Transsphenoidal surgery for pituitary adenomas

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Doctoral Thesis

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List of papers

This thesis is based on the following papers:


Abbreviations

ACTH    Adrenocorticotropic Hormone
ADH     AntiDiuretic Hormone
AUC     Area Under the Curve
CBTRUS  The Central Brain Tumor Registry of the United States
CI      Confidence Interval
CGH     Cushing-Guiot-Hardy
CRH     Corticotropin Releasing Hormone
CSF     Cerebrospinal Fluid
CT      Computer Tomography
DVT     Deep Venous Tromboembolism
FSH     Follicle-Stimulating Hormone
GH      Growth Hormone
HD      High-Definition
HUNT    Helse Undersøkelsen i Nord-Trønderlag
IGF-1   Insulin Like Growthfactor-1
IPSS    Inferior Petrosal Sinus Sampling
LH      Luteinzing Hormone
MRI     Magnetic Resonans Imaging
PE      Pulmonary Embolism
PRL     Prolactin
QALY    Quality Adjusted Life Years
RCT     Randomized Clinical Trial
ROC     Receiver Operated Characteristics
TSH     Thyroid-Stimulating Hormone
T4      Thyroxin
1. Introduction

1.1 The pituitary, a small but important organ

The pituitary is a seemingly small and extruded portion of the brain, lying underneath the proper cerebrum but inside the dura mater. It weighs only 0.6 grams, but evolution may have understood the importance of this organ as it is confined inside its own bony protection, the sella turcica. The pituitary is the conductor of the hormonal orchestra that maintains equilibrium in the body, and its function therefore affects every major organ system in the body. Tumours arising from the gland can produce hormones, so-called endocrine active tumours, or tumours that do not produce hormones, i.e., hormonally silent tumours. These tumours may therefore pose both a problem of local mass effect, pituitary deficiency and systemic hormonal hyperactivity, which make these tumours difficult to understand and necessitates a complex presurgical work-up, including endocrinologists, radiologists, ophthalmologists and neurosurgeons.

1.2 History of pituitary surgery

The first surgical attempt to remove a pituitary tumour was described by the British general surgeon F. T. Paul, of Liverpool. Paul, on February 2nd 1893, at the suggestion of Sir Victor Horsley of London, performed a subtemporal decompression in an acromegalic patient suffering from headache, visual loss and facial pain (1). The patient died 3 months later, and the autopsy revealed a tangerine-sized pituitary tumour. Horsley later operated upon 10 patients with pituitary tumours, using temporal and subfrontal approaches, and reported his results in 1906 (2). The first attempt to approach a pituitary tumour through a transsphenoidal approach was made by Hermann Schloffer in 1907 in Vienna (3). He used an extensive lateral rhinotomy to enter the nasal cavity, and then resected the septum and turbinates to obtain access to sella turcica.

In 1909, Harvey Cushing, who was an associate professor of surgery at Johns Hopkins University in Baltimore, described a refined variant of transsphenoidal surgery using a sublabial incision instead of a lateral rhinotomy (4). Further development of the transsphenoidal approach was performed by Oskar Hirsch, a rhinologist from Vienna, who described the first endonasal approach in 1910.
and later the submucosal transseptal route (5). Cushing employed the transsphenoidal approach to the pituitary in more than 200 operations. However, by the late 1920s, he had abandoned the transsphenoidal approach in favour of the transcranial subfrontal route (6). He could achieve a better decompression of the optic chiasm, a more complete evacuation of the sellar tumour, and a reduced risk of CSF leakage with the transcranial approach. Harvey Cushing had a tremendous impact on the practice of neurosurgery both in the US and in Europe, and the transsphenoidal route to the pituitary was more or less abandoned for the next 40 to 50 years (6).

One surgeon who did not want to abandon the transsphenoidal route was Norman Dott. He learned this method as a fellow of Cushing and brought it with him to Edinburgh, where he had performed 80 consecutive operations without any deaths by 1956 (7). Gerard Guiot came to Edinburgh in 1956, learned the procedure from Dott and later performed more than 1000 transsphenoidal procedures in Paris. Guiot had many fellows who trained with him in Paris. Among them was Jules Hardy from Canada, who brought transsphenoidal surgery back to North America. Hardy developed a set of instruments specially designed for transsphenoidal surgery and introduced the operating microscope for pituitary surgery in 1967. Hardy and Guiot once again popularized transsphenoidal surgery in Europe and North America, and since the 1970s, transsphenoidal microneurosurgery has been an integral part of neurosurgery. The procedure was for a long time called CGH (Cushing-Guiot-Hardy) after the three pioneers.

Transsphenoidal surgery continued to develop during the 80s and 90s with the development of the direct endonasal approach and extended approaches allowing surgery in the vicinity of the sella (8). Along the same line was the introduction of the endoscope into the sella, which was a spill-over from otorhinolaryngologists performing endoscopic sinus surgery, so called FESS surgery (functional endoscopic sinus surgery). Some centres developed the endoscopy assisted microsurgical transsphenoidal surgery (9), whereas others, such as Paolo Cappabianca in Naples, Hae Dong Jho in Pittsburgh and Giorgio
Frank in Bologna, developed fully endoscopic procedures (10-12). Over the years, the fully endoscopic procedure has gained popularity, and there has been a rapid increase in the number of surgeons using this method.

The strive for better control over the amount of tumour tissue removed in the suprasellar and parasellar areas led to the development of intraoperative imaging during transsphenoidal surgery. Different intraoperative imaging techniques have been used, such as CT, ultrasound and MRI. Groups that have been instrumental in the development of intraoperative MRI are Peter Black’s group in Boston, working with a 0.5-Tesla, “double donut” MRI, and Rudolph Fahlbusch’s group in Erlangen, working with a 1.5-Tesla MRI-scanner (13, 14). Both groups showed that they could obtain high-quality images during transsphenoidal surgery and that they could visualize tumour remnants that could be removed later during the same surgery.

Transsphenoidal surgery was first introduced in Norway in the late 1970s by Ragnar Nesbakken at Ullevål University hospital (15, 16) and later at The National Hospital by Tormod Kollevold (17, 18).

1.3 Epidemiology of pituitary adenomas
Pituitary adenomas account for approximately 15% of all primary intracranial tumours, preceded in frequency only by gliomas and meningiomas (19). In the latest report on primary brain and central nervous system tumours diagnosed in the United States in 2007-2011, non-malignant pituitary tumours accounted for 15.0% of all newly diagnosed primary brain tumours (20). The incidence of tumours of the pituitary was 3.3 per 100000; the vast majority of these are adenomas (20). Using data from the Norwegian HUNT 1 study, a general health survey conducted among adults in the county of Nord-Trøndelag in Norway in 1984-1986, the incidence of pituitary adenomas was 3.2 per 100 000 person-years (95% CI 2.4-4.3) (21), not differing significantly from the incidence cited in the latest CBTRUS report (20). Autopsy studies have shown that up to 25% of the population have clinically silent small pituitary adenomas. These tumours have
the morphology of non-functioning, lactotroph or gonadotroph adenomas and are identified after careful microscopic post-mortem examination (22).

Incidental finding
As the population's access to imaging of the brain and skull base increases, an increasing number of pituitary tumours are found incidentally; these are termed incidentalomas. A pituitary incidentaloma is a previously unsuspected pituitary lesion that is discovered on an imaging study performed for an unrelated reason. By definition, the imaging study is not performed for a symptom specifically related to the lesion, such as vision loss or a clinical manifestation of hypopituitarism or hormone excess. Rather, these imaging studies are performed to evaluate head trauma or symptoms such as headache or other head- or neck-related neurological or central nervous system complaints. In a recent publication for which MRI scanning was performed on 2000 healthy volunteers, a pituitary macroadenoma was detected in 6 subjects (0.3%) (23)

1.4 Classification of pituitary adenomas
A. Pathology
The pituitary is composed of two lobules, an anterior adenohypophyseal portion and a posterior neurohypophyseal portion. The two parts are morphologically, embryologically and functionally different. Pituitary adenomas arise from the anterior lobule, whereas tumours from the posterior lobe are very rare. The most common tumours encountered in the posterior lobe are metastases from malignant tumours elsewhere in the body (24).

