SURGICAL TREATMENT OF PITUITARY ADENOMAS

John A. Jane, Jr., MD, Professor of Neurosurgery and Pediatrics, CDW Room 3530, University of Virginia Health System, PO Box 800212, Charlottesville, VA 22908-0711, johnjanejr@virginia.edu
Michael P. Catalino, MD, MSc, Chief Resident, Department of Neurosurgery, University of North Carolina, 170 Manning Drive, Campus Box 7060, Chapel Hill, NC, 27599, michael.catalino@unchealth.unc.edu
Edward R. Laws, Jr., MD, Professor of Neurosurgery, Harvard Medical School, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, elaws@partners.org

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ABSTRACT

The overwhelming majority of pituitary adenomas are benign and present either with characteristic syndromes of excess hormone secretion or secondary to mass effect by the growing tumor. The common hypersecretory syndromes include Cushing's disease, acromegaly/gigantism, and hyperprolactinemia. Local mass effects on the pituitary can cause varying degrees of hypopituitarism. As the tumor grows beyond the confines of the sella turcica, the visual pathways are commonly affected and visual field deficits are present. Effective medical therapy is available for prolactin secreting adenomas. With the exception of these tumors, transsphenoidal surgery remains the first-line treatment for most other pituitary adenomas. Medical therapy for growth hormone secreting adenomas and for Cushing's disease continues to evolve.

CLASSIFICATION

Pituitary adenomas may be classified according to their clinical/radiographic characteristics (Table 1) and, more recently, their cell lineage (Table 2). Those tumors that measure less than 10 mm in diameter are considered microadenomas; macroadenomas are those 10 mm or larger (Fig. 1A, B, C, and D). Macroadenomas may also be sub-categorized as "giant" if their extent reaches far beyond the normal confines of the pituitary region or their greatest diameter exceeds 4cm (Fig 1E, F, and G). Pituitary adenomas may also be categorized based on their functional/secretory status. The hypersecretory adenomas cause distinctive clinical syndromes that include acromegaly/gigantism caused by growth hormone (GH) secreting adenomas, the classic Forbes-Albright syndrome (amenorrhea-galactorrhea) caused by prolactin (PRL) secreting adenomas, TSH-secreting adenomas, the occasional hypersecreting FSH/LH adenoma, and Cushing's disease/Nelson's syndrome caused by corticotropin (ACTH) secreting adenomas. The non-functioning adenomas (NFAs) are "silent" and only perturb the endocrine system due to mass effects on the normal gland causing hypopituitarism (decreased pituitary hormone production) and generally present either incidentally, because of visual loss, or with secondary subtle hormonal abnormalities. The new histopathological classification considers the majority of tumors to be clinically silent gonadotropin tumors staining for SF-1. The next category is the true null cell adenoma which stains for no pituitary hormones with none of the other transcription factors or hormones being detected.

Table 1. Clinical/Radiographic Classification Schemes of Pituitary Adenomas	
Scheme	**Features**
Microadenoma/ Macroadenoma	≤ 10 mmm/ > 10 mm
Non-Functioning adenoma	Endocrinologically inactive, patient may present with pituitary deficiency or cranial nerve deficits (CN 2 most commonly)
Functioning adenoma	Excess of pituitary hormone secretion: GH adenoma; PRL adenoma; ACTH adenoma; TSH adenoma; GH -PRL adenoma; FSH/LH adenoma (rare, most are non-functioning) Other plurihormonal hypersecretory adenomas

Abbreviations: CN = cranial nerve, GH = growth hormone, PRL = prolactin, ACTH = adrenocorticotropic hormone, TSH = thyroid stimulating hormone, FSH = follicle stimulating hormone, LH = luteinizing hormone

