSH stimulates the release of thyroxine and triiodothyronine by the thyroid gland. Elevated serum levels of these peripheral hormones are sensed by specific receptors on pituitary and hypothalamic cells. By this mechanism, TRH and TSH release is supressed in case of peripheral hormone excess (2).

Hormone levels can significantly raise above the normal set-point in patients suffering from secreting neuroendocrine PAs. These tumours are usually considered as autonomous functioning entities. Nevertheless, it is suggested that these tumours are still under some control of negative feedback. However, the so-called set-point of the tumour cells is higher than in physiological conditions (2).

Somatotropin release inhibiting factor, also known as somatostatin, can inhibit the pituitary secretion of growth hormone. Additionally, it has the ability to inhibit the secretion of TSH and prolactin (2).

Prolactin releasing inhibiting factors (PIF) refer to a number of hypothalamic peptides which are able to inhibit the secretion of prolactin. Dopamine turns out to be a powerful inhibitor of the prolactin secretion. All anterior pituitary hormones, except for prolactin, are under primarily positive control by the above mentioned hypothalamic releasing hormones. Prolactin on the contrary, is predominantly under tonic inhibition of PIF (2).

1.3 Pituitary adenomas

1.3.1 Definition

Despite significant morbidity that can be associated with PAs, they are defined as benign (i.e. do not metastasize) tumours arising from the adenohypophysis. PAs are also known as pituitary neuroendocrine tumours (3–7).

Pituitary carcinomas do metastasize. On imaging, they cannot be distinguished from an ordinary PA before metastasizing (6). Less than 1% of the pituitary neoplasms are carcinomas (8).

1.3.2 Epidemiology

PAs are without doubt the most common tumours arising from the pituitary gland (4,6). The differential diagnosis of sellar masses is described in section 1.3.5.1.

PAs are not exceptional: they account for 10-15% of all intracranial tumours and 25% of all surgically resected intracranial neoplasms (3–5). The improved and highly sensitive imaging techniques contribute to a higher detection rate and an increasing number of incidental findings. The exact incidence and prevalence of PAs is unclear (3,4). The incidence in literature varies from 1 to 7 per 100,000 persons (5). Autopsy studies suggest that the prevalence of PAs is 20% and even closer to 30% in individuals aged between 50 and 60 years old. It is important to be aware that the bulk of the adenomas found during autopsy were incidentalomas without any clinical impact. In the overall population, the prevalence of clinically relevant PAs rises with age and approximates 0.1% (3–5). So these benign PAs generally appear during adulthood and are rarely diagnosed during childhood (9). The average age at diagnosis is 39-44 years (5).

A small, insignificant pituitary lesion is present in 10-20% of the persons who do not exhibit any overt features of pituitary disease. The so-called incidentalomas are lesions discovered on magnetic resonance imaging (MRI) in an asymptomatic patient. In that case, the MRI was performed for an indication unrelated to pituitary disorders (3,4,10).

The majority of the PAs occur sporadically (4). Hereditary syndromes such as multiple endocrine neoplasia type I (MEN-I) account for less than 5% of all PAs (10). In about 40% of all individuals with the syndrome of MEN-I, a PA will develop during lifetime. Predisposing somatic mutations are identified in a significant minority (4).

1.3.3 Classification

PAs can be classified according to their size and invasion of adjacent structures, their histological characteristics and their ability to secrete hormones (3–5,9,11–13).

1.3.3.1 Size and Knosp grading system

Based on their largest diameter, PAs can be subdivided into three types: microadenomas (<1 cm), macroadenomas (≥1 cm) and giant adenomas (≥40 mm) (3,9,11–15).

The Knosp score is an internationally acknowledged classification system for PAs based on parasellar expansion and invasion of the cavernous sinus. The relationship of the tumour to the ICA is defined and graded 0, 1, 2, 3 (A or B) or 4 (see Figure 2). Grade 0 is assigned to a lesion where no invasion of the cavernous sinus is observed. To evaluate whether or not a grade 1 is present, a line connecting the centres of the intra- and supracavernous ICA is drawn. If a lateral extension is present, but it does not exceed this line, this PA is classified as a grade 1. The extension in the cavernous sinus in a grade 2 is more comprehensive than in a grade 1, but it does not pass the lateral tangent of the intra- and supracavernous ICA. As opposed to a grade 2, a grade 3 does extend lateral of this line. A grade 4 can be distinguished from a grade 3 by the presence of total encasement of the intracavernous ICA (16). The invasiveness is an important negative predicting factor to assess the outcome of surgical treatment: some studies proved that individuals with Knosp grades 3 and 4 are less likely to achieve complete resection and remission. Operating these kinds of invasive lesions is surgically challenging due to the many neurovascular elements in this area (10,12,17–19).

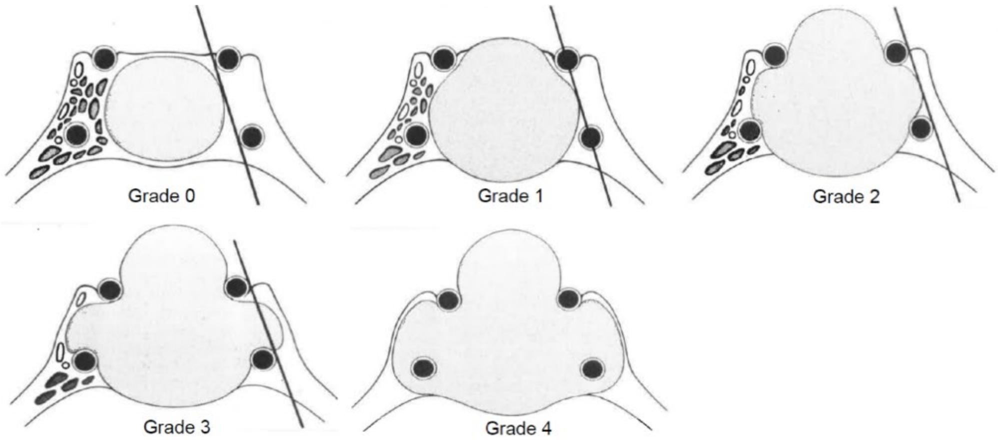

Figure 2. Knosp grading system (16)

1.3.3.2 World Health Organization (WHO) histological classification

The differentiation between chromophobic, acidophilic and basophilic adenomas based on their staining properties is outdated (6).

In 2017 the WHO classification of endocrine tumours was updated. Adequate classification requires immunohistochemistry using antibodies against commonly used diagnostic markers, hormones of the adenohypophysis (GH, PRL, ACTH, β-TSH, β-LH, β-FSH, and α-subunit of glycoproteins) and, pituitary transcription factors (PIT-1, SF-1 and T-PIT) involved in hormonal secretion and cytodifferentiation (6,19).

PAs arise from neuroendocrine cells. Certain transcription factors are associated with differentiation into one of the three main cell lineages: the acidophilic, the gonadotrophic or the corticotropic cell lineage. PIT-1 is an essential transcription factor that mediates differentiation into thyrotroph, lactotroph and somatotroph pituitary cells. SF-1 regulates differentiation into gonadotroph pituitary cells and T-PIT into corticotroph pituitary cells (19). Therefore PIT-1, SF-1 and T-PIT are cell lineage specific transcription factors that can be used as diagnostic tools, especially for NFPAs (19). The evidence that each subclass corresponds to a different prognosis and recurrence rate emphasizes the importance of these investigations (6). Only one study routinely used an assessment of transcription factors for tumour classification (20).

The 2017 WHO classification system defines seven categories of PAs: somatotroph adenoma, lactotroph adenoma, thyrotroph adenoma, corticotroph adenoma, gonadotroph adenoma, null-cell adenoma and plurihormonal and double adenomas (19,21). Somatroph adenomas for example, are defined as PAs that mainly produce GH and are derived from the PIT-1 cell lineage. Null-cell adenomas do not show immunoreactivity for a specific pituitary hormone and transcription factor (19). The pituitary cell lineage, rather than the hormone the adenoma produces or not, is the principal classifier (10,21).

1.3.3.3 Functional classification

In literature, PAs that are not associated with biochemical or clinical evidence of hypersecretion are often described as NFPAs. Hormonal excess syndromes also exist (2). However, following the latest WHO classification the concept of a “hormone-producing adenoma” is considered to be an obsolete term, because even NFPAs may produce small amounts of LH, FSH, the α-subunit of LH, TSH or ACTH (2,19). When a PA causes no endocrine hypersecretion syndrome in patients, the term “silent adenoma” seems more suitable. For example, most gonadotroph adenomas are considered to be clinically silent tumours. Among all silent adenomas, corticotroph adenomas seem to be the most common subtype. In these patients neither elevated ACTH levels nor Cushing’s disease is present (19).

1.3.4 Clinical manifestations

Although PAs can remain asymptomatic, a broad spectrum of clinical signs and symptoms can occur. Mass effects related to an increasing size and/or invasion, as well as syndromes of hypersecretion and pituitary deficiency, are observed (3,5).

1.3.4.1 Tumour expansion

PAs are able to extend superiorly (suprasellar) and laterally (parasellar), but also in a downward extension in to the sphenoid sinus. In this case, erosion of the sellar floor concomitant with dural perforation can cause cerebrospinal fluid rhinorrhoea (2).

Headache is a non-specific, but common symptom in patients with PAs. Stress on or invasion of the meninges and bony structures surrounding the pituitary gland is associated with headaches (2). A headache does not necessarily correlate with the size of the adenoma (3,9).

Visual deficit is another neurologic symptom, that unlike headaches, tends to correlate with the size of the adenoma. It can develop due to suprasellar expansion and subsequently put pressure on the optic nerve and/or chiasm. Bitemporal hemianopsia is a well-known complication linked to PAs that arises as the optic chiasm is compressed in the centre. Other compression patterns are associated with other types of visual field defects. It is possible that patients are not aware of their slow progression visual field loss until they get tested by an ophthalmologist. Other possible visual deficits are central scotomas, homonymous hemianopsia and asymmetric visual fields. A weakened visual acuity is reported in cases of persistent and significant compression or invasion of the optic nerve (1,3,9).

Parasellar expansion may involve cavernous sinus invasion affecting vascular components (encasement of ICA) and/or neuronal structures. Paresis or even paralysis of the extraocular muscles can arise when the oculomotor nerve, the trochlear nerve and/or the abducens nerve are damaged. Due to this compromised function, the patient can experience diplopia (9).

Temporal lobe epilepsy triggered by invasion or compression of the temporal lobe is a rare observation, since PAs are hardly able to reach the temporal lobe. Likewise, intracranial hypertension and occlusion of the ICA are documented, but very rare phenomena (2,22).

The acute manifestation of severe headache, hypotension or shock and bilateral visual deficits are suggestive for pituitary apoplexy. This acute vascular event is most commonly caused by a haemorrhage in the PA. The elevated pressure on the surrounding structures contributes to the loss of blood supply of the hypophysis. Eventually necrosis might occur, accompanied by (pan)hypopituitarism in some cases (23).

1.3.4.2 Deficiency of normal pituitary functions

Growth of a PA can compress the pituitary stalk, preventing dopamine and hypothalamic releasing hormones to reach the anterior pituitary (2). Loss of inhibition of prolactin release results in hyperprolactinemia. As elevated prolactin inhibits the GnRH release, central hypogonadism can be the result (3,4,24).

Hypopituitarism refers to an inefficient or ceased release of one or more anterior pituitary hormones. The term panhypopituitarism defines a status of deficient functioning of all the anterior pituitary axes. Because this phenomenon usually arises gradually and mild deficiencies may not cause overt clinical symptoms, hypopituitarism is often detected late (2,10). In case of a PA, multiple hypothalamic-pituitary axes are often involved (2).

1.3.4.3 Overproduction of hormones

PAs are frequently able to produce anterior pituitary hormones. In some cases, hormones are secreted in clinically significant excess. Three well-known hormonal excess syndromes are described: hyperprolactinemia, acromegaly and Cushing’s disease (2–4,25). Note that thyrotroph and gonadotroph adenomas can also be associated with a clinically significant excess of respectively TSH, FSH or LH, but this is uncommon. Occasionally, a PA can excessively produce more than one anterior pituitary hormone (e.g., GH and prolactin) (2).