Pituitary adenomas have traditionally been classified according to their light microscope appearance:

Chromophobe – the most common tumours, they were originally thought to be non-secretory, but it was later shown that they may produce prolactin (PRL), growth hormone (GH) or thyroid-stimulating hormone (TSH).

Acidophil – produce prolactin, TSH or, usually, GH

Basophil – produce gonadotropins (follicle-stimulating hormone (FSH) or luteinizing hormone (LH)) or adrenocorticotropic hormone (ACTH)
The modern pathologic classification is based on immunohistochemistry, which permits conclusive identification of the various cell types in the adenoma. The standard immunohistochemical battery includes the use of antibodies to GH, PRL, ACTH, TSH, FSH, LH and the alpha-subunit of the glycoprotein hormones (25).

Most pituitary adenomas arise sporadically or, rarely, as part of hereditary genetic syndromes. Molecular analysis of familial pituitary adenomas has provided significant insight into pituitary tumour genesis. Some specific genes have been identified that predispose to pituitary neoplasia, but these are rarely involved in the pathogenesis of sporadic tumours. One known genetic disorder that predisposes individuals to pituitary adenomas is multiple endocrine neoplasia type-1. This is a rare, autosomal-dominant disorder that gives rise to tumours in the parathyroid, pancreas and pituitary. It accounts for approximately 3% of all pituitary tumours (26). Lately there has been special focus on pituitary adenoma predisposition caused by germline mutations in the AIP gene, first described by a Finish group in 2006 (27). This condition has later been known as Familial Isolated Pituitary Adenomas (FIPA) and FIPA families account for around 2% of pituitary adenomas (28). The number of other identified genes is increasing. The possible resulting mechanisms of action involve abnormalities in signal transduction pathways, cell cycle regulators, growth factors and chromosome stability (29).

B. Clinical classification

Pituitary adenomas can be classified based on their secretory products. The most common tumours, constituting approximately 65% of all tumours, are the endocrine active tumours that produce one or two hormones that can be measured in the serum and causes distinct clinical syndromes (for more extensive information, see 1.5):

- Prolactin – amenorrhea, galactorrhea, infertility, impotence, etc.
- Growth Hormone – acromegaly or gigantism
- Thyroid Stimulating Hormone - secondary hyperthyroidism
Adrenocorticotropic Hormone – Cushing's disease or Nelson's syndrome

The other group of tumours are the endocrine inactive tumours, consisting of 5 subgroups

- Null – cell adenoma
- Oncocytoma
- Gonadotropin – secreting adenoma
- Silent corticotrophin – secreting adenoma
- Glycoprotein – secreting adenoma

C. Classification by size

Pituitary adenomas can also be classified based on their size

- Microadenoma – less than 10 mm in diameter
- Macroadenoma – more than 10 mm in diameter
D. Classification based on lateral growth

A simple and surgical relevant classification of pituitary adenomas is by their extent of lateral growth. There are many variants proposed for this classification, but the most used today is the Knosp classification (30) illustrated in figure 1.

Figure 1 Illustrating the 5 Knosp grades.

1.5 Clinical symptoms of pituitary adenomas

Pituitary adenomas are usually divided into secreting and non-secreting tumours. Non-secreting tumours do not present until they are large enough to cause neurologic symptoms due to their mass effect, whereas secretory tumours
present earlier due to the physiologic symptoms caused by the excess hormones they secrete. The symptoms and signs of pituitary adenomas can be divided into three main groups:

- endocrine symptoms
- mass effect symptoms
- pituitary apoplexy

**Endocrine symptoms**

Approximately 65% of pituitary adenomas secrete an active hormone (48% prolactin, 10% growth hormone, 6% ACTH and 1% TSH) (31).

Prolactin hypersecretion causes amenorrhea-galactorrhea syndrome, with infertility in females and impotence in males. It can be caused either by a prolactinoma, a neoplasia of pituitary lactotrophs or by the so called “stalk-effect” – a non-secreting tumour that puts pressure on the pituitary stalk and thereby reduces the hypothalamic inhibitory control over prolactin secretion.

Growth hormone oversecretion causes acromegaly in adults and gigantism in children and adolescence before closure of the growth plate.

ACTH hypersecretion causes an endogenous hypercortisolism, also termed Cushing’s disease. In patients who have undergone adrenalectomy, ACTH oversecretion might cause Nelson syndrome.

TSH hypersecretion is clinically detectable as a secondary or central hyperthyroidism.

LH and/or FSH hypersecretion will usually not produce a clinical syndrome.

Endocrine symptoms may also present as pituitary deficiency; this effect may be caused by the compression of the normal pituitary by a large non-secreting tumour. There seems to be a fixed order of sensitivity to compression of the hormone-producing cells, with growth hormone being lost first, followed by
gonadotropins, TSH and ACTH. Selective reduction of a single pituitary hormone is very rare in adenomas and points to some other cause, such as autoimmune hypophysitis, hypothalamic glioma or craniopharyngioma.

**Mass effect**

Growing pituitary adenomas may be detected by compression on their neighbouring structures

- dura and skull base – may give rise to headache
- optic chiasm – causes bitemporal hemianopsia and subsequent reduced visual acuity
- third ventricle – may cause obstructive hydrocephalus
- cavernous sinus – compression of the contents of the cavernous sinus (cranial nerves III, IV, V1, V2 and VI and carotid artery) may give rise to ptosis, facial pain and diplopia

**Pituitary apoplexy**

Pituitary apoplexy is a sudden intrasellar expansion due to haemorrhage and/or infarction within a pituitary tumour and adjacent pituitary gland (32). Seldom, a haemorrhage may occur in a normal pituitary gland. Symptoms of pituitary apoplexy include the following: sudden onset of headache, visual disturbances and loss of consciousness. The true incidence of apoplexy in an adenoma is difficult to assess; in one much-cited series, 3% of patients with macroadenomas had an episode of apoplexy (33).

1.6 Diagnosis of pituitary adenomas

**History and Physical examination**

General clinical and neurological examination directed at finding signs and symptoms of

- Endocrine dysfunction
- Visual field deficits
- Cranial nerve palsies
**Endocrinologic evaluation**

A thorough endocrine evaluation is necessary to verify type of tumour, to determine whether there is a need for hormonal replacement and to establish a hormonal baseline for endocrine follow-up after treatment. All axes need to be checked.

- **Adrenal axis screening**
  - 8 AM cortisol
  - 24-hour urinary free cortisol if hypercortisol is suspected
- **Prolactin levels**
  - Moderately elevated may indicated prolactinoma or a “stalk effect”
  - Significant elevation is indicative of a prolactinoma
- **Thyroid axis**
  - Free T4 and TSH
- **Growth hormone axis**
  - IGF-1
  - A single random GH level is not reliable
- **Gonadal axis**
  - Serum gonadotropins, FSH and LH
  - Sex steroids
    - Oestradiol in women
    - Testosterone in men
- **Neurohypophysis**
  - P-Na and P-osmolality
  - U-Na and U-osmolality
  - Check the ability to concentrate urine with water deprivation.