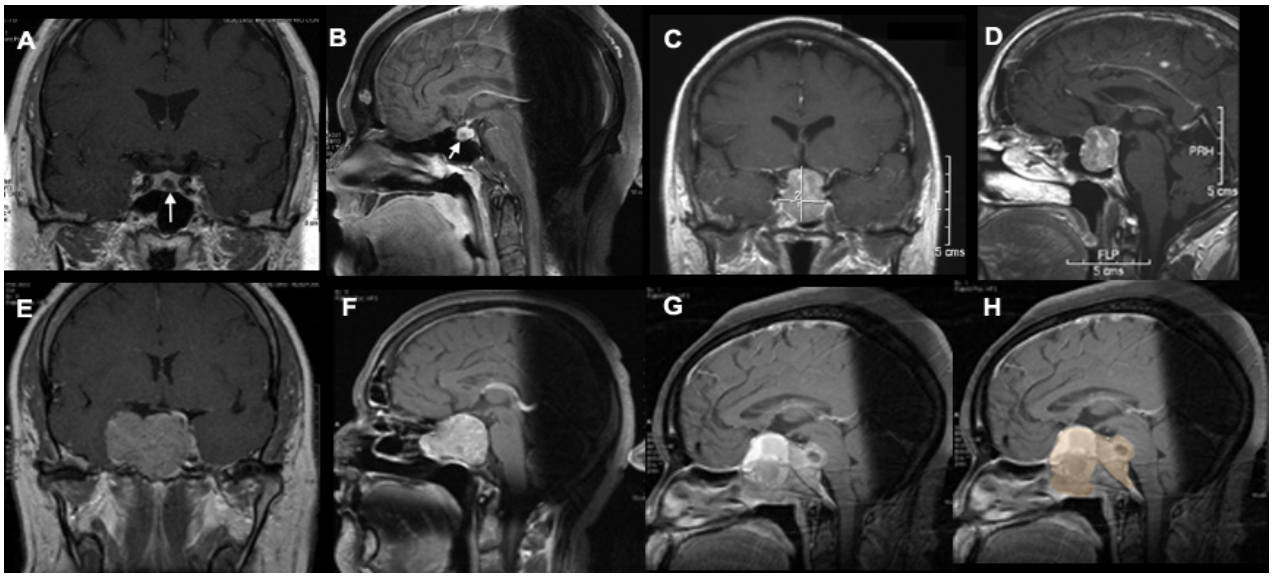

Figure 1. Tumor Classification based on size. Microadenoma: Coronal and sagittal T1 weighted MRIs with contrast with arrow indicating the location of the tumor (A and B). Macroadenoma: Coronal and sagittal T1 weighted MRIs of a typical macroadenoma (C and D). Giant invasive macroadenoma: Coronal and sagittal T1 MRIs with contrast in a patient in whom the tumor compresses the right temporal lobe and invades the sphenoid sinus (E and F). In another patient, the sagittal MRI reveals a tumor that has not only invaded the sphenoid sinus but compresses the brainstem; the tumor is highlighted (G and H).

The new cell lineage classification system of pituitary adenomas is a result of recent studies which have uncovered the shared transcription factor profiles present in adenoma cell lines (1). For detailed

information on the pathology and pathogenesis of pituitary adenomas, see the corresponding Endotext chapter. The most common transcription factor profile is PIT1, which is shared by somatotroph, lactotroph, and thyrotroph adenomas. PIT1 mediates differentiation, expansion, and survival of these three cell types (Table 2). In adenomas, evidence supports an HMGA mediated upregulation of PIT1 (2). HMGA genes are usually active during embryogenesis but not in normal adulthood (3). A new paradigm has evolved, which generally begins with transcription factor mediated monoclonal expansion of a single cell line followed by variable differentiation and retention of secretory capability. Patients harboring multiple pituitary adenomas present a unique scenario in which the true pathogenesis and pathogenetic process underlying neoplastic growth could involve distinct multicentric monoclonal expansion ("Multiple-Hit Theory") or adenoma transdifferentiation across cell lines ("Transdifferentiation Theory") (4).

