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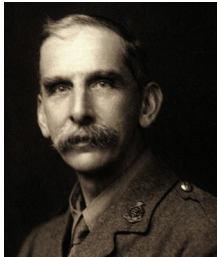
Pituitary adenoma

Aspects of outcome after surgical intervention

ERIK UVELIUS

DEPARTMENT OF CLINICAL SCIENCES, LUND | LUND UNIVERSITY





Sir Victor Horsley (pictured) is said to have performed the first surgical removal of a pituitary adenoma in 1889, years before the term hormone was coined. The technical evolution of pituitary surgery is ongoing, in part evaluated in the present thesis.



Pituitary adenoma

-aspects of outcome after surgical intervention

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Erik Uvelius



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DOCTORAL DISSERTATION

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Title and subtitle: Pituitary adenoma – aspects of outcome after surgical intervention		
<p>Abstract</p> <p>Disease of the pituitary may negatively affect patients in multiple ways. The present thesis evaluates four aspects of surgical outcome in patient's presenting with pituitary adenoma: the long-term effect on health-related quality of life (HRQoL) and work ability of a purely endoscopic transphenoidal approach compared to microscope-assisted surgery (Paper I); the efficacy of a betamethasone suppression test in determining remission after surgery of Cushing's disease (Paper II); the effect of 3-D endoscopy on surgical outcome (Paper III); and to find factors associated with reduced visual acuity (VA), post-operative improvement, and radiological measurements correlated with reduced VA in patients with non-functioning adenomas (Paper IV).</p> <p>For this purpose, retrospective cohorts (Paper I, II, IV) and a prospective cohort (Paper III) were assembled and analyzed. Data was extracted from patients' files and questionnaires.</p> <p>Paper I. Two hundred thirty-five patients were included (99 microsurgical and 136 endoscopic). HRQoL was not affected by surgical technique but showed a trend towards lower values compared to the general population. Females had lower ratings in all outcome variables.</p> <p>Paper II. The cohort consisted of 45 procedures in 28 patients. Plasma-cortisol after 24 hours with betamethasone was most accurate in predicting short- and long-term remission. Three-month remission with cut-off 107 nmol/L: sensitivity 0.85, specificity 0.94 and AUC 0.92 (95% CI 0.85–1). Five-year remission with cut-off 49 nmol/L: sensitivity: 0.94, specificity 0.93, and AUC 0.98 (95% CI 0.95–1).</p> <p>Paper III. Twenty-six patients having surgery with 2-D endoscopy were compared with 29 patients having surgery with 3-D endoscopy. Procedure time, complication rate, hospital stay, gross total resection rate and post-operative HRQoL were unaffected by surgical technique.</p> <p>Paper IV. The examined cohort contained 87 patients, 55% with reduced VA. VA improved in 54% and 77% of the best and worse seeing eye, respectively. About 50% of patients considered having normal pre-operative VA improved post-operatively in VA. Tumor height above the sella in the sagittal plane was the best radiological predictor of VA defects, cut-off 10 mm, sensitivity 0.88, specificity 0.64 and AUC 0.79 (95% CI: 0.69 to 0.89). Age, sagittal tumor height and visual field defects were risk factors of pre-operative VA deficits. No predictive factors of post-operative recovery were found.</p> <p>In conclusion, endoscopic surgery does not affect long-term HRQoL or the ability to return to work, although both are reduced among patients having had surgery of pituitary adenoma. Females seem to be at greater risk. A betamethasone suppression test after surgery of Cushing's disease can predict remission with a high accuracy without risk of adrenal crisis. No obvious outcome advantages were seen with 3-D endoscopy. VA deficits improve in 54% and 77% of the best and worse seeing eye following endoscopic pituitary surgery. Around half of patients will recover normal VA. Improvement can occur even in patients with severe VA defect, as no obvious factors associated with post-operative recovery were found.</p>		
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-aspects of outcome after surgical intervention

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Original Papers

- I. Quality of Life and Work Capacity Are Unrelated to Approach or Complications After Pituitary Surgery. Uvelius E, Castelo N, Kahlon B, Svensson C, Cervin A, Höglund P, Valdemarsson S, Siesjö P. *World Neurosurg.* 108:24-32. 2017.
- II. An early post-operative ACTH suppression test can safely predict short- and long-term remission after surgery of Cushing's disease. Uvelius E, Höglund P, Valdemarsson S, Siesjö P. *Pituitary.* 21:490-498. 2018.
- III. 3-D versus 2-D endoscopy in surgery of pituitary adenomas, evaluating patient gain using basic outcome parameters. Uvelius E, Siesjö P. *J Clin Neurosci.* 76:166-170. 2020.
- IV. Visual Acuity in Patients with Non-Functioning Pituitary Adenoma: Prognostic Factors and Long-Term Outcome after Surgery. Uvelius E, Valdemarsson S, Bengzon J, Hammar B, Siesjö P. *Manuscript.*

Abbreviations

3-D	Three-dimensional
5-ALA	5-aminolevulinic acid
ACTH	Adrenocorticotrophic hormone
AUC	Area under the curve
CSF	Cerebrospinal fluid
DI	Diabetes insipidus
FSH	Follicle-stimulating hormone
GH	Growth hormone
GTR	Gross total resection
HRQoL	Health-related quality of life
ICG	Indocyanine green
iMRI	Intra-operative magnetic resonance imaging
IGF-1	Insulin-like growth factor 1
IQR	Interquartile range
IPSS	Inferior petrosal sinus sampling
KPS	Karnofsky Performance Status Scale
LDDST	Low dose dexamethasone suppression test
LH	Luteinizing hormone
MCID	Minimal clinically important difference
MD	Median deviation
MRI	Magnetic resonance imaging
NFPA	Non-functioning pituitary adenoma
OCT	Optical coherence tomography
Pa-KPS	Patient-Karnofsky Performance Status
PitNET	Pituitary neuroendocrine tumor
RNFL	Retinal Nerve Fiber Layer
ROC-curve	Receiver operating characteristic curve
TSH	Thyroid-stimulating hormone
QoL	Quality of life
UFC	Urine free cortisol
VA	Visual acuity
VF	Visual field
VFI	Visual Field Index

Background

Historical aspects of pituitary surgery

The evolution of pituitary surgery took its first hesitant steps even before Ernest Starling coined the term hormone in 1905¹. At the time, the function of the pituitary gland was largely unknown². Galen of Pergamum, almost 2000 years earlier, stated that the pituitary was the route for evacuating mucus from the brain to the pharynx³. As a result, the pituitary is named after the Latin word for phlegm, pituita. The dogma of Galen was unquestioned until the 17-18th century when cadaveric studies showed that this evacuation was anatomically impossible⁴. Others also showed that the pituitary could enlarge and cause blindness and the pituitary was slowly considered a source of disease⁴.

Sir Victor Horsley, the first to bear the title brain surgeon⁵, is credited for the first successful pituitary operation, removing a pituitary tumor transcranially in 1889⁶. Contemporary indication for surgery would be mass-effect causing hydrocephalus and visual disturbances as the pituitary hormones and the secretory syndromes were unknown². As with all neurosurgical interventions at the time, the mortality and morbidity was high⁷.

The transsphenoidal route was first described in the late 19th century and the first successful transsphenoidal resection of a pituitary tumor was performed by Schloffer in 1907⁸. The procedure was nothing like the technique used today. The nose was lateralized via a lateral rhinotomy and parts of the orbital walls, septum and maxillary bone were removed⁶. Successively, surgeons developed techniques limiting the removal of tissues along the transsphenoidal corridor. Harvey Cushing later reported 231 cases operated via a sub-labial transphenoidal approach during 15 years with a, for the time, low mortality of only 5.6%². As could be expected, Cushing, considered the father of neurosurgery⁹, heavily influenced the field of neurosurgery and when he abandoned the transsphenoidal route to the sella in the 1920s, most of the neurosurgical community followed. For the remainder of his career, Cushing accessed the sella transcranially. In the field of medical history it is speculated that the transcranial route gave Cushing better access to suprasellar tumors and avoided infectious complications in an era with poor antiseptics and no antibiotics⁴.

A few otolaryngologists and neurosurgeons, though, kept the transphenoidal procedure alive⁶, amongst them Norman Dott who was taught the technique from Cushing. Dott developed a sphenoidal speculum with lighted tips, beginning the technical evolution that would go hand in hand with pituitary surgery in the future⁶. The rebirth of transphenoidal surgery during the 1960s is often attributed to neurosurgeons Guiot and Hardy who introduced fluoroscopy to define perioperative surgical anatomy⁶. Hardy was also one of the first surgeons to use the microscope in pituitary surgery, enhancing visualization in the narrow transphenoidal corridor, as he described in 1971¹⁰. At this time several other medical advances made transphenoidal pituitary surgery feasible. The pituitary hormones were now known and measurable, some were even available as hormone substitutes, and antibiotics had been introduced. The different secretory pituitary syndromes were described which widened the indication for pituitary surgery as Hardy introduced the term microadenoma and selective adenomectomy¹¹.

The microsurgical technique would remain largely the same until the introduction of the endoscope. Aforementioned Guiot was the first surgeon to use the endoscope in transphenoidal surgery. He abandoned the technique due to bad visualization during the 1960s¹². The rod-lens system, fiber optics and improved cameras made the technique clinically practical and the endoscope was used as an adjunct to microsurgery during the late 1970s and 1980s⁶. In 1992 Jankowski et al. were the first to describe the purely endoscopic transphenoidal technique in pituitary surgery¹³. Further development by today's surgeons such as specific endonasal instruments, techniques for repair of cerebrospinal fluid (CSF) leaks, neuronavigation and not the least, a scientific foundation has made endoscopic pituitary surgery what it is today^{6,14-17}.

Anatomy and physiology of the pituitary gland

The normal pituitary gland has a flattened, round shape, measuring no more than one centimeter in any dimension and weighing less than one gram¹⁸ (Figure 1). The gland is situated in the sella turcica of the sphenoid bone. Lateral, on both sides of the sella, are the cavernous sinuses, communicating with each other by intercavernous sinuses through the sella¹⁹. As the cavernous sinus contains cranial nerve III, IV, V1 and VI as well as the carotid artery, there is a close relation between these structures and the pituitary gland¹⁹. The posterior border of the sella turcica is the dorsum sellae. Anteriorly and inferiorly the sella is most often delimited from the sphenoid sinus by a thin sheet of bone. The pneumatization of the sphenoid sinus varies with individual and age¹⁹. Above the pituitary is the diaphragm sellae, a double sheet of dura mater

functioning as a barrier between the pituitary and the intracranial compartment. An opening in the diaphragma sellae enables the pituitary to communicate with the hypothalamus via the pituitary stalk²⁰. Above the diaphragm sellae is the chiasmatic cistern, roofed by the chiasm and optic nerves¹⁹.

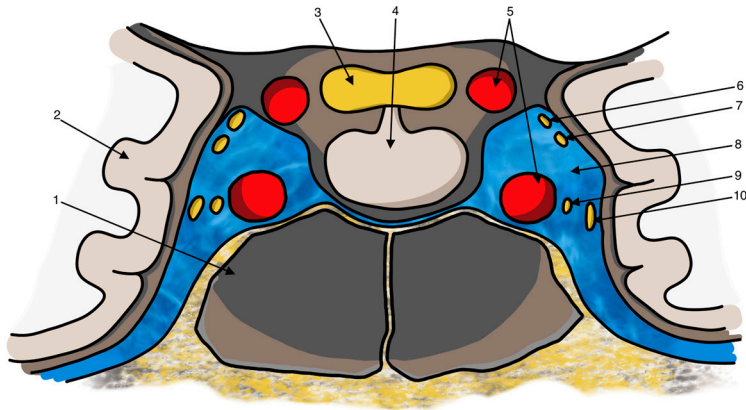


Figure 1. Gross anatomy of the pituitary gland, coronal view. 1: sphenoid sinus, 2: temporal lobe, 3: optic chiasm, 4: pituitary gland, 5: carotid artery, 6: oculomotor nerve (III), 7: trochlear nerve (IV), 8: cavernous sinus, 9: abducens nerve (VI), 10: ophthalmic nerve (V1).

The pituitary is divided into the adenohypophysis and the neurohypophysis with different embryology, though both of ectodermal origin²¹ (Figure 2). The adenohypophysis contains glandular tissue, comprising the larger part of the pituitary, responsible for the production of Adrenocorticotropic hormone (ACTH), Growth hormone (GH), Follicle-stimulating hormone (FSH), Luteinizing hormone (LH) and Thyroid-stimulating hormone (TSH). The adenohypophysis in turn can be divided into three parts, pars distalis, pars tuberalis and pars intermedia. The largest part is the pars distalis where the majority of hormones are synthesized. Pars tuberalis wraps around the pituitary stalk. It is speculated that the pars tuberalis is controlled by melatonin and important in photoperiodic control of hormone secretion^{22,23} thus incorporating a seasonal control of e.g. fertility²⁴. Pars intermedia, the smallest part of the adenohypophysis, with, if any, unknown function, is a remnant of the oral ectoderm from embryologic development of the adenohypophysis and the site of formation of pars intermedia cysts, aka Rathke's cleft cysts²⁵.

Pars nervosa of the neurohypophysis, contrary to the adenohypophysis, is of neural ectodermal origin and contains axons from cell bodies in the supraoptic and paraventricular nuclei of the hypothalamus. Oxytocin and vasopressin produced by these cells are transported through the axons via the pituitary stalk, also a part of the neurohypophysis, and stored in nerve endings in the neurohypophysis until released¹⁸.

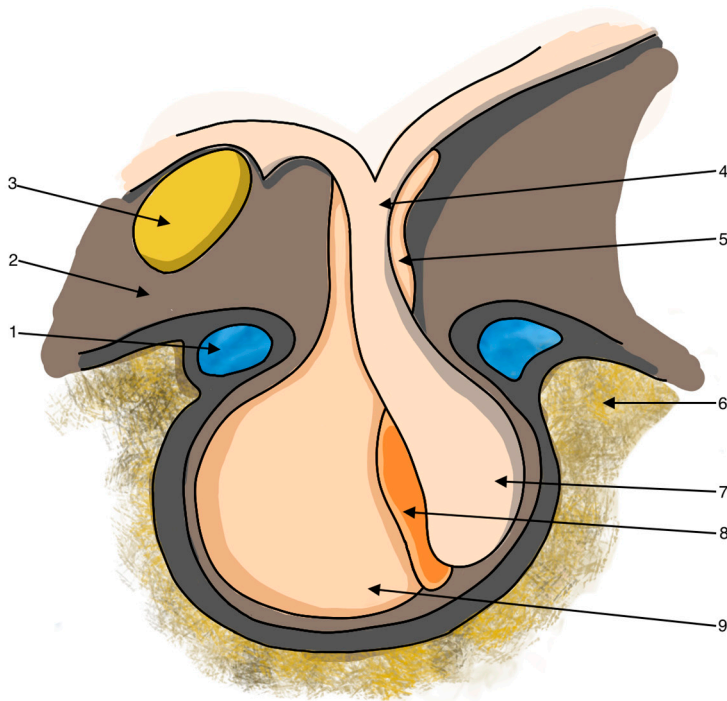


Figure 2. Anatomy of the pituitary gland, sagittal view. 1: intercavernous sinus, 2: suprasellar cisterns, 3: optic chiasm, 4: pituitary stalk, 5: pars tuberalis, 6: dorsum sellae, 7: neurohypophysis, 8: pars intermedia, 9: pars distalis.

The median eminence, the infundibular part of the hypothalamus, is one of the circumventricular organs devoid of blood-brain barrier enabling the hypothalamus to control pituitary function by means of neurosecretion via the hypophyseal portal circulation²⁶.

The pituitary gets its blood supply through the superior and inferior pituitary arteries, both branches of the internal carotid artery¹⁹. The superior pituitary arteries converge in the area of the pituitary stalk, creating the primary capillary network around the median eminence. Extensions then create the secondary capillary network in the adenohypophysis, thus completing the hypophyseal portal network¹⁸. The superior pituitary arteries supply the adenohypophysis while the neurohypophysis is supplied via the inferior pituitary arteries²⁷.

The pituitary secretes regulatory hormones controlling various systems in the human body, e.g. growth, fertility and electrolyte balance. Production of pituitary hormones is controlled by hypothalamic neurosecretory nuclei through secretion into the hypophyseal portal system, putting the central nervous system in control of the endocrine systems of the human body²⁸. This is achieved through positive- and negative-feedback loops in which hormones produced in peripheral target organs influence the production of hypothalamic factors as well as pituitary hormones. Neural inputs and circadian rhythm can also alter the hypothalamic-pituitary production of hormones¹⁸.

Pituitary adenoma

Epidemiology and classification

Pituitary adenomas are common tumors comprising 15% of all intracranial tumors²⁹. Adenomas are often categorized by size into microadenomas (<10 mm), macroadenomas (>10 mm) and sometimes giant adenomas (> 40 mm). More advanced classifications, e.g. Knosp³⁰, SIPAP³¹ and the Zurich Pituitary Score³² especially focus on lateral extension into the cavernous sinuses as such growth pattern reduces the success rate of transphenoidal surgery. The KNOSP classification is presented in Figure 3. Adenomas can also be divided into clinically functioning or non-functioning pituitary adenomas (NFPAs) based on secretion of functional hormones. NFPAs comprise non-functional gonadotroph adenomas, null cell adenomas with no immunohistological evidence of cell line origin and sometimes also includes silent adenomas³³. True functional gonadotroph adenomas are rare³⁴.

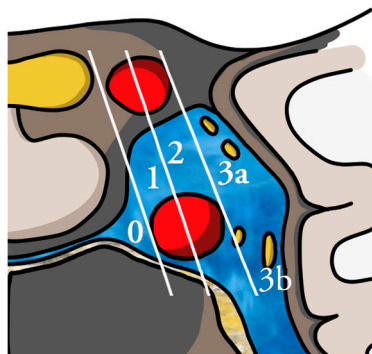


Figure 3. KNOSP classification. Tumor extending beyond the tangent lines (white lines) of the carotid artery grades the cavernous sinus invasion by adenoma into six grades. In grade 4 (not pictured) adenoma encircles the intercavernous carotid completely.

The annual incidence of pituitary adenoma is estimated at about 4/100 000 (western Sweden³⁵) with NFPAs (54%) and prolactinomas (32%) being most frequent while GH-producing adenomas (9%), Cushing's disease (4%) and TSH-producing adenomas (0.7%) are less common³⁵. The tumors, in general, are benign although pituitary carcinomas occur in a small minority (<0.5% of pituitary tumors³⁶). About 40% of patients present with macroadenomas³⁷. Peak incidence occurs between 30-60 years of age, earlier in women. A systematic review of post mortem- and imaging-studies show a general prevalence of 16.7%³⁸. Most patients never develop symptoms as the tumors remain small. The various effects of the pituitary adenoma causes a generally increased mortality³⁹, seen especially in Cushing's disease⁴⁰ and with Acromegaly⁴¹ but also reported for NFPAs⁴². The most common differential diagnoses are Rathke's cleft cysts, meningiomas and craniopharyngiomas⁴³.