**Visual evaluation**

A formal preoperative visual evaluation is mandatory in the presurgical work-up and should include both an evaluation of visual fields and visual acuity. Goldmann perimetry is the most widely used test for visual fields (34).
Neuroradiologic evaluation

A MRI of the brain and sellar region with multiplanar thin sections is the most important preoperative neuroradiologic evaluation. This imaging protocol provides axial, coronal, and sagittal sections of the sellar contents. Generally, the relationship between the lesion and the optic chiasm and visual pathways is easily recognized. Pregadolinium and postgadolinium images are recommended to ensure that primarily isointense lesions do not escape detection. This MRI will often show the adenomas relation to the normal pituitary gland. Most microadenomas have a low signal on T1-weighted images and high signal on T2-weighted images. Contrast enhancement is time dependent. Initially the normal pituitary will enhance to the greatest degree, but after approximately 30 minutes, the tumour and normal pituitary will enhance to similar degrees. Dynamic MRI scans have been attempted to look for tumours that are not observed on standard scans (35). Deviation of the pituitary stalk may also indicate on which side an isointense microadenoma is located. A cerebral CT-scan may be indicated for surgical planning as it shows the shape of the sphenoid sinus, the presence of septa in the sinus, and the presence of a septal deviation in the nose.

A specialized form of neuroradiologic evaluation is Inferior Petrosal Sinus Sampling (IPSS), performed by an interventional neuroradiologist and used in the work-up for endogenous Cushing’s syndrome. In this evaluation, microcatheters are advanced to the inferior petrous sinus and used to measure ACTH levels on both sides of the pituitary. IPSS is used in cases where a pituitary adenoma cannot be visualized on MRI. ACTH levels are measured before and after intravenous corticotropin releasing hormone (CRH) is given, and a central-to-peripheral ratio of more than two before CRH administration, or more than three after, is usually interpreted as positive for Cushing’s disease (36).
1.7 Treatment of pituitary adenomas

The therapeutic toolbox includes careful observation, medical treatment, surgical resection, conventional radiation therapy and radiosurgery. In each patient, the risk and benefit of each therapy must be carefully assessed, and an individual treatment plan should be provided.

The goals of treatment are

- to reverse endocrinopathy and restore normal pituitary function
- to eliminate the mass effect of the tumour
- to reduce the likelihood of tumour recurrence
- to obtain a definite histologic diagnoses

1.7.1 Observation

Careful observation with repeated MRI-scans, visual evaluation and endocrine evaluation may be a good treatment option for small non-functioning tumours without visual impairment and where there is no indication for surgical treatment. Studies have shown that only approximately 10% of non-functioning microadenomas and 24% of non-functioning macroadenomas will grow and require treatment (37).

1.7.2 Non-surgical treatment

*Medical treatment*

Medical therapy is first-line treatment for prolactinomas, and there can be a dramatic shrinkage of the tumour during treatment with dopamine agonists within days to weeks (38). The most commonly used dopamine agonists are as follows:

- bromocriptine, a dopamine agonist
- cabergoline, a selective D₂ dopamine agonist
- pergolide, a long-acting dopamine agonist

For growth hormone secreting tumours, surgery is still the primary treatment modality. However, medical treatment may be used as pre-treatment before surgery, (39) for those who are not cured by surgery and for those with
contraindications for surgery (40). There are different medical options, and a combination of medication gives the best result in some cases

- bromocriptine, a dopamine agonist
- octreotide/lanreotide/pasireotide, somatostatin analogue
- pegvisomant, GH receptor antagonist

Surgery is the primary treatment modality for patients with Cushing’s disease. There are some medical treatment options that can be used prior to surgery to control the symptoms of Cushing’s disease, including diabetes mellitus, hypertension, psychiatric disturbances etc. (41). There are different options for medical treatment, some of the most commonly used are as follows:

- ketoconazole, an antifungal agent that blocks adrenal steroid synthesis
- aminoglutethimide, inhibits an enzyme in the synthesis of steroids from cholesterol
- metyrapone, an enzyme inhibitor, inhibits cortisol synthesis
- mitotane, inhibits several steps in glucocorticoid synthesis
- cyproheptadine, a serotonin receptor antagonist, is effective in a small percentage of patients.

Transsphenoidal surgery is the first-line treatment for TSH secreting tumours, but octreotide may help in cases where the patient is not cured (42).

**Radiation therapy**

Radiation therapy, either given as conventional fractionated radiotherapy or as radiosurgery, is no longer routinely used as primary treatment of pituitary adenomas, but it may have a role as postoperative treatment in selected patients (43) (44). Radiation therapy should be reserved for those cases in which it is not possible to remove the recurrent tumour and growth is documented. Prolactinomas seem to have a very poor response to radiation therapy (43). Growth hormone-secreting tumours may have the best response, although the response is delayed for many years (45). The side effects of radiation therapy may be hypopituitarism with progression to panhypopituitarism over a period of
years, optic nerve and chiasma injury, memory disturbances and cranial nerve palsies (46).

1.7.3 Surgical treatment

Indication

A clear indication for surgery is progressive mass effect from a macroadenoma, causing visual impairment. The exception is prolactinomas, in which immediate and effective shrinkage can be achieved with medical therapy. The most urgent cases are pituitary apoplexies, for which abrupt vision loss, neurologic deterioration and collapse from acute adrenal insufficiency necessitates urgent glucocorticoid replacement and surgical decompression.

The secretory adenomas where surgery is the first-line treatment include Cushing’s disease (47), secondary hyperthyroidism and growth hormone hypersecretion. In the treatment of acromegaly and gigantism, one often uses a combination of surgical and non-surgical therapies (39).

Failure of prior therapy is also an indication for surgery. Patients who are initially treated with medical therapy for acromegaly or prolactinomas that have an insufficient response to medication or intolerable medication side effects are clear candidates for surgical therapy. A surgical resection may be curative or reduce the tumour burden, leading to a more favourable pharmacologic response. Patients who are initially treated with radiotherapy may also have a relapse after a number of years and require surgical therapy.

A relative indication for surgery is to obtain a definite histological diagnosis of a sellar tumour mass, e.g., in the case of a radiologically verified tumour in a patient with known history of a metastatic tumour.

Contraindications for surgery

Surgery for pituitary adenomas are in most cases minimally invasive microsurgical or endoscopic transphenoidal surgeries, and there are few
contraindications. Absolute contraindications for transsphenoidal surgery would be as follows:

- sinusitis or active systemic infection
- "kissing carotids", in which the horizontal distance between the two carotid arteries is less than 10 mm and there is insufficient space to perform surgery
- very poor general medical condition of the patient (48)

Relative contraindications for surgery would be

- severe cardiovascular compromise
- chronologic age of the patient
- severe endocrine disturbances
  - florid Cushing's disease
  - grave acromegaly
  - serious secondary hyperthyroidism

It will often be possible to improve the consequences of these endocrine disturbances with medication before surgery and thereby reduce the increased anaesthetic risk

*Choice of surgical method*

Approximately 95% of the pituitary adenomas can be resected through a transsphenoidal approach, either with a microscopic or an endoscopic technique. Other cases require a transcranial approach.

Factors that favour a transcranial approach are as follows:

- significant suprasellar and especially anterior or posterior extension of the tumour
- an hour-glass shape of a tumour, with a small opening in the diaphragma sellae
- if the tumour is suspected to be very firm in consistency, e.g., multiple previous surgeries
- if one is in doubt about the nature of the tumour (e.g., suspecting a meningioma)
Transsphenoidal surgery

The transsphenoidal approach to the sella turcica is a minimally invasive, direct approach through the air sinus system of the anterior skull base. It has become the access route of choice because it requires no brain retraction and provides direct visualization of the pituitary and adjacent structures.

The surgical technique has evolved over the years, with better illumination from modern microscopes and endoscopes, the use of endonasal rather than sublabial access to the sinus system, the use of better methods for reconstruction of the dura and sellar floor and the development of better micro-instruments for dissection and tumour removal.

