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Endoscopic Surgery for Pituitary Tumors

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KEYWORDS

• Endoscopic surgery • Pituitary adenoma • Tumor • Skull base surgery
• Center of excellence • Surgical video

KEY POINTS

- Endoscopic transsphenoidal surgery is first-line treatment of most pituitary adenomas.
- Multidisciplinary team work is key for all phases of treatment: indication, preparation, surgery, and postoperative care.
- Identification of anatomy and intraoperative risk assessment with adjustment of the surgical objective is essential for safe and effective surgery.
- Cushing's disease and giant adenomas often are highly complex surgeries.
- In addition to traditional outcome measures, like remission and complication rate, modern outcomes, like quality of life, accomplishment of the surgical goal, and health care usage, are important to monitor quality of care.

Video content accompanies this article at http://www.endo.theclinics.com.

INTRODUCTION

Transsphenoidal surgery is the front-line treatment of most pituitary adenomas.[1] After the first transsphenoidal pituitary surgery in the Netherlands was performed in the authors' hospital, it remained a focus point.[2] The authors have invested in organizing pituitary patient care in a multidisciplinary way, adopting the value-based health care principles with clinician-reported and patient-reported outcome measures. The authors work in a large-volume center, taking care of the whole spectrum of pituitary

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patients, including last-resort options for patients with complex (functional) pituitary adenomas and other parasellar lesions. Patient preference and individual risk/benefit assumptions are discussed during preoperative consultations using shared decision making after weighing treatment choices. In select cases, innovative imaging is used to optimally identify this individual benefit/risk balance. The authors believe that, if feasible, total resection of functional tumors without compromising pituitary function is imperative to improving ultimate health outcome of patients. This article describes the authors' philosophy, surgical technique, outcomes, and complications.

In the past decades, a transition from microscopic transseptal to an endoscopic, 2-nostril approach has been made. The surgical microscope is still the most important tool for the neurosurgeon, allowing great illumination, magnification, 2-handed surgery, and 3-dimensional view. Endoscopy for pituitary adenomas finds its origin in functional endoscopic sinus surgery, performed by ear, nose, and throat (ENT) surgeons. It is no surprise that adoption of the endoscopic technique was slow, due to the steep learning curve and the not immediately clear advantages of endoscopy. Although for midline microadenomas endoscopy offers little benefit, the endoscopic panoramic view is superior in terms of efficacy and safety for macroadenomas and tumors near the cavernous sinus.[3–5]

In the authors' center, transsphenoidal surgery has been performed exclusively endoscopically from 2007 onward. The entire procedure is always performed by a pair of 2 dedicated surgeons, either an ENT/neurosurgeon couple or 2 neurosurgeons. Because of the large surgical volume, recently well over 100 cases a year, and limited ENT surgeon availability and proper training of the neurosurgeons, the majority of cases is performed by 2 neurosurgeons. Dedicated equipment is needed, which includes not only endoscopes (0° and 30°), high-definition (HD) cameras, and monitors but also, among others, specialized drills, curettes, and dissectors. A Doppler ultrasound probe is used to identify the carotid artery. Even a routine pituitary adenoma surgery is equipment intense. The authors have protocolized the operation, which has improved efficiency and benefitted teamwork for the whole operating room (OR) team. It is also the authors' experience that greater surgical volume benefits quality of care and efficiency. They are strongly in favor of centralization of pituitary adenoma surgery, with a limited number of centers of excellence,[6,7] connected to a wide network for endocrine diagnostics, follow-up, and treatment.

CLASSIC AND NONTRADITIONAL INDICATIONS FOR SURGERY

At the authors' center, the indication for surgery is always discussed by a multidisciplinary team (MDT), where treatment objectives, alternative treatments, and timing of surgery are considered. An individualized approach to advantages or disadvantages of either treatment is discussed with the patient. In most cases, complete adenoma resection benefits the patient best, but sometimes tumor extension makes complete resection uncertain or with raised risks (**Fig. 1**). Perhaps it is here where experience, a large surgical volume, and surgery performed by 2 surgeons have the most impact on quality of care through better preoperative and intraoperative risk assessment. The surgical goal and expectations are defined preoperatively and this evaluation is discussed with the patient.

There may be a situation of high chance of total resection with very low chance of complications in microadenoma and small noninvasive macroadenoma. In invasive adenoma and small nearly undetectable adenoma remnants, however, the chances for surgical success are lower, and risk assessment is crucial to deciding optimal