Table 2. Cell Lineage Classification of Pituitary Adenomas (1)

Lineage	Cell type	Immunophenotype	Transcription factor profile
Acidophil	Somatotroph	GH ± PRL ± α-subunit	PIT1
	Lactotroph	PRL	PIT1, ER-α
	Thyrotroph	TSH-β, α-subunit	PIT1, GATA2
Corticotroph	Corticotroph	ACTH, LMWCK	TPIT
Gonadotroph	Gonadotroph	FSH-β or LH-β or α-subunit	SF1, GATA2
Unknown	Null cell	None	None

Abbreviations: GH= growth hormone, PRL= prolactin, TSH = thyroid stimulating hormone, ACTH = adrenocorticotropic hormone, LMWCK = low molecular weight cytokeratin

EPIDEMIOLOGY

Pituitary adenomas account for approximately 10 to 15% of surgically-treated primary tumors of the central nervous system (CNS) (5-9). The incidence appears higher in African Americans in whom pituitary adenomas account for over 20% of non-metastatic CNS tumors (10, 11). The incidence rate of pituitary tumors has increased from 2.5 to 3.1 per 100,000 per year (annual percentage change of 4.25%). Although the incidence varies according to age, sex, and ethnic group, between approximately 0.5 and 8.5 per 100,000 in the population are diagnosed annually with a pituitary adenoma (5, 12-14). In a large cohort study between 2004 and 2009, the largest incidence peak was 8.5 for males 75-79 years old (14). Autopsy series indicate that pituitary tumors are quite common, and that nearly 25% of the population may harbor undiagnosed adenomas (15, 16). The majority of these tumors are less than 3-5 mm in diameter and would not require medical or surgical intervention. More recent series using magnetic resonance imaging (MRI) of healthy subjects indicate that approximately 10% of the population harbors pituitary lesions. Some series report a higher rate of diagnosis among women of childbearing age, despite a similar incidence in women and men (5, 13). Because disruption of the hypothalamo-pituitary-gonadal axis in women is more evident than in men, women with pituitary adenomas may present to clinical attention at a higher rate, and earlier, than men.

Among the varying classes of adenomas, prolactinomas and non-functioning adenomas have the highest incidence, and account for nearly two-

thirds of all pituitary tumors. Prolactin-secreting adenomas comprise 40 to 60% of functioning adenomas and are the most common subtype of pituitary tumor diagnosed in adolescents (6). The majority of microadenomas occur in women in their second and third decades. Men generally present later, in their fourth and fifth decades, almost always with macroadenomas.

GH secreting adenomas represent approximately 20-30% of all functioning tumors. Nearly three quarters of GH secreting adenomas are macroadenomas. Approximately 40 to 60 individuals per million have acromegaly (17-19). Between 3 and 4 new cases per million are diagnosed annually (17-20). Most present in their 3rd to 5th decades after they have been developing symptoms and signs for many years (18). Acromegaly has been associated with an increased incidence of cardiovascular, respiratory, and cerebrovascular disease, as well as an increased risk of colon cancer. Studies have reported an increased risk of mortality compared to the unaffected population (17, 20). Although some studies report a higher incidence of several cancers, others have only confirmed an increased risk of colon cancer (21, 22). There is some evidence that mortality risk may be different between the sexes. Etxabe et al. found a higher mortality rate in men than in women (18). Other reports found similarly increased mortality in both sexes (23). Still others report increased risks of death in men from cardiovascular, respiratory, cerebrovascular, and malignant disease, but only from cerebrovascular disease in women (17).

ACTH adenomas account for 15 to 25% of all functioning adenomas and are the most common pituitary tumors diagnosed in pre-pubertal children (6). The majority of ACTH adenomas, regardless of age, are microadenomas. Approximately 39 individuals per million have Cushing's disease from an ACTH-secreting adenoma and the annual incidence is estimated at 2.4 per million (24). Cushing's disease is more common in women, most of whom present in their third and fourth decades (24, 25). There is a high incidence of hypertension and diabetes mellitus as well as higher vascular disease-related mortality (24, 26). Nelson's syndrome can develop after adrenalectomy in patients with Cushing's disease, as negative feedback is then lost to a previously unrecognized intrasellar ACTH adenoma. These patients may develop hyperpigmentation, and the ACTH-secreting pituitary tumors often become aggressive over time.