Hyperprolactinemia can remain silent or subclinical. Galactorrhoea occurs in roughly 35% of all women with biochemical hyperprolactinemia (26). Low levels of FSH and LH in women are associated with oestrogen deficiency, amenorrhoea and lowered sexual desire. In men central hypogonadism causes erectile dysfunction and gynaecomastia. In both sexes infertility can follow (3,4).

High levels of GH and insulin-like growth factor-I (IGF-I) can be linked with somatotroph adenomas and acromegaly. Gigantism can occur when GH excess is present at the moment the epiphyses are not closed yet. In adults enlargement of the hands, feet and jaw is frequently observed (4). Other clinical symptoms can arise such as hyperhidrosis, decreased sexual desire, asthenia and arthralgia (3). A diagnosis of acromegaly must always be treated as this syndrome is associated with important morbidity and a higher mortality rate compared to the general population (25).

Although corticotroph adenomas can be silent, they can be a cause of Cushing’s disease. An excess of ACTH could be assumed in patients presenting a so-called “moon face” and “buffalo hump”, plethora, central obesity, striae, lowered sexual desire, irritability, depression and muscle weakness. In women hirsutism and amenorrhoea can develop (3).

1.3.5 Diagnosis

1.3.5.1 Differential diagnosis

If an intrasellar mass is diagnosed on MRI, it will most likely be a PA. Although PAs are frequent, other lesions such as craniopharyngiomas and Rathke cleft cysts should be considered. Benign lesions (meningiomas), uncommon malignant tumours (germ cell tumours, gliomas, pituitary carcinomas, …), inflammatory masses, vascular malformations, cystic lesions, etc. can also be present (2,10).

Approximately 2% of all intracranial neoplasms are craniopharyngiomas. They can be discovered in the sellar or suprasellar region. Craniopharyngiomas most frequently occur in early life. Symptomatic craniopharyngiomas are generally treated by surgical excision. Despite these lesions being benign, recurrence is frequently observed (27,28).

Radiological investigations along with clinical assessment and biochemical analysis should help in the differential diagnosis (10). Evaluation of the complete pituitary function is recommended in order to detect or confirm hypopituitarism and/or excess secretion (2,3).

1.3.5.2 Ophthalmologic examination

Ophthalmologic examination can be considered if a PA is present, especially when the PA reaches the optic chiasm. Visual deficit can be present, without the patient being aware of it (3). In order to detect early visual field deficits, Goldman perimetry is the investigation of choice (2,10). Assessment by confrontation executed by a general physician can be valuable too (2). Long-term existence of a visual deficit diminishes the postoperative chance of improved visual function (10,22).

1.3.5.3 Radiological investigations

CT-scan

Computed tomography (CT) is inferior to MRI in evaluating lesions of the sellar and suprasellar region (22). Nowadays, CT is only indicated when MRI is not available or contra-indicated (e.g., cardiac pacemakers) (1,3,22). Both CT and MRI can lead to incidental findings of a pituitary mass (1).

MRI

When suspecting a PA, gadolinium contrast-enhanced magnetic resonance imaging (CE-MRI) is the golden standard (1,2,10,22). PAs are characterized by a lower affinity for gadolinium contrast compared to the normal pituitary gland. When a PA is strongly suspected, although CE-MRI shows a normal pituitary gland, dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) can be helpful, especially to detect a microadenoma (1,22). In some cases

DCE-MRI is useful in evaluating macroadenomas as well (e.g., invasion of the cavernous sinus) (29).

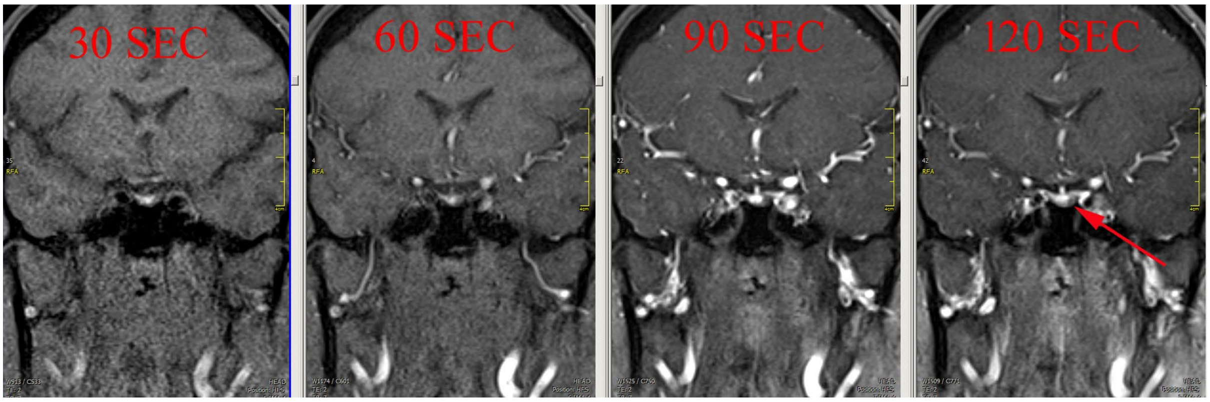

Figure 3. Dynamic contrast-enhanced MRI

In DCE-MRI several sets of images are obtained at multiple time points following contrast injection (e.g., after 30 sec, after 60 sec, after 90 sec and after 120 sec) (see Figure 3) (29,30). This imaging technique is based on the significant difference in the signal-time curves between normal pituitary tissue and PAs. The enhancement-curve of the normal pituitary tissue shows a faster wash-in compared to the PA (30). Approximately 30-80 seconds after contrast injection the normal pituitary gland is maximally enhanced, while the PA is still relatively dark (non-enhanced) (29,30). At this point of maximal image contrast, an adenoma can be recognised as a small dark region surrounded by major enhancement (white) (29). Subsequently the signal intensity of the adenoma gradually increases and eventually overtops the already decreased signal intensity of the normal pituitary tissue (31).

Interpretation together with other diagnostic findings is essential, because areas of different signal intensities might also represent other lesions than PAs (22).

Starting from a 4 mm diameter, microadenomas can be readily detected on MRI. Indirect signs suggesting a sellar mass include: deviation of the pituitary stalk, bulging of the pituitary content towards the optic chiasm or remodelling and thinning of the bony sellar floor.
Although a macroadenoma can be identified as a homogeneous mass on MRI, a heterogeneous mass can also indicate a macroadenoma. In this case a variable signal can occur due to cystic degeneration, necrosis or regions of haemorrhage (1).

If TSS has taken place, a time of about three to four months should pass to accurately evaluate the presence of any remaining tumorous tissue (1).

2-deoxy-2-[^{18}F]-fluoro-D-glucose positron emission tomography (^{18}F-FDG-PET)

^{18}F-FDG is phosphorylated by hexokinase and captured in metabolically active cells. This radioactive tracer can be detected on PET-scans. As the metabolic rate in the pituitary gland is low, normal pituitary tissue does not highlight on PET-images (32,33). In contrast, a PA might accumulate ^{18}F-FDG (32). In some cases, ^{18}F-FDG-PET is a valuable technique to identify PAs that were not visible on MRI (34). Regarding this, some studies recommend to use high-resolution PET-scan as a complementary diagnostic tool in case of a false negative MRI in order to detect small microadenomas. Nevertheless, it is important to notice that not all PAs show positive PET-scans because not all PAs accumulate ^{18}F-FDG (33,34). Finally, ^{18}F-FDG-PET can be valuable in the differentiation between fibrosis and remnant/recurrence following pituitary surgery (33).

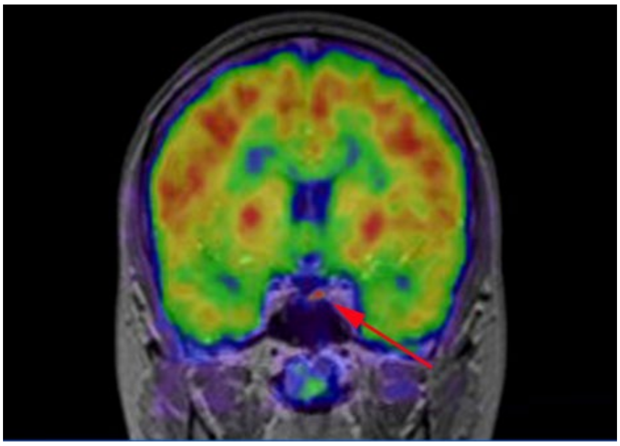

Figure 4. ^{18}F-FDG-PET

Simultaneous bilateral inferior petrosal sinus sampling (BIPSS)

For this technique, a catheter is advanced from the femoral vein to both petrosal sinuses, receiving the venous blood drained from the pituitary gland. Next, several blood samples (peripheral and from both petrosal sinuses) are taken for ACTH determination. After CRH injection, post-stimulation samples are collected and analysed (35).

BIPSS can be indicated to determine the origin (pituitary or ectopic) of ACTH-dependent hypercortisolism. For example, in case of an ACTH-secreting adenoma, the ACTH concentration is expected to be higher in a petrosal blood sample instead of a peripheral blood sample.

In some cases, MRI is not able to locate the PA responsible for the ACTH production. BIPSS can determine in which part (left or right) of the hypophysis the adenoma is situated, by comparing the ACTH levels in the left and right inferior petrosal sinus (35).

Although BIPSS is an invasive procedure performed by an interventional neuro-radiologist, complications (e.g. deep venous thrombosis, venous subarachnoidal hemorrhage) are rare (35,36).

1.3.6 Treatment

A wide range of approaches for PA treatment are available depending on the size and type of adenoma. In general three main therapy goals are described: reduction of mass effects by decreasing tumour size, substitution for deficient pituitary axes and correction of overproduction and corresponding symptoms (3). Whether medical treatment, surgery, radiotherapy or a combination is indicated, should be discussed on a multidisciplinary consultation, attended by a neurosurgeon, an ear, nose and throat (ENT) surgeon, an endocrinologist and a radiologist (2).

Surgery is to be considered in presence of a clinical hormonal excess or when compression-related symptoms occur. In case of prolactinomas, even though there is a hormonal excess, the first-choice treatment is medication. In case of tumour resistance or medication intolerance, surgery can be considered (2,15,37). For acromegaly and Cushing's disease, surgery is the therapy of choice. Particularly for relatively small adenomas, but also for larger adenomas, surgery can be a permanent cure. Extrasellar extensions can make it impossible to achieve a complete resection (2). The risks of TSS are discussed in section 1.5.

Radiotherapy is generally indicated when surgery fails to control the PA or when absolute contraindications for TSS exist. Stereotactic radiotherapy allows to precisely deliver a high dose of irradiation. The aim is to control the PA (e.g., in cases of hormonal hypersecretion), but mostly it does not eradicate the tumorous mass (2).

1.4 Surgery

1.4.1 History

In order to reach the pituitary gland, several approaches are described throughout history. In 1893 a first attempt was made using a temporal approach (38,39). Neurosurgeons agreed that new approaches were necessary as the transcranial approach was associated with a high mortality rate (39).

In 1907 Schloffer successfully resected a PA using a superior nasal transsphenoidal approach (see Figure 3) (5,40). After an incision around the left nostril was made, the nasal septum and a part of the sphenoid bone were consecutively removed in order to open the sphenoid sinus (39).