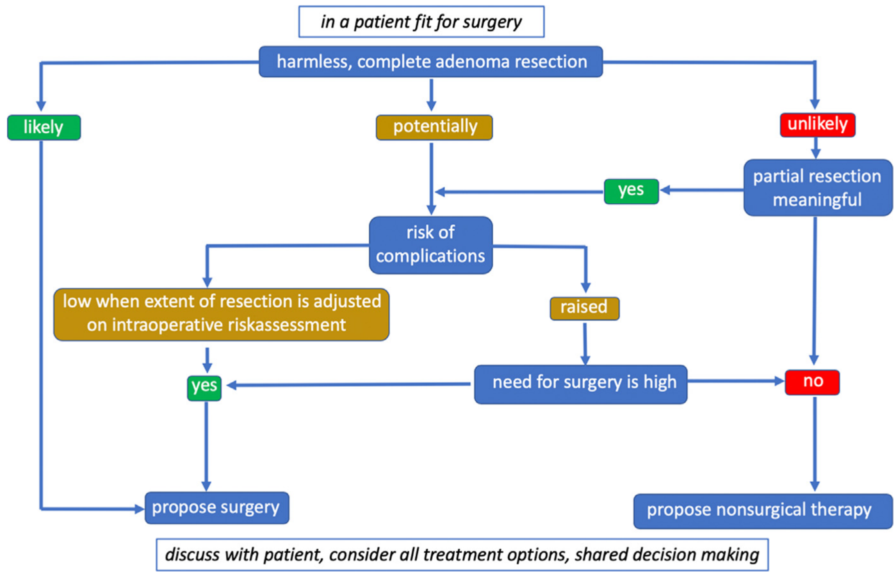

Fig. 1. Schematic representation of consideration of surgical therapy in a patient with a pituitary adenoma, who is fit to undergo surgery. If complete adenoma resection is likely and risks are low, surgery is proposed. When risks for complete resection are raised, surgery is proposed only when there is a high need for surgery (eg, Cushing's disease). Correspondingly when complete resection is possible, but uncertain, usually because of suspected cavernous sinus ingrowth or close relation to the stalk, surgery is proposed only when there is a high need for resection (eg, drug intolerance or resistance or decompression) and when it can be anticipated that risks can be kept low by adapting surgical strategy when faced with unfavorable adenoma consistency and unfavorable local anatomy. The planning of partial resection is based on a careful evaluation of anticipated risks and benefits (eg, preservation of pituitary function and risk of leaving remnant tissue) and the added value of surgery in the multimodality treatment algorithm.

treatment. When risk of complication is higher, alternative treatments (medication and radiotherapy) may be indicated. If, despite higher risks, there is a high need for surgery, the goal of treatment is defined explicitly and surgery planned accordingly.

In select cases, an incomplete adenoma resection is advised because it is expected that this is best for the patients, through lower complication rates and preserving pituitary function. Real cavernous sinus invasion[8] (Knosp classification grades 3B and 4) and certain growth patterns[9] are known to limit likeliness of complete resection. Surgery sometimes is offered, even when the chance of success is limited, for example, residual adenoma in cavernous sinus with uncertain invasion in functional tumors with severe symptoms or drug intolerance. In those cases, adjustment of the degree of resection to intraoperative risk assessment is key; for example, success may depend on the consistency of the tumor. Typically, intact pituitary gland function is deemed more important than residual adenoma. Repeat pituitary adenoma surgery has proved safe in the authors' hands and well tolerated by patients. The authors prefer repeat intervention instead of sella clean out in difficult Cushing's disease cases, trying to prevent irreversible hypopituitarism whenever possible.

There is a striking variance between centers in surgical indications for pituitary adenomas in different centers of excellence, depending on local experience and culture, availability of interventions, alternative strategies, and so forth (Boxes 1 and 2 list authors'

Box 1
Classic surgical indications for pituitary adenoma and (para)sellar tumors

Nonfunctioning adenoma
- Nonfunctioning adenoma with compression of the optic chiasm and visual field defects
- Nonfunctional adenoma that shows consistent growth over time and close to, or touching, the optic chiasm

Cushing's disease
- Cushing's disease with a visible adenoma on the MRI, or positive petrosal sinus sampling
- Recurrent disease, with resectable adenoma

Acromegaly
- Acromegaly, with an adenoma that is likely to be completely resected
- Acromegaly, with a large adenoma, where debulking is likely to improve medical treatment

Prolactinoma
- Prolactinoma, medication refractory
- Prolactinoma, medication intolerance
- Prolactinoma with new CSF leakage after tumor shrinkage under medical therapy

Thyrotropinoma
- Thyrotropinoma, with thyrotoxicosis

General
- Apoplexy with visual deterioration
- Unknown pituitary, or sellar lesion necessitating histologic diagnosis
- Other (para)sellar tumors, such as craniopharyngioma, Rathke cleft cysts, meningioma, chordoma, pituicytoma, metastasis, and so forth

Box 2
Nontraditional surgical indications of pituitary adenoma

Nonfunctioning adenoma
- Recent onset of pituitary insufficiencies surgical objective: increasing the odds of restoration of pituitary gland function

Cushing's disease
- Second reoperation for small, identifiable adenoma remnant/recurrence surgical objective: remission of Cushing's disease, while maintaining pituitary gland function

Acromegaly
- Reoperation for acromegaly if visible remnant/recurrence is resectable surgical objective: remission of acromegaly, while maintaining pituitary gland function, and reducing need of, potentially side-effect inducing medical treatment

Prolactinoma
- Prolactinoma as initial treatment
- Prolactinoma after a short (6-month) trial period of dopaminergic medication
- Prolactinoma, with recurrence after 2 years of medical therapy, as alternative to lifelong medical treatment surgical objective: remission of prolactinoma, while maintaining pituitary gland function, and omitting need of, potentially side-effect inducing medical treatment

General
- Apoplexy with either extreme headache, and/or (partial) ophthalmoplegia
- (Small) sellar mass with debilitating headache surgical objective: resecting sellar lesion, while maintaining pituitary gland function, hereby optimizing chances of symptom reduction

indications). Although in most guidelines, surgery is considered the initial treatment in acromegaly patients if safe and complete resection can be achieved,[10,11] this is perhaps the group where treatment strategies differ the most. The authors' center always has been surgically oriented, with medical treatment and radiation reserved for secondary or tertiary therapy. Upfront medical treatment sometimes is initiated to make surgery safer or more likely to succeed. The authors advise on surgery and reoperations as long as there is a chance to achieve total resection with low chance of complications. Patient preferences and individual situations are taken into account, however, and alternative treatment options have proved their efficacy and added value in the multimodality treatment of this difficult-to treat disease. The authors make a plea for a multidisciplinary consultation of every new patient with acromegaly, because they have encountered several cases in which surgical chances were assumed optimal at diagnosis, but after many years of SRL treatment, the remnant tumor is less likely to be totally resected.