Pathology

The majority of pituitary adenomas are incidental isolated cases⁴⁴. There is however a minority, accounting for five percent of cases, associated with hereditary non-syndromic entities such as Familial Isolated Pituitary Adenoma or syndromes e.g. Multiple Endocrine Neoplasia Type 1 and McCune-Albright syndrome⁴⁵. Somatic mutations in tumor suppressor genes and proto-oncogenes have been reported for several types of adenomas and might be targets of future medical therapies⁴⁶. The 2017 World Health Organization (WHO) classification of tumors of the pituitary gland focuses on detection of transcription factors to divide adenomas according to cell lineage and further stains to subdivide adenomas according to hormonal content^{29,47}. The addition of cell lineage will more often clarify the origin of silent adenomas as well as NFPAs compared to earlier classification⁴⁷. Several adenoma subgroups are marked as high-risk pituitary adenomas, suggesting an increased risk of invasiveness and recurrence⁴⁷. Increased mitotic count or Ki-67 might be suggestive of an aggressive or invasive adenoma⁴⁸. Pituitary carcinoma is diagnosed solely by the presence of metastases²⁹. Because of the significant morbidity associated even with non-carcinoma classified adenomas, there is increasing interest in updating the terminology and replacing pituitary adenoma with pituitary neuroendocrine tumor (PitNET)^{49,50}. PitNET would be consistent with the terminology used in other neuroendocrine tumors and reflects the impact of the tumor on the patient better^{49,50}.

Signs and symptoms

In general, pituitary adenomas cause symptoms by hypersecretion of pituitary hormones, compressing surrounding structures or causing hypopituitarism¹⁸.

Headache often occurs with pituitary adenoma, though causality is unclear⁵¹. Various kinds of headache have been reported, e.g. migraine like intermittent pain, neuralgic pain and cluster headache⁵². The headache is likely of multifactorial origin^{52,53}, often attributed to dural stretch, increased sellar pressure, biochemical factors and cavernous sinus invasion⁵⁴, though there is also an association with family history of headache⁵².

Compression of surrounding structures

The central anatomical location of the pituitary explains the variety of neurological deficits pituitary adenomas may cause. If the tumor expands upwards it will eventually distort the anterior optic pathways (Figure 4) causing bitemporal hemianopia or other visual field (VF) deficits^{19,55}. Depending on the spatial relationship of the chiasm and the tumor, compression may also cause junctional scotomas or homonymous hemianopia⁵⁵. Visual symptoms often develop over several months or years^{56,57}. Rapid visual deterioration, often in combination with headache, vomiting and ocular paresis may indicate pituitary apoplexy⁵⁸. The visual impairment caused by pituitary adenoma is more thoroughly reviewed in the section *Visual impairment due to pituitary adenoma* (page 43).

Lateral growth into the cavernous sinuses may cause compression and symptoms from cranial nerve III, IV, V1 or VI⁵⁹. Giant adenomas may cause hydrocephalus by obstructing the third ventricle⁶⁰.

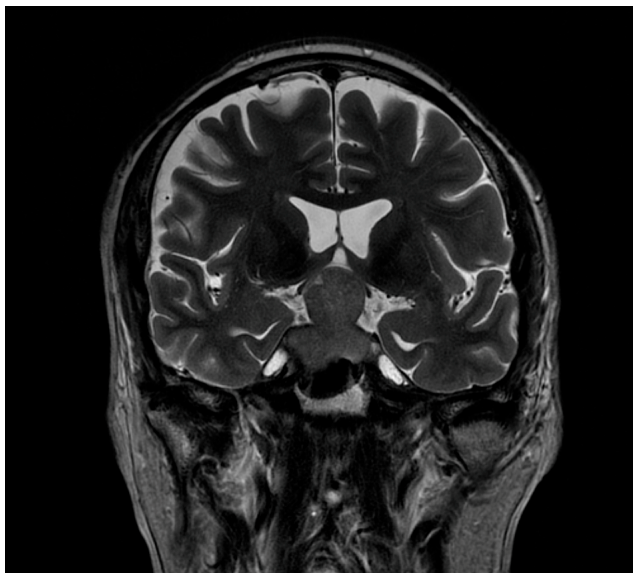


Figure 4. Macroadenoma causing severe distortion of the anterior optic pathways

Hypopituitarism

Pituitary adenomas cause hypopituitarism by compression of the pituitary gland, the pituitary stalk or the hypothalamus. Pituitary apoplexy can also cause rapid hypopituitarism by destruction of pituitary tissue.

Pre-operative hypopituitarism is associated with adenoma size⁶¹. Partial hypopituitarism, affecting at least one axis, is seen in 40-80% of macroadenomas⁶¹⁻⁶³, but also in a non-negligible minority of microadenomas⁶⁴. Panhypopituitarism occurs more seldom^{33,62}. GH and LH/FSH deficiencies are more common than ACTH and TSH insufficiencies^{33,65}. Hypopituitarism is most often reported with NFPA, most likely because hormone producing adenomas are diagnosed at an earlier stage with smaller tumor volume⁵⁹. Hypopituitarism is associated with increased morbidity and mortality^{66,67}.

Hypersecretion of pituitary hormones

Functional adenomas comprise around 50% of all adenomas³⁷ and are often diagnosed based on hormone specific signs and symptoms followed by static or dynamic endocrinological testing²⁸.

- Prolactinoma

Prolactin secreting adenomas, prolactinomas, are the most frequent of the functional adenomas³⁷. Females often present with amenorrhea, galactorrhea and infertility during fertile age while male patients present later in life, most often with impotence and decreased libido⁶⁸. As females often have more obvious symptoms, they often present with microadenomas, whereas male patients, with more obscure symptoms present with macroadenomas²⁸.

- GH-producing adenoma

In adults, with closed epiphyseal plates, GH-producing adenomas cause acromegaly while in adolescents they cause gigantism. Acromegalic symptoms develop insidiously, often resulting in late diagnosis several years after symptom onset⁶⁸. Patients often present with coarse facial features, lethargy, pain, peripheral neuropathies, sleep apnea, hypertension and diabetes mellitus²⁸. Acromegaly causes an almost two-fold general increased risk of mortality⁴¹, mainly because of cardiovascular disease but patients might also have an increased risk of developing neoplasia, mainly colorectal cancer⁶⁹.

- Cushing's disease

Cushing's disease, caused by ACTH-producing pituitary adenomas, results in an hypercortisolic state which negatively influences most organ systems⁷⁰. If left untreated, the disease bears a high mortality and morbidity⁴⁰. The symptoms are diverse, resulting in late diagnosis. Patients may present with central obesity, hypertension, diabetes mellitus, psychiatric illness, muscle and skin catabolism and osteoporosis⁷¹. The adenomas causing Cushing's disease are often small and not always visible on pre-operative magnetic resonance imaging (MRI) making surgical treatment challenging⁷⁰.

- TSH-oma

TSH producing adenomas are rarities with a incidence in Sweden of 0.03-0.15/100 000, comprising less than 1% of all adenomas^{35,72}. Patient present with symptoms of hyperthyroidism with clinical assays showing central hyperthyroidism with measurable levels of TSH, in combination with high levels of T3 and T4⁷³.

- Stalk effect

Macroadenomas can cause increased levels of prolactin by means of compressing the pituitary stalk, interrupting the inhibitory dopamine signaling from the hypothalamus, the so-called stalk effect⁵⁹.

Treatment

The goals of treatment are to reach biochemical control and to decompress nervous structures distorted by the adenoma. Except for prolactinomas and asymptomatic NFPAs, first-line of treatment is transphenoidal surgery^{74,75}.

Watchful waiting

A wait and see approach can be justified in some cases. Asymptomatic micro-prolactinomas, e.g. in pre-menopausal women without desire for pregnancy can be treated with oral estrogen contraceptives instead of dopamine agonists. As prolactinomas seldom increase in size without simultaneous increase in prolactin and the adenoma volume correlate with prolactin levels, patients can be followed by repeat sampling of prolactin as well as MRI and ophthalmologic examinations^{76,77}.

Non-symptomatic NFPAs can also be considered for conservative treatment. A summary by Huang and Moltich of 648 conservatively treated patients with NFPAs showed an increase in adenoma size in 18.4% (10% in microadenomas and 23% in

macroadenomas) during an observation period of 1-8 years⁷⁸. Interestingly, about ten percent of tumors decreased in size during follow-up. Spontaneous tumor reduction was more often seen with macroadenomas (12%) compared to microadenomas (7%). If symptoms or rapid growth, indicating the propensity for further future growth, occur during follow-up, surgery should be considered⁷⁹.

Surgical treatment

Endoscopic transnasal transphenoidal technique or various microsurgical transphenoidal approaches are used⁶⁸ and is considered first line of treatment of symptomatic NFPAs, Cushing's disease, GH-producing adenomas and TSH-omas⁸⁰. Non-functioning pituitary macroadenomas are often surgically treated because of visual deterioration or the impending risk of such³⁷. Some surgeons consider surgery an option to improve or normalize hypopituitarism, though success rate varies greatly^{62,65}.

Transphenoidal surgery of prolactinomas is second-tier treatment often considered only after failure of medical treatment caused by dopamine resistant tumors or disabling side effects. Patients with macroadenomas and the desire to become pregnant can sometimes be referred to prophylactic surgery or radiotherapy as the risk of tumor growth during pregnancy is high in this subgroup⁸¹. Also, some authors advocate surgery as treatment of microprolactinomas with low prolactin levels as the remission rate is high, thus avoiding, a potentially life-long medical treatment⁸²⁻⁸⁴.

Surgical technique does not vary with adenoma subtype although larger exposure may be required with larger tumors. Macro- and giant-adenomas can be reached via the transphenoidal route but transcranial approaches are also useful in this subgroup, especially in cases without sellar enlargement, extensive parasellar tumor extension, asymmetric suprasellar extension or fibrotic tumors.

Emergency surgery is sometimes warranted in patients with intracranial mass effect caused by pituitary apoplexy. Early surgery of apoplexy does not seem to improve visual outcome nor reduce post-operative hypopituitarism suggesting conservative management or semi-elective surgery are more relevant in these patients⁸⁵⁻⁸⁷ though early surgery is warranted in patients with rapidly deteriorating visual acuity (VA), VF or pronounced ophthalmological symptoms.

Pharmacological treatment

Various pharmacological treatments of all types of pituitary adenomas have been attempted. Dopamine agonists have shown great success in reducing prolactin levels and reducing tumor volume in prolactinomas and are now considered first line of treatment⁸¹. Dopamine agonists adds to the tonic inhibition from the hypothalamus

on prolactin secretion⁷⁶. It is speculated that dopamine agonists induce fibrosis that may prevent successful surgery and cause a higher rate of post-operative complications in cases where prolactinomas are subject to later surgical treatment^{88,89}. Other authors promote pre-operative medical treatment to increase the success of surgery⁹⁰. Rapid reduction in tumor size can sometimes cause CSF leaks in cases with large invasive prolactinomas where tumor shrinkage creates CSF fistulas through the eroded skull base after initiation of medical treatment⁹¹.

Although surgery is the primary treatment of GH-producing adenomas, medical treatment has a role after unsuccessful surgery. Individually adjusted treatment with one, or a combination, of somatostatin analogues, dopamine agonists and GH receptor antagonists are recommended in guidelines⁷⁵. Somatostatin analogues and dopamine agonists normalize Insulin-like growth factor 1 (IGF-1) in about 30% of cases each⁷⁵ while treatment with the one available GH receptor antagonist is reported to normalize IGF-1 levels in 97% after one year of treatment⁹². More than 60% showed normalized IGF-1, still after five years of treatment⁹³. Though no study has shown reduced anesthetic risk with pre-treatment of acromegalic patients with somatostatin analogues^{94,95}, guidelines recommend considering pre-operative treatment in patient with acromegaly-induced sleep apnea or heart failure⁷⁵ to reduce anesthetic risk. Also, four randomized controlled trials (RCT)⁹⁵ have all shown significant increase in short-term remission rate with pre-treatment though more recent studies failed to show improvement^{94,96}.

In patients with Cushing's disease, medical treatment is often an option only after failed surgery. There are several different drugs available, mainly steroidogenesis inhibitors, ACTH-secretion inhibitors and a glucocorticoid receptor antagonist. Steroidogenesis inhibitors, amongst others ketoconazole normalizes cortisol levels in 50% of cases by inhibiting enzymes in the production of cortisol⁹⁷. A majority of ACTH-producing adenomas express dopamine and somatostatin receptors, explaining why dopamine agonists and somatostatin analogues might have an ACTH reducing effect⁷¹. Dopamine agonists and somatostatin analogues have also been reported to reduce adenoma volume⁹⁸. Mifepristone, acting as a glucocorticoid receptor antagonists, controls the peripheral effects of hypercortisolism but does not reduce ACTH or cortisol levels⁸⁰.

There are reports of treatment of NFPAs with dopamine agonists in which treatment inhibits the growth of tumors compared to conservative follow-up of residual tumors after transphenoidal surgery^{99,100}. Somatostatin analogues, used as a proliferation inhibitor in cases of NFPAs, have only showed minor effects in small trials^{100,101}.

Increasing attention has been given to treating aggressive adenomas and pituitary carcinomas with temozolomide. Patients with aggressive tumor growth after failed surgery and radiotherapy are recommended treatment with temozolomide in European guidelines⁴⁸. Halevy et al. summarize eight patient-series with a total of 100 patients showing a response rate of 42%. Stable disease was seen in another 27%¹⁰². If continued growth occur, other cytostatic agents are recommended.

Radiotherapy

Conventional photon radiotherapy as well as various types of stereotactic radiosurgery including proton therapy can be used in patient unsuitable for surgery, after subtotal resection or in recurrent disease³⁷. Successful treatment with local control is achieved in a majority of patients at long-term follow-up regardless of adenoma type and type of radiotherapy^{28,74,103-105}. Biochemical improvement is seen over several years after treatment of functioning adenomas, e.g. one year after radiotherapy of Cushing's disease 28% were in remission, while five years after therapy 78% had normal cortisol levels¹⁰⁴.

It is important to limit the dose to surrounding neural structures, especially the chiasm which is particularly radiosensitive. Worsened optic neuropathy is seen in less than five percent of cases¹⁰⁴. Fractionated radiotherapy and increased distance between the chiasm and the tumor reduce the risk of radiotherapy induced optic nerve damage. Hypopituitarism can be expected in 20-40% of cases five years after treatment, regardless of radiotherapy modality, and will likely continue to increase in frequency with time^{74,104,106}. There has been reports of radiotherapy of pituitary adenomas causing ischemic strokes, though this risk might not be correlated to the treatment itself, rather by adenoma induced cerebrovascular risk factors and hypopituitarism^{107,108}. The risk of secondary tumor development seems to be increased compared to the general population though reported hazard ratios varies; Minniti et al. report a relative risk compared to the normal population of 7.0 for intra-axial tumors and 24.2 for meningiomas¹⁰⁹. Erridge et al. reports a relative risk of 5.7 and 9.9 compared to the normal population amongst males and females respectively¹⁰⁵. Younger age at radiotherapy also seem to be related to increased risk of developing secondary tumors¹¹⁰. In order to take account for other factors associated with pituitary adenomas, Sattler et al. compared the incidence of intracranial tumors between patients having surgery and post-operative radiotherapy to patients having surgery alone without detecting any difference in tumor incidence¹¹¹. The number of cases of secondary tumors are low, each case reported would change the risk ratios significantly in the aforementioned studies.

Current concept of endoscopic pituitary surgery

The evidence of superiority of any specific approach and surgical technique for e.g. exposure, instrumentation and reconstruction of the sella is weak and subject to preference of individual surgeons¹¹². The following text aims at giving a technical overview of the endoscopic transnasal transphenoidal surgical procedure.

Anesthesia

Oral intubation with packing of oropharynx is recommended to avoid risk of aspiration and post-operative nausea and vomiting¹¹³. The biology of pituitary adenomas can cause difficulties with intubation. Acromegalic patients often have false normal predictors of difficult intubation¹¹⁴ as well as severe obstructive sleep apnea and congestive heart failure, both adding to the risk of anesthesia¹¹⁵. Because of this, international guidelines suggest pre-treatment with somatostatin analogues prior to surgery in cases with severe obstructive sleep apnea or heart failure⁷⁵. Patients with Cushing's disease can present with electrolyte disturbances, obesity, hypertension and hyperglycemia, that need to be taken in to consideration by the anesthetist¹¹⁶. These patients are also in a hypercoagulable state with increased risk of pulmonary embolism and deep vein thrombosis during the perioperative phase¹¹⁷. As to TSH-omas, it is, as with other types of hyperthyroidism, recommended that hyperthyroid patients should be treated medically and having surgery in a euthyroid state to avoid a thyroid storm characterized by tachycardia, hyperthermia, confusion, gastrointestinal complaints and potentially cardiovascular collapse⁷³.

Pre-operative antibiotics

Pituitary surgery involves incising the respiratory tract, and is therefore classified as clean/contaminated surgery¹¹⁸, why antibiotics are recommended to reduce the risk of post-operative meningitis and sinusitis although evidence as to what substance should be administered and length of treatment is lacking¹¹⁹. A 2011 questionnaire study among pituitary surgeons show that a majority give prophylactic intravenous antibiotics for 24 hours or less. No study indicating that prolonged prophylaxis with per oral antibiotics after surgery decreases the risk of infection was found. In endoscopic sinus surgery, in ways closely related to endoscopic pituitary surgery, the use of any perioperative prophylaxis is questioned though antibiotics could be considered in cases of nasal packing to prevent toxic shock syndrome and sinusitis¹²⁰. This regime seems to be utilized by some centers also in pituitary surgery¹²¹⁻¹²³. Though even this has recently

been questioned in a systematic review of sinus surgery, which failed in showing any difference in infection incidence with or without prophylactic antibiotics¹²⁴.

Surgical technique

Pituitary surgery is most often team work between neurosurgeon and rhinologist with input from anesthetist and scrub nurse. There is an increased use of endoscopic surgery though little evidence suggest that experienced microsurgeons should transition from microscope to endoscope^{125,126}. The following text focuses on fully endoscopic transnasal transphenoidal pituitary surgery.

Technical equipment and setup

With indication of surgery and patient consent, a decision of surgery is taken. Pre-operative MRI and CT used independently or fused are often utilized in image guidance systems to increase the appreciation of the surgical anatomy, thus reducing the risk of complications¹²⁷. Anatomical variations such as kissing carotids or a conchal sphenoid sinus could motivate another surgical approach¹²⁸.

After anesthetic induction and packing of the oropharynx, patient is positioned supine with a slight rotation of the neck towards the surgeon. A pin clamp can be used to decrease unintended movement of the head and increase the accuracy of image guidance, but is not mandatory¹²⁹.

The procedure can be divided into a nasal-, sphenoid- and sellar-stage followed by sellar reconstruction¹³⁰. Each stage is further reviewed below.

Surgical procedure

Nasal stage (Figure 5)

The rhinologist begins the procedure with decongestion of the nasal mucosa or submucosal local anesthetics. The nasal anatomy is appreciated with a rigid endoscope inserted along the floor of the nasal cavity reaching the choana. The middle turbinate is lateralized and the sphenoid ostium is identified in the sphenoid recess above the choana^{19,129}. Any anatomical variants, e.g. septal deviation, concha bullosa or septal spina, are corrected if needed and should not affect surgical access¹³¹. The same procedure can then be performed on the contralateral side.