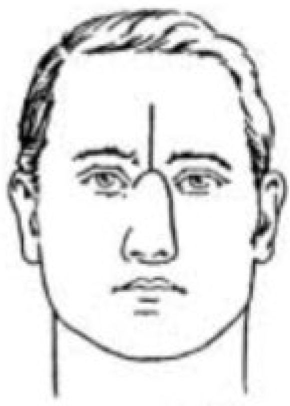

Figure 5. Superior nasal transsphenoidal approach-Schoffler (39)

Avoiding rhinotomy, a direct endonasal transsphenoidal approach was described in 1909 by Hirsh (38,39). Nearly one

year later, Halstead introduced a sublabial gingival incision to reach the sphenoid sinus. Cushing also contributed to an improved transsphenoidal procedure (39,40).
In the 1950s, Guiot initiated intraoperative fluoroscopy in order to improve the accuracy of the transsphenoidal approach (38,39). Microsurgery was introduced in the 1960s by Hardy and provided substantial advantages compared to the transcranial approach that dominated until the 1950s (5,38,39,41).
A refinement of the endonasal transsphenoidal approach involving minimal posterior nasal mucosa dissection without turbinate resection, was implemented in 1987 by Griffith and Veerapen (5,38,39).
In 1992 Jankowski for the first time successfully removed a PA using ETSS (5,42).

1.4.2 Microscopy versus endoscopy

The transsphenoidal approach has become the method of choice for operating on PAs (15). Although microscopic TSS has been frequently and successfully performed as a standard surgical treatment for PAs, ETSS is gaining favour (15,43,44). Several theoretical advantages of this technique have encouraged surgeons to make a transition from microscopic to fully endoscopic surgery (15,43,45,46). In order to do this, neurosurgeons should be trained in this different technique, which involves a steep learning curve. Close cooperation with an ENT surgeon trained in endoscopic surgery, may facilitate the procedure (43). This is also known as a 4-handed technique (47).

A major advantage of the endoscopic technique over microscopy is the improved visualisation during the surgery (15,43–46). For a growing number of surgeons, the panoramic surgical view provided by the endoscope is preferable to the conical view of the microscopic technique, because the endoscope allows a superior visualisation of the tumour and surrounding structures (45,46). Additionally, the angled endoscope (30°, 45° or 70°) makes it possible to look around corners and, in turn, visualize regions (e.g., the suprasellar and parasellar area) which are not visible using the microscope (40,42,43). Also, the endoscopic technique allows advancement of the lens and illumination into the sellar cavity, facilitating detection of residual tumour (45,46).

An advantage of microscopy over endoscopy is that microscopy establishes a continuous view, whereas in endoscopy a cloudy vision can occur, for example, in case of a major bleeding. This implicates that a major bleeding is more easily controlled in microscopy (43,46). Additionally, the microscopic technique can offer depth perception, which is not possible in 2-dimenional endoscopy (45). Three-dimensional (3D) endoscopy is supposed to improve the precision of actions in the anterior-posterior direction, generating a shortened learning curve for the surgeons (15,43).

Theoretically a superior viewing in endoscopic surgery implicates an improved identification of the tumour mass, neurovascular elements and other surrounding structures (46). Regarding this, a decreased complication rate in endoscopic pituitary surgery versus microscopy, could be expected. However, it is still uncertain if surgical outcomes are significantly different between these two techniques (44,46). Some studies demonstrated in endoscopy versus microscopy a more complete tumour removal, a shorter length of operation and hospitalization, improved patient outcomes (especially in presence of cavernous sinus invasion), less postoperative complications and patient discomfort (15,43–45,48,49). On the contrary, other studies reported no significant difference in major surgical outcomes between the endoscopic and the microscopic technique (15,43,48).

The occurrence of inconsistent results may be a consequence of variations between remission criteria, different healthcare centres and most importantly variations in surgeon’s experience (46). Experience of the surgeon in a certain technique (endoscopic or microscopic) is an important factor positively affecting the remission rate and complication rate. When a surgeon switches from a microscopic to an endoscopic technique a transient augmentation of perioperative complications might be observed (43).

Several studies demonstrated the effectiveness and safety of endoscopic pituitary surgery. Although, long-term follow-up studies are needed to confirm the central role of endoscopic pituitary surgery in the surgical treatment of PAs (15,45).

1.4.3 Electromagnetic neuronavigation

Neuronavigation systems have been developed to make image-guided surgery possible (50). One of these systems is the electromagnetic (EM) guided neuronavigation system. This tool provides extra information to plan surgical trajectories and to assess tumour margins or anatomical structures during the surgery (51). It enables to show the tip of an instrument at depth live on digital anatomical images during the surgery. Because the instruments are tracked by this neuronavigation system, it is possible to follow these in the virtual brain (50–52). A linkage between the anatomical structure and digital images is made in order to recreate a 3D brain structure during the surgery. An accurate localisation of e.g., the ICA can be provided by neuronavigation (50).

1.5 Complications

Although this endoscopic transsphenoidal technique is routinely used internationally, complications can emerge at every step in the surgery (9). Fortunately, this is a minimally invasive technique leading to a small amount of complications (38,40).

Low complication rates can be acquired by well-coordinated multidisciplinary teamwork and are positively affected by surgical experience (9,53,54). Many other factors are also associated with the amount of complications, such as the biological structure of the adenoma, the localisation of the lesion, the extent of removal and damage to surrounding tissue. Invasion by the adenoma can be a negative factor. The relationship of some lesions to the surrounding structures and their size are reasons why it is not always possible to reduce the number of serious and potentially fatal complications (38).

The complications can be divided and assessed in a few groups: CFS leak, rhinological complications, meningitis, endocrine complications, vascular and visual complications (9), coma and death (18).

1.5.1 CSF leak

A major cause of morbidity subsequent to TSS for PAs is persistent cerebrospinal fluid leakage. Headache, meningitis, pneumocephalus and intracranial hypotension can occur because of this persisting CSF rhinorrhoea (55,56).

When the surgeon investigates the anatomic structures nearby the diaphragm sella or manipulates the tumour, the diaphragm, arachnoid or suprasellar cistern may be harmed (9,14).
Besides the destruction of the enclosing tissue structures (5), other reasons that contribute to persistent CSF leaks are: failure to detect an intraoperative CSF leak or insufficient primary repair (57). Once the surgery is over, changes in intracranial pressure might cause CSF leakage (14).

The suspected CSF rhinorrhoea can be tested for β-2 transferrin or β-trace protein to confirm the CSF fistula (14,55,58).

Further treatment of the leak depends on the incidence of intraoperative CSF leak, the volume and the surgeon's preferred techniques (55).

Although there are many treatment options for a postoperative CSF fistula, it is preferable to prevent the occurrence of it. Avoiding an intraoperative CSF leak is the first step in prevention of persistent CSF leakage. This is possible by using gentle manoeuvres when dissecting the adenoma close to the diaphragm sellae, so the diaphragm sella stays intact (9,56). Another precaution is adequate sellar floor reconstruction, as it is proven that the progress in reconstructive techniques lowered the incidence of a postoperative CSF leak (38,59). If an intraoperative CSF leak arises, it should be treated immediately (9). Endoscopy is more sensitive than microscopy in identifying an intra-operative CSF leak (44).

1.5.2 Rhinological complications

1.5.2.1 Nasal vascular complications or epistaxis

Repetitive passage of instruments through the nasal cavity is obligatory in ETSS. This could lead to trauma to the nasal mucosa and endonasal blood vessels (59). Extra caution is important when performing mucosal dissection in the region of blood vessels. Knowing their localisation is mandatory. The sphenopalatine artery reaches the nasal cavity through the sphenopalatine foramen. Here the sphenopalatine artery branches in the posterior lateral nasal branches and the posterior septal branches (9,38).

As patients are operated under moderate low blood pressure, the dissected area has to receive extra attention at the end of the surgery to verify haemostasis and prevent early postoperative epistaxis (56). It is known that in the early postoperative hours and days, when the blood pressure normalises, bleeding can occur from previously coagulated and/or noncoagulated vessels (9).

1.5.2.2 Hyposmia

Olfactory disorder is a possible postoperative nasal complaint after endonasal transsphenoidal resection of PAs (5,56,60). Different degrees of hyposmia and anosmia might occur (5,9,56).

Injury and compression of the nasal mucosa contribute to ischemia which is often the cause of olfactory disorder. Excessive coagulation of the haemorrhagic mucosa and insufficient protection of nasal mucosa are other causes. Especially damage to the turbinal and septal mucosa should be avoided, because this area consists of the olfactory nerve fibres (5,9).

To protect the olfactory nerve endings in the nasal mucosa, it is safe to operate at a range of 10 mm from the cribriform plate beside the nasal septum and 15 mm from the cribriform plate aside the turbinates (5).

Postoperative subjective and objective examination as regular assessment of the nasal cavity should be emphasized to control nasal mucosa inflammation and avert olfactory disorder (5).

1.5.3 Meningitis

Postoperative meningitis is a severe complication of endoscopic nasal TSS for adenoma excision (17,56,61). Clinical signs include the development of headache, neck stiffness and fever (9,38).

This potentially fatal complication is strongly associated with CSF leak and can occur after lumbar drainage (9,12,52,55–57,61,62). Although meningitis can also occur in patients without CSF leakage (40,56,61).
Prevention of CSF leaks is an important aim in order to diminish the rate of meningitis (38,56,57,61). Therefore, meticulous closure and repair of the skull base is necessary (38,57,61).
Avoiding contamination by a lumbar drain that is kept in place too long, can be achieved by shortening the time of lumbar drainage and using it only for severe CSF leakage (62).

Another major decrease in this complication rate can be observed with increased experience of the surgeon, adequate antibiotic prophylaxis protocol, washing of the nasal cavity with antiseptic solutions and always rechecking of the reconstruction (9). The back and forth of the endoscope sheds directly against the nostrils. That is why a thorough preoperative decontamination of the nostrils and nasal fossae should be considered (56).

Some studies observe higher rates of meningitis as the operation time increases (38,56).

Patients with postoperative signs of meningism, raised protein and/or decreased glucose levels in the CSF and elevated white blood cells in the cerebrospinal fluid are considered to have bacterial meningitis (56).

1.5.4 Pituitary insufficiency

The aim of endoscopic transsphenoidal excision of PAs is to remove the tumour while the endocrine function is preserved or normalised (40,57).

An evaluation of the preoperative and postoperative pituitary activity is necessary to assess the occurrence of endocrine complications related to the surgical procedure (38,52,54,60,62,63). The examination of the pituitary function is based on the basal status and stimulation tests for all hormones of the pituitary gland. Urine analysis is useful for the diagnosis of diabetes insipidus (DI) and SIADH (52,63,64).

New postoperative endocrinological dysfunctions can be divided in anterior and posterior pituitary deficiency (38,56,63).

1.5.4.1 Anterior lobe insufficiency

Although a major goal during surgery is preserving the normal pituitary function (52), postoperative anterior pituitary insufficiency is a complication reported frequently in literature (9,13,14,38,54,56,59,60,62,63).

A worsening of the pre-existing anterior pituitary disfunction can occur, or patients with normal pre-operative pituitary function can develop a new anterior lobe dysfunction (38,54,56,59,62,63). It can affect one or more hormonal axes (9,38,56). Panhypopituitarism is attributed to patients suffering from more than three types of hormonal deficit. The strongest predictor of the loss of a new axis is the size of the tumour (56).

Complications associated to glandular damage are initially remarkably transient. Even a simple manipulation of the pituitary gland might cause a brief form of anterior lobe deficiency. Frequently a recovery of this temporary hormone deficiency occurs spontaneously within 6 months (9,59).

There are several preventable causes for anterior pituitary failure related to surgery. Excessive use of the tumour aspirator in the sellar cavity, for example. Other reasons are the undue manipulation and excision of normal pituitary tissue neighbouring the adenoma and thermal injury to the hypophysial gland because of coagulation (9,14,60). Therefore, coagulation must be avoided in the vicinity of the infundibulum. An alternate way to restore haemostasis close to the stalk is the use of Surgicel® (9,60).

Compression due to macro- or giant adenoma might thin the normal pituitary tissue (60,62). This leads to difficulties during the resection in distinguishing the adenoma from the pituitary gland, which lies below or around the tumour. To prevent the easily occurring injury of the pituitary during surgery, a preoperative MRI should be planned to assess the relationship between the adenoma and normal gland. The incidence of damage to the normal pituitary tissue could be reduced by the use of a scraper ring for the excision of the adenoma. The use of an angled endoscope enables the visualisation of residual tumour and also prevents injury of the normal pituitary tissue (60).