The authors' surgical attitude also is shown in surgical indications that are nontraditional (see **Box 2**). They recently started a study about surgery as initial treatment of patients with a small or medium-sized prolactinoma (Zandbergen IM, Najafabadi AHZ, Pelsma ICM, et al. The ProlaC & PRolaCT studies – a study protocol for a cohort and multiple Randomized Clinical Trials study design in Prolactinoma, submitted). Dopaminergic therapy, the traditional first-line treatment of prolactinoma, may have more side effects than previously recognized, at least in a substantial proportion of patients, whereas surgery has become safer; therefore, a comparison between the 2 treatment options is timely.[12,13]

Perhaps even more controversial is early surgery in non-functioning lesions not yet compressing the optic chiasm, with the main goal restoring pituitary gland function instead of accepting hypopituitarism and waiting for tumor growth and optic chiasm compression. Traditionally, restoration of gland function was an unexpected beneficial side effect of surgery,[14] not its aim. The authors have not yet properly investigated this indication, but initial clinical experiences support the concept that in select cases early surgical intervention can restore gland function. When surgery is considered anyways, in a patient with recent-onset pituitary gland dysfunction, the authors attempt to do the surgery with little delay in an attempt to maximize the chances of restoring gland function.

Another indication that has been a cause of debate is the optimal treatment strategy for apoplexy.[15] In a patient with extensive sellar bleeding/infarct and visual field defects, surgery is standard of care. The authors, however, treat almost all apoplexies as an emergency; patients often have severe headache, partial ophthalmoplegia, and loss of pituitary gland function. The authors aim to perform surgery within 24 hours after admission, reduce the headache, and optimize the odds of restoration of cranial nerves and pituitary gland function. In a patient with apoplexy, without headache, and only partial third nerve palsy, a conservative, careful, wait-and-observe approach (with hormone replacement for adrenal insufficiency when needed) usually also results in good recovery of the ophthalmoplegia. Headache, in a patient with pituitary adenoma or cyst, without accompanying apoplexy, is a symptom the authors encounter with some frequency. Predicting headache relief after surgery is unreliable[16] and as a solitary surgical goal often denied. In patients with daily, incapacitating headache and a sellar mass or cyst, however, the authors have offered surgery as a last-resort treatment and have obtained occasional good, lasting effects.

IMAGING

Imaging of the pituitary gland and stalk, optic nerves, chiasm, cavernous sinuses, sella turcica, sinuses, and nose is extremely important for a surgeon to assess surgical risks and likelihood of success. Modern imaging of the pituitary adenoma, with various magnetic resonance imaging (MRI) techniques, is key to identifying (residual) functional adenomas and tumor extensions.[17] A thin-sliced computed tomography (CT) scan of the skull base is performed to identify the exact bony anatomy, in particular the degree of pneumatization, optic canals, bony covering of carotids, sphenoid septations, septum deviation, and size of turbinates (Fig. 2). Postoperative imaging is done mainly for future referencing for the assessment of possible recurrence. Differentiating between normal postoperative changes in the resection cavity and residual adenoma can be difficult on initial postoperative MRI.

SURGICAL SETUP

Surgery is done under general anesthesia, in supine position, with the head elevated. An endotracheal tube is placed in the left corner of the mouth; usually, no gastric, arterial, or bladder catheter is placed. Intranasal decongestion and local anesthesia are achieved by applying a mixture of cocaine (dosage 4 mg/kg; maximum, 200 mg), adrenaline, xylometazoline, and lidocaine on 6 small gauzes (patty), which are placed on both sides adjacent to the nasal septum (upper, middle, and lower meatus) under direct vision.

Positioning of surgeons, OR nurse, and anesthesiology team in the OR is important to allow optimal, somewhat ergonomic, working posture for all. The authors perform the surgery with 2 standing surgeons positioned on the right side of the patient at the level of the shoulder (Fig. 3). They both look at a large HD monitor on the left side of the head of the patient. The OR nurse is on the left side of the patient, while anesthesiology is placed as far cranial on the left side as possible. At least 1 additional surgical monitor is placed for the OR nurse to follow the procedure. This setup works well for the authors and allows doing the surgery quickly and safely. A common variation in the setup is with 1 surgeon placed on the right side of the head and 1 surgeon on the left side.

A zero degree endoscope is used and fitted with a lens rinsing system. Endoscopes are used for visualization only; instruments are passed separately into the nose. Technically, therefore, this is endoscopic-assisted surgery and not endoscopic surgery.

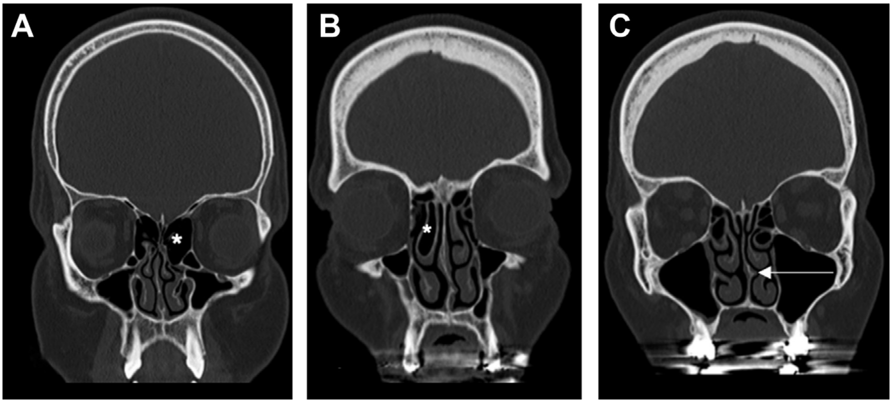

Fig. 2. Three different coronal CT scans with anatomic variations, which narrows the surgical access to the sphenoid sinus. (*A*) Strong pneumatized bulla ethmoidalis (*asterisk*). (*B*) Concha bullosa on the right side (*asterisk*). (*C*) Spur of the septum (*arrow*).