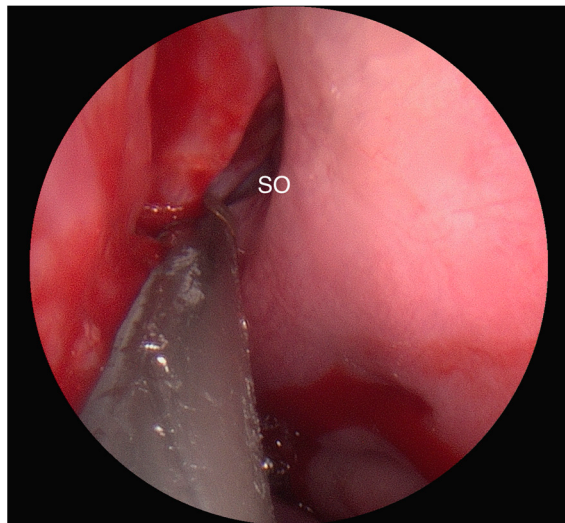


Figure 5. Nasal stage. The sphenoid ostium (SO), in the sphenoid recess, is visible above and to the right of the instrument.

Sphenoid stage (Figure 6)

If septal flaps or rescue flaps will be used, these are harvested and stored in the choana^{132,133}. The mucosa around the sphenoid ostia is otherwise coagulated and the bony rostrum of the sphenoid is exposed. The nasal septum is fractured anterior to the sphenoid and removed by back biting forceps creating a single working corridor¹³⁰. Care is taken not to injure the sphenopalatine arteries, entering the nasal cavity from the pterygopalatine fossa in the lower lateral part of the sphenoid face posterior to the middle turbinate^{19,129}. The sphenoid ostia are extended laterally and inferiorly by bone punches finalizing the sphenoidotomy. The sphenoid sinus is often divided by septations which needs to be removed to reach the sella. Lateral septa can often be

followed towards attachments along the carotids. Care should be taken as hasty removal of these septa could create fractures causing injury to the carotid arteries.

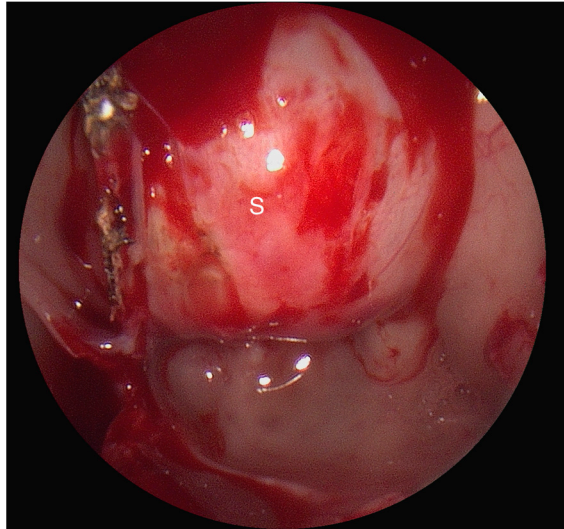


Figure 6. Sphenoid stage. After anterior sphenoidotomy and removal of sphenoid septa, the sella (S) is visible.

Sellar stage (Figure 7 and 8)

The endoscope is often controlled by the assistant and positioned in the upper part of one nostril so the lead surgeon can perform two-handed surgery using both nostrils. Anatomical landmarks in the sphenoid sinus should be appreciated before entering the sella. The optic protuberance and the carotid protuberance are separated by the lateral optico-carotid recess, created by pneumatization of the optic strut¹⁹. It is important to remember that these protuberances are not always covered by bone¹⁹. Coagulation and removal of the mucosa over the sella limits post-operative hemorrhage. The sellar face and floor is often thinned by the adenoma and might even be absent. The anterior wall of the sellar floor is fractured by gentle compression or drilling, and removed with a bone punch. The size of the opening depends on the size, shape and consistency of the adenoma. The exposed dura mater is incised and resection using ring curettes and aspiration commences. Image guidance can be used to identify direction to microadenomas¹³⁴. With macroadenomas, the inferior and lateral parts of the adenoma should be removed first to prevent the diaphragma sellae descending to early, limiting the surgeons view. This will also enable the CSF pressure on the cranial side of a patent diaphragma sellae to push the adenoma into the sella for further removal. Valsalva maneuver which increases the intracranial pressure can further aid the descent¹³⁵. After removal, the cavity is inspected with straight and angled endoscopes, often visualizing

the normal pituitary. The sellar stage is finalized with a Valsalva maneuver to detect CSF leaks before deciding on sellar reconstruction.

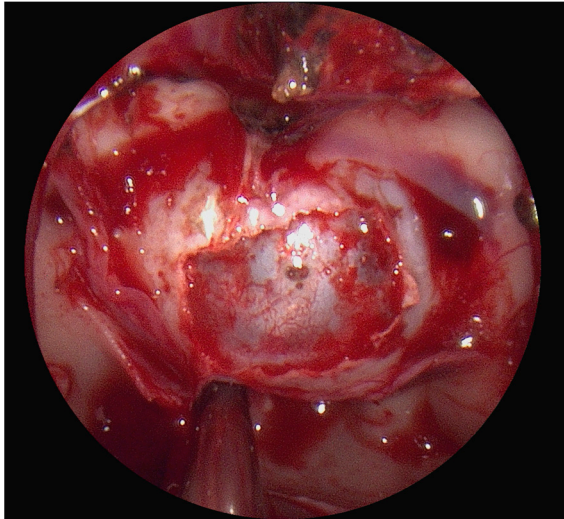


Figure 7. Sellar stage 1. The anterior wall of the sella is removed and the dura is exposed.

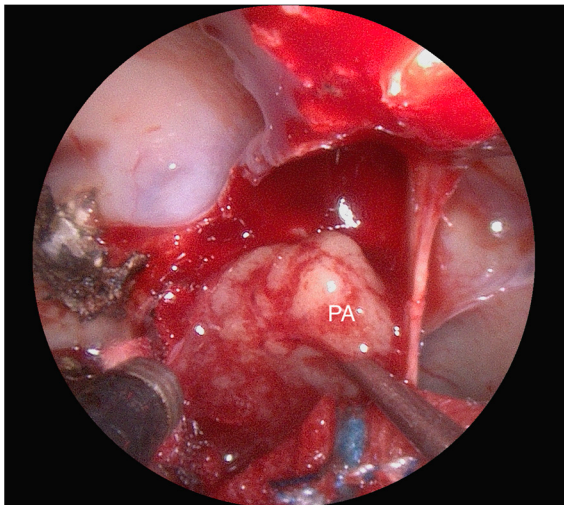


Figure 8. Sellar stage 2. The dura has been cut and pituitary adenoma (PA) is removed with ring curettes.

Reconstruction of sella

The strongest indication for reconstructing the sella is intra-operative CSF leak¹²⁹. It is also suggested that reconstructing the sella could reduce the risk of symptomatic secondary empty sella and late CSF fistulas in cases without intra-operative CSF leaks^{129,130}. The dead space created after adenoma removal is normally filled with arachnoid membranes and CSF herniating from the suprasellar cisterns. If scar tissue and arachnoid adhesions between the optic apparatus and the diaphragma sella are present, the optic apparatus in the suprasellar space is at risk of downward herniation as well. This, together with arachnoiditis and microvascular damage can cause delayed visual deterioration after initially successful surgery¹³⁶. The incidence of symptomatic secondary empty sella is low and only small case series are published^{136,137}. As to delayed CSF leaks in cases without obvious intra-operative CSF leak, the incidence is reported to be 0.7-3.4%¹³⁸⁻¹⁴¹. Since sellar reconstruction decreases the rate of post-operative CSF leaks in cases with intra-operative leaks it is reasonable to expect an reduction of post-operative CSF leaks also in cases with no intra-operative leaks if sellar reconstruction is utilized¹³⁸. Regardless, surgeons motivation to seal the sella is considerably lower if no intra-operative CSF leak is seen¹⁴⁰. Certain patient factors could motivate the surgeon to be more thorough in the reconstruction of the sella to prevent CSF leak. Large body habitus, high body mass index (BMI), chronic obstructive pulmonary disease, use of continuous airway pressure (CPAP) therapy, absent sellar bone, known post-operative nausea and vomiting, reoperation and finally previous radiotherapy, are factors indicating increased risk of post-operative CSF leak⁸⁰.

The most efficient way to reconstruct the sella is a matter of debate. Many techniques have been described, utilizing combinations of vascularized nasoseptal flaps^{132,133}, fat grafts¹⁴², fascia lata¹⁴³, dural substitutes¹⁴⁴, sometimes covered with bone, polyethylene- or titanium-mesh and reinforced by different tissue glues¹⁴³. All techniques seem reasonable effective in the hands of the respective surgeon.

To reduce the pressure exerted on the reconstruction by CSF one could expect a decreased CSF pressure to reduce the risk of CSF leaks. This is most easily achieved by a lumbar drain, though invasive and not without risks¹⁴⁵. In a survey amongst American pituitary surgeons, a majority did not use lumbar drain in routine pituitary surgery¹²³. Meta-analyses have not shown any significant decrease of CSF leaks in anterior skull base surgery when using lumbar drains^{146,147} though there might be an advantage in larger defects in endoscopic skull base approaches¹⁴⁸.

Post-operative care

The initial post-operative care can take place in an intensive care unit, high dependency unit or normal ward depending on individual department guidelines¹²³. Immobilization varies in the same way, though the use of lumbar drains is associated with prolonged bed rest^{123,149}. In accordance with the reasoning around lumbar drains it is often suggested that patient should avoid activities causing increased intracranial pressure, therefore treatment with stool softeners and antiemetics is initiated and patient are encouraged to avoid heavy lifting, sneezing and other strenuous activities after surgery^{80,122}.

The risk of symptomatic thromboembolic events after pituitary surgery is around one percent¹⁵⁰⁻¹⁵² which is lower than numbers reported for craniotomy and other forms of CNS neoplasia^{153,154}. There is though, a marked multifactorial increased risk in patients with Cushing's disease^{117,155}. Considering pituitary patients often present with other risk factors for venous thromboembolism¹⁵⁶ and undergoes, sometimes, lengthy procedures with blood loss followed by bed rest or fluid and electrolyte disturbances¹⁵¹, guidelines on perioperative venous thromboembolism prophylaxis after craniotomy^{154,157} could be used as no specific guidelines exists for pituitary surgery.

Nasal morbidity is ubiquitous after pituitary surgery. Crusting is present in almost 100% of cases, nasal discharge in almost half of cases and reduced sense of smell in about ten percent of cases¹⁵⁸. Nasal debridement is often initiated a few days post-surgery to reduce formation of synechias and crusting¹⁵⁹. Saline irrigation can be used for humidification and cleaning of the nasal mucosa¹⁶⁰.

Patients are often discharged two to four days after surgery¹⁶¹.

Future technical advances

The technical evolution is ongoing. Still, it remains to be seen if any of the techniques described below will influence the efficacy of pituitary surgery in any major way.

Intra-operative MRI (iMRI)

There is still a lack of evidence showing superiority of endoscopic pituitary surgery regarding resection rate. High-field iMRI enables detection of residual tumor in the cavernous sinuses, microadenomas and decompression of the optical apparatus suggesting a possibility to increase the rate of gross total resection (GTR)¹⁶³. Several studies show further resection after iMRI as residual tumor was found in 20-50%¹⁶³⁻¹⁶⁵. This increase in resection rate seem to correlate with an increase progression free survival, at least for NFPAs¹⁶³, and in a few reports increased endocrinological remission after surgery of functional adenomas¹⁶⁷, motivating the prolonged procedure time and cost.

Optic visualization of adenoma

Even though the use of iMRI increases the rate of GTR, the technique is time-consuming and expensive, causing other alternatives to be sought. The fluorescent properties of porphyrins from metabolized 5-aminolevulinic acid (5-ALA) used in glioma surgery¹⁶⁸ has recently been suggested as an adjunct also in pituitary surgery. Amongst others cell lines, pituitary adenoma cells have been shown to accumulate the fluorescent porphyrin in a laboratory setting¹⁶⁹ making it possible to identify residual adenoma the same way as in glioma surgery¹⁷⁰, and also opening for the possibility of photodynamic therapy¹⁷¹. Eljamel et al.¹⁷⁰ used a laser spectrophotometric probe on the pituitary after opening of the dura and managed to identify the location of six out of six MRI-negative adenomas. Another study only showed fluorescence in eight percent of adenomas¹⁷².

Indocyanine green (ICG) is another substance with fluorescent properties if excited by near-infrared light¹⁷³. ICG binds to plasma proteins and stays in the vascular compartment thus enabling intra-operative fluorescent angiography. The technique is well established in vascular neurosurgical procedures e.g. to ascertain occlusion of clipped aneurysms¹⁷⁴. ICG in pituitary surgery can be used to identify the carotid arteries, hypophyseal arteries as well as intercavernous sinuses¹⁷⁵. The technique can also, through detection of regional variation in blood flow, capillary density and differences in accumulation in adenoma tissue vs normal pituitary, delineate pituitary tissue from adenoma¹⁷⁶⁻¹⁷⁹.

Three-dimensional (3-D) endoscopy

With the evolutionary transition from microscope-assisted microsurgery to endoscopic technique in pituitary surgery, surgeons have gained the ability to “look around corners” with increased detail perception. At the same time, stereoscopic vision has been lost because of the monocular endoscope. Though the first attempt of 3-D endoscopy was made during the 1990s¹⁸⁰ it is only during recent years that technology has caught up, creating narrow tubed 3-D endoscopes with high definition screens, thus enabling the possibility of stereoscopic vision yet retaining the advantages of endoscopic surgery (Figure 9). Stereoscopic vision might increase surgeons task accuracy thus reducing complications and procedure time. Patient series evaluating 3-D endoscopy in pituitary surgery generally show small measurable advantages. Barkhoudarian et al.¹⁸¹ show, in a retrospective cases series of 160 patients of whom 115 patients had pituitary adenoma, a significantly reduced mean adenoma resection time with 3-D endoscopy (147 and 174 minutes for 3-D and 2-D endoscopy, respectively) while two smaller series¹⁸² fail to show a reduced procedure time. Hajdari et al.¹⁸³ evaluated 2-D and 3-D as well as standard definition versus high definition visualization in a study of 170 patients

showing no difference in resection rate or complication frequency between the techniques. Non-comparative case series of 3-D endoscopic cases indicate that the technique is safe and provides increased depth vision and dexterity^{184,185}. The subjective appreciation of the increased depth perception is harder to measure though the aforementioned studies report more direct application of surgical tools and reduced movement of endoscope and tools to receive tactile depth cues^{181,182} as well as and increased anatomical understanding^{184,186}. Although the advantages of the 3-D technology can be hard to appreciate, no study has shown negative results with the new technique.



Figure 9. 3-D endoscopy. Using 3-D goggles surgeons gain the ability of depth perception through the monocular endoscope.

Surgical outcome and quality of life (QoL)

The concept of surgical outcome

Surgical outcome implies the effect of surgical intervention on a population or individual. This evaluation can be done on several levels. When examining quality of health-care, the conceptual model of Donabedian¹⁸⁷ illustrates three levels: structure, process and outcome. Structure refers to measurements of the infrastructure of care, e.g. facilities, equipment and training, while process defines the interaction between

patient and the health care system, e.g. indication of surgical procedure and waiting time. Outcome, as mentioned, refers to the effect of health care intervention on an individual or population. Donabedian illustrates the many levels that can be measured in determining the effect of a surgical procedure as well as the complexity of the health system and the many factors that could affect outcome. For example, the health-care system in which procedures are performed can be funded in ways that could affect both patient selection and cause bias in reported outcome^{188,189}.

Early studies focused on mortality, general morbidity, negative outcome and length of stay when assessing surgical outcome¹⁹⁰. With time, the refinement of surgery has decreased the mortality of major surgical intervention in developed countries to 0.4-0.8%¹⁹¹ making mortality an important but insufficient marker in procedures without high mortality rates¹⁹². Surgical complications can be defined as any deviation from normal post-operative course¹⁹³ and is one type of negative outcome, while post-operative sequela and failed surgery are other examples of negative outcome¹⁹³. Sequelae, meaning successful surgery without complications, though leaving patient with anticipated loss of function, e.g. complete resection of motor cortex tumor causing expected post-operative weakness. Surgery not achieving the intended goal is considered failed surgery.

Outcome parameters should be standardized and easily quantifiable¹⁹⁴, preferably decided via international consensus, e.g. criteria of cure after surgery of acromegaly¹⁹⁵. Generally, the inter-rater variability should be low, the test should be easy to use, set up in a way that it measures what it is intended to measure and should be able to detect change over time, finally the test should have a low ceiling and floor effect, thus being able to detect change over the full spectrum of possible results¹⁹⁴. In data management, selection of statistical methods should be appropriate to variable type and skewness of data¹⁹⁶. A statistically significant result indicates that the likelihood of the result is above an accepted threshold of uncertainty, thus not occurring by random but attributed to a certain factor. The effect could very well be too small to make any clinical difference for the patients even though proven statistically significant¹⁹⁷. This especially interesting in patient-reported outcome measurements where minimal clinically important difference (MCID) determines the smallest change considered meaningful for the patient. The MCID value is unique to every patient group regardless if the same patient-reported outcome tool is used¹⁹⁸.

Conventional outcome measures after pituitary surgery

Gross total resection of pituitary adenomas can be achieved in 60-80%¹⁹⁹⁻²⁰¹. Growing evidence, in the form of consistent results of several meta-analyses, show improved

GTR with endoscopic technique¹⁹⁹⁻²⁰¹. Messerer et al. suggest that the endoscopic technique specifically increases the resection of high KNOSP-grade tumors and macroadenomas²⁰². A 2012 meta-analysis reports a mean GTR of 47% after surgery of NFPAs²⁰³. Almutairi et al. show a GTR of 71% after endoscopic surgery compared to 61% with microsurgery in a meta-analysis from 2018²⁰⁴. Two other papers indicate that a majority of patients with residual tumor show continuous growth during follow up (61% and 75%, respectively)^{205,206}.

Post-operative improvement of pituitary function is reported in about 25% of cases with pre-operative hypopituitarism⁶¹. Low age, no intra-operative CSF leak and, amongst patients with NFPAs, absence of pre-operative hypertension are factors associated with improved pituitary function after surgery⁶¹.

Pre-operative headache is reported to resolve in 49-100% after surgery while worsened headache is reported in 0-15% of cases^{53,207,208}. Inconsistent factors associated with improved headache after surgery are young age, functional adenomas, NFPAs and micro-adenoma^{53,207,208}.

The lack of consistent remission criteria adds an uncertainty to the comparison of results after surgery of Cushing's disease²⁰⁹. There is general consensus that the goal of treatment is to eliminate signs and symptoms of hypercortisolism⁷⁴. Surgical success varies with surgeon's experience and finding of adenoma on pre-operative MRI^{210,211}. In general, studies report surgical cure in 30-90% cases²¹¹⁻²¹⁵, although with various definitions of remission and follow-up time. The higher figures are reported for microadenomas while remission after surgery of macroadenomas is reported in 43-60%²⁰⁹. Recurrence is reported in up to almost 50% of cases²⁰⁹. Macroadenomas reoccur more often and earlier than microadenomas. Repeat surgery is reported to be successful in around 50% of cases²¹⁶⁻²¹⁸.