1.5.4.2 Posterior lobe insufficiency

Diabetes insipidus

DI is a frequent complication of ETSS (12,40,54,56,60). Especially in macroadenomas postoperative PDI is not rare, because it is realistic that the posterior pituitary gland has been destroyed completely (52,62).

The aetiology of DI might be surgical trauma affecting the release of antidiuretic hormone, inflicting a temporary dysfunction (9,38). Even a simple manipulation, displacement or stretching of the pituitary tissue, stalk and/or skull base structures can cause DI (9,38,56,60).

Risk factors for development of long-term postoperative DI are being younger than 50 years old and the occurrence of an intraoperative CSF leak (56,65). GTR and tumour size (>1 cm) are related to TDI. One-third of the patients who developed TDI evolved to PDI (65).
The patients will suffer from polyuria and polydipsia (56). Serious signs of DI include dehydration and convulsions. These symptoms can regularly be prevented by a successful management of the complication (9).

Postoperatively serum sodium, urine output and urine analysis are meticulously observed for signs of DI (14,52,63). Patients suffering from post-surgery DI will present an augmented urinary loss, often defined as >250-300 mL/h for three consecutive hours, urine specific gravity of <1.005 and a serum sodium of >145 mEq/dL (52,56,65,66).

Syndrome of inappropriate antidiuretic hormone secretion

Inappropriate secretion of antidiuretic hormone is a plausible complication after endoscopic transsphenoidal PA resection (38). It is due to a posterior lobe insufficiency (25).

Close monitoring of the serum sodium, urinary sodium, plasma and urinary osmolality, urinary output is essential to detect signs of SIADH (and DI) (52). In case of hyponatraemia, increased urine osmolality and decreased plasma osmolality SIADH should be considered (23,60,64). Consequences of severe hyponatraemia are vomiting, abnormal somnolence and cardiorespiratory distress (64).

Patients are at risk of SIADH until 10 days after their pituitary surgery (52).

Triple phasing is possible in patients with severe damage to the posterior pituitary gland or stalk as result of the surgical manipulation. They exhibit first a period of DI, followed by SIADH and eventually return to PDI (52).

1.5.5 ICA injury and intracranial haemorrhage

A severe complication of endoscopic transsphenoidal pituitary operations is injury of the ICA, because it can cause a major bleeding (9,38,52,56). Damage to this artery can also cause stroke (because of thrombosis/embolism), vessel spasm, subarachnoidal haemorrhage, carotid cavernous fistula, pseudoaneurysm and death (56,67,68).

Injury of the ICA can result in a partial resection or no resection of the adenoma, because it disallows to continue the surgery (56).

Aneurysms of the ICA should be investigated preoperatively because they can cause major bleeding during surgery (9,63). Neuronavigation systems and Doppler techniques play an important role in the avoidance of ICA injury by helping to localise the ICA and facilitating a safer exposure (9,14,38,52,56,60).

1.5.6 Visual complications

Visual complications might arise after ETSS (37,61). Damage to the optic nerves and chiasm can occur through trauma, over-packing with sellar closure material, haemorrhage and ischemia, due to occlusion of the vascularisation of the optic chiasm (52,56,61). Visual acuity and visual field are regular parameters tested in literature to evaluate visual deterioration (42,54,56). Rarely a newly induced transient diplopia can also be observed postoperatively (56).

Patients who already suffer from preoperative visual impairment are more susceptible to additional optic nerve dysfunction because most of them have large adenomas with suprasellar extension (37,61).

Permanent decreased visual acuity is often observed in cases of compressive intrasellar bleeding. These bleedings are frequently seen in patients with suprasellar extension of their adenomas (56). Nevertheless, visual deterioration can be transient too (37,42,56).

1.5.7 Coma

Coma is a very rare complication which can occur after ETSS (9,60).

1.5.8 Death

Death is a very rare, but possible complication of ETSS (5,54,62,69).

Causes of death related to this type of surgery are, for example, injury of the ICA and meningitis (54,56).

Although, in cases with a deadly outcome, death was not always directly related to the operation (14,38,40). For instance, the occurrence of cardiovascular complications (14,38,40).

1.6 Objective

Many studies have already been conducted to assess the success of pituitary surgery. We evoke this again because not every study is 4-handed, techniques evolve continuously, in the past endoscopy was not used routinely, not every surgeon uses the transsphenoidal approach and of course each centre has its own individuality and specificity.

Also, with every extra study the total study population of patients who underwent an endoscopic transsphenoidal pituitary surgery grows. This benefits the representability of the results reported in literature.

This study is a step forward in creating more efficient patient files and clear reporting. Ideally, the Access form used in this study is coupled to the electronic patient file. This results in less typing (more is ticked) and in an easier way to keep track of the results of this team of surgeons. Updates can be made easily.

The form facilitates the identification of trends in complications and outcomes. This knowledge is useful in developing preventive measures and pointing out steps that need more training (e.g., if it is seen that the frequency of complications is high) or in confirming good medical practice. Therefore, this study is an ideal opportunity for benchmarking. This is why it is important to do research on the results of the 4 years' experience in 4-handed endoscopic transsphenoidal pituitary surgery performed by dr. F. Dewaele and prof. dr. T. Van Zele who work together in close cooperation with endocrinologist prof. dr. B. Lapauw.

2 METHODOLOGY

2.1 Procedure of investigation

In order to begin research, permission of the ethical committee of the University Hospital of Ghent was required. An admission was sent to the ethical committee through Bimetra Clinics (clinical research centre Ghent) and approval for this study was acquired in September 2017. Together with this approval, access to the electronic patient files of the endocrine, neurosurgical and ear-nose-throat department of the University Hospital of Ghent was received.

A survey list of all patients who underwent endoscopic transsphenoidal pituitary surgery in the Ghent University Hospital between January 2012 and July 2018 was made up. Only patients with PAs were extracted from this list. The overwhelming majority of these surgeries were performed by a duo of surgeons: neurosurgeon dr. F. Dewaele and ENT surgeon prof. dr. T. Van Zele.

Every patient received a letter with an opting-out formula. The letter, drafted according to the template of Bimetra Clinics, informed the patients about the aim of the study. In this letter patients were informed that no extra clinical tests needed to be done, but that their electronic patient file regarding their pituitary surgery would be consulted. The patients needed to respond to the letter if they did not agree to participate. The refusal period lasted for two weeks. Two patients preferred not to participate in this study, so they were excluded.
Meanwhile, a literature review was performed (see section 2.3). This review investigated the most frequent complications and cure rates of ETSS in international studies. The aim was to find keywords and search terms to run through the patient files efficiently and to formulate the research questions of this master's thesis. A definition list was set up, based on this information and the advice of the supervisors (see addendum 2).The gathered information, together with the expertise of the surgeons, was used to select descriptive criteria in order to create a form in Access to describe every case of the patient population. The new form was based on a pre-existing form. There was already a rough draft of the form available, which was subjected to a complete revision. As soon as the form (see addendum 1) was completed, it was possible to further investigate the cases of the patients.

Initially, the anatomopathological file was looked into to ensure that the patients had a PA. This implicates that patients with other kinds of parasellar and sellar lesions, such as craniopharyngiomas and chordomas for example, were excluded. In this way, an initial patient population consisting of 82 patients was built up. The retrospective search could be performed by exploring the electronic patient files.

Some patients did not receive their follow-up at the Ghent University Hospital. This led to incomplete information regarding those patient files when building the database. To avoid missing data, these patient files were consulted in CoZo ("*Collaboratief Zorgplatform")* under supervision of the doctors involved in this research. CoZo is a Belgian initiative to establish open communication between doctors active in different treatment centres. By this means, more accurate information could be gathered. Since CoZo is a Belgian initiative, this application does not support exploring files of patients who were followed up in the Netherlands or other countries. Most of the patients who were followed in the Netherlands were treated in the hospital of Terneuzen. In order to get access to their patient files, the hospital in Terneuzen was contacted. However, it was not possible to retrieve their patient files.

The data found in the electronic patient files were registered into the Access database. Every patient was exhaustively described by completing the newly developed form with numerous describing parameters (see addendum 1). The filling out of the forms was not in every case a clear matter, especially when incomplete reports and/or contradictions in the patient files were observed. These patients needed extra interpretation by the doctors in this research. In this manner, the database was built. The MRI-images were evaluated by a radiologist to determinate the Knosp score, the size of the adenoma and the presence of cystic structures in the adenoma.

The final Access database was analysed to visualise trends and to perform data-analysis. These results were compared to the results found in literature by statistical software. By this means, the cure and complication rates of surgery performed by dr. Dewaele and prof. dr. Van Zele could be objectively evaluated.

2.2 **Clinical methods**

Two surgeons, an ENT surgeon and a neurosurgeon, worked together during the operations. The ENT surgeon is positioned on the left side of the patient, while the neurosurgeon stands on the right side. They usually approach the patient by the right nostril. The binostril approach is seldom used. It is only used in cases of complex adenomas.

Classically, the first part of the surgery is mainly performed by the ENT surgeon. The second part, the actual tumour removal, is done by the neurosurgeon. However, in this 4-handed surgery, the two surgeons are each able to perform the complete surgery on their own. For example, the actual tumour removal can be performed by the neurosurgeon as well as by the ENT surgeon. Here, the two surgeons assist each other while they take turns in performing parts of the operation. This is a unique configuration where both the surgeons share the same experience.

Figure 6. Configuration of the neurosurgeon and the ENT surgeon in the operating room

Good visualisation is important during the surgery. In this operation, this is achieved by an EM guided neuronavigation system. An Ultra High Definition endoscope is used to visualise the tumour tissue and surrounding structures. The images created by the endoscope and the neuronavigation system are projected on monitors during the operation.

The surgical procedure contains the following steps:

- The patient is half seated in supine position, while his head is fixated by a Mayfield skull clamp.
- Hydrocortisone 100 mg, dexamethasone 5 mg i.v. and a prophylactic dose of cefazoline 2 g are administered preoperatively.
- Ten minutes in advance, cottonoids soaked in cocaine and levorenine are placed in both nostrils for decongestion and local anaesthesia.
- The MRI-based neuronavigation is set up.
- Isobetadine is used for disinfection of the nose and face. An alcohol based solution is used for the fat graft area (e.g., abdomen).
- After the removal of the cottonoids, an endoscopic exploration of the nose can be performed. The conchae nasales are moved laterally.
- A mucosal flap ented on the a. nasoseptalis is made. The use of a nasoseptal flap is performed when a CSF leak is expected.
- The posterior, bony segment of the nasal septum is resected.
- The entrance of the sphenoidal sinus is identified and opened.
- The anterior wall of the sella is opened by the incision of periosteum.
- After the incision of the dura mater, an intrasellar view is obtained.
- The diafragm sellae and the pulsating ICAs should be identified.
- The lesion is differentiated from the normal pituitary gland and subsequently resected by curettage. The resected fragments are aspirated and sent for anatomopathological analysis.
- The 30-degree endoscope is used for further exploration.
- The resection is ended when the surgeons believe there is a gross total removal or no further resection is possible due to plausible complications.

- A fat graft is dissected from the abdomen in cases where a CSF leak is suspected.
- The fat graft is placed in the resection cavity covered by bone. Subsequently the previously made mucosal flap is placed. The reconstruction of the sellar floor is finalized using gelfoam and Tissucol.
- A Merocel is placed in the right nostril.

Afterwards the patient is transferred to the intensive care unit, where he stays one night. The next day the patient goes to the department of neurosurgery. During the last days of hospitalisation, the patient stays at the department of endocrinology. There, endocrinological investigations (e.g., morning cortisol, IGF-I, TRH- (Protirelin®) and LHRH-stimulation tests (Relefact®)) are performed one week after surgery to verify the anterior pituitary function. In postmenopausal women, a LHRH-stimulation test is not routinely conducted. After this control, normally the patient can be discharged. Preferably, the patients receive a MRI immediately postoperatively.

One month postoperative, a new hormonal evaluation is carried out to measure the basal cortisol level. New stimulation tests are only performed if there is an indication for it, based on the one week postoperative hormonal tests.