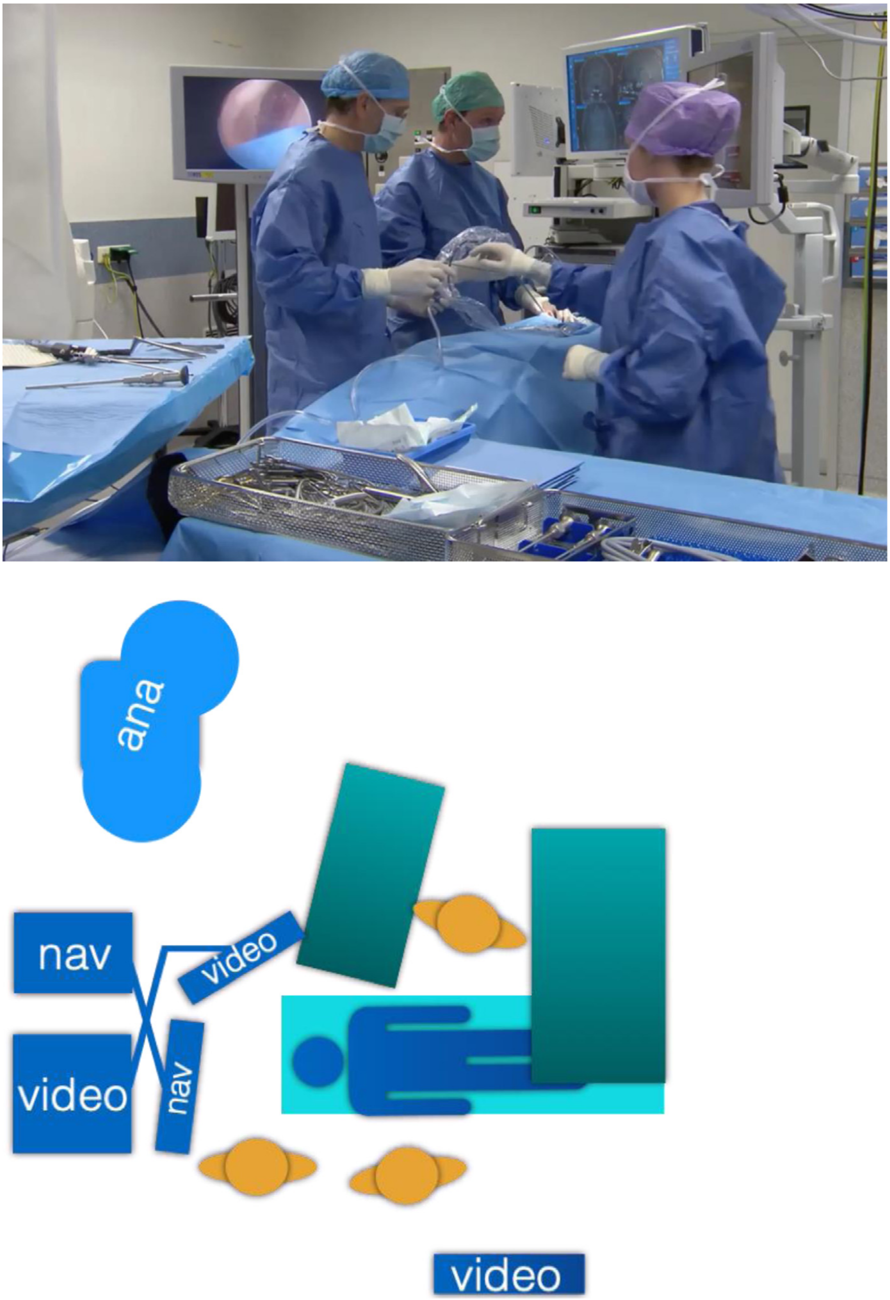

Fig. 3. Picture and schematic drawing of setup in the OR for endoscopic pituitary adenoma surgery. ana, machine of anesthesiologist; nav, navigation.

The initial steps of surgery are done with the surgeon holding the scope in 1 hand and an instrument in the other. Once the sphenoid sinus is opened on both sides and a posterior septectomy is performed, a 2-handed surgical technique is used. For this, 1 surgeon is the scope driver and the other is using both hands for surgery, similar to when a microscope is used for visualization. The endoscope is placed in the upper quadrant of the right nostril to provide ample space for surgery. The benefit of performing surgery with a handheld endoscope, compared with a rigid scope holding system, is dynamic visualization. Delicate movements of the scope, in and out, allow for better 3-dimensional understanding of anatomy. Furthermore, the scope driver can optimize visualization at all times, while allowing sufficient space for surgical instruments to maneuver. So-called sword-fighting can occur, when the endoscope and instruments compete for the narrow space in the sphenoid. Usually, this is easily solved by enlarging the opening of the anterior sphenoid wall. Magnification of the image is done simply by moving the endoscope closer to the object. With the HD scopes and monitors, the quality of the image is at least as good as with modern microscopes. Last, but not least, the authors favor surgery performed by 2 surgeons, because not infrequently it is the scope driver who identifies anatomic landmarks before the operating surgeon, which increases safety.

An electromagnetic (EM) neuronavigational system is used in all cases. Optic systems are less practical, because the line of sight often is obstructed by the endoscope. EM navigation systems have enough accuracy to be useful during surgery. The most important reason to always use the system is that it is hard to predict in which cases it can possibly have a benefit. Furthermore, the authors find that the reliability of the navigational system is better when used routinely.

APPROACH OF THE SELLA

Using the septum, nasal floor, turbinates, and choanae, the first surgical step is to identify the right sphenoid ostium. Usually, it is sufficient to carefully lateralize the middle turbinate, without the need to resect it. With a monopolar needle, an incision is made in the mucosa of the face of the sphenoid, just below the ostium, toward the septum. The length of this incision is arbitrary but should be at least as long as the length of the posterior septectomy. The mucosa inferior to this incision is reflected downward; the mucosa superiorly provides a free mucosa graft. This septal incision is always made, to always allow for mucoseptal flap harvesting. This so-called rescue flap[18] rarely is needed for pituitary adenoma surgery but the authors find it good practice to have this closure option available in all patients and in this way conserve the septal branches of the sphenopalatine artery. Injuries of these branches can result in (late) postoperative epistaxis.