In contrast to Cushing's disease, there is consensus as to what defines remission after surgery of GH-producing adenomas¹⁹⁵. Remission criteria have successively become more stringent making comparisons over time difficult²¹⁹. Surgery of microadenomas reach remission in 70-90% of cases while surgery of macroadenomas are successful in 20-60% of cases^{28,75}. Recurrence occur around 10% of patients^{68,209} and repeat transphenoidal surgery achieved remission in almost 60% of cases²²⁰.

Surgical treatment of prolactinomas seem to incur a lower rate of disease control than surgery of other adenoma subtypes. Several authors report a disease control of microadenomas in around 70%^{84,221,222} and 15-40% in patient with macroadenomas^{81,84,221}. Recurrence is fairly common at around 20% over ten years of follow-up⁸¹.

Transphenoidal resection of pituitary adenoma is a safe procedure. Mortality is low, reported between 0 and 1.2%^{112,223-226}. Nasal complications such as epistaxis, pain and reduced olfaction often recover a few months after surgery²²⁷. The risk of symptomatic thromboembolic events after transphenoidal pituitary surgery is around one percent^{112,150-152} which is lower than numbers reported after craniotomy^{153,154}. Post-operative hemorrhage, either as delayed epistaxis or post-operative hemorrhage in the tumor cavity occurs in 0.2-3% and 0-2.5%, respectively^{112,223-226}. An even lower incidence of cranial nerve sequelae, stroke and vasospasm is reported⁸⁰. The use of nasoseptal flaps is suggested to diminish the amount of epistaxis as the flaps are pedicelled over the spared sphenopalatine artery⁸⁰. Dreaded intra-operative carotid injuries, thankfully, occur in only 0.1-2% in published series^{112,223-225}.

Post-operative reduction of function of the anterior pituitary is reported in 2.2-13.7%^{61,228-230} and post-operative panhypopituitarism in 0.23%-2.6%^{61,229}. Little et al. published their results from a prospective multicenter study comparing endoscopic and microscopic surgery, indicating a reduced rate of post-operative hypopituitarism with endoscopic technique (post-operative anterior pituitary insufficiency after microscopic surgery and endoscopic surgery occurred in 28.5% and 10%, respectively, $p < 0.001$)¹¹². Jahangiri et al. compared normalization of pituitary axes six weeks and six months after surgery showing improvement with time of three axes, the male reproductive axis (26% and 36% respectively), thyroid axis (30% and 49% respectively) and IGF-1 axis (9% and 22% respectively)²³⁰. No prognostication of recovery can be given based on which axis is affected as studies show a large variation in recovery of the different axes^{61,63,230}.

Post-operative temporary diabetes insipidus (DI) occurs in around 20% of cases^{231,232} while persistent DI one year after surgery is seen in 0-4% of cases^{61,229,231,233}. In general, inconsistent risk factors for DI are intra-operative CSF leak²³¹, ACTH-producing adenomas^{231,232} and micro-adenoma^{231,232}. Tumor size and reoperation are not proven risk factors²³¹. Resolution of DI occurred within eight months in 95% of cases²³². Considering the aforementioned numbers, it should be noted that different papers use different follow-up time, making it hard to compare the rates of anterior hypopituitarism and DI.

CSF leak requiring further surgery is reported in 0.3-3 of cases^{138,140,141,234}. Delayed CSF leaks in cases without obvious intra-operative CSF leak are uncommon and seen in 0.7-3.4% of cases.¹³⁸⁻¹⁴¹ Paluzzi et al. show a reduction of post-operative CSF leaks from 11.5% to 3.0% after the introduction of nasoseptal flaps²³⁴. The reported incidence of complications with the use of nasoseptal flaps in a recent meta-analysis are: septal perforation 0-14.5%, mucocele formation 0-4% and flap necrosis 0-1.5%. Given the low incidence of CSF leak with pituitary adenomas one could question if the use of nasoseptal flaps is motivated in standard cases.

Post-operative meningitis after pituitary surgery is uncommon, reported in less than 1% of cases^{138,140,141,234}. Magro et al. showed a strong correlation between meningitis and both intra-operative and post-operative CSF leak²³⁵ while Jin et al. reports correlation between diabetes mellitus, reoperation, CSF leak and endoscopic approach and the risk of post-operative meningitis²³⁶. Post-operative rhinosinusitis occurs in around two percent of cases^{237,238}.

The concept of QoL

With reduced mortality and morbidity, more patients are left with the burden of chronic disease^{191,239}. Under some circumstances, treatment can be initiated without aiming at prolonging life but relieving symptoms or improving function. As the medical evolution continues, more treatment options are available, further emphasizing the need to distinguish pros and cons with treatment alternatives. Evaluating the effect of treatment under any of these circumstances should not only evaluate objective mortality and morbidity, but also review the subjective well-being of the patient. This well-being can be considered as quality of life²⁴⁰. In 1947 health was defined by the WHO as the state of complete physical, mental and social well-being and not merely the absence of disease or infirmity²⁴¹. This definition is the foundation of the multidimensional conceptualization of health status as satisfaction over multiple dimensions of health²⁴². Health status, appreciated in a cultural and socioecological context covering both physical, material, social and emotional well-being, can define the broader concept of QoL²⁴⁰. Health related quality of life (HRQoL) is considered the part of QoL related to health and lack of disease²³⁹. Several definitions exist, e.g. aspects of self-perceived well-being that are related to or affected by the presence of disease or treatment²⁴². Health status, QoL and HRQoL are intertwined, often used interchangeably and each challenging to define^{239,242,243}. A myriad of generic HRQoL tools have been developed, e.g. SF-36²⁴⁵ and EQ-5D²⁴⁴ attempting to quantify the generic HRQoL or self-perceived health status²⁴². Following this, disease- or site-specific and domain-specific HRQoL instruments have followed. Disease-specific scales focus on symptomatology unique to a disease or treatment modality, e.g. the Anterior Skull Base Nasal Inventory-12 (ASK Nasal 12), evaluating the effect of signs and symptoms after endonasal skull base surgery²²⁷. Domain specific scales, on the other hand, focus on symptomatology in specific domains of HRQoL and can be used on different groups of patients, e.g. Hospital Anxiety and Depression scale²⁴⁶ focusing on detection and measuring severity of emotional disorders.

Pituitary adenoma and QoL

A systematic review published in 2015, including 102 papers, shows a general decrease in generic HRQoL in patients with symptomatic pituitary adenoma regardless of adenoma type, though GH- and ACTH-producing adenomas present with the largest reduction in HRQoL²⁴⁷. Indicating a multifactorial cause of impaired HRQoL, any of the following factors may correlate with reduced HRQoL in subtypes of adenoma^{247,248}
Prolactinoma: reduced reproductive status, sleep disturbances, hypopituitarism. NFPA: reduced visual function, pain, age, female gender and hypopituitarism. Acromegaly: Increased IGF-1 levels, pharmacotherapy with multiple drugs, radiotherapy, muscle- and joint-pain, hypopituitarism and female gender. Finally, with ACTH-producing adenomas female gender, increased age and hypopituitarism correlate with reduced HRQoL.

Surgical treatment of different types of adenomas can improve HRQoL^{247,249,250}. This improvement, shown to occur as early as one to three months post-surgery^{249,250}, often follows a temporary reduction in HRQoL. Site specific sinonasal QoL tools (SNOT-22²⁵¹ and ASK Nasal-12²²⁷) return to pre-operative base line within three months²⁵²⁻²⁵⁴. The established correlation between health status and sinonasal QoL indicates that the initial reduction in HRQoL is caused by sinonasal post-operative complaints²⁵³. A prospective multicenter study assessing sinonasal morbidity by the ASK Nasal-12 found superiority of endoscopic technique compared to microscopic approach three months post-surgery but not before or after²⁵⁵. Interestingly, the authors later published a paper determining the MCID of the ASK Nasal-12, which was shown to be higher than the median difference published between endoscope and microscope in the previously mentioned study²⁵⁵, forcing the authors to conclude that the difference between groups in the earlier study was not clinically meaningful²⁵⁶.

Though HRQoL improve after surgery, for NFPAs²⁵⁷, GH-²⁵⁸, and ACTH-producing²⁵⁹ adenomas, treatment does not allow patient to reach HRQoL baseline values of the general population. This suggests a remaining negative effect of the adenoma, presumably mediated by the long-standing exposure to abnormal hormone levels or dislocation of neural structures, even as long as 10-15 years after decompression or normalization of hormone levels²⁵⁷⁻²⁶⁰. It is important to note that these results are not consistent and there are studies not identifying an altered HRQoL in adenoma patients compared to controls²⁴⁷.

Visual impairment caused by pituitary adenoma

Background and symptoms

The anterior visual pathways are situated just above the pituitary gland in the suprasellar cisterns¹⁹. Compression of these structures by suprasellar growth, or parasellar growth encroaching the extraocular motor nerves in the cavernous sinuses, may cause various forms of visual impairment. As the adenoma needs to reach a certain size to compress the chiasm, microadenomas and even smaller macroadenomas seldom cause visual deficits⁵⁵. A 2017 meta-analysis report that 28-100% of patients present with VF deficits whereas 14-86% present with reduced VA²⁶¹. Ophthalmoplegia, most commonly oculomotor nerve palsy, can be seen in 2-15% of cases^{205,262}. The main subjective complaint in surgical series of NFPAs is visual dysfunction, seen in 38-72%²⁶³. One fourth of all NFPAs are initially diagnosed by ophthalmologist⁵⁶. Likely, because of the slow growing nature of NFPAs and unspecific symptoms⁷⁸, the mean duration of symptoms of any kind before diagnosis is reported to be 1.9 ± 2.9 years⁵⁶ whereas median duration of visual symptoms at diagnosis is 6-24 months²⁶⁴⁻²⁶⁶ with increasing age being the only factor associated with further delayed diagnosis²⁶⁶. Patients can be unaware of visual impairment, as patients not reporting visual symptoms may show VF deficits in formal neuro-ophthalmological examination^{79,267}. In all, there are inconsistent findings in regard to the effect of symptom duration on severity of visual deficits²⁶³. Asymmetric defects, including unilateral defects, are seen in a majority of cases, likely caused by interindividual variation in growth of the adenoma and position of the optic chiasm²⁶⁷⁻²⁶⁹. A post-fixed chiasm could present with monocular symptoms whereas a pre-fixed chiasm can cause homonymous hemianopia²⁷⁰. As the chiasm is situated in a pre- or post-fixed position in up to 25% of cases^{268,271,272} it is not remarkable that combinations, most often including bitemporal defects, of VF defects are common, even including nasal field defects^{267,269}. The variation in the position of the chiasm is likely contributing to the mild visual symptoms sometimes seen with very large adenomas²⁶⁸. The true bitemporal hemianopia, respecting the vertical meridian, might be less common than initially believed^{267,269} (Figure 10).

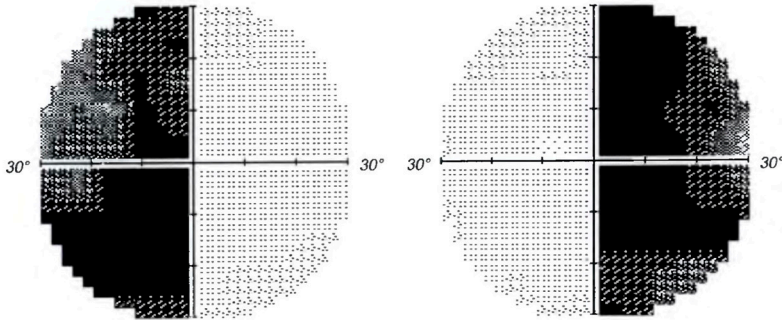


Figure 10. Visual field defects. The true bitemporal hemianopia illustrated here, might not be as common as initially believed.

Adenoma size has been correlated to pre-operative visual impairment in multiple studies^{55,57,264,268,273-276}. Specifically, Ikeda et al. show that adenoma lifting the chiasm 8 mm and 13 mm or higher above reference lines drawn from planum sphenoidale to the top of the posterior clinoids in a sagittal plane; and to a line connecting the top of the intracavernous carotid arteries bilaterally in a coronal plane, respectively, correlate with the occurrence of visual impairment. Similar results are described by other authors as well^{268,273,276}. In addition, tumor volume have been correlated to visual impairment without increasing accuracy, likely due to interindividual growth patterns, poor volumetry or calculating whole adenoma volume including para- and infra-sellar components^{268,274,276,277}.

Reduction in color perception, dyschromatopsia, was seen in around half of patients with macro adenomas in two case series^{264,278}. Red-green deficiencies are most common which is suggestive of optic nerve compression²⁷⁰. Dyschromatopsia is often combined with a decline in VA as the major pathway for color information runs through the central VF²⁷⁰.

Loss of retinal nerve fibers causes optic atrophy²⁷⁰. As there is no grading system, fundoscopic signs such as disc pallor and retinal vascular alterations are subjective. Thus, the incidence of atrophy varies markedly, ranging between 16-71%²⁶³. Additionally, some authors have showed correlation between atrophy and severity of visual deficits, while others have not²⁶³. Optical coherence tomography (OCT), a laser-based technology produces a cross sectional image of the retina. Measuring the retinal nerve fiber layer (RNFL) thickness will give an objective measurement of optic nerve atrophy⁸⁰. Blanch et al. show that OCT analysis of the ganglion cell complex, the three inner-most retinal layers, can detect subtle cell loss before clinically detectable VF deficits occur, suggesting OCT could be used as a tool of surveillance²⁷⁹.

Other forms of deficits can occur. Junctional scotomas, comprised of VF defects suggestive of ipsilateral optic nerve compression and contralateral superior quadrant VF defects⁸⁰, are present in a minority of cases. Historically this phenomenon has been attributed to compression of Wilbrand's knee, nasal retinal fibers crossing over into the contralateral optic nerve before entering the chiasm. This explanation, as well as the existence of Wilbrand's knee, has lately been questioned²⁶³. Post-fixation blindness occurs in patients with severe bitemporal hemianopia where the VF behind the point of fixation is part of the bilateral blind temporal fields. Patients with strabismus can experience the hemislide phenomena where either a strip of the VF is lost or duplicated as the alignment of the VF is lost⁸⁰.

The pathophysiology of visual symptoms caused by pituitary adenoma

It has been well accepted that bitemporal hemianopia and later further VF defect and reduced VA occurs after inferior compression of the optic chiasm²⁷⁰. There is still, however, ongoing debate as to how this injury occurs and why the crossing fibers are selectively injured early on^{280,281}. Pressure applied to a nerve may cause loss of function by conduction block in several ways, including ischemia, reduced axoplasmic transport due to disrupted cytoskeleton, remyelination and axotomy²⁸⁰. Ischemia and loss of axoplasmic transport may improve immediately or a few days after decompression, whereas demyelination requires at least a month to improve²⁸². There will be no recovery after axotomy²⁸⁰, though central plasticity may still improve visual perception²⁸³. Clifford Jones et al. noted that demyelination was seen within one week of applied pressure by a balloon to optic nerves in cats²⁸². A combination of demyelination and remyelination was seen after five weeks, despite pressure still being applied. This could suggest rapid improvement of function once chronic compression is removed as, at least partly, remyelinated fibers are in place even before decompression. The size of lesion in the compressed nerve correlated to the volume of the balloon, but, more interestingly, not to the number of injections used to inflate the balloon. Thus, a balloon that was incrementally increased in size or fully inflated at once resulted in the same type and size of lesion. Whether this also applies to the sudden increase in pituitary size with pituitary apoplexy compared to a slowly growing adenoma is unclear. In experimental spinal cord research, distension of nervous tissue has been correlated to demyelination and ischemia²⁸⁴. Similar processes have been suggested also in the anterior optic pathways. Several authors have suggested the histological changes in compressive optic neuropathy to be caused by ischemia^{285,286}. Amongst others, Bergland et al.²⁸⁶ analyzed the arterial blood supply of several hundred human specimen and found the chiasm to receive its arterial blood from two groups of arteries, a superior and an inferior group. The central part of the chiasm, with the

decussating nasal retinal nerve fibers, receive its blood supply only from the inferior group, making it more vulnerable to compressive ischemia. In another theory, McIlwaine et al.²⁸¹ suggest the force applied to the decussating fibers is larger, as the contact area between axons is smaller compared to the parallel non-decussating lateral fibers. Kosmorsky et al.²⁸⁷ assumed this would be the result if pressure in the chiasm was equal in central and lateral parts. In a cadaveric study they measured pressure in different parts of the chiasm, showing a higher pressure in the central parts, suggesting that also increased fiber density is an explaining factor of the theory of McIlwaine et al.

Recovery of vision after surgical decompression

The aforementioned studies of the pathophysiology of visual impairment suggests two to three phases of improvement after decompression of the anterior visual pathways^{270,282,288}

- Early fast phase

Improvement seen directly after surgery to one-week post-surgery. Mechanism is thought to be restoration of conduction in fibers with conduction block caused by ischemia and reduced axoplasmic transport.

- Early slow phase

Improvement seen one month to four months post-surgery. Explained by remyelination of compressed demyelinated axons.

- Late phase

Improvement seen six months to three years post-surgery. Less often described or studied. Axonal or central plasticity could be involved as well as further improvement of the factors described in the early phases²⁸³.

The previously mentioned 2017 meta-analysis showed an overall full recovery and improvement of VF deficits in 40% and 80%, respectively. VA improved in 68% of cases. Worsening of VF deficits and VA occurred in 2 and 5%, respectively²⁶¹. Deterioration is most often explained by post-operative intrasellar hemorrhage²⁸⁹, while surgical manipulation causing deficits is less often reported^{290,291}. Barzaghi et al. report improvement of color perception in 50% of cases²⁶⁴.

Predicting favorable outcome is of great interest in aiding decision making in regards to surgical intervention. Unfortunately, results are not uniform as there is great heterogeneity in the way VF deficits and VA are graded and reported. Also, there is no consensus at what time follow up should be performed²⁹². Some studies report

significant influence of symptom duration on visual recovery²⁶⁶, while others have not^{265,273}. Symptom duration consists of two time periods, time until diagnosis and time from diagnosis to surgery. The former is inherently difficult to measure, while the second might be less important in non-apoplectic cases²⁸⁹. Dekkers et al. report no deterioration when VA was measured twice preoperatively with a median of 4 (range 1-45) weeks between examinations, suggesting it is safe, but not recommended, to wait up to a month before surgical intervention²⁹³. Age as predictive factor shows again various results. Messerer et al. report lower improvement in the elderly, possibly due to reduced neuronal reserves and larger tumors²⁹⁴. Luomaranta et al. also note reduced improvement in the elderly compared with younger patients with the same visual deficits²⁷⁶. Others report obvious improvement amongst the elderly after surgery, though from a baseline of lower visual functions^{290,295}. Severe pre-operative impairment of VA or VF is likely correlated to reduced chance of post-operative recovery^{264,265,273}, though there are examples of studies not supporting this as well²⁶³. Similar inconsistent results are seen with tumor height and volume^{264,268,273}. It has been suggested that size is a pseudo-marker for other factors, such as growth rate and anatomy of the chiasm²⁶³. Jacob et al. described RNFL thickness as an independent factor related to the probability of post-operative improvement²⁹⁶. Several authors have showed nearly full recovery of vision, both VA and VF, in patients with preserved preoperative RNFL thickness²⁹⁷⁻²⁹⁹ prior to surgery. Danesh-Myer et al. also show that patients with reduced RNFL improve later in the post-operative time period than patients with normal retinal thickness³⁰⁰. Finally, one article report higher improvement rate of visual deficits in patients with normal pre-operative color perception compared with patients with compromised color perception²⁶⁴.