The second MRI takes place three months postoperatively. Further follow-up consists of a yearly endocrine consult and MRI, but this depends on the needs of the patient.

In 2017 the 4th edition of the World Health Organization classification of endocrine tumours has been announced. Immunohistochemistry remains an ancillary diagnostic tool, but also routinely assessment of transcription factors is recommended (6,21,70). As this study has a retrospective nature, investigations in order to apply the new classification system were not routinely conducted in the past. Consequently, this new classification system could not be applied in this research. Since only one study uses the new classification based on transcription factors, a problem in the comparison of results in literature would arise (20).

2.3 Literature review

The databases PubMed, Embase, Web of Science and Google Scholar were primarily used in the search for publications. Keywords (MeSH-terms/Emtrees) and Boolean operators were combined to narrow down the amount of hits. A further selection was made from these hits based on relevance, title, abstract and publication date. To provide information that is up to date, articles older than ten years were withheld from this literature review. Exceptions were allowed only when recent alternatives were not available. Index terms related to the articles and the number of citations were also considered.

Another method used to search for publications was provided by the function “Similar articles” on PubMed (also known as the “snowball-method”). Other articles were found by means of references in already included studies.

Because of the language barrier, articles only in English, French and Dutch were selected.

2.4 Statistical analysis

SPSS (Statistical Package for Social Sciences) was used to perform data analysis. The Chi-square test or Fisher’s exact test were used to evaluate the differences between the various subgroups: microadenomas versus macro- or giant adenomas, complications versus no complications, remnant versus no remnant and hormonal control versus no hormonal control. The learning curves were created with Microsoft Office Excel. To evaluate characteristics between the early and the late operated group the Student’s T-test was used. A normal distribution in continuous variables (e.g., age) was confirmed with the Kolmogorov-Smirnov test.

Based on comparisons of patients with microadenomas versus macroadenomas or giant adenomas, patients with or without complications, patients with or without a remnant and patients with or without hormonal control and several possible risk factors were identified.

For most variables the statistical significance level is considered $p<0.05$. In some cases $\alpha=0.01$ was used.

3 RESULTS

3.1 General characteristics

From January 2012 to July 2018, 82 patients were submitted to ETSS for a PA at the Ghent University Hospital. The study sample consists of an equal amount of women and men (Table 1). In the studied population, the age at the moment of the operation varied from 12 to 80 years (mean age was 51±15.9 years old). The mean follow-up was 29 months±22.2 months (range 6 days–74 months). In studies evaluating the endoscopic transsphenoidal technique for PAs the mean follow-up ranged from 3 to 61.5 months (5,60,62,63,70,15,17,24,37,39, 51,58,59). Of the 82 patients, eight patients (9.8%) received pituitary surgery in the past. In the studied sample, NFPAs were more prevalent than FAs (see Table 1). The GH-producing adenoma was the most common subtype in patients with a FA. Other subtypes ranked by decreasing prevalence are: ACTH-producing adenomas, prolactinomas, mixed GH/PRL-producing adenomas and TSH-producing adenomas.

Preoperative hormonal deficiency of one or more axes was present in 34 patients (41.5%). The LH-axis was the most affected, followed by the TSH-axis. Preoperative complaints reported by patients and radiological parameters can be found in Table 1.

Table 1. General characteristics in 82 patients

	N	%		N	%
Patient characteristics			***Radiological parameters***		
Total amount of patients	82	100	KNOSP 0	17	20.7
Woman	41	50	KNOSP 1	24	29.3
Patient with previous surgery	8	9.8	KNOSP 2	18	22
Adenoma characteristics			KNOSP 3	13	15.9
Incidentaloma	15	18.3	KNOSP 4	10	12.2
NFA	43	52.4	Radiologic compression optic chiasm	45	54.9
FA	39	47.6	Radiologic invasion cavernous sinus	63	78.8
Acromegaly	20	24.4	Cystic component in the adenoma	30	38
ACTH-producing PA	13	15.9	***Preoperative complaints***		
Prolactinoma	3	3.7	Visual deficit	32	39
TSH-producing PA	1	1.2	Diplopia	5	6.2
Mixed GH/PRL producing PA	2	2.4	Headache	31	37.8
Microadenoma	16	19.5	Pituitary based amenorrhea in women	7	20
Macroadenoma	62	75.6	Decreased sexual desire	7	10.6
Giant adenoma	4	4.9	Galactorrhoea	5	6.1
Preoperative hormonal deficiency	34	41.5	Seizure	2	2.5
Preoperative GH deficiency	7	8.5	Apoplexy	4	4.9
Preoperative ACTH deficiency	15	18.3			
Preoperative TSH deficiency	17	20.7			
Preoperative LH deficiency	27	32.9			

N Number of patients, *%* Percentage of 82 patients

The mean duration of surgery (DoS) was 158±55.7 minutes and the mean length of hospital stay was 11±4.8 days. The mean DoS reported in studies evaluating ETSS varied from 58 to 255 minutes (42,43,49,56,72). In ten cases (12.2%) a nasoseptal flap was used.

3.2 Postoperative outcomes

3.2.1 Ophthalmologic outcomes

32 patients (39%) presented themselves with a preoperative visual deficit. Five patients (6.2%) had diplopia preoperatively. The combination of a visual deficiency and diplopia was present in three patients (3.7%). In total, 34 patients suffered from preoperative visual deficit and/or diplopia. Twenty-seven patients (87.1%) in this group experienced a postoperative visual improvement. Four patients (12.9%) did not experience a recovery of normal sight. Postoperative visual data is missing in three patients. According to literature, rates of postoperative visual improvement range from 70.1% to 87.0% (18,37,52,54,56).

The adenoma size, cavernous sinus invasion and optic chiasm compression by PAs in persons with a preoperative visual deficit and/or diplopia, are shown in Table 2. They all had an adenoma that invaded the cavernous sinus. None of them had a microadenoma. In two patients, data about cavernous sinus invasion were missing. According to Kim et al., visual recovery is associated with adenoma size (54).

Table 2. Adenoma characteristics in 34 patients with preoperative visual deficit and/or diplopia

	N	%
Microadenoma	0	0
Macroadenoma	30	88.2
Giant adenoma	4	11.8
Invasion of the cavernous sinus	32	100
Compression of the optic chiasm	29	85.3

N Number of patients, *%* Percentage of 34 patients

3.2.2 Recuperation of hormonal deficiency

34 patients (41.5%) suffered preoperatively from a hormonal deficit of at least one hormonal axis. Among these 34 patients, 11 patients (32.4%) had a complete recovery, while partial recovery was seen in 20 patients (58.8%). Three patients (8.8%) did not experience a recovery of a hormonal axis.

In literature, hormonal recovery rates (partial and/or complete) vary between 0% and 56% (18,38,54,56,62).

The number of patients with a specific hormonal deficiency is shown in Table 3. The number of patients who postoperatively recuperate from a specific hormonal deficit is also given in

Table 3. In literature, 51.1% of preoperative ACTH deficient patients recovered postoperatively. The percentage of TSH deficient patients preoperatively who recover is 30.1%. The preoperative LH deficit is most common, but is also most likely to recover. The preoperative gonadal deficiency was the most common deficient axis in literature too (54,56).

Table 3. Specific hormonal deficit and recovery in 34 patients with preoperative hormonal deficiency

	Deficiencies (N=34)	Recoveries (N=Patients with specific deficit)
Preoperative deficit GH, N (%)	7 (20.6)	3 (42.9)
Preoperative deficit ACTH, N (%)	15 (44.1)	7 (46.7)
Preoperative deficit LH, N (%)	27 (79.4)	13 (48.1)
Preoperative deficit TSH, N (%)	17 (50)	3 (17.6)

N Number of patients, *%* Percentage of patients

In this study, no significant association between hormonal recovery and adenoma size could be found (see Table 4). Kim et al. states that hormonal recovery is not related to size (54).

Table 4. Hormonal recuperation rates in microadenoma and macro- or giant adenoma

	Microadenoma (N=16)	Macro- or giant adenoma (N=66)	P-value
Recuperation of all preoperative deficient hormonal axes, N (%)	0 (0)	11 (34.4)	1.000
Recuperation of at least one hormonal axis, N (%)	1 (50)	19 (59.4)	1.000

N Number of patients, *(%)* Percentage within the microadenoma group or macro/giant adenoma group

3.2.3 Hormonal control of FAs

Of the 39 patients with a FA (47.6%), 14 (39.9%) achieved hormonal remission. In the other 25 cases (64.1%) hormonal levels did not normalize in the follow-up period. However, a decrease in hormonal levels was sometimes observed. In this series, the disease control rate was higher in patients with Cushing's disease (69.2%) versus patients with a GH-producing PA (20%). None of the three patients with a prolactinoma achieved hormonal control. In this study, one TSH-producing PA was diagnosed, in which cure was not achieved. In Table 6 disease control rates, in each subgroup of FAs, are compared to results found in literature.

Table 5. Comparison of hormonal remission rates

	N	GH-producing PA (%)	ACTH–producing PA (%)	PRL-producing PA (%)	TSH-producing PA (%)	GH/PRL producing PA (%)
Bex et al. (73)	125	34	-	-	-	-
Gondim et al. (40)	228	70.7	71.4	85.3	100	-
Hazer et al. (25)	-	64.5	-	-	-	-
Martins dos Santos et al. (12)	-	39.1	-	-	-	-
Palluzi et al. (37)		65.3	82.5	54.7	-	-
Pennacchietti et al. (15)	140	68.7	77.7	-	-	-
Wang et al. (60)	166	66	69	85	86	-
This study	39	20	69.2	0	0	50

N Number of patients, *%* Percentage of patients

There is a significant difference in size and invasion of the cavernous sinus, between the group that achieves postoperative hormonal control and the group that does not (see Table 6).

Table 6. Hormonal control of FA vs. no hormonal control in 39 patients with a FA

	Hormonal control (N=14)	No hormonal control (N=25)	P-value
Microadenoma, N (%)	10 (71.4)	6 (24)	0.004
Macroadenoma or giant adenoma, N (%)	4 (28.6)	19 (76)	
Invasion cavernous sinus, N (%)	4 (28.6)	18 (72)	0.009
No invasion cavernous sinus, N (%)	10 (71.4)	7 (28)	

N Number of patients, *(%)* Percentage of patients

Further analyses in the acromegaly group showed that 16 (80%) of these 20 patients had a macro- or giant adenoma and also 16 (80%) had invasion of the cavernous sinus. This is in contrast to the 13 patients with Cushing's disease: only two patients (15.4%) had a macro-or giant adenoma and two patients (15.4%) had cavernous sinus invasion.

3.2.4 Remnant

In 43 cases (55.1%), complete tumour removal was achieved. In the other 35 (44.9%), a remnant, with or without clinical significance, was detected on postoperative MRI. In four patients, data about a possible remnant were missing. GTR was obtained in 61 patients (74.4%). In literature, the rate of GTR varies from 60% to 94% (15,18,38,40,62,63,71). Focussing on NFPAs, the GTR ranges between 62% and 97% (37,40,52,54,63).

No remnant was visible on several postoperative images in half of the patients who had a FA and did not achieve hormonal control after surgery (N=25).

Table 7 shows GTR rates and the presence of a remnant, in each category of the Knosp grading system. The presence of a remnant is significantly different in each Knosp grade (P<0.001). Some studies proved that individuals with Knosp grades 3 and 4 are less likely to achieve complete resection and remission. Invasiveness is an important negative predicting factor to assess the outcome of surgical treatment (10,12,17–19).

Table 7. GTR and remnants in 82 patients

	Knosp 0 (N=17)	Knosp 1 (N=24)	Knosp 2 (N=18)	Knosp 3 (N=13)	Knosp 4 (N=10)
GTR, N (%)	16 (94.1)	21 (87.5)	18 (100)	5 (38.5)	1 (10)
Remnant, N (%)	2 (12.5)	7 (31.8)	6 (35.3)	11 (84.6)	9 (90)

N Number of patients, *(%)* Percentage of patients in specific Knosp grade

The characteristics of the adenoma, in the remnant and no-remnant group, are shown in Table 8. The adenoma size, invasion of the cavernous sinus and the incidence of previous surgery were significantly different between both groups.