Even though this is an excellent surgical route to reach sella turcica, it has its limitations. The long and narrow surgical corridor creates a very limited space in which to move the instruments and to actually perform the surgery; the long corridor makes lateral and suprasellar visibility limited; the important neighbouring structures, such as the optic chiasm and carotid arteries, necessitate great care during the dissection; and the lack of landmarks inside the tumour makes it difficult to be certain how much of the tumour has been removed.

The cure rate for hormone-producing macroadenomas is in the range of 30-60% (39). In non-functioning macroadenomas radical surgery is obtained in 40 – 60%. The percentage of patients needing reoperations is 5-30%, the risk of complications after reoperations is markedly increased, and the long-term mortality in patients with recurrent tumours is markedly increased (49). All of these data indicate the need to strive for more radical surgery. The following strategies may contribute to more radical surgery:

- immediate postoperative MRI
- intraoperative MRI
- intraoperative ultrasound
- neuronavigation on preoperative MRI/CT
- endoscopic endonasal techniques
- experienced surgeons

When we began to perform immediate postoperative MRI scans, within the first 48 hours after surgery, we occasionally experienced a discrepancy between the postoperative MRI and the surgeon's report (Figure 2). It is well known from earlier intracranial tumour studies that the estimation of resection grade with postoperative MRI is more reliable than the surgeon's report (50).

Figure 2. Preoperative and immediate postoperative T1-weighted images, showing a small resection of a large non-functioning adenoma.

Surgical techniques
The patients examined for this thesis were operated upon between September 2002 and February 2011. In this period, we performed both microscopic and endoscopic transsphenoidal surgeries. Intraoperative MRI was used in some of the patients.

Microscopic transsphenoidal surgery
Before 2005/2006, the standard microsurgical endonasal transseptal approach was used. The right nostril was entered, an incision was made in the anterior portion of the septum, and a dissection of the mucosa from the septal cartilage and bone was performed. The anterior wall of the sphenoid sinus was opened bilaterally, and any septum in the sphenoid was removed as necessary. The floor of the sella was opened with a high-speed drill, and the tumour was removed
with standard instruments, such as curettes, dissectors, suction and micro forceps. After tumour removal, the floor of the sella was reconstructed in most cases. The materials and techniques used for the floor reconstruction depended on the intraoperative findings and the surgeon’s preference. In paediatric patients with small nostrils, a sublabial approach was used. All of the patients received nasal packing that was removed on the first postoperative day.

*Endoscopic transsphenoidal surgery*

Beginning in 2005, the endoscopic endonasal transsphenoidal approach was gradually introduced. One or both nostrils were entered, depending on the space available and the need for exposure during surgery. Standard Storz endoscopes (180/4 mm) with 0°, 30° and 45° angulations (attached to cameras) were used. In the later period of the study, the endoscopes were attached to high-definition (HD) cameras. Based on personal preference, some surgeons used a fixed endoscope support, whereas others did not. The middle turbinate was lateralized to improve access to the sphenoethmoid recess and the sphenoid ostium, that was identified and enlarged to allow the passage of the endoscope and surgical instruments. Septa in the sphenoid sinus were removed as necessary. Tumour resection was performed with standard surgical instruments, such as curettes, dissectors, suction and micro forceps, depending on tumour size and firmness. In tumours with parasellar extensions, an ultrasonic Doppler probe was used to localize the internal carotid arteries. As a result of the broader view that was possible with the endoscope, the opening of the sella was extended, which made the closure of the sella floor more challenging. Sella floor reconstruction was most often performed in a multilayer fashion with different autologous and artificial materials. A vascularized nasal septal flap was also used as needed.
Figure 2. The surgical set-up in an endoscopic transsphenoidal surgery

Figure 3. Illustration of the difference in the sagittal and coronal working areas between the microscopic transsphenoidal and endoscopic transsphenoidal surgical approaches. The blue colour represents the working area.
Figure 4. A patient with a Knosp grade 3 tumour was operated upon with endoscopic transsphenoidal surgery in September 2010. The two upper pictures show the preoperative tumour, the two middle pictures were taken the day after surgery, and the two lower pictures were taken in February 2015, showing no residual tumour, with a 4.5 year follow-up.
Intraoperative MRI

Intraoperative MRI was introduced nearly 20 years ago, and many scanners and surgical techniques have been developed (51). Most described scanner configurations require transportation of either the patient or the scanner, which is time-consuming, labour-intensive, and makes it difficult to maintain sterility and anaesthesia. A Signa SP/i 0.5-Tesla MRI scanner that was installed at The Intervention Centre-OUS in 1996 has primarily been used for biopsies and glioma surgeries. The ‘double-doughnut’ configuration of this scanner is designed to make it possible to operate inside the imaging field. The disadvantages of this scanner are its relatively low field strength of 0.5 Tesla and the requirement for nonmagnetic instruments and microscopes. We developed a system in which we operated just outside the MRI tunnel and slid the patient approximately 50 cm into the scanning position. We used the standard microsurgical, endonasal technique. This approach provides good access to the sella and the clivus; however, it has the limitation of no direct visualization of the suprasellar and parasellar regions. At the end of resection, but before closure, a new MRI was performed. In cases with remnant tumour accessible for resection – the resection was continued.
All of the patients were given 2 g of cephalothin at the beginning of surgery for infection prophylaxis. In patients with suspected hypersensitivity to cephalothin, 600 mg of clindamycin was used instead.

Postoperative care
All of the patients were kept in the postoperative unit overnight for careful monitoring of neurologic function (visual field, visual acuity and cranial nerve function), electrolyte balance and water balance.
According to our experience with the use of intraoperative MRI, we began to routinely perform postoperative MRI scans within 48 hours after surgery. Traditionally, the usefulness of early MRI validation of transsphenoidal surgery has been questioned due to difficulty in interpreting the images. Precluding factors in this procedure can include the material used to close the sella, haemostatic agents left in the cavity, and the difficulties in discerning both blood from the tumour remnants and the re-expanded pituitary gland from the tumour tissue (14). Our experience with iMRI has taught us to use T1 with contrast enhancement and T2 as a postoperative control. At our institution, an early MRI control is performed within 48 hours after all transsphenoidal procedures that are not performed in the iMRI. Learning the extent of tumour resection from this objective evaluation immediately after surgery is extremely important, especially for less experienced surgeons.

All patients, except for those with Cushing’s disease, are given an intraoperative intravenous (IV) hydrocortisone infusion of 12 mg/h (Solu-Cortef®) until 8 AM on the first postoperative day. Thereafter, cortisone is administered orally, starting with 50 mg x 4 and tapering over a 7-day period to a maintenance dose of 12.5 mg x 2. The patients are maintained on this dose until a scheduled 6-12 weeks postoperative follow-up in the Department of Endocrinology. Cushing’s disease patients were not prescribed any postoperative steroids unless they showed clinical symptoms of hypocortisolism or serum cortisol values <100 nmol/L at discharge. The patients were mobilized and prescribed low molecular-weight heparin subcutaneously beginning on the first postoperative day until they were fully mobilized.

1.8 Complications after surgery for pituitary adenoma

The minimally invasive nature, the lack of an external scar and lower morbidity and mortality compared with transcranial approaches make the transsphenoidal approach to the pituitary appealing both to the patient and to the surgeon (52). Transsphenoidal surgeries for pituitary tumours are among the safest procedures in neurosurgery, and almost certainly the safest major intracranial procedure (53). When developing and adopting new surgical techniques, it is
necessary to know your previous success rates and complication rates to be able to judge whether the changes you made have positive or negative results.

It may be useful to divide complications after transsphenoidal surgery into three different categories:
- nasal complications
- endocrine complications
- surgical complications

Nasal complications include anosmia, chronic sinusitis and septum perforation. Endocrine complications include new anterior lobe deficits, diabetes insipidus and SIADH. Surgical complications include postoperative CSF-leakage, meningitis, neurological deterioration, vascular complications and surgical mortality.