CLINICAL PRESENTATION

Advances in neuroimaging, namely CT, CT angiography and particularly magnetic resonance imaging (MRI) have improved the visualization of the pituitary region. Increasing numbers of adenomas are diagnosed incidentally during the evaluation of sinus disorders (15%), trauma (19%), and stroke (15%), among others. These "incidentalomas" are not necessarily asymptomatic. Visual deficits are present in 5-15% of cases and up to 50% when formal testing is employed (27). Some degree of pituitary dysfunction is found in up to 15-30% (27, 28). More than one third are macroadenomas and, of these, approximately 30% will show significant enlargement over time (28-31). Small asymptomatic incidental microadenomas are less likely to have clinically significant growth and often can be followed over time with repeated MRIs.

Although increasing numbers of tumors are diagnosed incidentally, pituitary adenomas more often present secondary to hypersecretion, hypopituitarism, or mass effect (Table 3).

Table 3. Presenting Features of Pituitary Adenomas

Hypersecretion GH-secreting adenoma: Acromegaly ACTH-secreting adenoma: Cushing's disease/Nelson’s syndrome Prolactin-secreting adenoma: Amenorrhea-galactorrhea TSH-secreting adenoma: Secondary hyperthyroidism
Pituitary insufficiency Symptoms: diminished libido, infertility, fatigue, weakness Gonadal dysfunction, Hypothyroidism, Adrenal Insufficiency, Somatotroph Insufficiency
Mass Effect (symptoms related to compressed adjacent structures) Optic chiasm: bitemporal visual field deficit and diminished visual acuity Cavernous sinus: trigeminal nerve, facial pain; cranial nerves III, IV, VI, diplopia, ptosis, mydriasis, anisocoria Pressure on dura or diaphragma sellae: headache Hypothalamus: behavior, eating, and vigilance disturbances (somnolence) Temporal lobe: complex partial seizures, memory and cognitive disturbances
Incidental Discovered during the evaluation for headaches, trauma, nasal sinus disorders, dizziness

Hypersecretory Syndromes

(For detailed descriptions see corresponding chapters in Endotext)

Acromegaly induces characteristic growth hormone-induced structural changes in physiognomy. There is an insidious coarsening of facial features with an enlarged forehead, enlarged tongue, malocclusion of the teeth, and prognathism (Fig 2). Patients' hands and feet also enlarge. Many patients may develop excessive sweating (hyperhidrosis). The external hypertrophy of tissue is paralleled throughout the body. Enlargement of the tongue and hands is common. Patients may suffer from enlarged organs (visceromegaly) and overgrowth of joints and cartilage, along with high blood pressure, cardiomyopathy, congestive heart failure, sleep apnea, spinal canal narrowing (facet hypertrophy), and carpal tunnel syndrome. Significant numbers of patients with acromegaly also have impaired glucose metabolism and diabetes mellitus.