The connection between the cartilaginous septum and the vomer is broken and the mucosa of the left face of the sphenoid elevated. A small chisel is used to break out the central part of the vomer and gain access to the sphenoid sinus. Next, the left nostril is entered and middle turbinate lateralized. As an option, another free mucosa flap is taken at the back of the nasal septum. A small strip of septal mucosa always is left superiorly, because of the olfactory nerve fibers, which may be recognized by a more orange color of the mucosa. The anterior wall of the sphenoid is opened extensively in all directions, tailored to the specific needs of the patient. In patients with adenomas with extensive suprasellar growth, superior opening of the anterior wall of the sphenoid is enlarged, whereas with cavernous sinus invasion, lateral opening is more extensive. When needed, the inferior one-third part of the superior turbinate is cut, allowing it to be reflected laterally for the duration of the surgery.

The bony septations in the sphenoid show a lot of variation, although often they are attached at the level of the carotid artery. This is why these septations are best drilled away carefully and not broken and removed. Force may cause carotid artery injury. Septations are removed and mucosa over the sella is opened as curtains, or fully removed, to allow for optimal bony anatomy identification. It is essential to identify on both sides the following structures, prior to commencing to the next phase (Fig. 4):

- Carotid artery
- Optic canal
- Medial opticocarotid recess
- Lateral opticocarotid recess
- Sella floor
- Tuberculum sellae
- Planum sphenoidale

SELLAR PHASE

To benefit from the panoramic view the endoscope offers, a larger bony opening of the sella is preferred. The authors have noticed that a major cause of incomplete adenoma resection was a too limited sellar bony opening. The technique is to outline the extend of the opening with a drill, until the cutline is eggshell thin and then break it and remove a small bone flap. Bony opening is tailored to pathology. When an adenoma is adjacent to the medial wall of the cavernous sinus, the bony opening on that side is extended over the cavernous sinus. This technique allows safe bony removal, even over the cavernous sinus and carotid artery. Correspondingly, tuberculum sellae, or even the first part of the planum sphenoidale bone, is removed for adenomas with suprasellar growth.

Before the dura is cut, anatomic reorientation is performed, and the location of both carotid arteries is confirmed. Doppler and neuronavigation may be useful for this. Dura opening is done with a disposable microblade, making sure to keep distance from the cavernous sinuses and carotid arteries. The intercavernous sinus inferior and/or superior sometimes may need bipolar coagulation. With the superior cuts, the authors try to avoid cutting into the cerebrospinal fluid (CSF) that often is here in a dural fold. The

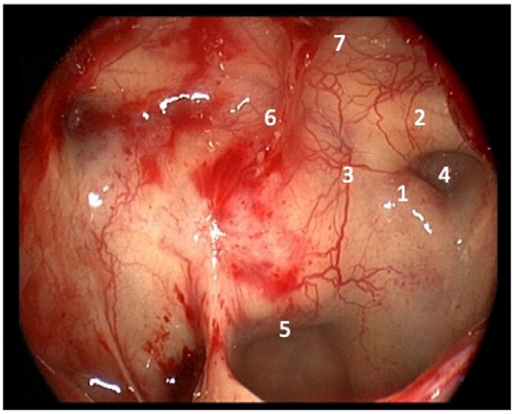

Fig. 4. Endoscopic view of the bony anatomy of face of sella in well-pneumatized sphenoid. 1, Carotid artery; 2, optic canal; 3, medial opticocarotid recess; 4, lateral opticocarotid recess; 5, sella floor; 6, tuberculum sellae; and 7, planum sphenoidale.

dura of the sella floor also is cut, to get wide exposure of the sellar content. Because of the wide bony opening, the dura edges can be mobilized, allowing direct visual intrasellar inspection.

Bleeding during resection of the pituitary adenoma is venous and, therefore, usually limited. This venous bleeding, however, does obstruct good visibility of the resection planes. Bleeding, usually from the cavernous sinus or intercavernous sinus, is best prevented or stopped before adenoma resection is continued. Packing with hemostatic agents works well and, in more persistent bleeding, injection with a specialized product Floseal (Baxter Health Care, Deerfield, IL, USA) or Surgiflo (Ethicon, New Brunswick, NJ, USA) may be needed to get full hemostasis.

In macroadenoma, the pituitary gland often is displaced laterally and superiorly, so that the adenoma is first encountered after dura opening (**Fig. 5**, Video 1). With dissectors and blunt ring curettes, the borders of the adenoma are dissected first and then the adenoma is removed in a piecemeal fashion. Early identification of the adenoma edges is crucial to limit the risk of damage to the pituitary gland and tearing of the arachnoid at the level of the diaphragm sellae. In some more firm adenomas, extracapsular resection is possible.[19] In this technique, the adenoma edge is dissected all around, without piecemeal removal. Although this surgical technique has a high chance of complete adenoma resection, it also has a higher chance of inadvertently removal or pituitary gland injury. After selective adenoma resection, intrasellar inspection is performed to assess completeness of tumor removal. In adenomas with large suprasellar components, a 30o endoscope is used to inspect the superior compartment. Placing the patient in Trendelenburg position raises the CSF pressure, which pushes the suprasellar compartment of the adenoma downward, sometimes allowing resection of residual adenoma.