Another way to divide complications is into mortality, major morbidity and lesser morbidity. In recent years, the complication rates in centres of excellence in pituitary surgery are a mortality of approximately 1%, major morbidity approximately 3% and lesser morbidity approximately 5% (54).

1.9 Results after surgery for pituitary adenomas
Non-functioning adenomas
The outcome regarding visual function after transsphenoidal surgery is usually excellent, and the quality of life is among the best in the field of neurosurgical tumours (48). However, many patients will have tumour remnants after surgery (44), and tumour recurrence is not infrequent. Large and giant macroadenomas pose the greatest challenge to the pituitary surgeon and carry the highest risk of serious complications (55).

GH-secreting adenomas
The criteria for biochemical cure of acromegaly is not standardized and has changed over the years, making outcome figures for acromegaly difficult to compare. However, it seems that transsphenoidal surgery results in remission in
a large percentage of patients with microadenomas without invasive growth. GH-producing macroadenomas extend often laterally, with invasion into the cavernous sinus, making them difficult to cure with surgery (39). The development of medical treatment for acromegaly has been rapid and successful; therefore, there are now possibilities for adjuvant therapy that have few side effects and high effectiveness (40).

In the last consensus (2009) of the Acromegaly Consensus Group, optimal disease control is now defined as IGF-I level (determined by a reliable standardized assay) in the age-adjusted normal range and a GH level less than 1.0 µg/litre from a random GH measurement (using an ultrasensitive assay). In patients with acromegaly undergoing surgical management of GH-secreting tumours, oral glucose tolerance test (OGTT) can be used to assess the outcome. There is substantial evidence suggesting that nadir GH levels less than 0.4 µg/litre (with ultrasensitive assays) may define control in these circumstances. In the case of discrepant biochemical results, multiple GH sampling may be useful (56).

ACTH secreting adenomas
There are numerous methodologies for determining biochemical remission of Cushing’s disease, however there is no international consensus on the criteria for remission. The most used criteria for remission are as follows: Clinical resolution of symptoms, normal 1 mg overnight dexamethasone suppression test (DST), normal urinary 24 h free cortisol and normal late-night salivary cortisol level (57). A high proportion of patients will be cured with transsphenoidal surgery, with the best results in microadenomas visible on MRI scans. As there are no effective medical treatments, the only other option to relieve the burden of Cushing’s disease is to perform a bilateral adrenalectomy, a mutilating surgery that requires life-long glucocorticoid replacement, but that is occasionally necessary (58).

TSH-secreting adenomas
These adenomas are very rare, and there are few reports of results after surgery, but it appears that half of patients go into remission after transsphenoidal
surgery, and one can achieve even better control with the addition of radiotherapy (59).

2. Aims of the study

This study was undertaken to investigate the results after surgical treatment for pituitary adenomas in our department.

Specific aims:

**Paper I:**

- To evaluate whether the use of iMRI improves the grade of radical tumour resection in transsphenoidal surgery for pituitary adenomas.
- To study whether endocrine function could be improved after surgery for macroadenomas.
- To evaluate the effect of transsphenoidal surgery with intraoperative MRI on postoperative visual fields and visual acuity.

**Paper II:**

- To determine and compare the complication rates and the overall survival rates after transsphenoidal microscopic and endoscopic surgery for pituitary adenomas.
- To identify risk factors for complications.
- To identify risk factors for reduced survival.

**Paper III:**

- To evaluate the role of the early postoperative S-cortisol levels as a prognostic marker for short- and long-term remission in Cushing's disease.
- To retrospectively review our short and long term results after surgery for Cushing's disease.
3. Material and methods

Ethics
All data from the three retrospective studies were based on data extracted from our approved tumour database (prospectively registered from 2003) and from chart reviews. The patients were not subjected to any additional tests or visits for the sole purpose of these studies. The collection of data was approved by the "patientsombud" at Oslo University Hospital. The data were saved according to the instructions of the data protection officer at Oslo University Hospital.

Patients
This is a retrospective study of patients operated upon for pituitary adenomas at Oslo University Hospital. The data were prospectively collected in a database for all operated CNS-tumours. Additional information was retrieved from electronic chart reviews as needed. During the period of September 2002 - February 2011, 506 transsphenoidal surgeries for histologically verified pituitary adenomas were performed at our hospital; all of them are included in this thesis. We have routine follow-up data on all the patients who underwent surgery in this period. The patients described in papers I and III are subgroups of the total population of operated patients, and are also part of the total population in paper II.

Surgery
Transsphenoidal surgery was performed on standard clinical indication, and as described in detail in part 1.7.3.

Endocrine evaluation
Preoperative endocrine evaluation was performed at the Section for Specialized Endocrinology, Oslo University Hospital, the Department of Endocrinology, Aker University Hospital or the Department of Endocrinology, Akershus University Hospital. The postoperative endocrine evaluation was performed at the same institutions at 3, 6 and 12 months postoperatively and every year thereafter.
Registration of complications

For the study of complications, the following patient characteristics were recorded: age (at surgery); gender; adenoma type (non-secreting or GH-, ACTH-, TSH- or prolactin-producing); tumour size (microadenoma (<10 mm) or macroadenoma (≥10 mm)); preoperative visual deficit, preoperative hormone substitution (glucocorticoid, thyroxin, growth hormone, gonadotropins or antidiuretic hormone (ADH)); primary surgery or reoperation; number of previous surgeries for pituitary adenoma; vital statistics and time of death.

The following postoperative complications were recorded: visual deterioration; neurological deterioration other than visual deterioration; cerebrospinal fluid (CSF) leakage requiring lumbar drainage or surgical repair; reoperation for haematoma; meningitis (requiring antibiotics for ≥7 days, positive bacterial cultures were not necessary); carotid artery injury and deep venous thrombosis (DVT)/pulmonary embolism (PE).

Furthermore, the hospital (Rikshospitalet or Ullevål), surgical technique (microsurgical or endoscopic) and number of surgical procedures per surgeon were recorded. The surgeons were divided into 2 groups for comparison. One group consisted of the most experienced pituitary surgeon at our institution (high-volume surgeon), and the other unit comprised the remaining surgeons (low-volume surgeons).

MRI evaluations

In paper I, all of the patients had standard preoperative MRI-scans performed in the 1.5 Tesla Siemens MRI-scanner, and 3 months-control was performed in the same scanner. In addition, all of these patients had intraoperative MRI scans performed in the GE Signa 0.5 Tesla scanner. The iMRI scanning time was 3 minutes and 30 seconds per series performed. The pre-operative and intra-operative scans consisted of T1-coronal, T1-sagittal, T2-coronal and T2- sagittal imaging series and lasted approximately 14 minutes. After the completion of the surgery, we added T1-coronal and T1-sagittal series with contrast; the post-operative scan-time was therefore 21 minutes. In addition to the time
consumption of the scans, approximately 3 minutes was required for transport in and out of the scanner. Thus, in a typical case with one re-exploration, the use of iMRI added approximately 60 minutes of operating time.

Patients in papers II and III were scanned according to our standard pituitary protocol, which consists of coronal, sagittal and axial T1 series with and without gadolinium enhancement, in addition to coronal and sagittal T2 series. The neuroradiologists Per Kristian Hol and Sumit Roy were part of our research team and were pivotal in the evaluation of the MRI scans.

Statistical analysis
Standardized statistical analyses were performed with Student’s t-test to identify between-group differences.

In paper II, we used univariate and multivariate Cox and logistic regression analyses after ascertaining that the assumptions of these models were fulfilled. Survival curves in paper II were generated using the Kaplan-Meier estimator. The log-rank test was used to compare different survival curves. Survival curves for the general population were created using life tables from Statistics Norway (www.statbank.ssb.no) that were matched by age, cohort and gender.