Aims

The focus of this thesis is surgery of pituitary adenomas and various ways of evaluating the outcome of surgical intervention. The specific aims of the included papers are

- I. To study the long-term effects of a purely endoscopic transsphenoidal approach compared to transsphenoidal microscope-assisted pituitary surgery with regard to pre-operative findings and surgical factors for the final outcome of generic HRQoL and work capacity.
- II. To examine the efficacy of a 48 hours, 2 mg/day betamethasone suppression test in determining remission after surgery of Cushing's disease.
- III. To evaluate the effect of 3-D endoscopy on general surgical outcome and HRQoL compared to the conventional endoscopic technique.
- IV. To analyze pre-operative factors associated with reduced VA in patients with NFPA, factors associated with post-operative improvement and normalization of VA as well as radiological measurements correlated with reduced VA. The overall aim is to extend knowledge on risk factors and outcome of VA in NFPA patients and thereby to improve pre-operative patient counseling.

Methods

Paper I

Study design and clinical material

The patient material comprised adult patients having had transphenoidal surgery for pituitary adenoma during 1996-2009 at Skåne University hospital in Lund, Sweden, the sole center for pituitary surgery in a region with a catchment area of 1.7 million inhabitants. Retrospective data was extracted from the Swedish National Pituitary Registry. The selected study period covered the transition from microsurgery to fully endoscopic transphenoidal surgery in 2004 and allowed for five-year follow up. Only cases with histologically confirmed adenoma were eligible for inclusion. Deceased patients, patients living abroad or under secrecy as well as patients that had undergone transcranial procedures were also excluded. Eligible patients were sent questionnaires concerning self-assessment of HRQoL, performance level assessed by EQ-5D-3L and the Karnofsky Performance Status Scale (KPS), and questions about work capacity. Additional clinical data was collected from medical records. Ethical approval was obtained from the regional ethical review board in Lund (reference number 2012/374). Initial data intended to compare 200 patients having had microsurgery to 200 patients having had purely endoscopic surgery. After exclusions 311 questionnaires were sent and 284 patients accepted inclusion. Due to data management errors, 49 more patients were later excluded because of disease other than pituitary adenoma, transcranial surgery or endoscopy before transition date. The final study population was 235 individuals. To detect any bias in patients' willingness to respond, by factors such as treatment result, gender or age, patients surgically treated during the study period but not participating in the study were reviewed and are presented as a comparison of basic data from the Swedish National Pituitary Registry (n=131).

Prevalence of citizens in the hospital catchment area able to work was extracted from official Swedish statistics for comparison³⁰¹. A cross-sectional study including almost 10 000 individuals of the general population in two Swedish provinces was used in an unmatched comparison of HRQoL³⁰².

Definitions of complications and outcome

Significant bleeding was defined as hemorrhage affecting the surgical procedure, prolonging surgery, causing prematurely aborted surgery, or causing neurologic deterioration. Meningitis was defined as clinical signs of bacterial meningitis that motivated treatment with antibiotics. CSF leak was defined as post-operative rhinorrhea requiring insertion of a lumbar drain or reoperation. DI necessitating medication at one-year follow-up defined post-operative permanent DI. Pituitary functional outcome, as evaluated by the treating endocrinologist, was assessed one year after surgery. The endocrinologist's and radiologist's interpretation of follow-up blood samples and magnetic resonance imaging at one year after surgery defined patients as cured or not cured.

EQ-5D-3L

The EQ-5D-3L is a two-part generic HRQoL instrument²⁴⁴. First, five different dimensions of HRQoL (mobility, self-care, usual activities, pain and anxiety) are rated according to the grade of problems experienced (1: no problems, 2: some problems or 3: extreme problems) giving a five-digit HRQoL-profile. This profile can be summarized as a single number (EQ-5D-index) where 1 is the best QoL imaginable and 0 is death. Negative values are possible. The EQ-5D-index is calculated by subtracting numerical points from the best health imaginable. These points vary by social and cultural factors and are calculated from reference materials in different countries. At the time of publication of the current paper there was no Swedish reference material. Sweden has historically used the reference material from the United Kingdom, as was done in the current paper. Secondly, patients are asked to grade their health on visual analogue scale (EQ-5D-VAS) between 0 and 100, 100 being the best health state imaginable and 0 being the worst health state imaginable.

Karnofsky Performance Status Scale

The Karnofsky Performance Status Scale (KPS) was introduced in the nineteen-forties to quantify the effect of chemotherapy³⁰³. KPS has been widely used in neuro-oncology when prognosticating disease or determining if patients are fit for surgery or chemotherapy. KPS is a scale with 11 points correlating to different percent values of the patients' functional status ranging from 100% (no symptoms, no signs of disease) to 0% (death). KPS was used as a patient-reported outcome assessment tool (Pa-KPS).

Statistical methods

All statistical analyses were performed with the free statistical software R³⁰⁴. Fisher's exact test was used for proportions. Continuous variables assumed to be normally distributed were analyzed with t-tests. Mann-Whitney test was used in ordinal or continuous skewed data. Associations between pre-operative or surgical factors and post-operative outcome variables were analyzed with linear and logistic univariate regression analysis. Factors with $p < 0.1$ were included in multivariable regression models along with age and gender as basic factors regardless of significance in univariate analysis. Surgical technique was also included as this was the principal parameter of investigation. Follow-up time was included without showing significance since the follow-up time was expected to be diverse. P -values < 0.05 were considered significant.

Paper II

Study design and clinical material

Data was retrospectively collected from medical records of patients diagnosed with Cushing's disease between 1998 and 2011 in the catchment area of Skåne University Hospital. The diagnosis of Cushing's disease was confirmed by a consultant endocrinologist by a combination of clinical examination, dexamethasone suppression tests and urine free cortisol (UFC). Inferior petrosal sinus sampling (IPSS) was performed in a majority of patients before primary surgery. The study period was selected to allow at least a five-year follow-up period. Pediatric patients, adult patients unfit for surgery due to severe comorbidity, lack of follow up and patients not tested according to protocol were excluded.

The 48 hours, 2mg/day betamethasone suppression test, including biochemical analyses and glucocorticoid substitution utilized is outlined in Table 1. Like dexamethasone, betamethasone is a potent synthetic glucocorticoid, which does not interfere in biochemical assays measuring plasma or urine cortisol. Betamethasone was used as the substance was available and familiar by staff in the neurosurgical ward where the patients were attended to after surgery. Betamethasone and dexamethasone both exhibit long effect duration, similar anti-inflammatory effect and negligible mineralocorticoid effects. Equipotency is reported at 1–1.25 mg dexamethasone per 1 mg betamethasone³⁰⁵.

Table 1. Protocol of glucocorticoid substitution and analyses used in the 48h, 2 mg/day betamethasone suppression test. Glucocorticoid substitution was given three times daily (8 AM, 2 PM and 8 PM). Samples for biochemical analyses were taken prior to the morning dose (8 AM). The success of surgery was evaluated on postoperative day four. If the patient was in remission continuous substitution with hydrocortisone was prescribed. If surgical success was not achieved substitution was discontinued.

	Preop day 1	Day of surgery day 0	Postop day 1	Postop day 2	Postop day 3	Postop day 4
Glucocorticoid substitution	Hydrocort 100 mg im 11 pm	Hydrocort 50+50+50 mg iv	Hydrocort 50+25+25 mg iv	Betamethas 1+0.5+0.5 mg p.o.	Betamethas 1+0.5+0.5 mg p.o.	Hydrocort 20+10+10 mg p.o. (or no supplements*)
Biochemical analyses	-	-	-	P-cortisol + P-ACTH	P-cortisol + P-ACTH + UFC	P-cortisol +P- ACTH

Hormone analyses and chemical assays

The included chemical analyses were plasma levels of cortisol and ACTH as well as UFC. Samples were collected from the days after surgery and four times during follow-up: three and 12 months, five years after surgery and at last known follow-up. As assay methods varied over time, plasma cortisol and UFC levels were recalculated by equations provided by the laboratory to fit the current reference ranges used at the main laboratory (Skåne University Hospital). Different methods were used to measure plasma ACTH but no conversion algorithms were available. Therefore, ACTH results were divided, in analogy with Invitti et al³⁰⁶, into five groups based on relation to the reference range of the method used. Group 1: values below 50% of the lower reference limit, group 2: between 50% below lower reference limit and the lower reference limit, group 3: values within lower half of reference range; group 4: values within upper half of reference range, group 5: values above upper reference limit.

Post-operative follow-up and definitions of remission and recurrence

Plasma levels of morning cortisol and ACTH along with UFC and/or overnight 1 mg low dose dexamethasone suppression test (LDDST) were analyzed according to endocrinologist's preference at follow-up three months after surgery and then yearly as well as at time of suspected recurrence. Remission was defined as decreasing clinical signs and decreasing symptoms of hypercortisolism in combination with laboratory test (UFC, morning plasma cortisol and ACTH, and/or an overnight 1 mg LDDST with significant plasma cortisol suppression). Unclear cases were always evaluated with overnight 1 mg LDDST to determine remission. As to recurrence, signs and symptoms in combination with incomplete suppression in an overnight 1 mg LDDST, a flat 24-hour plasma cortisol curve and/or UFC above reference range measured twice, defined recurrence. The outcome of biochemical testing, clinical signs and symptoms formed

the basis for the endocrinologist's compiled evaluation to determine remission or recurrence. These evaluations were reassessed by the authors based on the laboratory results and correlated well with the endocrinologist's previous conclusions.

Statistical methods

A two-sample t-test and Fisher's exact test were used in determining differences between primary operations and reoperations. The two-sample t-test was used for continuous variables while Fisher's exact test was chosen due to the low numbers involved and used for proportions. Receiver operating characteristic (ROC) curves illustrated sensitivity and specificity of post-operative assays in determining immediate post-operative success and predicting remission at follow-up. The Youden index was used to determine optimal cut-off values with highest sensitivity and specificity. In the analyses, sensitivity equals the test's ability to correctly predict patients in remission whereas specificity in this setting is the test's ability to identify patients with later recurrence. Sensitivity and specificity were considered equally important. Area under the curve (AUC) of the ROC curves with 95% confidence interval were calculated to determine the predictive power of the laboratory analyses. AUC values between 0.7 and 0.9 indicate moderate accuracy whereas AUC values over 0.9 indicate high accuracy. ROC curves were created for both primary surgeries and reoperations as well as both combined, for remission at three month, 12-month, five-year and last known follow-up. Linear and logistic univariate and multivariable regression analyses were performed to determine factors influencing remission, and thus might motivate subgroup analysis to determine if specific patient groups needed individual biochemical cut-off values. Factors with $p < 0.1$ in univariate analyses were included in multivariable regression analysis. The following factors were analyzed: Age, primary procedure or reoperation, gender, surgical technique (microsurgery or endoscopic surgery), the use of IPSS, occurrence of complications after surgery as well as category of adenoma (non-visible, micro- or macro-adenoma). p -values < 0.05 were considered significant. Specific ROC curves were to be plotted for the subgroups showing significance in multivariable regression analysis.

Paper III

Study design and clinical material

Prospective data was collected from medical records of patients undergoing primary transsphenoidal endoscopic surgery of pituitary adenoma before and after the

introduction of 3-D endoscopy at the Department of Neurosurgery, Skåne University Hospital, Sweden. The study was performed under ethical approval from the Regional Ethical Review Board in Lund (Ref. No: 2015/138). After giving written consent participants completed the EQ-5D-3L questionnaire, measuring pre-operative QoL. Patients were then followed three months post-surgery with the same questionnaire and an MRI of the sella to determine the extent of resection. A two-dimensional (2-D) HD-endoscope (Karl Storz, Germany) was used for all 2-D cases before the department transitioned to 3-D endoscopy (Karl Storz, Germany) in HD-resolution. To avoid erroneous results because of the reported learning curve of endoscopic surgery¹⁴, there was a three-month transition period where the 3-D endoscope was used parallel to the 2-D endoscope to familiarize surgeons and staff with the technique. Patients from this time period were not included in the study. All surgical procedures were performed under general anesthesia in supine position with a pin head holder and neuronavigation (StealthStation, AxiEM, Medtronic, USA) with both computed tomography and MRI of skull and brain.

Statistical methods

Patients, divided by having 2-D or 3-D surgery, were compared in regards to surgical time, perioperative blood loss, post-operative complications, time as inpatient, grade of resection and QoL. GTR was defined as complete absence of suspected pathological tissue in the sella and parasellar spaces and only estimated in cases with visible adenoma on pre-operative MRI. Pathological tissue was defined as tissue with the same attenuation as the adenoma tissue pre-operatively. Adenoma volume, pre-operatively and on MRI three months post-operatively, were determined with volumetry by the computer software OsiriX³⁰⁷ after which percentage of resection could be calculated. Statistical methods were selected according to parameter. Student's t-test, Mann-Whitney test and Fischer's exact test were used where appropriate. Medians and non-parametric tests were used if data was skewed. Multivariable regressions determined the effect of 3-D endoscopy on surgical outcome. P-values<0.05 were considered significant. As to complications, hemorrhage was defined as bleeding effecting the surgical procedure, i.e. the need for use of topical hemostatic agents or causing prolonged surgery. Meningitis was defined as clinical signs of bacterial meningitis motivating treatment with antibiotics. CSF leak was defined as post-operative rhinorrhea requiring insertion of a lumbar drain or reoperation. Post-operative pituitary insufficiency was defined as insufficiency of at least one axis compared to pre-operative function and presented as a compound evaluation by a consultant endocrinologist at follow-up three months post-surgery.

Paper IV

Study design and clinical material

Data was retrospectively collected from medical records of adult patients (≥ 18 years of age) with histologically confirmed NFPA's abutting the optic apparatus and having undergone transphenoidal surgery as primary treatment between May 2009 and June 2015. Reoperations were excluded to avoid confounders from previous surgery. The study period was selected to allow for five years of follow-up. During the study period 111 primary procedures were performed. The study was performed under ethical approval from the Regional Ethical Review Board in Lund, Sweden (Ref. No: 2012/374). After written consent was obtained from all patients alive, 101 patients were reviewed. Further exclusions, resulted in a study population of 87 individuals. All procedures were performed with a fully endoscopic transphenoidal technique.

Pre-operative and post-operative ophthalmology review (at three months, one to two years and five years after surgery) included best corrected VA (Snellen chart), VF testing with either automated static perimetry with Humphrey Field Analyzer alternatively Octopus perimetry, or with kinetic Goldmann perimetry. Slit lamp examination and fundoscopy were performed as well as extraocular motility testing. Normal VA was defined as a Snellen decimal notation 0.8 or higher³⁰⁸. VA below normal was categorized into mild visual impairment (Snellen notation 0.7 to 0.3), moderate visual impairment (Snellen notation 0.3 to 0.1) and severe visual impairment (Snellen notation ≤ 0.1) according to ICD-10³⁰⁹. Significant change was classified as two rows or more on the Snellen chart. Median deviation (MD) and Visual Field Index (VFI), both global indices of VF compared to the normal population, were noted in patients examined pre- and post-operatively with perimetry using the Humphrey Field Analyzer. In patients having perimetry by other methods, only interpretation by the ophthalmologist was recorded (graded as worsened, unchanged, improved or normalized VF).

All patients had a pre-operative MRI-scan. Adenoma height was measured from the upper limit of the adenoma to a line drawn from planum sphenoidale to the top of the posterior clinoids in the sagittal plane, and to a line connecting the top of the intracavernous carotid arteries bilaterally in the coronal plane, as described by Schmalisch et al.²⁶⁸. Adenoma volume and volume above aforementioned coronal and sagittal lines were determined with slice-by slice volumetry with the computer software OsiriX³⁰⁷. A post-operative MRI, three months after surgery, determined if the optic apparatus was decompressed.

Statistical methods

As NFPA affects the anterior visual pathways, data from each eye could not be considered independent. Consequently, eyes were categorized by best or worse pre-operative VA and analyzed accordingly throughout the follow-up. Thus, patients with reduced VA in any eye were compared with patients with bilateral normal VA. Continuous variables are presented as mean \pm standard deviation if not skewed, categorical variables as number (%) and finally ordinal and skewed continuous variables are presented as median (interquartile range). To determine differences between patients with and without reduced VA, t-test was used for continuous variables and Mann-Whitney test for skewed or ordinal data. Fischer's exact test or Chi-squared test were used for dichotomous categorical variables. Logistic multivariable regression determined factors associated with pre-operative VA and factors predicting improvement in VA after surgery. P-values < 0.05 were considered significant. ROC curves illustrated sensitivity and specificity of tumor heights and volumes in determining pre-operatively reduced VA and post-operative recovery. The Youden index was used to determine optimal cut-off value with highest sensitivity and specificity. Area under the ROC curves (ROC-AUC) with 95% confidence interval were calculated to determine the predictive power of the analysis. AUC values between 0.7 and 0.9 indicate moderate accuracy whereas AUC values over 0.9 indicate high accuracy.

Results

Paper I

Study population

A total of 366 transsphenoidal surgical procedures for pituitary adenoma were performed, 153 were microsurgical, and 213 purely endoscopic. Out of these patients, 235 were included (Figure 11).

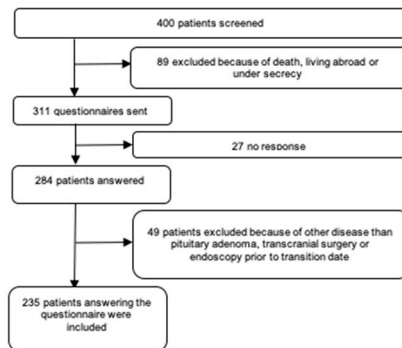


Figure 11. Inclusions and exclusions in Paper I.

The remaining 131 patients are presented as a comparison regarding basic data to examine potential inclusion bias. The mean age was equal between both surgical techniques, but there was a significant difference in gender profile, with a majority of female patients in the microsurgical group compared with a minority in the endoscopic group ($p=0.01$). Pre-operative pituitary insufficiency was significantly more frequent in the endoscopic group (39% and 63% in the microsurgical and endoscopic group, respectively, $p<0.001$). There was also a larger proportion of macroadenomas and giant adenomas in the endoscopic group, resulting in a larger mean tumor volume, though not reaching statistical significance. NFPA was the most common adenoma type in

both groups. As expected, follow-up time differed between groups (median follow-up: 173 and 88 months after microsurgery and endoscopy, respectively).