According to literature, cavernous sinus invasion, adenoma size and previous surgery are associated with incomplete tumour removal (40,54).

Table 8. Remnant versus no remnant in 82 patients

	Remnant (N=35)	No remnant (N=43)	P-value
Microadenoma, N (%)	1 (2.9)	14 (32.6)	0.001
Macroadenoma or giant adenoma, N (%)	34 (97.1)	29 (67.4)	
Invasion of cavernous sinus, N (%)	32 (94.1)	29 (67.4)	0.004
Previous surgery, N (%)	7 (20)	1 (2.3)	0.02

N Number of patients, *(%)* Percentage of patients in the remnant or no-remnant group

3.3 Postoperative complications

In this series, 17 patients (20.7%) suffered from transient or permanent complications, caused by ETTS. The possible complications are shown in Table 9. In literature, overall complication rates range from 9.1% to 26.9% (38,40,54,61).

The most common complication in this series is a newly induced hormonal dysfunction. Postoperative haemorrhage, perioperative ICA injury, severe epistaxis, postoperative decreased visual acuity, coma and dead did not occur. Two patients presented a nosebleed, but they were not considered as a “true” epistaxis, in conformity with the definition.

Table 9. Postoperative complications in 82 patients

	N	%
Postoperative complications	17	20.7
Hyposmia	1	1.2
Meningitis	1	1.2
SIADH	2	2.4
TDI	7	8.5
PDI	1	1.2
Panhypopituitarism	1	1.2
Postoperative CSF leak	4	4.9
Newly induced hormonal dysfunction	10	12.2
Postoperative haemorrhage	0	0
Transient coma	0	0
Peroperative ICA-injury	0	0
Epistaxis	0	0
Revision epistaxis	0	0.
Postoperative decreased visual acuity	0	0
Death	0	0

N Number of patients, *%* Percentage of patients

Table 10 shows a comparison between the complication rates found in literature and this series.

Table 10. Comparison of postoperative complications

	N	Epistaxis %	Hyposmia/ Anosmia %	CSF Leak %	Meningitis %	ICA injury %	TDI %	PDI %	SIADH %	Hormonal worsening %	Visual worsening %	Death %
Berker et al. (9)	570	0.7	1.4	0.7	0.7	0	4.6	0.7	1.1	2.1	-	-
Charalampaki et al. (63)	134	1.4	12	3.3	-	0.7	6.7	1.3	-	7.5	-	0.7
Dallapiazza et al. (59)	80	1.3	13	2.5	-	1.3	-	5	-	-	-	0
Gondim et al. (38)	301	1.9	0	6	0.6	0.9	-	1.3	-	11.6	-	1
Halvorsen et al. (61)	238	-	0.2	5	3.4	0.4	-	-	-	-	2.1	1.3
Kim et al. (54)	331	-	-	2.4	-	-	9.1	3	2.1	32.9	2.7	0.3
Magro et al. (56)	300	2.3	4.7	2.7	3.3	0.3	5.1	6.2	-	13.7	2.4	0.7
Messerer et al. (62)	82	4.9	-	12.1	3.7	-	-	8.5	-	14.6	0	0
Paluzzi et al. (37)	555	1	2.1	5	0.9	0.3	-	2.5	0.7	3.1	0	0.2
Wang et al. (60)	1,166	1.7	1.5	0.6	1	-	6.3	0.7	-	1.3	0.4	-
Zhong et al. (14)	326	1.5	-	4	0.3	0.3	3.1	0.6	-	7.1	-	0.6
This study	82	0	1.2	4.9	1.2	0	8.5	1.2	2.4	12.2	0	0

N Number of patients

Comparing patients with or without postoperative complications, no statistic significant differences were found in adenoma characteristics (see Table 11). The number of patients who were submitted to previous surgery, was higher in the group with postoperative complications (10.9%) versus the group without complications (5.6%). However, this difference is not significant (P=1.000). Literature states that higher complication rates are present in patients with previous surgery, large PAs and invasive PAs (38,54).

Table 11. Complications versus no complications in 82 patients

	Complications (N=18)	No-complications (N=64)	P-value
Microadenoma, N (%)	4 (23,5)	12 (18,5)	0,732
Macroadenoma or giant adenoma, N (%)	13 (76,5)	53 (81,5)	
Invasion of the cavernous sinus, N (%)	12 (70,6)	51 (81,0)	0,340
Previous surgery, N (%)	1 (5,9)	7 (10,8)	1,000

N Number of patients, **%** Percentage of patients in the complication or no-complication group

Newly induced hormonal deficiency was significantly different in microadenomas versus macro- or giant adenomas (see Table 12). Although, postoperative CSF leaks occurred more in macro-or giant adenomas, it was not a statistically significant result.

Literature states that the adenoma size is the most powerful predictor of loss of a new hormonal axis (56). Also, macroadenomas are more frequent associated with CSF leaks than microadenomas (9,38,56,60).

Table 12. Complication rates in microadenomas and macro- or giant adenomas

	Microadenoma (N=16)	Macro- or giant adenoma (N=66)	P-value
PDI, N (%)	0 (0)	1 (1.5)	1.000
Postoperative CSF leak, N (%)	0 (0)	4 (6.1)	0.581
Newly induced hormonal dysfunction, N (%)	6 (37.5)	4 (6.1)	0.003

N Number of patients, *(%)* Percentage within the microadenoma group or macro/giant adenoma group

3.4 Further policy

42 patients (47.5%) were under control with permanent medication. Of these 42 patients, seven (16.7%) required medication because of a persisting hypersecretion, 24 (57.1%) because of a hormonal deficiency and 24 (57.1%) because of growth.

In three cases (3.7%) repeat surgery was necessary. Two patients (2.4%) needed repeat surgery because of a PA remnant. One of these patients had a macroadenoma. The other had a giant adenoma. These surgeries were conducted one day postoperatively. One (1.2%) patient with a persisting ACTH-producing PA received a bilateral adrenalectomy.

Postoperative radiotherapy was needed in five cases (6.1%) because of growth of the remnant. In the study of Gondim et al., 1% of patients received postoperative radiotherapy (40).

3.5 Learning process

In 2012, a switch to the fully endoscopic technique operating PAs was made at the Ghent University Hospital. Presence of impaired postoperative outcomes, following this switch in technique, is evaluated by the drawing of several learning curves. Missing values were excluded from these learning curves.

In literature, the number of patients needed to be operated, in order to reach a plateau on the learning curve, varies from 13 to 100 patients (49,54).

The DoS decreased significantly with increasing number of patients operated (Pearson correlation coefficient, -0.311; P=0.005 with α=0.01). Figure 7 shows a reduction in DoS, comparing the first ten cases (205.7 min) to the following ten (156 min). However, from this moment on, the DoS is only slightly decreasing over time.

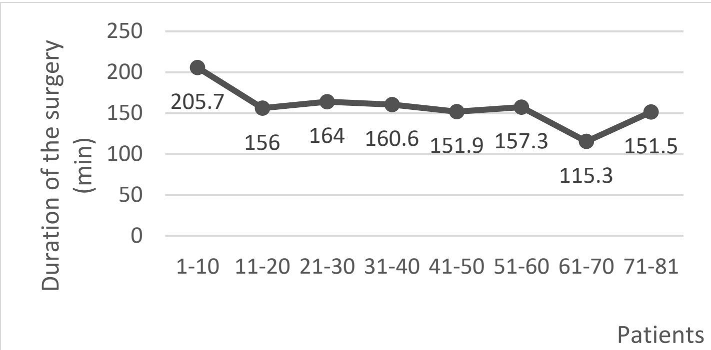

Figure 7. Learning curve: duration of the surgery

The length of hospital stay did not decrease significantly with increasing experience (Pearson correlation coefficient, -0.210; P=0.060 with α=0.01). Figure 8 visualizes the length of hospital stay (days) in function of the increasing number of patients operated.

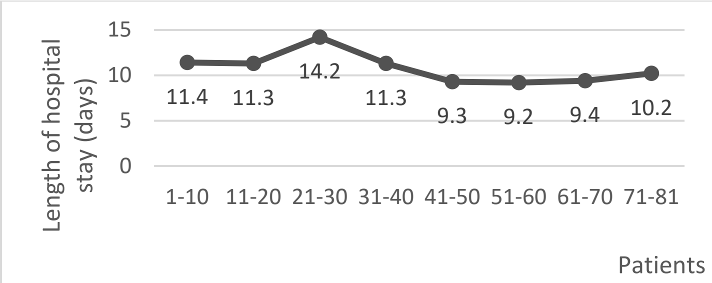

Figure 8. Learning curve: length of hospital stay

A postoperative CSF leak did not occur after the number of 37 surgeries (see Figure 9).

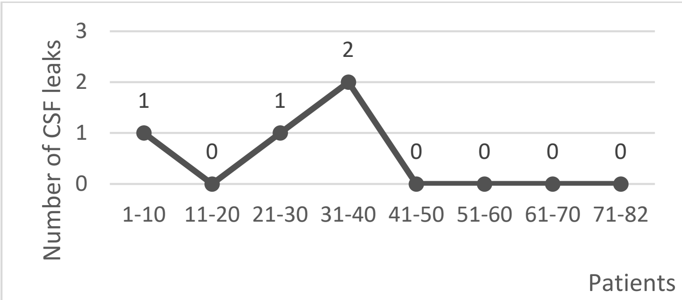

Figure 9. Learning curve: number of CSF leaks

Qureshi et al. reported a mean number of patients needed to be operated in order to become proficient in ETTS (49). Based on this number, the 82 patients in this study were separated in two groups.

No significant differences in age, gender, size and preoperative visual complaints (diplopia or visual deficit), were observed between the first or early group (N=36) and the second or late group (N=46). Also, the radiological invasion of the cavernous sinus was not significantly different between the early group (69.4%) and the late group (86.4%). Only the general complication rate (P=0.013) and newly induced hormonal dysfunction (P=0.004) were significantly different in the early and late group (see Table 13).

Table 13. Complications rates in the early group vs. the late group

Complications	Early (N=36)	Late (N=46)	P-value
General complication rate, N (%)	12 (33.3%)	5 (10.9%)	0.013
CSF leak, N (%)	3 (8,3%)	1 (2.2%)	0.315
PDI, N (%)	1 (2.8%)	0 (0%)	0.439
TDI, N (%)	5 (13.9%)	2 (4.3%)	0.231
Meningitis, N (%)	1 (2.8%)	0 (0%)	0.439
Transient coma, N (%)	0 (0%)	0 (0%)	-
SIADH, N (%)	1 (2.8%)	1 (2.2%)	1.000
Panhypopituitarism, N (%)	1 (2.8%)	0 (0%)	0.439
Hyposmia, N (%)	0 (0%)	1 (2.2%)	1.000
Newly induced hormonal dysfunction, N (%)	9 (25%)	1 (2.2%)	0.004
Remnant, N (%)	14 (40%)	21 (48.8%)	0.435

N Number of patients, *%* Percentage of patients

4 DISCUSSION

4.1 Analysis of the results

4.1.1 General characteristics

The follow-up duration in this study (29 months±22.2 months) is comparable to the follow-up in other studies, evaluating the endoscopic transsphenoidal technique. However, the follow-up in patients operated in 2017 or 2018 is rather short in order to evaluate long-term outcomes.

The mean DoS (158±55.7 minutes) fell within the mean ranges found in literature. When comparing the DoS between different centres, it is important to take the experience of the surgeon(s) into account as the lack of experience might lengthen the DoS (43).

4.1.2 Postoperative outcomes

4.1.2.1 Ophthalmologic outcomes

84.4% of patients with a preoperative visual complaint, experience visual improvement postoperatively. This result is in accordance with the superior rates found in literature.