In paper III, the data are summarized as counts, percentages, means and medians as appropriate. T-tests robust for unequal variances are used. Due to the correlational structure of the repeated intra-individual cortisol measurements, the confidence intervals were calculated according to Morey (60). The time trend of cortisol was investigated using logistic regression and area under the curve (AUC) of the cortisol values over time, nadir values and slope until nadir. The nadir value was further investigated as a classifier for remission using receiver-operating-characteristics (ROC) curves. The optimal cut-off was calculated by finding the maximum Youden index over all of the nadir values. The confidence interval for the AUC in the ROC was calculated using bootstrapping techniques. A confidence interval for the ROC AUC excluding 0.5 was considered significant. Excel 2010 (Microsoft) and R version
3.0.3 (61) were used for all of the statistical analysis. A p-value <0.05 was considered significant.

Sensitivity, specificity, positive predictive value and negative predictive value were calculated using this table.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Present</th>
<th>Absent</th>
<th>Total</th>
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<td><strong>Test</strong></td>
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<td>Positive</td>
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<td>Negative</td>
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<td>c+d</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>a+c</td>
<td>b+d</td>
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</table>

Sensitivity was calculated as $\frac{a}{a+c}$, specificity as $\frac{d}{b+d}$, positive predictive value as $\frac{a}{a+b}$, and negative predictive value as $\frac{d}{c+d}$. The Youden index was calculated as $(\text{sensitivity} + \text{specificity} - 1)$, giving a value between 0 and 1, where 0 indicates a test with very low predictive value and 1 indicates a perfect test with high predictive value.

4. Synopsis of results

4.1 Paper I

Twenty patients with macroadenomas (16 non-functioning, three growth-hormone secreting and one pharmaco-resistant prolactinoma) were selected for surgery in the intraoperative MRI. The mean tumour diameter was 27 mm (range: 11–41 mm). The mean parasellar grade according to the Knosp classification was 2.3. Pre-operative coronal and sagittal T1- and T2-weighted images were obtained. The transsphenoidal tumour resection was performed at the edge of the tunnel of a Signa SP 0.5-Tesla MRI. The surgeon aimed for a radical tumour resection, which was followed by an iMRI scan. When a residual tumour was visualized and deemed resectable, an extended resection was performed, followed by another iMRI scan. This procedure was repeated until the imaging results were satisfactory.
In all of the patients, we were able to obtain images to assess the extent of resection and to classify the resection as either total or subtotal. After primary resection, eight out of 20 cases were classified as total resections. A second resection was performed in 11 of 12 cases classified as subtotal resections, and in four of these, total resection was achieved. A third resection was performed in three of the remaining seven cases with subtotal resections, but we did not achieve total resection in any of these cases. Therefore, the use of iMRI increased the number of patients with total resection from 8/20 (40%) to 12/20 (60%). The only observed complication was a transient spinal fluid leakage.

4.2 Paper II
All transsphenoidal procedures for histologically verified pituitary adenomas performed between September 2002 and February 2011 at our institution were included in this study. The data were obtained from a prospectively collected database and from chart reviews. No patients were lost to follow-up, and the median follow-up period was 28 months. There were 506 transsphenoidal procedures performed on 446 patients. There were 268 microscopic and 238 endoscopic procedures, and there were 352 non-functioning and 154 hormone-secreting adenomas. A total of 73% of the procedures were primary surgeries, and 27% were repeat surgeries for tumour recurrence. The overall complication rate was 9.1%. The 3 most frequent complications were cerebrospinal fluid (CSF) leakage (4.7%), meningitis (2%) and visual deterioration (2%). Multivariate analyses showed that the overall risk for complications increased with older age, surgery for recurrent tumours and surgery performed by a low-volume surgeon. There was no significant difference in the overall complication rate between the microsurgical and endoscopic techniques. The surgical mortality was 0.6%, and the overall survival rates at 1 and 5 years were 95% and 90%, respectively. The only negative predictor of survival was older age.

4.3 Paper III
This single centre, retrospective study consisted of 19 consecutive patients with Cushing's disease undergoing transsphenoidal surgery. S-cortisol was measured every 6 hours postoperatively without any glucocorticoid replacement.
At three months follow-up, 16 patients (84%) were in remission; at 12 months, follow-up, 18 patients (95%) were in remission; and at the final follow-up (mean 68 months), 13 patients (68%) were in remission. The mean postoperative S-cortisol nadir was significantly lower in the group of patients in remission than in the non-remission group at three months, but there was no difference between those in long-term remission and those in long-term non-remission. The 5-year recurrence rate was 26%, showing the need for regular clinical and biochemical follow-up in this patient group.

5. General discussion

5.1 Intraoperative MRI

The first paper of this thesis shows that the use of intraoperative imaging to guide surgery led to an increased grade of resection. We achieved this without inflicting a higher complication rate. We achieved primary radical surgery in 40% of the patients (eight out of 20), and we showed that complete resection is more easily achieved in smaller tumours that have little or no parasellar extension. The use of iMRI increased the percentage of patients who received radical surgery from 40% to 60%. To be able to compare the results to other studies of transsphenoidal surgery, it is necessary to know the size of the tumours and the degree of parasellar extension. Eight of ten patients in paper I exhibited normal pituitary hormonal activity after surgery (80%). In the small subgroup of patients with growth hormone-producing tumours (three patients), there was a 100% correlation between the intra-operative imaging results and the post-operative hormonal status.

A PubMed search of “intraoperative MRI AND pituitary adenoma” in December 2014 resulted in 254 references. These publications are from a relatively small number of institutions, namely, those who have the equipment installed. The cost of installation and running of these systems limits the availability of this technique to only the wealthiest part of the world. A growing number of publications indicate increased resection grade with the use of iMRI (13, 14, 62-78).
The use of iMRI increases the length of surgery; in paper I, the use of iMRI increased the total surgery time by approximately 60 minutes. In a procedure that normally takes 60-90 minutes, this is a considerable increase in surgical time. This longer duration may lead to an increased risk for postoperative infections, although this was not proven for iMRI. If one can achieve more radical surgery and a longer progression free survival, it may be worth the added length of surgery (62).

As the use of iMRI is relatively new, there are few studies on long term-outcome. One centre that began to use the iMRI early is the Erlangen group, led by Prof Fahlbuschh (79), and they have recently published a study with long-term follow-up. Eighty-five patients were followed for a mean of 5.6 ± 1.9 years, and the authors concluded that the use of iMRI for transsphenoidal resection leads to low recurrence rate. Even in cases of invasive tumours, distinctly more patients showed long-term tumour-free follow-up. The authors also found that tumour remnants detected by iMRI are at high-risk to grow within 5 years after surgery (63).

In the evolution of transsphenoidal surgery, intraoperative imaging modalities, such as intraoperative fluoroscopy and cisternography, have been attempted to increase the extent of resection and to make surgery safer (16, 80). One promising new technique is the use of intraoperative ultrasound. With the development of dedicated transnasal probes, this method may represent an improvement being much simpler to use and more cost-effective method than iMRI (81, 82). Another available tool for intraoperative imaging is a portable CT-scanner, or a fixed CT-scanner located in the operating room. This technique has shown promising results (83), and in some studies, it has been shown to be as accurate as iMRI and to be significantly faster and less expensive (84).

The recent advances in flat panel technology has made it possible to obtain CT-scans with the use of a rotating C-arm, and this technique has been used for postoperative control scans in pituitary surgery. The results are promising, both for resection control and for ruling out complications, such as haematomas (85).
5.2 Endoscopic versus microscopic transsphenoidal surgery
Starting in 2005, the endonasal endoscopic transsphenoidal technique was gradually introduced in our clinic as an alternative to the microscopic transsphenoidal approach to the pituitary. In paper II, we showed that there was no significant difference in the overall complication rate between the two methods, although there was a trend towards more complications in the endoscopy group (p=0.006). We have not yet analysed the grade of resection or remission rates in the two groups.