In microadenoma, the exposed surface of the pituitary gland can look completely normal (**Fig. 6**, Video 2). Based on preoperative imaging, a small cut then is made in the gland at the location where the adenoma is expected. There currently are no techniques for intraoperative imaging of the gland, but neuronavigation (merging CT and MRI) can help based on preoperative imaging. Sometimes gentle palpation of the gland surface with an instrument also may provide information about the localization of the adenoma. After a cut is made in the pituitary gland, again the edges of the microadenoma are identified and dissected. Often the consistency of the microadenoma is

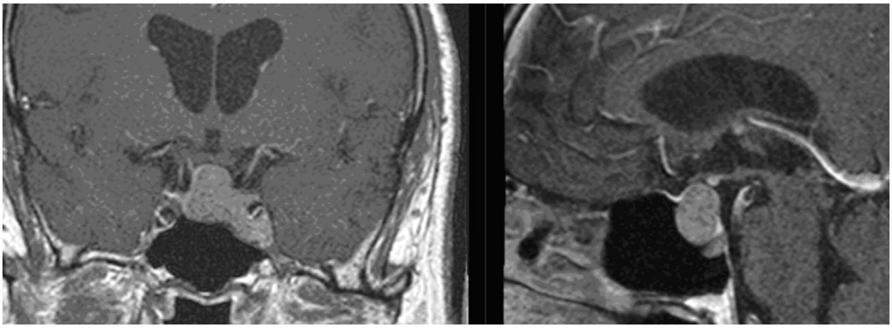

Fig. 5. A 68-year-old male patient with a growing macroadenoma that abuts the chiasm, with recent-onset partial hypopituitarism. Coronal (*left panel*) and sagittal (*right panel*) MRI show extension of the adenoma into the left cavernous sinus. The postoperative course was uneventful with recovery of pituitary function. A postoperative MRI showed small cavernous sinus residual adenoma on the left side. For surgical video, see Video 1.

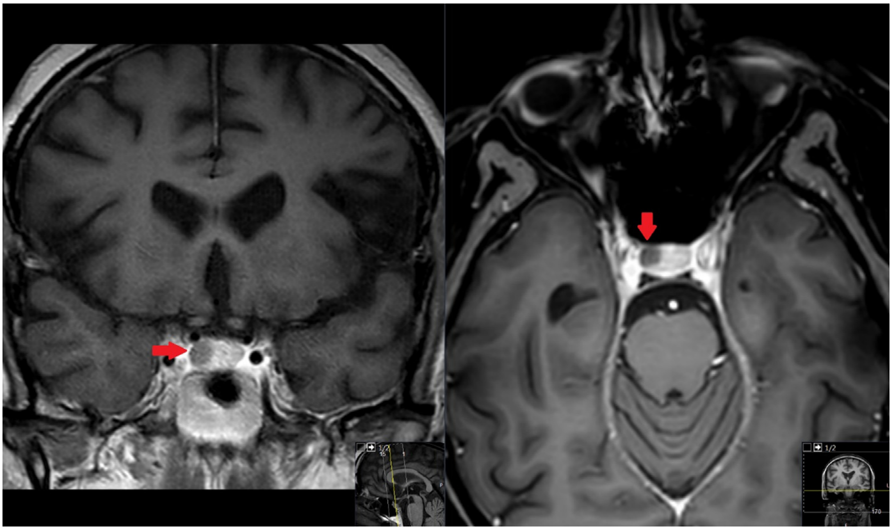

Fig. 6. An 18-year-old female patient with severe Cushing's disease (cortisol, 1376 nmol/L) due to a microadenoma located on the right side of the sella. Coronal (*left panel*) and axial (*right panel*) MRI show the location of the adenoma (*arrows*). Postoperative course was uneventful with recovery of symptoms, biochemical remission, without the need for hormone replacement except for hydrocortisone (10 mg, 5 mg, 5 mg over the day). Pathology showed ACTH positive adenoma. For surgical video, see Video 2.

soft, limiting the option of extracapsular dissection. With small ring curettes the adenoma is removed and the resection cavity explored. The authors try to visually inspect the entire cavity, to assess completeness of resection. It can be useful to fill the resection cavity with saline and dive into the cavity with the endoscope, rinsing continuously for detailed inspection.[20]

CLOSURE

When selective adenoma resection is performed without CSF leakage, closure can be simple. The authors normally place a collagen foam material in the opening of the resection cavity, to close it off. In macroadenoma with extensive exposure of the arachnoid, it is wise to be stricter about closure. The authors have had patients without CSF leakage during surgery, who started leaking a couple of days later, sometimes provoked by a sneeze or other activity causing rise in intracranial pressure. In these patients, CSF leakage is prevented by filling the resection cavity with autologous fat tissue, harvested from a paraumbilical 2-cm incision and held in place by fibrin glue. In all these cases, unless removed, the sphenoidal mucosa is draped over the sella to promote remucosalization.

In patients with a CSF leak during surgery, a more stringent closure technique is crucial. There are many variations in closing techniques; the authors rely mostly on the following technique. The arachnoidal tear is closed by placing a small piece of abdominal fat in the opening and secured by several drops of fibrin-glue. Subsequently, the closure is reinforced by filling the resection cavity with small pieces of abdominal fat, taking care not to overpack it. In larger CSF leaks, the next layer is 1 or 2 pieces of fascia lata. This can be an autograft or may be available from donor tissue. Finally, the free mucosa graft that was harvested at the beginning of the surgery is placed on top and again secured with drops of fibrin glue. Only in a patient with a larger defect and reconstruction are fatty gauzes placed in the sphenoid to hold the reconstruction in place. A mucoseptal flap is not used for pituitary adenomas. Lumbar drains are not placed and postoperative bedrest is refrained from.