In the questionnaire cohort, complications after microscopic surgery were seen as follows: CSF leaks (11%), DI (7%), meningitis (5%), and influential bleeding (5%). After endoscopic procedures, CSF leaks were seen in 6.5% of cases, DI in 7.5% of cases, meningitis in 4.5% of cases, and influential bleeding in 7.5% of cases. Gender, age, and functional adenoma did not influence the complication frequency. Decreased pituitary function after surgery was seen in 32% of patients after microsurgery compared with 15% of patients after endoscopic procedures. Overall, no significant differences in complication frequencies were seen between the two surgical techniques, nor was there any relation between any of the studied outcome variables and the occurrence of complication or reoperation because of complication. Patients not answer the questionnaire were generally older with smaller tumors. The complication frequencies were not significantly different between patients answering, or not answering the questionnaires.

QoL outcome

Pa-KPS was not significantly higher at follow-up compared with estimated pre-operative values. Pa-KPS before surgery (endoscopy 87, microsurgery 85) and at follow-up (endoscopy 92, microsurgery 90) were both slightly, but not significantly, higher in the endoscopic group. Surgical technique and patients' age did not influence pa-KPS at follow-up, nor did complications or reoperation because of recurring tumor. Among patients of working age at surgery, none of the studied outcome factors (return to work, length of sick leave, permanent sick leave and EQ-5D-3L-parameters) showed significant correlation to pa-KPS at follow-up.

The most affected EQ-5D-3L dimensions, in both microsurgical patients and endoscopically treated patients, were pain and anxiety. Self-care was least affected.

The EQ-5D-index was not influenced by surgical technique, reoperation, or complication, but was significantly lower among female patients (median among females and males regardless of surgical technique, 0.8 and 1.0, respectively, $p < 0.001$). Not returning to work after surgery was significantly related to lower EQ-5D-index ($p < 0.001$).

Overall, median EQ-5D-VAS tended to be rated higher after endoscopic surgery ($p = 0.09$). There was no difference related to surgical approach between males or females separately regarding EQ-5D-VAS. However, when calculated regardless of the surgical technique, EQ-5D-VAS was lower among female patients (median values among females and males regardless of surgical technique, 80 and 80 (sic), respectively;

p=0.006). As with EQ-5D-index, not returning to work was a significant factor for lower EQ-5D-VAS values (median values among patients returning and not returning to work, 80 and 60, respectively, p<0.001).

Work related outcome

The proportion patient of working age at time of surgery was significantly higher in the microsurgical group (84% vs. 71% after endoscopic surgery). Patients of working age working was also significantly higher in the microsurgical group (95% vs. 80% prior to endoscopic surgery, p=0.02). The median sick leave after surgery was six weeks regardless of surgical technique, though endoscopic surgery was associated with a shorter sick leave among male patients (median sick leave after endoscopic surgery and microsurgery: four weeks (IQR 12 weeks) and six weeks (IQR 13 weeks), respectively. Female patients had a longer median sick leave regardless of surgical technique (median sick leave 8 weeks, IQR 18 weeks), though differences between gender and surgical techniques were not statistically significant.

Surgical technique did not influence the return to work frequency (return to work after microsurgery and endoscopic surgery: 72% and 78%, respectively; p=0.28). Return to work after surgery was significantly less likely among female patients (p=0.02). Among patients of working age, 10% (n=11) and 13% (n=10) had permanent sick leave after microsurgical and endoscopic surgery respectively. The majority of these patients were females (76%).

Table 2 illustrates proportions of patients working divided in age groups. Data are compared with official Swedish statistics showing the proportion of work-able citizens in our region 2012³⁰¹. There was a significant decrease in work capacity among females 40-49 years of age having had pituitary adenoma surgery (p=0.03). All age groups of females had a, nonsignificant, lower work ability compared with the general population, whereas all age groups of men showed nonsignificant increased work-ability.

Table 3 presents an unmatched comparison between the present EQ-5D-3L results and an HRQoL study of the Swedish general population³⁰². Problems are generally distributed similarly between patient in the present study and the general population, with highest frequency of problems in the pain and anxiety dimensions. The reported rates of problems, though, in the mobility, self-care, and usual activities dimensions are significantly higher in the present patient cohort. The pain dimension shows a significantly lower reported rate of problems after pituitary surgery compared with the general population. When EQ-5D-index and EQ-5D-VAS are compared, male patient

ratings are on the same level as the general population (EQ-5D index and EQ-5D-VAS in the questionnaire cohort amongst males, 0.86 and 79, respectively; EQ-5D-index and EQ-5D-VAS in the general population amongst males; 0.86 and 80, respectively). Female patient ratings, on the other hand, are lower than those of the general population (EQ-5D-index and EQ-5D-VAS in the questionnaire cohort amongst females, 0.74 and 70.2, respectively; EQ-5D-index and EQ-5D-VAS in the general population among females, 0.82 and 79, respectively).

Table 2. Comparison with official Swedish work statistics. Upper table showing percentage of the general population unable to work divided by age and gender. Lower table showing patients in patient cohort. Female patients had a lower percentage of work ability compared to the general population; the difference was significant among 40-49 year olds. All ages of male patients had a (not statistically significant) higher rate of work ability. ^aP-values calculated with Fisher exact test regarding difference between the general population and the patient cohort.

Official statistics						
Age group	40-49		50-59		60-64	
	Male	Female	Male	Female	Male	Female
Working, n	71276	68968	59650	58632	24642	23347
Not working, n	18247	16352	15469	16970	11840	13987
% Not working	20.4	19.2	20.6	22.4	32.5	37.5

Questionnaire cohort						
Age group	40-49		50-59		60-64	
	Male	Female	Male	Female	Male	Female
Working, n	10	9	11	20	12	6
Not working, n	0	7	2	6	3	7
% Not working	0	43.8	15.4	23.1	20.0	53.8
P-value ^a	Ns(0.23)	S (0.03)	Ns (0.90)	Ns (0.94)	Ns (0.45)	Ns (0.35)

Table 3. EQ-5D-3L comparison to a cohort of the general Swedish population. Columns showing proportions of patients reporting any problems in the different EQ-5D-3L dimensions divided by surgical technique (column 1-3) and the general population (column 4). The general population consists of 6093 individuals 20-74 years of age. P-values refer to the comparison between all 235 surgically treated patients and the general population. ^aP-values calculated with Fisher exact test.

	Microsurgery (n=99)	Endoscopy (n=136)	Surgical techniques, combined (n=235)	General Population ³⁰² (%)	p-value ^a
Mobility, problems, n(%)	22 (22.2)	24 (17.9) 2 missing excluded from analysis	46(19.6) 2 missing excluded from analysis	8.2	S(<0.0001)
Self-care, problems, n(%)	5 (5.1) 1 missing excluded from analysis	4(3.0) 1 missing excluded from analysis	9(3.8) 2 missing excluded from analysis	1.2	S(0.003)
Activity, problems, n(%)	27(27.6) 1 missing excluded from analysis	25(10.6) 1 missing excluded from analysis	52(22.1) 2 missing excluded from analysis	6.9	S(<0.0001)
Pain, problems, n(%)	37 (37.4)	45 (34.1) 4 missing excluded from analysis	82(34.9) 4 missing excluded from analysis	48.1	S(<0.0001)
Anxiety, problems, n(%)	33(33.3)	49 (36.3) 1 missing excluded from analysis	81(34.9) 1 missing excluded from analysis	29.6	NS(0.11)

Paper II

Study population

After exclusions, 28 patients, undergoing 45 surgical procedures, were included (Table 4). The median age of participants was 49.5 years and the majority were females (71%). Patients having primary and reoperations were similar in regards to age, gender and surgical technique. Two patients were later diagnosed with pituitary carcinoma. In 21% of primary operations and in 35% of reoperations no adenoma was located on pre-operative MRI. Eleven patients (39%) had a macro-adenoma. Pathology reports showed findings of adenoma after primary procedures and reoperations in 93% and 87%, respectively. All adenomas were ACTH positive on immunohistochemical staining.

Table 4. Patient demographics. Basic demographics of patients divided by primary surgery and reoperation where no significant differences were seen between the groups. ^aTwo sample t-test. ^bFisher exact test.

	Primary surgery (n=28)	Reoperations (n=17)	p-value
Age, years, median (range)	49.5 (23-77)	42 (28-64)	0.62 ^a
Female gender, n (%)	20 (71)	8 (47)	0.11 ^b
Surgical technique, n (%)			
Microsurgery	7 (25)	2 (12)	0.29 ^b
Endoscopy	21 (75)	15 (88)	
Adenoma category, n (%)			
Not visible on MRI	6 (21)	6 (35)	0.67 ^b
Micro-adenoma	11 (39.5)	8 (47)	0.49 ^b
Macro-adenoma	11 (39.5)	2 (12)	0.12 ^b
Missing	0 (0)	1 (6)	0.38 ^b
Procedures / patient, n (%)			
1 procedure	15 (54)		
2 procedures	9 (32)		
3 procedures	4 (14)		

Surgical complications were rare. Reoperation did not carry a significantly higher risk of complications. One patient experienced persistent post-operative DI. Except for the need of glucocorticoid substitution after successful surgery, no other case of reduced pituitary function was found according to endocrinological follow-up. No adrenal crises were observed.

Surgical results

Twelve of 28 patients (43%) showed five years or longer remission at last follow-up (median 116 months) after one surgical intervention. Three patients were not considered in remission after primary surgery but never became candidates for further surgical intervention. Thirteen of the patients underwent a total of 17 reoperations (nine patients had one reoperation and four patients had two reoperations) due to residual disease or recurrence. Four patients showed long term remission after a second or third procedure, thus, in total, long-term remission (five years or longer) was seen in 16 patients (57%) after surgical treatment, including patients cured after repeat surgery. All 16 remained in remission at last known follow up (median 110 months). Four patients, not considered cured according to direct post-operative assessment, fulfilled remission criteria at three months. However, only one of these patients was in remission five years after surgery. Two patients who, by endocrinologist's assessment, indicated immediate post-operative remission showed recurrence at three-month follow-up. Median follow-up time, between first surgery and either last known follow-up, recurrence or death, was 71 months (range 3 to 206 months). All recurrences occurred within 54 months of surgery. Nine (20%) procedures were initially deemed successful but patients later had recurrences.

Results of the 48 hours, 2 mg/day betamethasone suppression test

In summary, the best predictors in determining remission were plasma cortisol after 24 and 48 hours with betamethasone. ROC-curves with sensitivity and specificity at the optimal plasma cortisol cut-off and AUC in predicting three months and five years remission are presented in Figure 12. Cut-off values after reoperations as well as primary procedures and reoperations combined are also shown in Figure 12. Plasma ACTH and UFC analyses are not shown as ROC-curves since they all had lower sensitivity, specificity and lower accuracy, or had larger number of missing values. As there were cases where patients showed remission first three months after surgery, and long-term follow-up was considered more important than 12-month remission the following analyses were focused on three month and five-year remission. The cortisol cut-offs for 12-month prediction (data not shown) were similar to those for three-month. No recurrences were seen later than 54 months after surgery, thus values of last follow-up equal five-year remission values.

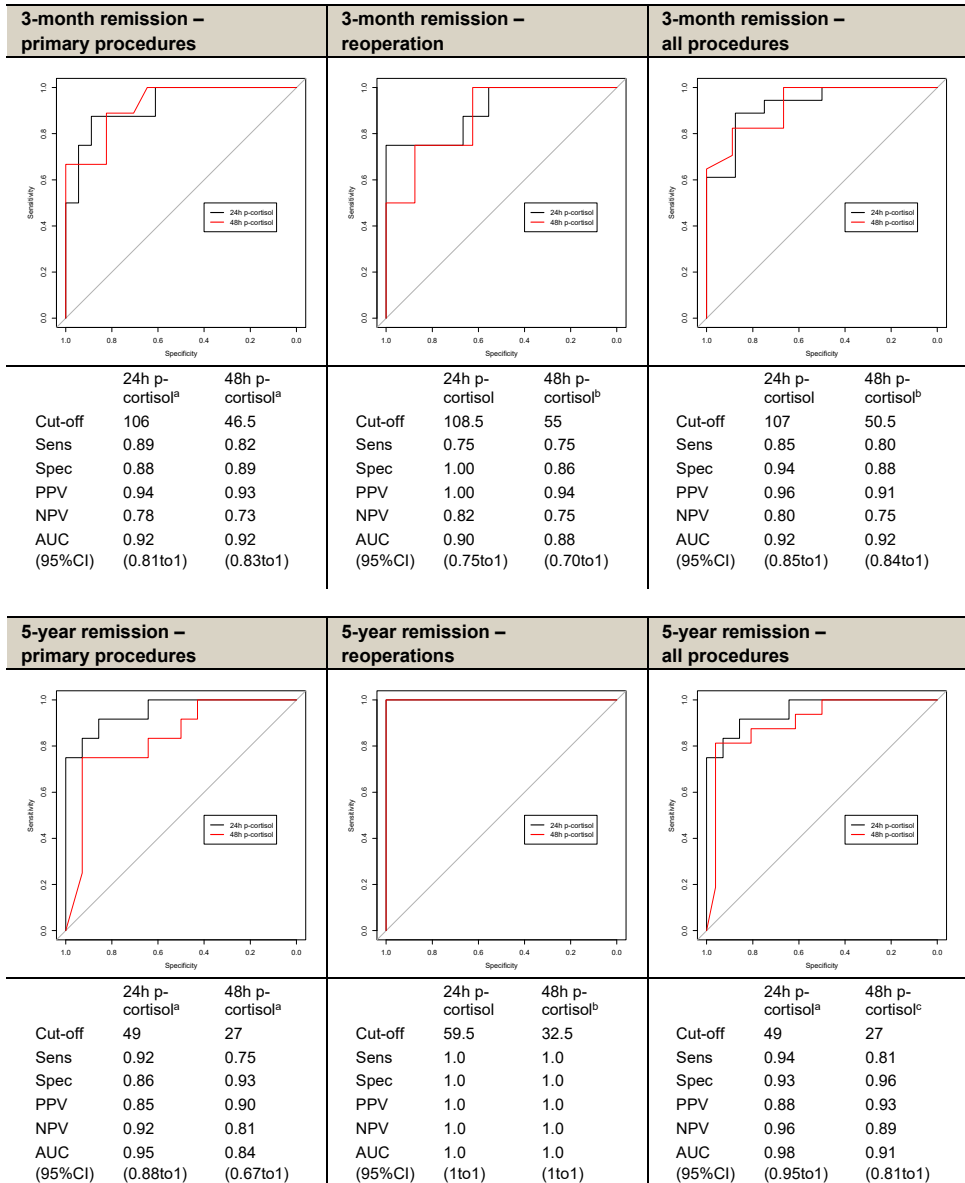


Figure 12. ROC curves with optimal cut-off values and corresponding sensitivity, specificity and AUC for the two best predictors of remission. First column: ROC-curves for primary procedures (n=28) and the ability of plasma cortisol levels after 24 h and 48 h with betamethasone to predict remission after three months and after five years. Second column: ROC-curves for reoperations (n=17). Third column: ROC-curves for all procedures (primary intervention and reoperations combined, n=45) The data indicates that the optimal cut-off values are not influenced by primary surgery or surgery after failure or recurrence. Plasma-cortisol in nmol/L. ^a2 missing values, ^b1 missing value, ^c3 missing values.

Using other cut-off values such as 140 nmol/L (the originally reported normal suppression level of a LDDST) and 83 nmol/L (the cut-off value used by Chen et al.³¹⁰ in predicting long-term remission) lacks in specificity. The suppression cut-off used in diagnosis of Cushing's disease, 50 nmol/L, was close to the cut-off level with the highest sensitivity and specificity in our series (49 nmol/L). Finally, cut-off 25 nmol/L exemplifies that a more stringent suppression level will cause a low level of true positives and larger number of false negatives, in other words a high specificity at the expense of sensitivity.

Factors influencing remission

In univariate analyses of both three-month remission and five-year remission, gender, the use of IPSS and age in the upper quartile showed $p < 0.1$ and were included in multivariable analysis. In multivariable regression analysis, male gender was the only factor significantly associated with lower remission rates in either short or long-term follow-up, $p = 0.002$ and 0.047 , respectively.

Paper III

During the study period, 12 months of 2-D endoscopy were followed by 12 months of 3-D endoscopy, separated by three months when introducing the 3-D technique. Twenty-six patients underwent primary procedure with the 2-D endoscope and 29 patients had surgery with the 3-D endoscope. The American Society of Anesthesiologist (ASA) grade was three or higher in seven (27%) and eight (27.5%) of the 2-D and 3-D cases respectively, indicating similar medical status of patients prior to surgery. Surgeons experience was equal over the case series as the senior author partook in all procedures. Patient demographics and EQ-5D-3L QoL parameters before surgery were similar with no statistically significant differences (Table 5).

There was no change in complication frequency based on type of endoscopy. All cases of hemorrhages were intra-operative with no post-operative sequelae. No arterial injuries occurred. All cases of post-operative CSF-leak required surgery. We noted a higher rate of new pituitary insufficiency after 3-D endoscopy though statistically non-significant (new post-operative insufficiency after 2-D and 3-D surgery: 3.5% and 17.2% respectively, 95% CI -0.33 to 0.06, $p = 0.4$). At the same time, no patient in the 3-D group experienced DI at follow-up, whereas three patients (12%) were diagnosed with DI after 2-D surgery. Complication data is presented in Table 6.

Table 5. Demographic and clinical data of the patients in Paper III.

	2-D endoscopy (n=26)	3-D endoscopy (n=29)
Age, years, mean (SD)	54.2 (14.4)	60.1 (16.8)
Female gender, n (%)	12 (46.2)	11 (37.9)
ASA-grade, ≥ 3, n (%)	7 (26.9)	8 (27.6)
Non-functioning adenoma, n (%)	18 (69.2)	19 (64.3)
Acromegaly, n (%)	5 (19.2)	6 (21.4)
Cushings disease, n (%)	1 (3.8)	3 (10.7)
TSH-producing n (%)	2 (7.7)	0 (0)
Prolactinoma, n (%)	0 (0)	1 (3.6)
Macroadenoma, n (%)	22 (85)	21 (72)
Adenoma volume, median cm³ (range)	2.8 (0-23.7)	2.6 (0-16.6)
Pituitary insufficiency, any axis, n (%)	13 (50.0)	15 (51.7)
Knosp-grade		
0	1 (4)	7 (24)
1	3 (12)	5 (17)
2	5 (19)	8 (28)
3	13 (50)	5 (17)
4	4 (15)	4 (14)
EQ-5D-3L, pre-operative values		
<i>Dimensions:</i>		
Mobility, problems, n (%)	4 (15.4)	9 (31.0)
Self-care, problems, n (%)	0 (0)	3 (10.3)
Usual activities, problems, n (%)	2 (7.8)	8 (27.6)
Pain/discomfort, problems, n (%)	18 (69.2)	13 (44.8)
Anxiety/depression, problems, n (%)	14 (53.8)	12 (41.4)
EQ-3D-Index, median (range)	0.796 (0.264-1)	0.744 (0.183-1)
EQ-5D-VAS, median (range)	80 (30-100)	70 (20-95)

The pre-operative median tumor volume was similar in both groups (2.8 and 2.6 cm³ with 2-D endoscopy and 3-D endoscopy, respectively). MRI three months after surgery indicated gross total resection in 15 (60%) and 14 (54%) after 2-D and 3-D surgery, respectively. Four patients, one patient in the 2-D group and three patients in 3-D group, presented without visible adenoma on pre-operative MRI. All four patients had been diagnosed with Cushing's disease.