The advantage of the endoscopic approach is its minimal invasiveness; the improved visualization with a greater field of view, giving access to tumours that could not be reached previously; and the possibility of “looking around corners” with angled endoscopes. The disadvantages are the lack of stereoscopic vision and the need for a second surgeon to hold the endoscope to be able to work with both hands.

There are numerous reports that have attempted to elucidate whether there is any difference in the outcome between microscopic and endoscopic pituitary surgery, and most studies have been single-armed series without proper controls (86-88). To my knowledge, there has been no large, prospective, randomized clinical trial (RCT) comparing transsphenoidal microsurgery and endoscopic surgery. It is unlikely that such an RCT will be performed. Thus, we must rely on other types of studies, such as institutional studies reporting their experience with both methods, meta-analyses of published series and cost-effectiveness studies.

*The simultaneous use of microscopic and endoscopic surgery at the same institution*
There are two studies to date comparing microscopic and endoscopic surgery performed simultaneously at the same institution, and both are from the same institution. This institution has one experienced neurosurgeon performing microscopic procedures and another experienced neurosurgeon performing
endoscopic procedures (89, 90). The authors first compared patients with acromegaly and found that the outcome did not differ between the endoscopic and microscopic techniques, and postoperative remission was achieved in 20 of 23 microadenomas (87%) and 59 of 90 macroadenomas (66%). Regardless of the mode of resection, patients with high preoperative GH levels and Knosp scores were less likely to achieve remission. Moreover, the rate of complications was the same, except for self-reported sinusitis and alterations in taste or smell, which were significantly higher in patients treated with the endoscopic technique (90). These authors have also published a series of non-functioning adenomas in Knosp grade 0-2 patients, meaning that the tumours had not infiltrated the cavernous sinus. They found that there were significantly more intraoperative CSF leaks in the endoscopic group (58% versus 16%), but there was no difference in the incidence of postoperative CSF-leakage (12% microscopic, 7% endoscopic). The length of hospitalization was significantly shorter in patients undergoing endoscopic approach (2.4 days vs 3.0 days). At 1 year follow-up, 83% (25 of 30) of patients in the microscopic group had no evidence of residual tumour, and 82% (36 of 44) of those in the endoscopic group had no evidence of residual tumour. However, nearly 30% in each group were lost to follow-up (89). The authors of these studies have not published their results on the group of patients were one would expect the greatest advantage of the endoscopic technique, namely, large tumours with suprasellar extension and Knosp grades 2-4.

The endoscopic endonasal technique for transsphenoidal surgery was introduced during the study period of paper II, and we could therefore determine whether this shift in surgical technique had any impact on the complication rate. There was no significant difference in the overall complication rate between the new endoscopic approach and the traditional microscopic method, although there was a non-significant trend towards an increased frequency of complications in the endoscopic group. By including all of the patients who underwent surgery with the new endoscopic technique, the problems related to the learning curve were simultaneously incorporated. Thus,
as more experience with the endoscopic technique is gained, one can anticipate a further decrease in the number of complications.

**Meta-analyses**

Many meta-analyses have been published, with the first in 2009. The authors pooled their own data with that reported in the literature and collected a total of 821 patients. There were very few complications reported, and they concluded that the results of their meta-analysis support the safety and short-term efficacy of endoscopic pituitary surgery (91). Two meta-analyses published in 2010 and 2011 both found that major outcome measures, such as resection grade and hormonal outcome, were the same but that there were fewer complications, shorter hospital stays and less patient discomfort in the endoscopy group (92, 93). In 2012, the meta-analysis performed by DeKlotz was even more in favour of the endoscopic approach, finding a superior rate of gross total resection (79% versus 65%, P<0.0001) and less postoperative CSF leakage (94). In contrast, a meta-analysis published in 2013 concluded that there were no advantages of the endoscopic technique over the microscopic technique and that the incidence of reported vascular complications was higher in the endoscopy group (95). This analysis has been highly criticized by leading neurosurgeons for “deeply flawed methodology” (96-98). The latest meta-analysis included 1014 patients, and the authors concluded that the rate of gross tumour removal was higher in the endoscopic group than in the microscopic group, and their results indicated that the endoscopic transsphenoidal approach was safer and more effective than microscopic surgery in the treatment of pituitary adenomas (99). One might criticize this meta-analysis in that we are still in an early era of endoscopy and that any meta-analysis looking backwards will include a learning curve. Therefore, one may conclude that now is not the time for meta-analyses but for prospective, randomized studies (100). In paper II, we presented our data on complications after microsurgical and endoscopic transsphenoidal surgery, and we hope that these data will be incorporated in future meta-analyses.
Cost–effectiveness analysis

There have been some attempts to determine whether there is an economic difference between microscopic or endoscopic pituitary adenoma surgery. The first of these was published in 2012 as part of a study on the cost of acromegaly (101). Another study on the cost-effectiveness of the two methods was performed using the Markov decision tree model, using effectiveness and probability data from a single meta-analysis of 38 studies. These authors found that the cost of the endoscopic approach was $17,244.63 and produced a total of 24.30 QALYs. The microscopic approach cost a total of $23,756.60 and produced a total of 24.20 QALYs. In summary, it was found that the endoscopic approach was less costly and more effective; an incremental cost-effectiveness ratio was therefore not calculated. The sensitivity analysis demonstrated a 79% certainty that the endoscopic approach is the most cost-effective method (102).

Why is it so difficult to show differences in results, complication profile or effectiveness between the two different methods? One reason might be that the grade of resection is already so high and the complication rate so low that a new and potentially better method must be used in a very large, standardized series to be able to observe a statistically significant difference. Another point worth noting is that the endoscopic technique is still very new, and a learning curve is present in most published series. This fact means that the results when using the technique improve during the study period.

Combination of endoscopy and iMRI

Is there an added benefit of combining iMRI and endoscopy, or do the two techniques both give a better view of potentially hidden tumour remnants and therefore have the same superiority to standard microsurgical technique? This question has been analysed in a retrospective study of 446 transsphenoidal pituitary adenoma surgeries at a single institution between 1998 and 2012. Combining endoscopy and iMRI increased the extent of resection compared to conventional transsphenoidal microsurgery. Multivariate Cox regression revealed that reduced extent of resection gave a shortened progression-free survival for near- versus gross-total resection and sub- versus near-total
resection. Complication comparisons between microscopy, endoscopy, and iMRI revealed increased perioperative deaths for endoscopy versus microscopy (4/209 and 0/237, respectively), but this difference was non-significant considering multiple post hoc comparisons (103).

5.3 Population based studies versus single surgeon series
In Greenberg’s Handbook of Neurosurgery it is stated that the surgical cure rate for hormone-producing adenomas is low and that radical resection of macroadenomas is seldom achieved (104). Is this the case, or is it the excellent results reported by single-centre, single-neurosurgeon series that reflects reality? It is important to be aware that there are two very different ways to recruit patients; referral based – where patients are referred to a surgical centre independent of where they live, and population-based – where patients are allocated to surgery in the area where they reside. The referral-based system is the system in the US, and the population-based system is used in Scandinavia and central Europe, although there is a trend towards referrals out of the geographic location of the patients in these countries. In a referral-based system, it seems to be more difficult to follow patients, and it is not unusual to have 20 to 30% lost to follow-up (105, 106). In contrast, in population-based studies, patients tend to return to the centres were they were operated upon, giving a higher rate of follow-up, and in many instances, such as in our studies, one will achieve follow-up data on most patients. It is also worth considering which patients are lost to follow-up. One assumption is that patients who are not satisfied or not in remission will seek another centre and do not come back for follow-up visits.