The visual outcomes were not always unambiguously reported in the patient files. For example, in some instances the patient files mentioned a postoperative visual improvement without mentioning a preoperative complaint. Also, in patients with a short follow-up period (e.g., patients operated in 2017 and 2018) and no visual improvement postoperatively, it was difficult to estimate the visual outcome. It is still possible that these patients will gain recovery of their sight after the follow-up period. This might even lead to an underestimation of the cure rate.
The duration of the visual deficit preoperatively was not analysed because of the retrospective design of this study. This could have been a factor predicting visual recovery after the surgery.

Table 2 demonstrates that the adenomas associated with preoperative visual deficit or diplopia, are rather large. These findings can be explained by the fact that an adenoma needs a certain volume to interfere with the optical nerves (54).

As in this study no patients with a microadenoma had visual complaints preoperatively, it was not possible to investigate the presence of a significant relation between tumour size and visual recovery. Regarding the results of Kim J. et al., it is possible that tumour size is a predictive factor for visual recuperation (54).

4.1.2.2 Recuperation of hormonal deficiency

Recovery of all preoperative deficient hormonal axes is achieved in 32.4% of patients. A partial improvement can be seen in 58.8% of the hormonal impaired patients. These cure rates are higher than those found in literature. Messerer et al. (62) had the highest rate (56%). This was a combination of partial and total recovery. Compared to Messerer et al., in this study the result would be 91.2%, still much higher than his score.

The most common preoperative deficit is the deficiency of the LH-axis and this result is in accordance with literature. Compared to the other axes, the highest recovery rate is seen in the LH-axis.

It must be mentioned that in some cases of middle-aged women, it was dubious whether to count the patient as “deficient for the LH-axis” or as “menopausal”. Especially since in (assumed) menopausal women, no postoperative LHRH-test was executed. For example, a supposedly menopausal woman regained her menstruations after the surgery. Because no test of the gonadal axis was performed, this preoperative deficiency was missed initially. Therefore, it is recommended to interpret the outcomes of the LH-axis cautiously in menopausal aged women. Nevertheless, this will not have influenced the results gravely.

Another difficulty in making the distinction between a recovery or no recovery is the short follow-up time in some patients. Some patients were lost to follow-up short after their operation or received their surgery very recently. The possibility that a hormonal axis recovers after a longer period, leads to some uncertainties in the database.

Furthermore, no significant correlation between the size of the adenoma and postoperative recuperation of a hormonal axis could be observed, as found in literature (54).

4.1.2.3 Hormonal control of FAs

Compared to literature, the hormonal control rate (39.9%) in patients with a FA is relatively low. Various explanations are worth mentioning.

To begin with, only three options were present in the Access form evaluating a postoperative hormonal axis: “full remission”, “no full remission” and “missing”. For example, several patients with a GH-producing PA experienced a decrease in GH and/or IGF-I levels postoperatively. Yet, these cases were not classified as “full remission”, as the peripheral hormone levels did not completely normalize. Considering this, it is advisable to add the extra option “partial remission”.

Also, cases in which the hormonal recovery did not last for the whole follow-up period, were classified as “no full remission”. For example, a patient with an ACTH-producing PA, achieved a complete remission during the first three months following surgery. An increased ACTH-level was observed four months postoperatively. Despite his initial remission, he was not registered as “full remission”. In this case “recurrence” was also checked in the Access form.
However, it is possible that after several years postoperatively patients might still cure. For example, in this series one patient experienced a normalisation of GH and IGF-I levels 4 years postoperatively. Regarding this, the hormonal remission rates in this study could be an underestimation in patients with a short follow-up.
Those examples emphasize the importance of a long-term and standardised endocrine follow-up in order to accurately evaluate hormonal axes postoperatively.

While the remission rate of patients with an ACTH-producing PA (69.2%) was in line with those found in literature, the remission rate of patients with a GH-producing PA (20%) was rather low (see Table 5). This can be explained by the high number of macro- or giant adenomas (80%) and cavernous sinus invasion (80%) in the patients with a GH-producing PA. Those numbers (both 15.4%) were much lower in patients with an ACTH-producing PA. Increasing adenoma size and cavernous sinus invasion are related to incomplete resection (see section 4.1.2.4). Also, the size of the adenoma was related to hormonal control in case of a FA.
The low remission rate in patients with a TSH-producing PA (0%), prolactinoma (0%) and mixed GH/PRL-producing PA (50%) should be cautiously interpreted as the number of patients in these subgroups was very low. For example, only one patient with a TSH-producing PA was included in this study. Hormonal remission was not obtained within the follow-up period, resulting in a remission rate of 0%. If remission would be achieved, the remission rate would have been 100%. Re-evaluating hormonal remission rates in a larger study sample is therefore recommended.

4.1.2.4 Remnant

The GTR rate in this study (74.4%) is in line with results found in literature. Remarkably is the difference between this GTR rate and the amount of patients without a remnant (55.1%). Several authors defined GTR as “no residual tumour mass according to postoperative imaging (and to the intraoperative surgeon’s view)” (54,56,71). In this study, GTR was checked in the Access form when the surgeons considered that all residual tumour mass was eliminated. In some patients, despite the negative intraoperative judgement of the surgeons, a residual mass was still present on postoperative MRI. In this case, the parameter remnant was also checked in the Access form. This explains why patients can have a remnant as well as GTR.

Several reasons can explain why the percentage of patients with a remnant (44.9%) in this study is higher than GTR rates found in literature.
First, the criteria for having no remnant were very strict. For example, patients with a small suspected lesion on postoperative MRI were categorised as having a remnant, even though immediate postoperative MRI showed no remnant.

Second, a large number of patients (78.8%) in the studied population had cavernous sinus invasion. Resecting tumours in this area is surgically challenging (71). In this study, the presence of a remnant was significantly different in each Knosp grade. These findings support Zoli et al. who found a negative correlation between the Knosp grade and the rate of GTR (18). Furthermore, Gondim et al. showed that the maximum tumour size is an important predictive factor of the extent of tumour excision (40). This statement supports the hypothesis that the high number of patients with large adenomas in this study (80.5% had a macro- or giant adenoma) negatively affects the excision rate.

Third, in conformity with several articles, a steep learning curve is inherent to mastering the endoscopic technique (43,63). For example, Kim et al. documented a significant increase in GTR after 100 cases of experience (54). This study investigated the 82 cases immediately following the transition to the endoscopic technique.

Furthermore, in some cases the radiologist, the endocrinologist or the neurosurgeons doubted the presence of a remnant on postoperative MRI (e.g., differentiation with scar tissue). Also, contradictions were found in the electronic patient files. In these circumstances, even though it is possible a remnant was not present, the variable “remnant” was registered as “missing” in the database. This was also done when no postoperative MRI was existing (e.g., in patients operated in June or July 2018).

Finally, a significant association between cavernous sinus invasion and incomplete adenoma resection was found (P=0.004). Also, previous surgery (P=0.02) and adenoma size (P=0.001) seem to affect the presence of a remnant. These findings strengthen the evidence that cavernous sinus invasion, previous surgery and adenoma size are predictors of incomplete resection (40,54). So, the high number of patients with macro- or giant adenoma’s (80.5%) and cavernous sinus invasion (78.8%), contributed to the large amount of remnants.

In order to facilitate the comparison of resection rates with literature, it is not recommended to dichotomize (e.g., remnant or no remnant present, GTR or no GTR), but to distinguish different degrees of resection (gross total, near total, sub total or partial) (56,71). For example, Hwang et al. considered a suspicious remaining enhancing area on postoperative MRI as "near total removal", when in this study it would have been classified as "remnant" (71).

Furthermore, it is important to notice that despite the presence of a remnant, in some cases a patient can be considered cured clinically.
For example, in case of a FA the main goal could be to bring hormone levels back to normal without causing deficiency. However, a remnant is an important reason for persisting high hormone levels postoperatively (60). Remarkably, in some FAs, the hormone levels postoperatively did not normalize, although the adenoma was completely resected, according to several postoperative MRI-images. This fact illustrates that whether or not a remnant is present, this is subordinate to postoperative hormonal control in FAs. One of the reasons for persistent disease in absence of a remnant on postoperative imaging, might be that the remnant is too small to detect on MRI or ectopic hormone secretion is present (74).

In case of NFPAs, decompression of the optic nerve could be the primary purpose of surgery, rather than GTR, as these adenomas are mostly slow-growing benign tumours (52,56).
In case of large adenoma masses, some surgeries were only performed as a debulking procedure.

4.1.3 Postoperative complications

The general complication rate in this series is 20.7%. This number lies in the range of complication rates found in literature (38,40,61).

Specific complication rates are comparable to those in literature. Except for SIADH, a slightly higher complication rate (2.4%) was observed in this study. The range in literature was 0.7% to 2.1%. However, it should be noted that only three out of the ten studies used for comparison of complication rates, described the rate of SIADH. More studies are needed to evaluate this complication accurately.

The complication rate of TDI in this study lies within the range in literature.
This complication is often slightly overestimated. Patients are easily considered suffering from TDI. The reason for that is that the patient might be "overfilled" as a preoperative measure. If the patient was administered a lot of fluid preoperatively, it is normal that he has a higher urinary loss postoperatively. If the patients exhibit any early sign of TDI, they are instantly administered Minirin® and this is a criterium to confirm a case of TDI.
In order to avoid this overestimation, the registration of TDI cases only starts from the postoperative stay at the endocrinologic department. So, if the patient received Minirin® in the

first postoperative days, on the intensive care unit or neurosurgery department, he or she was not registered as a case of TDI.
The definition of TDI and PDI differs from study to study. This is an additional reason why complication rates in literature might be different. This definition problem occurs in some complications in this study.

In opposition to this study, Wang et al. also included patients who suffered from transient decrease of smell in their definition of hyposmia (60). Other articles even used different definitions for hyposmia (56,61).

Differences in the definition of epistaxis and death are also encountered. This study only considers nosebleeds as epistaxis if an intervention was necessary. The lower complication rate might be attributed partially to this strict definition that is not applied in every article.
No deaths related to the surgery were reported in this study. Although one of the patients passed away, this was not related to the surgery. Some studies might also include those cases.

This study has a score of 0% for visual worsening and this is in line with literature. However, it is worth mentioning there was one patient who had a decrease of visual abilities, because of a thrombosis, but this was not related to the surgery.

The reason why the rate of newly induced hormonal deficiency is not lower, is that the postoperative examinations for hormonal deficiency are performed more thorough than those performed preoperatively.
In this study the size of the adenoma did not significantly correlate with the general complication rate, though it seems to affect the presence of newly induced hormonal dysfunction. This result is in line with the results of Magro et al., stating that tumour size is the strongest factor predicting new loss of a hormonal axis (56).

Unfortunately, intra-operative CSF leaks are not reported in this study. Even though it might have been an interesting complication to analyse.

4.1.4 Further policy

Since the need for medication, surgery and radiotherapy depends on the outcomes of the surgery, a reference is made here to section 4.1.2.

4.1.5 Learning process

Some authors found that the amount of operations needed to be performed in order to reach significant advantages of the endoscopic technique (over the microscopic technique), was more than 82 cases (54,63). In this regard, the postoperative outcomes (e.g., operation time, postoperative complications, GTR) in surgeries performed by dr. Dewaele and prof. dr Van Zele, might still improve.

Figure 7 confirmed the statement that operation time improves with the increasing number of patients operated.
Figure 8 showed an increase in length of hospital stay to 14.2 days in the 3th group. This transient rise can be explained by one patient who had an extremely long hospital stay of 52 days, due to a complication. If this patient would be excluded from the calculations, a significant correlation between increasing experience and decreasing length of hospital stay, might be found.
Figure 9 demonstrated that only two cases of CSF leak occurred and these appeared in the first 37 surgeries.

A significant decreased general complication rate (P=0.013) and rate of newly induced hormonal dysfunction (P=0.004) between early operated patients and late operated patients supports the hypothesis that increasing experience goes hand in hand with a decreasing complication rate. Note that this significant decrease could be reported, even though the number of invasive PAs was higher in the late group than in the early group.