The use of the 3-D endoscope did not affect procedure time or length of hospital stay. Patients spent a median of four days in hospital regardless of endoscopic technique (Table 7).

The proportions of reported problems in EQ-5D-3L dimensions were all equal between the two techniques pre- and post-surgery. Post-operative EQ-5D-index and EQ-5D-

VAS values were both significantly increased at follow-up three months post-surgery, regardless of endoscopic technique. Regression models did not show any effect of 3-D endoscopy on post-operative QoL (EQ-5D-index and -VAS) three months after surgery.

Table 6. Surgical Complications. ^aDefined as bleeding affecting the surgical procedure, e.g. the need for use of topical hemostatic agents or causing prolonged surgery.

	2-D endoscopy (n=26)	3-D endoscopy (n=29)	95% CI, p-value
Infection, n (%)	0 (0)	3 (11.3)	-0.25 to 0.04, p=0.27
Haemorrhage^a, n (%)	20 (76.9)	22 (75.9)	-0.22 to 0.25, p=1
Blood loss, ml, median (range)	175 (0-1500)	200 (25-1500)	-75 to 100, p=0.5
Intraoperative CSF-leakage, n (%)	9 (34.6))	10 (34.5)	-0.25 to 0.25, p=1.0
Postoperative CSF-leakage², n (%)	2 (7.7)	2 (6.9)	-0.14 to 0.15, p=1.0
Diabetes Insipidus, n (%)	3 (11.5)	0 (0)	-0.04 to 0.27, p=0.20
Anterior lobe insufficiency, new postoperative, n (%)	1 (3.8)	5 (17.2)	-0.33 to 0.06, p=0.25

Table 7. Surgical results. ^aOnly including cases with adenoma visible on preoperative MRI.

	2-D endoscopy (n=26)	3-D endoscopy (n=29)	95% CI, p-value
Gross total resection^a, n (%)	15 (60)	14 (54)	-0.20 to 0.39, p=0.67
Total Procedure time, median (range), minutes	148 (85-480)	157 (110-249)	-20 to 44, p=0.45
Time at hospital, median (range), days	4 (3-7)	4 (2-10)	-1.4 to 0.18, p=0.13
EQ-5D-3L, post-operative values			
<i>Dimensions:</i>			
Mobility, problems, n (%)	4(15.4)	6(20.7)	-0.29 to 0.19, p=0.87
Self-care, problems, n (%)	0(0)	3(10.3)	-0.29 to 0.19, p=0.87
Usual activities, problems, n (%)	3(11.5)	7(24.1)	-0.36 to 0.11, p=0.39
Pain/discomfort, problems, n (%)	11(42.3)	15(51.7)	-0.39 to 0.21, P=0.67
Anxiety/depression, problems, n (%)	7(26.9)	10(34.5)	-0.35 to 0.20, p=0.75
EQ-3D-Index, median (range)	0.848(0.656-1)	0.761(0.09-1)	-0.2 to 0.00, p=0.33
EQ-5D-VAS, median (range)	90(30-100)	80(20-98)	-12 to 5.0, p=0.61

Paper IV

Study population

The mean age of the 87 patients included was 62 ± 14 years with 31 patients (36%) being females. Reduced VA, in one or both eyes, was present in 48 patients (55%) and VF defects in 71 patients (82%). Bitemporal VF defects were common while unilateral defects occurred in less than 10% of patients. Patients presenting with reduced VA were older than patients with normal VA (65 years and 58 years, respectively, $p=0.01$). Post-operative MRI confirmed adequate decompression of the optic apparatus in 93% of patients.

Visual acuity

Amongst patients with affected VA ($n=48$), median VA was 0.7 (range 0.3 to 1.3) in the best eye and 0.4 (range from light perception to 0.7) in the worse affected eye. Ten patients (21%) presented with severe VA impairment and 12 patients (25%) with moderate impairment. There was a notable asymmetry in VA amongst these patients as no patient demonstrated severe VA impairment in both eyes (best eye range: 0.4 to 1.0) and only two patients had moderate bilateral impairment.

Post-operative deterioration of VA was seen in 5 patients (6%). All cases were asymmetrical, with reduction occurring in only one eye. Out of these patients, two had pre-operative reduction of VA and both regained pre-operative VA levels one year after surgery. Three patients with normal pre-operative VA experienced VA reduction after surgery, out of these, two had regained full VA one year after surgery, leaving only one patient (1.1%) with permanent post-operative reduction in VA in one eye.

Radiological correlation between adenoma and reduced VA

The median tumor volume was significantly larger in patients with reduced VA, 8.5 (5.5 to 10.6) and 4.4 (3.2 to 8.3) cm^3 in patients with and without reduced VA, respectively, $p<0.001$. Additionally, the median volume above the sagittal line was 2.7 (1.9 to 5.1) cm^3 in patients with reduced VA compared to 1.1 (0.7 to 2.4) cm^3 in patients without ($p<0.001$). Mean height of tumor growth above the sagittal line was 13.5 ± 4.4 mm and 9.2 ± 3.3 mm in patients with and without affected VA ($p<0.001$). Similar results were seen comparing the coronal volume and coronal tumor height. The radiological measurements on pre-operative MRI are presented in Table 8.

Table 8. Summary of radiological measurements on preoperative MRI. ^ameasurement above a line connecting the top of the intracavernous carotid arteries bilaterally in the coronal plane. ^bmeasurement above a line drawn from planum sphenoidale to the top of the posterior clinoids in the sagittal plane.

	Reduced VA (n=48)	Unaffected VA (n=39)	P-value
Adenoma volume, cm ³ , median (IQR)	8.5 (5.5-10.6)	4.4 (3.2-8.3)	<0.001
Adenoma volume above coronal line ^a , cm ³ , median (IQR)	4.5 (3.3-6.7)	2.8 (1.9-4.1)	<0.001
Adenoma volume above sagittal line ^b , cm ³ , median (IQR)	2.7 (1.9-5.1)	1.1 (0.7-2.7)	<0.001
Vertical adenoma height, coronal ^a , mm, median (IQR)	18.2 (15.4-20.7)	14.0 (12.0-17.6)	<0.001
Vertical adenoma height, sagittal ^b , mm, median (IQR)	13.5 (10.9-15.5)	9.2 (6.9-11.3)	<0.001

ROC curves illustrating the sensitivity and specificity of aforementioned radiological measurements in predicting pre-operative reduction in VA are presented in Figure 13. The best test accuracy, determined by highest AUC, was seen with tumor height above the sagittal line (AUC 0.79 (95% CI: 0.69 to 0.89), cut-off: 10 mm, sensitivity 0.88, specificity 0.64) indicating a moderate test accuracy. In general, the different measurements of volumes and tumor heights were equally accurate. There were no significant differences between any of the curves in pairwise analysis of ROC-AUC. In attempting to identify a cut-off value predicting post-operative improvement, only low AUC, sensitivity and specificity were noted, indicating low test accuracy in predicting recovery of VA after surgery.

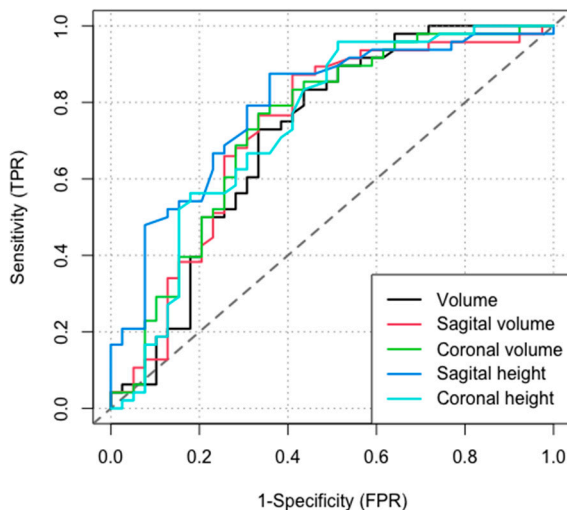


Figure 13. ROC-curves illustrating sensitivity and specificity of tumor measurements on preoperative MRI in predicting preoperative reduction in VA.

Pre-operative factors associated with reduced VA

Median MD and VFI were both significantly lower in patients with reduced VA. This could also be seen in logistic regression models when adjusting for multiple factors in the best and worse eye separately. Furthermore, regressions showed that increasing tumor height in the sagittal plane, increasing age and low MD of the worse eye (in patients having had pre-operative perimetry with the Humphrey field analyzer), were significant factors associated with reduced VA prior to surgery.

Post-operative improvement in patients with reduced VA

Thirteen patients with pre-operative reduction in VA were lost to first follow-up. At three-month follow-up, improved VA of the best eye was seen in 17/35 patients (49%) of which 15/35 (43%) had regained normal VA. An additional two patients showed significant improvement at next follow-up at one to two years, and three patients showed further improvement compared to three-month follow-up. Thus, 19/35 patients (54%), in total, improved in VA of the best eye post-surgery. Median VA improved from 0.7 (0.5-0.8) pre-operatively to 0.9 (0.65-1.0) one to two years after surgery ($p < 0.001$). No further improvement at five-year follow-up was seen. Change in median VA during follow-up is presented in Figure 14.

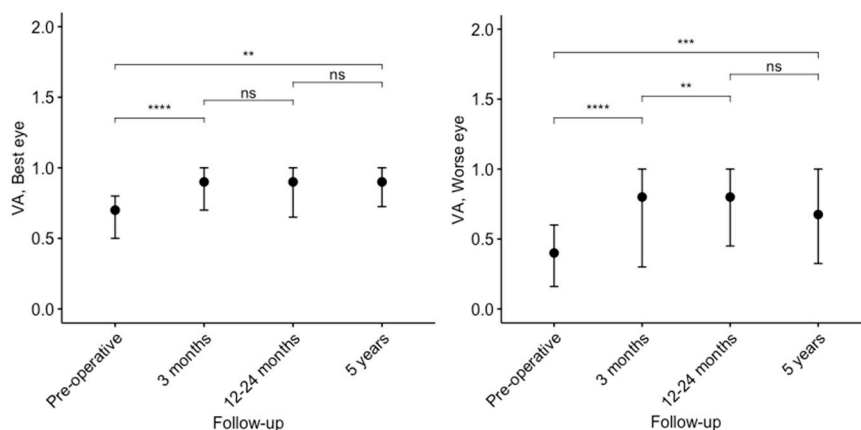


Figure 14. Change in median VA during follow-up in best (left) and worse (right) eye separately.

The VA of the eye with the lowest pre-operative VA showed improvement in 25/35 patients (71%) three months after surgery, and 19/35 (54%) of these had fully restored VA. Only a minority, a further two patients, showed new improvement at next follow-up one to two years after surgery, although eight patients showed additionally better

VA compared to first follow-up. In total 27 patients (77%) improved in VA of the worse eye. Median VA of the worse eye improved from 0.4 (0.16-0.6) pre-operatively to 0.8 (0.45-1.0) one to two years after surgery ($p<0.001$, Figure 14). No further improvement of VA at five years follow-up was observed. Normalization of VA was seen with all levels of reduced pre-operative VA, though more common in patients with mild pre-operative impairment (50%) compared to patients with moderate (25%) or severe impairment (30%). This difference did not reach statistical significance.

Regression analysis did not show any factor significantly predicting improvement. Having one eye with normal VA did not significantly affect the likelihood of improvement of the affected eye. Age, grouped by quartiles, did not indicate that increasing age negatively influenced the likelihood of post-operative VA recovery. Improvement in the worse eye was seen as follows: age 18-52 years: 80% ($n=4/5$), 53-63 years: 57% ($n=4/7$), 64-72 years: 69% ($n=9/13$), and finally age above 73 years: 80% ($n=8/10$) at follow-up one to two years post-surgery, $p=0.74$.

Post-operative improvement in VF in relation to VA

Improvement of VF, when pre-operatively affected, was seen in 48/54 patients (89%). In patients with and without reduced VA, improvement was seen in 31/36 patients (86%) and 17/18 patients (94%) during follow-up, respectively ($p=0.65$). Further improvement at follow-up one to two years after surgery only occurred in patients with reduced pre-operative VA ($p=0.002$). The overall rate of full VF recovery was 31%, seen in 21% and 50% with and without reduced pre-operative VA, respectively ($p=0.01$).

Outcome in patients with normal pre-operative VA

Twenty patients (51%), considered having no VA impairment according to the ICD-10 criteria, improved in VA during follow-up. Median VA, in this subgroup, increased from 0.8 (0.8-1.0) prior to surgery to 1.0 (0.8-1.0) one to two years post-surgery, though statistical significance was not reached ($p=0.08$). The majority, 15 patients, improved prior to the three-month follow-up.

Discussion

The pituitary has a central role in the homeostasis of the human body and an anatomical location with important neural structures in the surroundings^{19,28}. Consequently, diseases of the pituitary gland may affect the individual patient in multiple ways. Tumor growth may cause hypopituitarism, visual deterioration and headache while hypersecreting adenomas cause specific syndromes resulting in severe comorbidities and symptoms from a variety of organ systems⁴⁴. Patients having surgical treatment may experience hypopituitarism, and, thankfully rare, severe complications such as meningitis, hemorrhage and stroke⁸⁰. All these factors may impair patient's functions and QoL²⁴⁷. Successful treatment will not elicit full recovery in all patients²⁵⁷⁻²⁵⁹ as hypopituitarism may persist as well as negative effects of previous supraphysiologic hormone levels in GH and ACTH-producing adenomas. Complications as well as radiotherapy could negatively affect HRQoL even after surgical cure. It is vital to evaluate and substantiate current treatment regimens to increase efficiency in contemporary treatment, avoid exposing patients to unnecessary intervention and harm as well as optimizing patient's expectation and understanding of treatment alternatives. The present thesis aims at evaluating outcome of four different aspects in patients presenting with pituitary adenoma.

Development of surgical technique: from microscope to 3-D endoscopy

There are several inherent difficulties in performing research in the field of surgery³¹¹⁻³¹³. While the evaluation of pharmacological innovations is structured and centered around large randomized control trials, surgical innovation is often developed, refined and evaluated alternately, with obvious difficulties in randomization and blinding as well as adjusting for patient and physicians' preferences and experience, e.g. most patients want the most modern treatment available³¹³. Once a new technique has gained ground it is difficult, and sometimes considered unethical, to find comparative materials with similar non-surgical factors, e.g. historical controls could be subject to a less developed anesthetic technique and therefore experience less positive outcome³¹².

In all, surgery is a craft, improved through practice and experience³¹¹ Non the less, surgical treatment should be critically reviewed and evaluated to achieve its goal in an efficient and safe way. In the case of pituitary adenoma surgery, safe decompression of surrounding neural structures, normalization of hormone secretion without causing neurologic decline, hypopituitarism or recurrences is the main goal, while at the same time improve, or at least not cause further reduction in HRQoL⁸⁰.

Paper I revealed no significant change in complications frequencies with the introduction of endoscopic pituitary surgery. Nor did we note any change in outcome or complication frequency over time when evaluating each surgical technique divided in two subgroups according to time of surgery. These findings would argue against a significant bias from the, previously described¹⁴, steep learning curve of endoscopic pituitary surgery. We did though, observe a higher rate of females having microscope-assisted surgery. Assuming male patients with NFPA's present with larger tumors, this group might have been subject to transcranial surgery prior to the transition to endoscopic surgery, in part explaining the gender difference. This could also explain the presence of larger mean tumor volume and increased proportion of macroadenomas and giant adenomas in patients having endoscopic surgery. If anything, this fact would have introduced a bias in favor of microsurgery as larger tumors, operated transcranially before the transition to endoscopy in 2004, were not included in the series of patients selected for transphenoidal microsurgery. Although larger tumors are more prone to cause CSF leaks, decreased pituitary function, and other complications^{61,80,314}, no significant difference was seen between the two techniques in terms of complications. Rather, endoscopy was associated with a trend toward lower frequencies of CSF leaks, meningitis, and postoperative hypopituitarism, even though larger tumors were subject for endoscopic surgery, suggesting that transphenoidal endoscopic surgery is less prone to complications.

Three-dimensional endoscopy, a further evolution of endoscopic technique, was evaluated in Paper III. This study, which, to our knowledge is the first prospective study comparing 2-D and 3-D endoscopy, failed to show obvious advantages for patients with 3-D endoscopy using basic outcome parameters. Previous retrospective series evaluating 3-D endoscopy in pituitary surgery generally show small measurable advantages. Barkhoudarian et al. show, in a retrospective cases series of 160 patients of whom 115 patients had pituitary adenoma, a significantly reduced mean adenoma resection time with 3-D endoscopy (174 and 147 min for 2-D and 3-D endoscopy, respectively)¹⁸¹ while two smaller series¹⁸² fail to show reduced procedure time. Hajdari et al. evaluate 2-D and 3-D as well as standard definition versus high definition visualization in a study of 170 patients, showing no difference in resection rate between the techniques³¹⁵. None of the studies show any change in complication frequency with 3-D endoscopy^{181,315,316}.

Non-comparative series of 3-D endoscopic cases indicate that the technique is safe and provides increased depth perception and dexterity^{184,185,317}. The subjective appreciation of increased depth perception is harder to measure, though the aforementioned studies report a more direct application of surgical tools and reduced movements of endoscope and tools to receive tactile depth cues^{181,182}. Others describe an increased anatomical understanding^{184,186} and a reduced learning curve¹⁶². No study reports inferiority of 3-D endoscopy in any capacity¹⁶². Preclinical simulator studies^{162,318,319} all indicate reduced execution time and an increased depth awareness with 3-D neuroendoscopy. Some also report increased task accuracy^{318,319}.

With 3-D endoscopy in general, the effect of surgeon's experience varies in different reports. Studies indicate that experienced surgeons adapt to the new depth perception faster and have the most to gain from the new technique^{320,321} though others suggest that novice endoscopists have the biggest use of the new technique as experienced surgeons, with time, have developed and fine-tuned the ability of spatial awareness based on different depth cues^{322,323}. No clinical study addresses this question specifically for pituitary surgery although Barkhoudarian et al.¹⁸¹ note an improvement of non-quantifiably aspects of neuroendoscopy of surgeons in training (e.g. movement of the endoscope and 3-D perception). The main advantage of increased depth perception is more likely found in more complex anatomy in extended transphenoidal skull base procedures though this remains to be proven.

Development of a prediction test for Cushing's disease

The results of Paper II indicate that a postoperative betamethasone suppression test is a safe and accurate way to predict both short- and long-term remission after transphenoidal surgery of Cushing's disease. The usefulness of the betamethasone test is underlined by the high accuracy that was achieved even though the heterogeneous material included a large proportion of macroadenomas and cases of pituitary carcinoma. Cut-off values were equal regardless of primary or repeated surgery. Furthermore, considering no pre- or peri-operative factor, except for gender, significantly influenced remission and that the assay used to measure plasma cortisol had no gender specific reference range, we consider the cut-off values universal in regard to preoperative factors.