PATHOLOGY-SPECIFIC SURGICAL ISSUES

Cushing's disease

Surgery for Cushing's disease almost always is complex. The adenoma can be invisible on MRI. Visible adenomas may have extensions that are not always visible on the MRI. In rare cases, there may be multiple adenomas present, which is why some surgeons place several vertical cuts in the nonadenomatous part of the pituitary gland. The sellar dura can be infiltrated and cause a recurrence.[21] A small remnant or recurrence eventually can cause reoccurrence of symptomatic Cushing's disease. Completeness of resection, therefore, is essential. Typically, the first surgical attempt is the most likely to succeed; therefore, this should be done only by experienced surgeons, after extensive preoperative imaging and with a low threshold to do a wide, bilateral inspection of the sella.

Acromegaly

Adenomas in patients with acromegaly usually are larger than in Cushing's disease, with a high number demonstrating an invasive growth pattern.[11] To allow better medical treatment, partial resection of the adenoma also can be beneficial and is something the authors often consider when treating invasive adenomas. For unknown reasons, acromegaly adenomas tend to grow more in the inferior than the superior direction. Surgeons, therefore, should be aware of the possibility of small adenoma remnants in the clivus.

Prolactinoma

Surgery for prolactinomas usually is straightforward as long as the adenoma is reasonable in size[22] (**Fig. 7**, Video 3). A recent report showed that prolactinomas next to the cavernous sinus had lower remission rates than more centrally located adenomas.[23] This has not yet been replicated, however, and is not the authors' experience.

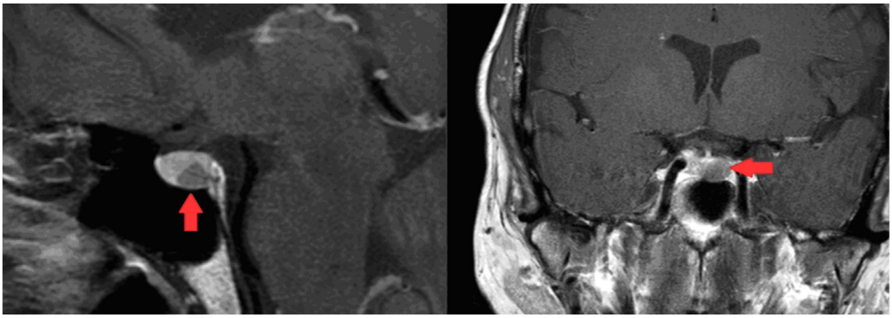

Fig. 7. A 45-year-old female patient with a microprolactinoma on the left side of the sella, treated medically for 4 years, with side effects and persistent disease. Sagittal (*left panel*) and coronal (*right panel*) MRI show location of adenoma (*red arrow*). Postoperative course was uneventful with complete recovery of symptoms, normal prolactin level, and normal pituitary function. Pathology showed a prolactin positive adenoma (growth hormone negative). For surgical video, see Video 3.

Giant Adenoma

Surgery for a giant adenoma (diameter >4 cm), is associated with a much higher risk profile compared with other pituitary adenoma operations. A feared complication is bleeding/apoplexy in tumor remnant, causing acute stretching of the optic chiasm and/or hypothalamus. Emergency surgical evacuation through a craniotomy often is required to try to reduce permanent damage. In an attempt to reduce this risk, the authors sometimes perform a combined approach,[24] through both endoscopic transsphenoidal and microscopic transcranial approach (**Fig. 8**) and/or endoscopic transventricular approach. Although the authors' experience with the combined approach is limited, they believe a combined approach in select, giant adenomas is safer than a staged combined approach or only transsphenoidal operation.

POSTOPERATIVE CARE

Careful postoperative monitoring is essential, because transient postoperative fluid disbalance occurs frequently. At day 2 after surgery, patients start rinsing the nose twice a day with saline solution, which is continued for 6 weeks. Recently, the authors introduced a short-stay protocol for preoperatively classified as low-risk patients, discharging patients 2 days after surgery under supervision of a trained pituitary case manager. Patients are screened daily to assess for potential complications. In this group, but also in the historical cohort, the reason encountered most frequently for readmission was syndrome of inappropriate antidiuretic hormone secretion (SIADH), which is present in 43% of readmissions (overall readmission rate was 17% vs 10%

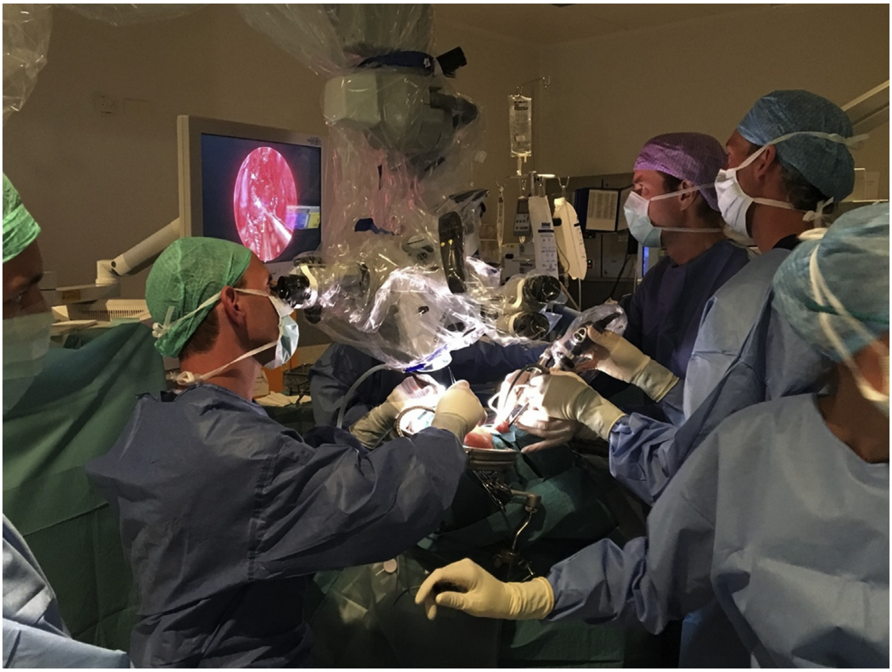

Fig. 8. Picture of setup in the OR for combined endoscopic transsphenoidal and microscopic transcranial pituitary adenoma surgery. Two surgeons perform the endoscopic transsphenoidal approach (*right*), while 1 surgeon does the microscopic cranial approach (*left*).