4.2 Limitations and strengths

4.2.1 Limitations

Not every possible postoperative complication following ETSS was included in this database. For example, postoperative sinusitis and intraoperative CSF leak were complications mentioned by several studies (37,38,63,69), but not routinely analysed in this master's thesis. Also, parameters assessing general medical complications were not incorporated. For example, some studies mentioned pneumonia, arrythmia, myocardial infarction, etc. (37,64,73).

This is a retrospective analysis. Information to build the database was gathered by exploring electronic patient files. Occasionally, data were not found or dubious and were registered as missing data. Especially in patients receiving follow-up abroad (e.g., the Netherlands, Congo), data regarding long-term outcomes were missing.

Sometimes it was difficult to fit each patient into the Access form. In those cases, supervisors of this study needed to be consulted. For example, patients with decreased, but not normalised, hormone levels (see section 4.1.2.3).

The follow-up period was in most cases quite long, but some patients had a shorter follow-up.

Although, this study did not investigate a small sample size (82 cases), much larger groups are studied in literature (e.g., Wang et al. included 1,166 cases) (60).

4.2.2 Strengths

A broad scope was pursued. Outcomes in both FPAs and NFPAs were evaluated. These outcomes include the presence of a remnant as well as ophthalmologic outcomes, hormonal recoveries and hormonal control rates. Special attention was given to postoperative complications. Also, learning curves were drafted and predictors of postoperative outcomes were investigated.

The operations were executed in a 3th line centre, known to receive more challenging cases. For example, 78.8% of patients had invasion of the cavernous sinus. In this sample, even a patient occurred who had invasion of the ventricles. Over 80% of patients had a macro- or giant adenoma. 9.8% of the study population already received previous surgery. These characteristics are typical for more demanding cases (10,12,17–19,71).

This study did not apply strict inclusion criteria. All patients in need of surgery because of a PA at the Ghent University Hospital were included. Surgically challenging cases were not excluded. Therefore, the results in this study provide a representative outcome of ETSS. Possibly, stricter inclusion criteria were applied in other studies.

In Belgium, the 4-handed configuration between a neurosurgeon and an ENT surgeon is rather unique. Probably, this is one of the few studies evaluating ETSS in Belgium.

4.3 Recommendations

As the Ghent University Hospital is a 3th line centre, frequently the follow-up is provided by the referring endocrinologist. Regarding this, easy communication and data exchange between this reference centre and the smaller peripheral centres seems to be essential for surgeons to assess the outcome of their surgery.

Gathering the data of patients registered in electronic patient files was an intensive process.

For easier prospective research in the future, the Access form is a useful tool to be filled out in the preoperative consultation and completed postoperatively. The use of this form ensures correct and complete registration of patient information. Afterwards, the data could be easily exported to excel for simple analysis and to SPSS for more advanced evaluation. Benchmarking is important to monitor the quality of performance and consecutively identify possibilities for improvement.

To enable the comparison of postoperative outcomes with other studies, it is important to determine fixed definitions for “cure”, “hormonal control”, etc. These definitions are not always the same in the studies which were available.
Also, in order to properly evaluate long-term postoperative outcomes, a longer follow-up is recommended in this study as well as in literature.
For further recommendations see section 4.1.

4.4 Conclusion

In this study, some prognostic factors for specific postoperative outcomes were observed: adenoma size, Knosp grade, previous surgery and invasion of the cavernous sinus.

The performance of the surgeons of the Ghent University Hospital was comparable to literature. The hormonal recovery rates in this research, were higher than those reported in earlier studies. The ophthalmologic cure rates reach the better rates found in literature. Also, the score of postoperative general complications was similar to other studies. The rates in literature regarding remnants and hormonal control of functioning adenomas were slightly better than in this study. However, the result for remission of ACTH-producing adenomas was comparable. Also, these rates were better than those for acromegaly and this is in line with other research. While evaluating these results, it is important to keep in mind that this study included challenging cases and partial success rates were not taken into account.

A comparison between the early and the late operated group shows a lower number of complications in the late operated group. This confirms the statement that the increasing experience of the surgeons leads to better results. This can also be observed in the decreased duration of surgery. Since literature states that the surgeons are still in a learning phase, their results might even improve. The newly developed Access form is a useful tool to track the performance of these surgeons. Analysis of the Access database makes further improvement possible.

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ATTACHMENTS

1. Access form
2. Definition list
3. Abbreviation list

FACULTY OF MEDICINE AND HEALTH SCIENCES

1. ACCESS FORM

General preoperative information

Id (Nieuw)
UZ_id
Date of birth
Gender
Date of diagnosis
Incidental
Previous surgery
Microadenoma
Macroadenoma
Giant macroadenoma
KNOSP
Radiological compression chi
Radiological cavernous sinus

Cystic component
Fibrous
Histology
Headache
Visual Deficit
Diplopia
Galactorrhea
Decreased sexual desire
Amenorrhea
Acromegaly
Seizure
Apoplexy

Histology PRL % 0
Histology TSH % 0
Histology GH % 0
Histology ACTH % 0
Histology LH % 0
Histology FSH % 0

Surgery

Date of surgery
Length of stay
Duration of surgery 0
Approach
Extracapsular
Nasoseptal flap
Peroperative carotishemorrhage

Postoperative complication

Meningitis
Coma
Hyposmia
Panhypopituitarism
Anterior lobe insufficiency
Transient Diabetes Insipidus
Permanent Diabetes Insipidus
SIADH
CSF-leak
Revision CSF-leak
Date revision CSF-leak
Postoperative hemorrhage
Epistaxis
Revision epistaxis
Date revision epistaxis
Postoperative decreased visual acuity

visual improvement postop

Postoperative follow-up

Postop Imaging
Date last control
GTR
Rest
Recurrence
Date of recurrence

Hormonal evaluation

Preop producing

Acromegaly GH

Cushing ACTH

Prolactinoma PRL

TSH producing adenoma

Mixed GH/PRL

Postop producing

Elevated GH

Elevated ACTH

Elevated PRL

Elevated TSH

Elevated mixed GH/PRL

Preop hormonal deficiency

Deficient GH

Deficient ACTH

Deficient LH

Deficient TSH

Postop hormonal deficiency

Deficit GH

Deficit ACTH

Deficit LH

Deficit TSH

Further policy

Conservative

Surgery

Date of surgery

Radiotherapy

date of radiotherapy

Medication

Reason for further policy

Stable

Growth

Producing

Visual deficit postop

Headache

Hormonal deficit

Comments

2. DEFINITION LIST

Amenorrhoea	The patient has no longer a menstrual cycle due to a deficient gonadal axis. Menopausal women are not reported.
Cerebrospinal fluid leak	The patient has a CSF leak if a sample of his/her nose secretions tested positive for β-trace protein.
Conservative treatment	The postoperative treatment is conservative if the patient is completely cured or has a remnant without any clinical implications. In this case the patient does not need any additional treatment.
Date of diagnosis	This is the date of the diagnosis of the pituitary adenoma. In case of a recurrence, the recurrence date is not noted here. This represents the date when the diagnosis was documented for the first time.
Diabetes Insipidus	Patients are considered to suffer from diabetes insipidus if the symptoms occur during their hospital stay at the endocrinological department and the patient is administered Minirin®. This complication can be transient or permanent: The diabetes insipidus is transient if this complication disappears within 3 months postoperatively. If the symptoms persist longer than 3 months, the patient has permanent diabetes insipidus.
Diplopia	The patient sees double. Because of his double vision, he sees two images of a single object.
Duration of the surgery	The time between the start of the incision and the end of the suturing.
Epistaxis	The patient has a nosebleed, which requires a (balloon) tamponade or cauterisation. Nosebleeds which do not require these interventions are not taken into account. E.g., a nosebleed which requires an aspiration or cleaning does not count as an epistaxis.
Giant adenoma	The adenoma has a size larger than 40 mm.
Gross total removal	In this case, the surgeons assumed that al residual tumour tissue was removed after control with the endoscope during the surgery. Gross total removal is per definition reported in microadenomas.
Hormonal control	A patient who has preoperative a producing pituitary adenoma, is under hormonal control if the high hormone levels normalise postoperatively. This observation is made at the end of the follow up period.
Hormonal deficit/deficiency	The patient has at least one deficient hormonal axis.
hyposmia	The patient has a persisting decrease of smell postoperatively.
Incidentaloma	A pituitary adenoma that is found by chance during a medical investigation. This investigation is performed in order to detect another pathology. E.g., a patient, who did not present any symptoms relatable to the presence of a pituitary adenoma, received a MRI of the head on which a pituitary adenoma could be detected. The indication for the MRI could be, for example, a transient ischemic attack or a cerebrovascular accident. Headache, for example, is a symptom that can be related to a pituitary adenoma. If a pituitary adenoma is detected on a MRI performed for headache, this adenoma is not reported as an incidentaloma.
Length of hospital stay	The number of days the patient stays in the hospital because of the surgery. The day before the surgery takes place is included.

Macroadenoma	The adenoma has a size larger than 10 mm.
Microadenoma	The adenoma has a size smaller or equal to 10 mm.
Newly induced hormonal deficiency	The patient has preoperatively no specific hormonal deficiency (that is known) and has a postoperative hormonal deficiency of that axis.
Partial recovery	This can be the case for a patient who had a preoperative hormonal deficiency in multiple axes, if he had postoperatively a recovery of at least one axis, but not of all his deficient axes.
Postoperative complications	Patients who have at least one postoperative complication are covered by this definition. By this means, the calculation of the postoperative complication rate is based on the number of patients with at least one postoperative complication and not on the number of postoperative complications. This is important since it is possible that one patient has multiple postoperative complications.
Postoperative visual decrease	The patient has a visual worsening directly due to injury by the surgeons.
Preoperative visual deficit	A preoperative visual shortcoming caused by the pituitary adenoma such as visual field deficiency and blurry vison. Diplopia is not included in this definition.
Previous surgery	Previous surgery of the pituitary was performed in this patient. (Any other surgeries are not taken into account.)
Recurrence	Recurrence is reported in two instances: – Postoperatively there was no remnant detectable on MRI, but after a period new adenoma tissue appeared. – Postoperatively there was no remnant detectable on MRI and the patient was cured. After a period the disease recurred, but still no new adenoma tissue was present.
Remnant	A remnant is present if an MRI, made at least two months postoperatively, shows any residual adenoma tissue. In cases where the radiologists doubted the presence of a remnant (e.g., differential diagnosis between remnant and postoperative fibrosis), this was considered as missing information.

3. ABBREVIATION LIST

^{18}F-FDG-PET	2-deoxy-2-[^{18}F]-fluoro-D-glucose positron emission tomography
3D	Three-dimensional
a.	Arteria
ACTH	Adrenocorticotropic hormone
BIPSS	Bilateral inferior petrosal sinus sampling
CE-MRI	Contrast-enhanced magnetic resonance imaging
CRH	Corticotropin releasing hormone
CSF	Cerebrospinal fluid
CT	Computed tomography
DCE-MRI	Dynamic contrast-enhanced magnetic resonance imaging
DI	Diabetes insipidus
DoS	Duration of surgery
EM	Electromagnetic
ENT	Ear, nose and throat
ETSS	Endoscopic transsphenoidal surgery
FA	Functioning adenoma
FAs	Functioning adenomas
FSH	Follicle stimulating hormone
GH	Growth hormone
GnRH	Gonadotropin releasing hormone
GTR	Gross total removal
ICA	Internal carotid artery
ICAs	Internal carotid arteries
IGF-I	Insulin-like growth factor-I
LH	Luteinizing hormone
MEN-I	Multiple endocrine neoplasia type I
MRI	Magnetic resonance imaging
NFPA	Non-functioning pituitary adenoma
NFPAs	Non-functioning pituitary adenomas
PA	Pituitary adenoma
PAs	Pituitary adenomas
PDI	Permanent diabetes insipidus
PIF	Prolactin releasing inhibiting factors
PIT-1	Pituitary transcription factor 1
SF-1	Steroidogenic Factor-1
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
T-PIT	T-box family member pituitary transcription factor
TDI	Transient diabetes insipidus
TRH	Thyrotropin releasing hormone
TSH	Thyroid stimulating hormone
TSS	Transsphenoidal surgery
WHO	World Health Organization