Even though the test was performed as a 48 hours suppression test, the best accuracy in predicting long-term remission was assessment of plasma cortisol after 24 hours with betamethasone. Application of this test, with a 49 nmol/L cut-off, yields a sensitivity of 0.94 and a specificity of 0.93. AUC 0.98 with a narrow 95% confidence interval,

also indicates a high diagnostic accuracy. A test result with suppression below 49 nmol/L will correctly predict five-year remission in 88% of cases. Applying this method and cut-off on the present series of patients and using it as the sole predictor of future remission, suppression of plasma cortisol below cut-off was seen after 17 procedures. Two of these patients had recurrences, while, five years after surgery, 15 patients (88%) were still in remission. This could be compared with procedures after which suppression did not reach cut-off value (n=26). In the latter group, eight patients were considered in remission by endocrinologist's compiled assessment after surgery. None of the eight were in remission five years after surgery.

All though dexamethasone suppressions tests are often used during follow-up of Cushing's disease²⁰⁹, we found only two studies reporting results of early LDDST for prediction of remission after surgery. Chen et al. report 174 patients recruited over a 20-year period showing a 93% chance of five-year remission if suppression in an overnight LDDST was below 83 nmol/L³²⁴. With reservation to methodological differences in cortisol assays, applying the cut-off 83 nmol/L to our patient series gave inferior specificity. Atkinson et al. retrospectively reviewed their series of 63 patients where LDDST was used during the first week after surgery in determining remission. Forty-five patients reached early remission of which ten patients later had recurrent disease. Suppression to undetectable levels was more common amongst patients still in remission (88.9%) versus patients with recurrences who suppressed below detectable levels in only 50% of cases³²⁵. However, these studies used different strategies to define and diagnose remission, highlighting the fact that different remission criteria are practiced. If incorporating undetectable levels of plasma cortisol as cut-off, or further lowering the plasma cortisol cut-off, exemplified with cut-off 25 nmol/L in we see enhanced specificity on the expense of sensitivity with increasing numbers of false negative results.

We use hydrocortisone substitution perioperatively and during the first days after surgery with a half-life of 1–2 hours. Extending the betamethasone test over 48 hours should eliminate analytical interference from peri-operative hydrocortisone substitution. In addition, this protocol might also overcome the possibility of altered glucocorticoid metabolism as has been reported for dexamethasone³²⁶. With this in mind, we expected the results after 48 hours with betamethasone to show the highest accuracy in predicting remission. However, the 24 hours result seemed to yield slightly better predictions than the 48 hours result. This could be by chance or by the fact that little is known of how surgery affects the response of either normal pituitary or residual adenoma in postoperative suppression tests. Furthermore, the fact that the 24 hours data seemed superior to the 48 hours data argues against an interference from perioperatively administered hydrocortisone. Thus, a shorter 24 hours test may well be used instead of the 48 hours test making the test applicable even with shorter hospital stays.

Many institutions rely on plasma cortisol nadir in predicting remission. Low plasma cortisol nadir has showed high correlation with remission, although with variable cut-off values as well as definitions of long-term remission³²⁷⁻³³⁵. Measuring plasma cortisol nadir requires withholding glucocorticoid substitution with the risk, although apparently minor^{328,329,331,333}, of acute hypocortisolism. We have found no reports of serious adrenal crisis post-surgery in the literature, but we would expect withholding cortisol to be more labor intensive in retaining a high level of patient safety^{328,332,336}. As we never pause substitution, extensive monitoring is not needed to avoid adrenal crises.

Surgical results and QoL

As the patient's perspective of medical intervention has come in to focus so has the concept of quality of life²⁴⁷. The major findings in Paper I are that neither HRQoL nor work capacity is significantly different with endoscopic transsphenoidal surgery compared with microsurgery in long-term follow-up.

As shown in Table 3 on page 62, higher rates of reported problems with the mobility, self-care, and usual activities dimensions of EQ-5D-3L are noted long after pituitary surgery compared to the general population. This finding is consistent with the report by Andela et al. in which pituitary adenomas can influence all dimensions of HRQoL²⁴⁷. The noted significant relationship between lower HRQoL (EQ-5D-index and EQ-5D-VAS) and the likelihood of return to work indicates that the reduction of HRQoL actually influences patients' life and livelihood, though Paper I has not attempted to confirm causality.

Short-term follow-up after endoscopic surgery shows reduced HRQoL²⁵⁵. Site-specific sinonasal QoL is decreased but seems to normalize and reach preoperative baseline values within three months of surgery^{253,337}. Little et al. describe the relationship between sinonasal QoL and general health status with the conclusion that the reduction of HRQoL after surgery is caused by sinonasal symptoms²⁵³. Even though health status reached the same levels as before surgery, this preoperative baseline level might be reduced compared with the general population according to studies of HRQoL and pituitary adenomas²⁴⁷. Based on these short-term findings and our present long-term results, we conclude that the surgical technique per se does not, in any major way, influence the HRQoL or work ability of patients surgically treated for pituitary adenoma in either a short-term or long-term perspective. The main effect on HRQoL does not seem to be associated with choice of surgical technique but rather with the endocrinological and compressive effects of the pituitary adenoma itself, as the diagnosis of pituitary adenoma often is preceded by several years of symptoms and

exposure to abnormal hormone levels^{338,339}. The changes caused by these abnormalities, such as arthropathy and hypertrophic cardiomyopathy with acromegaly or cardiovascular risk factors with Cushing's disease, persist long after hormone levels are normalized³³⁹⁻³⁴¹.

Social benefit systems vary over the world, resulting in different sick leave times, why one should be careful to draw any conclusions from absolute sick leave length. However, the nonsignificant difference between the surgical techniques regarding length of sick leave could be expected to be global. We found only one study addressing work ability after pituitary surgery. Pikkarainen et al. show in a study from Finland, regarding well-being and work ability among patients treated for Cushing syndrome, that 81% returned to work after surgery and 11% retired because of disability³⁴¹. Regardless of surgical technique, 76% in the present series of patients returned to work, whereas 11% (n=21) received permanent sick leave after surgery. The frequency of permanent sick leave is fairly equal between different adenoma types (Acromegaly 10%; NFPA 9.4%; Cushing's disease 6.7% and prolactinoma 5.9%). The socioeconomic consequences are considerable. A total of 251 working years were lost in the group of 21 patients who never returned to work. The issue is especially important among female patients, since 76% of patients on permanent sick leave after surgery were females. Female gender turned out to be a significant factor for lower EQ-5D index, lower chance of return to work, longer convalescence and higher rate of permanent sick leave, despite similar tumor and patient characteristics and equal complication rates compared to males. Gender was the only factor showing significant correlation to all outcome measures in univariate analyses, indicating influence on outcome even if multivariate analysis did not show statistical significance. This finding is in line with many previous reports in which female gender is associated with decreased HRQoL in pituitary patients^{257,260,342}, although there are studies that do not show any impact of female gender^{258,343}.

As to VA, paper IV aims at extending current knowledge regarding the effect NFPA specifically has on VA. In our series of 87 NFPA patients, preoperatively impaired VA and VF was found in 55% and 82% respectively. Specifically, decreased VA was seen more often among older patients and was also related to sagittal tumor height and severity of VF defects. Most importantly, improvement in VA after surgery was noted in the best and worse seeing eyes in 54% and 77%, respectively. Improvement was most often noted among those with mild VA impairment but was also seen among those with moderate or even severe preoperative reduction in VA. Recovery of VA was seen over all ages, also among the oldest patients. Overall, most of the recovery was observed already at three months postoperatively without obvious further improvement at follow-up one to two years and five years after surgery.

Predicting outcome is of great interest in aiding preoperative decision-making and patient counseling. Patient age, symptom duration, preoperative VA and VF, surgeons experience, grade of resection and finally tumor size have all, inconsistently, been associated with surgical outcome^{261,264,265,269,273,288,344-346}. Similar to our findings, a 2017 meta-analysis shows a pooled VA improvement rate of 67.5%²⁶¹. With the ICD-10 definition of normal VA being a Snellen decimal notation 0.8 or above³⁰⁹ we report similar rates of improvement. Notably though, half of our patients considered to have unaffected VA according to the ICD-10 definition, still showed improvement beyond the level of normal VA. Population-based evaluations of VA show Snellen decimal 0.97 being the median VA for 70-82 year old's while mean VA for younger adults varies around 1.3³⁴⁷ which would suggest Snellen decimal 0.8 being a crude estimation of normal VA and might underestimate the true prevalence of VA deficits in patients with NFPA.

It has been suggested that the improvement of visual impairment after decompression of the anterior visual pathways has two or three phases^{282,288}. An early phase, seen immediately after surgery to one week post-surgery, likely caused by removal of conduction block caused by ischemia and reduced axoplasmic transport, is followed by a second phase one month to four months post-surgery explained by remyelination. Finally, further improvement seen six months up to three years post-surgery is less often described or explained²⁸⁸. These phases have been demonstrated in clinical practice regarding VF defect^{265,288} where the majority of improvement, as well as all cases of complete recovery, was seen during the initial six months after surgery^{265,288}. One of these studies did, however, note significant improvement in VF defects as late as five years post-surgery²⁶⁵ whereas the other, similar study, reported only tendencies of improvement beyond six months of surgery²⁸⁸. No similar improvement phases have been shown for VA restitution. Dekkers et al. explored the recovery of VA up until one year after surgery for NFPA, noting a mean VA increase from 0.65 to 0.82 (right eye), and from 0.60 to 0.88 (left eye)²⁹³. Just over half of the patients showed continuing improvement between three and 12 months.

Our present results confirm an early phase of VA recovery and extend previous knowledge²⁹³, by our longer follow-up period, indicating a possible improvement of VA in some patients as late as one to two years after surgery (Figure 14, page 71). However, we did not find any further improvement at five-year follow-up, which should be conveyed to patients in pre- and postoperative patient counseling.

The pathophysiology of visual decline caused by pituitary adenoma is multifactorial²⁸⁰. Distension of nervous tissue in experimental spinal cord research, has been correlated with ischemia and demyelination²⁸⁴. Adding to this is the anatomical weakness of the blood supply of the central parts of the chiasm²⁸⁶. Considering these facts, one might theorize that an adenoma with larger suprasellar volume, and thereby larger contact

surface to the chiasm, could cause increasing tension in the axons of the anterior visual pathways. If so, suprasellar tumor volume could be expected to show higher correlation with VA than just the suprasellar tumor height. However, our present results could not confirm this hypothesis. In fact, volumetric measurements, resulting in ROC AUC between 0.73 and 0.74, did not add to the predictive power of linear radiological measurements of sagittal and coronal tumor height. Additionally, suprasellar extension in the sagittal plane was the only tumor measurement being a significant risk factor for preoperative reduction in VA. The present study results indicate that adenomas reaching 10 mm above the sagittal reference line may predict preoperative reduction in VA with a sensitivity of 88% and a specificity of 64%.

Although we did find increasing age to be associated with reduced VA prior to surgery, we did not find age to be predictive of VA improvement following surgery as VA recovery was seen also among our oldest patients. In contrast, in a recent paper, patient age was the only significant predictor of VA improvement following transsphenoidal surgery as younger age correlated to better prognosis³⁴⁸. The significant negative correlation between increasing age and VA improvement following surgery in that study, might, as the authors point out, be explained by coexisting ophthalmologic comorbidities. In our series, patients with severe ophthalmological comorbidity (n=6) were excluded.

The question arises why the predictions of surgical outcome on visual functions are not more accurate. In part, this is likely explained by the great heterogeneity in the way VF defects and VA are graded and reported^{261,265,276,349}. Additionally, the effect of ophthalmological comorbidity cannot be excluded. The anatomical location of the chiasm relative to the sella and the direction of tumor growth should also be taken into consideration as visual defects can be noted with smaller tumor extension if the chiasm is situated directly superior to the sella²⁶⁸.

Strengths and weaknesses

Paper I, II and IV all have a retrospective design with risks of recollection errors, loss of follow-up and irregularities in follow up protocol. In Paper I, the use of work-related outcome and instruments such as pa-KPS with limited number of grading steps might limit this weakness whereas the follow-up time is diverse. A lot can happen in a person's life that affects HRQoL or work ability over the years. However, the material is large and no age variation related to the outcome measurements were noted. Paper I does not consider the exact cause of decreased work capacity (e.g., decreased visual acuity, fatigue, cognitive decline, or psychiatric disorders). Again, because the series of patients

is fairly large, we assume that the factors causing decreased HRQoL and work capacity are similar in both groups. Because EQ-5D-3L has only three grading steps, minor changes in HRQoL might go undetected, but we believe that this quick and easy scale has a clear advantage with respect to higher inclusion frequencies. In paper II, the presented betamethasone suppression test lacks validation material as all patients tested with the presented protocol were included in the study. As the test shows high accuracy and no risk of adrenal crises, the protocol is of value to patients having had surgery of Cushing's disease. Paper III is, to our knowledge, the first prospective evaluation of 3-D endoscopy of pituitary adenoma, strengthening conclusions of previous retrospective data. Paper IV presents long term data of VA after surgery of pituitary macroadenoma valuable in preoperative patient counseling.

Future perspectives

The overall aim of the present thesis is to improve the care of patients with pituitary adenomas. The presented results add knowledge on the efficacy of endoscopic pituitary surgery. The betamethasone suppression test could be utilized with dexamethasone and thus achieving the goal of generalizability and constitute a valuable and easy-to-use addition to the existing repertoire of clinical tests of pituitary function. The suppression test should be validated in larger patient materials, inherently difficult considering the low incidence of Cushing's disease.

Noting that female patients fare worse in terms of HRQoL and work ability after pituitary surgery as well as the results regarding recovery of VA after surgery might be valuable in preoperative counseling of patients considering pituitary surgery. In the future, further evaluation of the impact of gender on recovery after pituitary surgery is warranted as the obvious risk of reduced HRQoL in female pituitary patients is costly both for society and the individual patient.

It would be valuable to further evaluate the VA recovery in patients considered having normal acuity prior to surgery and to clarify if the reduction in VA, within what is considered normal VA, causes loss of function in individual patients.

Finally, the rapid evolution of endoscopic pituitary surgery, since the first report 26 years ago, is likely to slow down as it is now standard of care. Hopefully further evolution and evaluation of sellar reconstruction will clarify the risk and benefits with nasoseptal flaps and various tissue glues. In general, the likely evolution of treatment of pituitary adenomas will be in the hands of endocrinologist and oncologists based on individualized treatment with future medical treatment, e.g. immunotherapy.

Conclusions

- The choice between microscope-assisted surgery and endoscopic surgery does not influence HRQoL or work-related outcome in long-term follow-up, although both are decreased in patients treated for pituitary adenomas compared to the general population. Females seem to have a greater risk for decreased HRQoL and work ability.
- A fully endoscopic surgical technique is equal, or better, than conventional microsurgery concerning the risk of complications, with a trend toward lower complication rates, even for patients with larger tumors.
- A 48 hours, 2 mg/day betamethasone suppression test after transphenoidal surgery of Cushing's disease can predict short- and long-term remission with a high accuracy and without the risk of adrenal crisis.
- A prospective cohort study fails to show obvious outcome advantages with 3-D endoscopy in pituitary surgery using basic parameters including post-operative HRQoL. This indicates that the clinical advantage with 3-D endoscopy is less than that reported in preclinical simulator environments.
- Around half of patients who present with reduced VA will have a chance of full VA recovery. All patients, independent of age and degree of VA reduction, have potential for improvement, as we found no single factor predictive of recovery. Improvement will likely occur during the first months after surgery, but VA can, unlike VF, in some cases improve up until one to two years after surgery. Finally, using the ICD-10 criteria for normal VA, Snellen notation above 0.8, might underestimate the presence of impaired VA in patients with NFPA.

Populärvetenskaplig sammanfattning

Under storhjärnan, ungefär mitt i huvudet sitter den ärtstora hypofysen, en övergripande styrkörtel som kontrollerar hormonproduktion från bland annat binjurar, sköldkörtel och äggstockar. Godartade hypofystumörer, så kallade hypofysadenom, kan orsaka sjukdom och symtom på flera olika sätt. Överproduktion av styrhormon kan leda till sjukdom och tumörer som inte producerar hormon kan trycka på den normala hypofysen och orsaka bortfall av hypofysens funktion. Stora tumörer kan också trycka på omkringliggande delar av centrala nervsystemet, framför allt synnerverna, och orsaka huvudvärk, synnedsättning och blindhet.

Hypofysadenom är tillgängliga för kirurgisk behandling. Tidigare genomfördes operationerna genom skallbenet och senare genom näsan och näsans bihålor med mikroskop. Under 1990-talet utvecklades tekniker för att nå hypofysen via tithålskirurgi genom näsan, endoskopisk hypofyskirurgi. Denna teknik har använts under 16 år vid neurokirurgiska kliniken i Lund. De vetenskapliga arbeten som utgör denna avhandling värderar fyra olika aspekter av endoskopisk hypofyskirurgi och dess effekt på patienterna.

I delarbete I värderas långtidseffekter på livskvalitet och arbetsförmåga jämfört med den tidigare kirurgiska tekniken, med mikroskop, utan att påvisa någon förändring med den nya tekniken. Resultaten tyder dock på att den nya tekniken är säker, möjligen har färre biverkningar än tidigare teknik och att livskvalitet hos patienter med hypofysadenom är lägre än i befolkningen i stort, speciellt hos kvinnor.

I delarbete II undersöks hur effektivt ett lokalt utvecklat endokrinologiskt test är för att förutse bot efter operation av hypofysadenom som producerar styrhormon för binjurarna, så kallad Cushings sjukdom. Arbetet visar att testet har god träffsäkerhet och kan förutse långtidsbot med hög träffsäkerhet.

I delarbete III värderas om tithålskirurgi med 3D-glasögon och ökad djupkänsla leder till förbättrade operationsresultat hos patienter med hypofysadenom. Studien visar tyvärr ingen effekt av denna nya teknik.

I delarbete IV eftersöks faktorer som kan förutse påverkad synskärpa hos patienter med stora hypofysadenom. Vi sökte också faktorer som kunde förutse förbättring av

synskärpa efter kirurgisk behandling. Över hälften av patienter med stora hypofysadenom hade påverkad synskärpa. Det sämsta ögat förbättrades i nästan 80% av fallen efter kirurgi. Stora tumörer påverkade synen mer än små. Även de med normal synskärpa innan operation kunde få bättre synskärpa efter operation. Vi kunde inte finna några faktorer som kunde förutse chans till förbättring efter operation.

Sammantaget är hypofysadenom en vanlig godartad tumör i centrala nervsystemet som kan påverka drabbade patienter på många olika sätt både på kort och lång sikt. Det aktuella avhandlingsarbetet bidrar med kunskap som kan vara till glädje för framtida patienter i valet av kirurgisk behandling och ge korrekta förväntningar på behandlingens effekt.

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To some of you. You should know that the choice between microscope-assisted surgery and endoscopic surgery does not influence health-related quality of life or work-related outcome in long-term follow-up. A 48 hours, 2 mg/day betamethasone suppression test after transphenoidal surgery of Cushing's disease can predict short- and long-term remission with a high accuracy and without the risk of adrenal crisis. No obvious advantages with 3-D endoscopy were found and that around half of patients who present with reduced visual acuity will have a chance of full VA recovery.

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