In paper II, we report complications on all patients operated upon with transsphenoidal surgery in a defined population of 2.6 million inhabitants in a given time period, with follow-up data on all patients. Norway is well suited for population-based epidemiological studies because of the country’s stable population and public health care system. Fifteen different surgeons acted as the main surgeon in these 506 procedures, illustrating the challenges of running a population-based neurosurgical service that should be available every day of the
year. On the other hand, the results reported in paper III are for a single-surgeon series of elective patients. The strength of this study is that we have long-term follow-up on all patients. The results in paper III are positive and show a high remission rate, as is often observed in series reported for a single dedicated neurosurgeon, as opposed to population-based studies.

A population-based study from the Munich metropolitan area in Germany on the results of surgery for Cushing’s disease included 120 patients operated upon in three tertiary university centres and multiple smaller neurosurgical centres, with a mean follow-up period of 79 months. These authors found that after primary surgery, 71% achieved remission, 29% experienced persistent disease and 34% experienced disease recurrence, with a mean time to recurrence of 54 months. These results show that 46% achieved long-term remission after primary surgery for Cushing’s disease. After a second surgery, 42% achieved remission, 58% experienced persistent disease, and disease recurred in 40%, with mean time to recurrence of 42 months. These results show that only 25% achieved long-term remission after a second surgery (107).

Another population-based study on hormone-producing tumours is the Norwegian POTA study on pre-treatment with octreotide in newly diagnosed acromegaly. This was a prospective, randomized study including all newly diagnosed patients with acromegaly in Norway. The overall remission rate at three months was 34%. There were surprisingly little difference in the cure rates between micro- and macroadenomas, with remission rates of 40% and 33%, respectively (39).

The results reported in these studies probably reflect those that could be expected in every-day surgical practise in neurosurgical departments in the Western world. Moreover, these data show the need for the further development of surgical techniques and the justification of adjuvant treatments, such as medication, radiotherapy and bilateral adrenalectomy.
5.4 Complications as a marker for quality

Quality assessment programs were introduced in the industry many decades ago and have slowly been adopted in health care systems in recent years. The rising cost of health care and obvious differences in clinical practises has propelled the need to quantify the health care offered. The incidence of postoperative complications is still the most frequently used surrogate marker of quality in surgery (108). Norwegian health authorities has developed a set of quality indicators to measure the quality of treatment of disease and survival; five out of six of these are complications, namely, the number of patients being amputated during treatment for diabetes, 30-day survival after hospitalization of any cause, 30-day mortality after hospitalization for myocardial infarction, 30-day mortality after hospitalization for cerebral insult, and 30-day mortality after hospitalization for femur fracture (109). These criteria tell us how important it is to know the complication rate for a given surgery to be able to conclude anything about the quality of the care.

Over the years, there has been a change in the attitude towards treating pituitary adenomas, with an increased focus on trying to accomplish radical surgery. When we sought to study our pituitary surgery results and started to work on paper II, it quickly became evident that we should look at our complication rate as a marker of quality of care, especially as we had changed our surgical technique in the period studied. The purpose of adopting a new surgical technique is to accomplish a less invasive, more radical surgery with fewer complications. Moreover, striving for radical resection must be carefully balanced against the risk and ramifications of surgical morbidity. Hence, it is essential for all surgeons and departments to review their complication and success rates when a new surgical technique is implemented.

However, the definition of complications in surgery still lacks standardization, hampering the interpretation of surgical performance and quality assessment. Many authors have tried to define what should be regarded as a complication, and one of the more useful was proposed by Clavien and co-workers in 1992 (110). They defined “negative outcome” by differentiating between complications, failure to cure, and sequelae. Complications were defined as “any
deviation from the normal postoperative course", and a severity score for complications was proposed. Sequelae were defined as something inherent in the procedure and that is likely to occur. In our setting, this would, for example, be a transient anosmia or a persistent endocrinologic deficit after resection of a non-functioning macroadenoma. Diseases or conditions that remain unchanged after surgery are not complications but rather a failure to cure. In our setting, this would be the case with Cushing's disease not going into remission after transsphenoidal surgery or incomplete resection of a non-functioning macroadenoma.

Other authors later made attempts to provide a more sophisticated definition of complications, defining a complication as "an undesirable, unintended, and direct result of an operation affecting the patient which would not have occurred had the operation gone as well as could reasonably be hoped" (111). This definition can absolutely be debated. Using this definition, a postoperative venous thrombosis would not be regarded as a complication as it is not a direct result of the operation, and an incomplete resection may be regarded as a complication because "had the operation gone as well as could reasonably be hoped" the whole tumour would be removed. The causal relationship between surgery and an unwanted incident might also be difficult to establish and might lead to an underreporting of surgical complications.

As we can see, it is important to agree on a definition of what is a complication before starting to report numbers for the occurrence of complications. We have more or less used the definition from Clavien and co-workers in defining what is a complication in our work (110).

6. Conclusions and future aspects

6.1 Conclusions

- Intra-operative MRI is a useful tool during transsphenoidal surgery for pituitary adenomas. Using this procedure, good results were achieved in regard to the extent of tumour resection and endocrine and visual outcomes; a low complication rate was also achieved.
• Learning from an objective evaluation of the extent of resection with an early MRI scan after surgery is important, especially for less experienced surgeons, and may improve the results after transsphenoidal surgery.

• Transsphenoidal surgery for pituitary adenomas is relatively safe, with an overall complication rate of 9.1% and a low mortality of 0.6%.

• There was no significant difference in the complication rate between the endoscopic and microscopic techniques.

• Predictors of having a complication were older age, surgery for recurrent tumours and surgery performed by a low-volume surgeon.

• The only negative predictor of survival was older age.

• The overall survival rates at 1 and 5 years were significantly lower for the patients undergoing transsphenoidal surgery than for the control population, most likely because of the pituitary disease per se.

• We achieved a high cure rate with transsphenoidal surgery for Cushing’s disease in this series of consecutive patients, with 95% being in remission at one year.

• The recurrence rate of Cushing’s disease was high, with a 5-year recurrence rate of 26%, demonstrating the need for thorough clinical and biochemical follow-up.

• The mean S-cortisol nadir was significantly lower in the remission group than in the non-remission group at three months, but low postoperative S-cortisol did not predict long-term cure.

6.2 Further aspects
Transsphenoidal surgery has a relatively short history in Norway, with the first procedures performed in 1979, but there have been great advances in surgical skills and methods over the years.

Evaluation and surgery for potentially endocrine active tumours is a field where interdisciplinary cooperation is of great importance, and arenas for this has been created at most institutions with routinely pituitary meetings. This
interdisciplinary approach for treatment of patients has been transferred also to the research arena, including not only endocrinologists and neurosurgeons, but also ophthalmologists, pathologists, neuroradiologists and basic science research labs. At our institution this kind of cooperation has already resulted in increasing our understanding of the biology of these tumours, and explored new treatment modalities (112-119). This interdisciplinary cooperation needs to be deepened and formalised including formalized bio banks for tumour tissue, given increased possibilities for research on receptor expression and activation and genetic factors. It will also be important to continue our work on intraoperative imaging, both regarding MRI but also implementing new imaging techniques. A local interdisciplinary cooperation should also be used to continue and deepen a national cooperation between the centres treating these patients to continue to develop national guidelines and studies (39, 47, 120).

We are now entering an era where an increasing amount of anterior skull base surgery can be performed with endonasal endoscopic techniques. To be able to continue these innovations, we must continuously develop our surgical skills with constant rehearsal and cadaveric courses and continuously maintain quality control with prospective databases.

We have documented that these innovations has so far been in the best interests of the patients, and as the surgery changes, it is important to continue to monitor our results and complications to avoid future risks. We have now established definitions and databases that serve as a starting point for further improvement.
7. References

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