in the short stay and historical control group, respectively).[25] Recent studies show that a reduction of readmission can be achieved by introducing a strict postoperative fluid restriction (1–1.5 L) during the first 2 weeks after surgery.[26,27]

OUTCOMES

For the assessment of outcomes, it is important to periodically evaluate quality of care through plan-do-check-act cycles. At the authors' center, this is done through weekly case discussions with the pituitary MDT and by periodic result evaluations. The authors have published both retrospective[5,28] and prospective[29] analyses of the outcomes and are continuing prospective outcome measurements. For the periodic evaluations, 2 different approaches to address outcomes are used: the 3-tier model of value-based health care[30] and a surgical goal assessment (de Vries F, Lobatto DJ, Verstegen MJT, et al. Novel surgical outcome classification integrating efficacy and safety, as applied to functioning pituitary adenoma surgery, submitted for publication). Based on the authors' experiences with the prospective outcome measurement, they have developed a dedicated system in the electronic patient record, which enables registering and evaluating outcomes as a part of regular clinical and outpatient care. Outcomes all are registered and automatically extracted from the source. These include the more classic outcomes, such as endocrine function, remission, postoperative remnant, visual function, and so forth, but also postoperative complications as well as the innovative, patient-reported outcomes. A selection of results of a prospective cohort of 103 patients treated at the authors' center that were categorized through the 3-tier model of value-based health care are presented by Lobatto and colleagues[29]. These figures are a work in progress and will be adjusted with new data being entered in the database. Results are highly dependent on case mix (complexity of cases), as is specified in detail in the article by Lobatto and colleagues[29].

Tier 1: Health Status Achieved or Retained

Tier 1, health status achieved or retained, includes outcomes that matter most to patients and includes outcomes, such as mortality, remission, and degree of resection, and also patient-reported outcomes.[30] Mortality in pituitary adenoma surgery generally is low for pituitary adenoma surgery; however, it occasionally does occur. Degree of resection generally is high, with complete resection possible in 70% of cases. Short-term remission rates among all functioning tumors at the authors' center are 69%, with 93% of patients obtaining improvement of hormone excesses. After endoscopic surgery for Cushing's disease, 83% were in remission. Both 5-year and 10-year recurrence-free survival rates were 71% (95% CI, 55%–87%).[5] In patients with ophthalmologic manifestations, complete visual recovery was achieved among 46% and partial recovery in 52%, whereas only 1 patient (2%) did not improve after surgery.[29]

The authors found a clinically relevant self-perceived improvement on disease burden in 41% of patients, which lags behind other outcomes.[29] This indicates that although physician-reported outcomes are important, the patient-reported outcomes should complement the outcome set. It shows the impact of a pituitary tumor on the daily lives of patients for which targeted interventions could lead to greater improvement on the long term.

Tier 2: Disutility of Care or Treatment Process

Tier 2, disutility of care or treatment process, includes length of stay, return to activity, treatment-induced complaints, and complications (described later).[30] Median length of hospital stay was 3 days (interquartile range 2–5).[29] In total, short-term return to work was high (86%); however, work disability among patients with pituitary tumors is substantial.[31] Nasal disability after treatment initially is high, however, in general, returning to baseline after 6 weeks.[29]

Tier 3: Sustainability of Health

Tier 3, sustainability of health, includes the long-term effects of treatment.[30] When initial surgery does not lead to remission, the authors often explore the options of early reoperation, with extensive new imaging. The need for long-term hormone replacement for pituitary insufficiency is substantial among patients with pituitary adenomas, the majority of pituitary function loss already occurring due to the tumor and not due to the intervention. Most patients present with pituitary dysfunction preoperatively (51%), and long-term hormone replacement ultimately remains necessary in 51% of patients.[29]

COMPLICATIONS

Although complications frequently occur after pituitary tumor surgery, most complications are transient. The authors differentiate between neurosurgical complications and endocrine complications. Although neurosurgical complications potentially are more life-threatening, the incidence of major neurosurgical complications usually is very low and patients often are hampered more by the endocrine consequences of the disease/complications. A systematic review performed by the authors' group found an increased risks of complications for patients of older age as well as for those patients with larger, invasive, and previously irradiated tumors.[32]

In the authors' published series, the most common complication is transient diabetes insipidus (26.2%), followed by SIADH (12.6%). Permanent diabetes insipidus was present in 7.8% of patients. For the onset of new pituitary deficiencies, it is important to differentiate between tumor types, because larger/giant adenomas and craniopharyngiomas have a higher chance of manifesting with postoperative pituitary deficits compared with functioning tumors. As with outcomes, the complication rate is dependent on surgeon volume and experience[33] and also is based on the complexity of the condition (see also **Fig. 1**). Thanks to monitoring of the complication rates, outcomes, and baseline characteristics, the MDT now is able to better appraise surgical risks at the preoperative consultation and together with the patient decide the treatment strategy.

SUMMARY

Endoscopic transsphenoidal surgery for pituitary adenomas is a safe and highly effective first-line treatment that is well tolerated by patients. Reoperations are more complex but generally still well tolerated, but these procedures require optimal preoperative planning and intraoperative risk assessment to maximize chances of success and minimize risks. This article presents the authors' philosophy, surgical techniques, and outcomes in a high-volume pituitary adenoma center. Three surgical videos illustrate the different procedures. The authors' experience has reinforced their belief that a multidisciplinary approach, experience, and surgical volume are key to delivering high quality of care.

DISCLOSURE

The authors have nothing to disclose.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.ecl.2020.05.011.

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