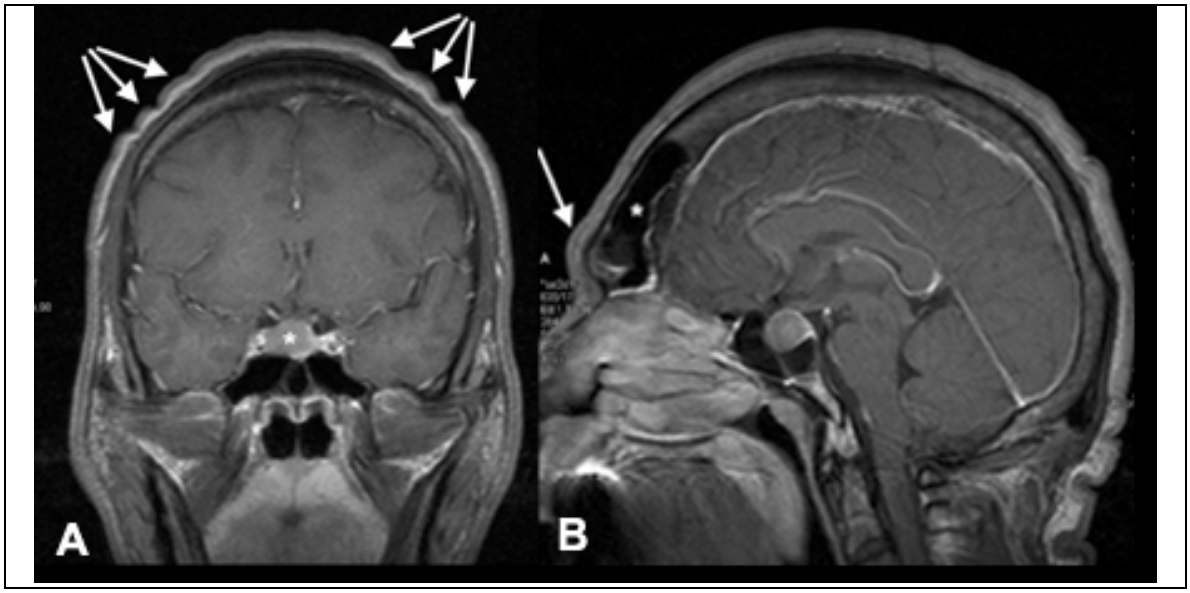

Figure 2. Acromegaly. A. Coronal T1 weighted MRI with contrast in a patient with an intrasellar GH secreting adenoma. Arrows indicate the common finding of "cutis gyrata". B. Sagittal T1 weighted MRI in the same patient with arrows indicating the frontal bossing and the enlarged frontal sinus, and * the tumor.

Cushing's disease causes changes in body habitus with characteristic increased weight gain, truncal obesity, "buffalo hump", enlargement of supraclavicular fat pads and moon facies. Skin changes are also common and include purple striae, easy bruisability, ruddy complexion, and increased body and facial hair. Patients suffer from fatigue, proximal muscle weakness, osteoporosis, psychological/psychiatric disorders, high blood pressure, and impaired glucose metabolism. They often have headache, menstrual disorders, and cognitive and emotional dysfunction.

Women with prolactinomas classically present with amenorrhea or oligomenorrhea and galactorrhea. Most are in their childbearing years, and are more likely to pursue medical attention for infertility and menstrual irregularity. Men, and women beyond their reproductive years, more often have headache, visual symptoms, sexual dysfunction, and signs of decreased pituitary function. Amenorrhea and galactorrhea are not specific to prolactinomas, however. Prolactin secretion is under constant inhibitory control from the hypothalamus. Any lesion that imposes pressure upon the portal venous connection of the pituitary stalk (infundibulum) connecting the hypothalamus and pituitary gland can interrupt these inhibitory dopaminergic signals. This, in turn, causes an increase in serum prolactin levels, and mimics a prolactinoma, i.e., a 'pseudo-prolactinoma'. In such cases serum prolactin levels are usually only moderately elevated. As a general rule, serum prolactin levels over 200 ng/ml (3600mU/L) are indicative of prolactinomas (32).

Hypopituitarism

Tumor growth impairs the normal secretory function of the anterior pituitary and causes hypopituitarism. Common complaints include diminished sex drive, fatigue, weakness, and hypothyroidism. Pituitary insufficiency generally develops slowly over time.

However, acute pituitary insufficiency may occur in the setting of pituitary apoplexy, a condition in which the tumor infarcts or has internal bleeding (Fig 3). Pituitary tumor apoplexy can be particularly devastating, because it combines acute hypopituitarism and adrenal insufficiency with a rapidly expanding intracranial mass, and often causes visual loss or even sudden blindness.

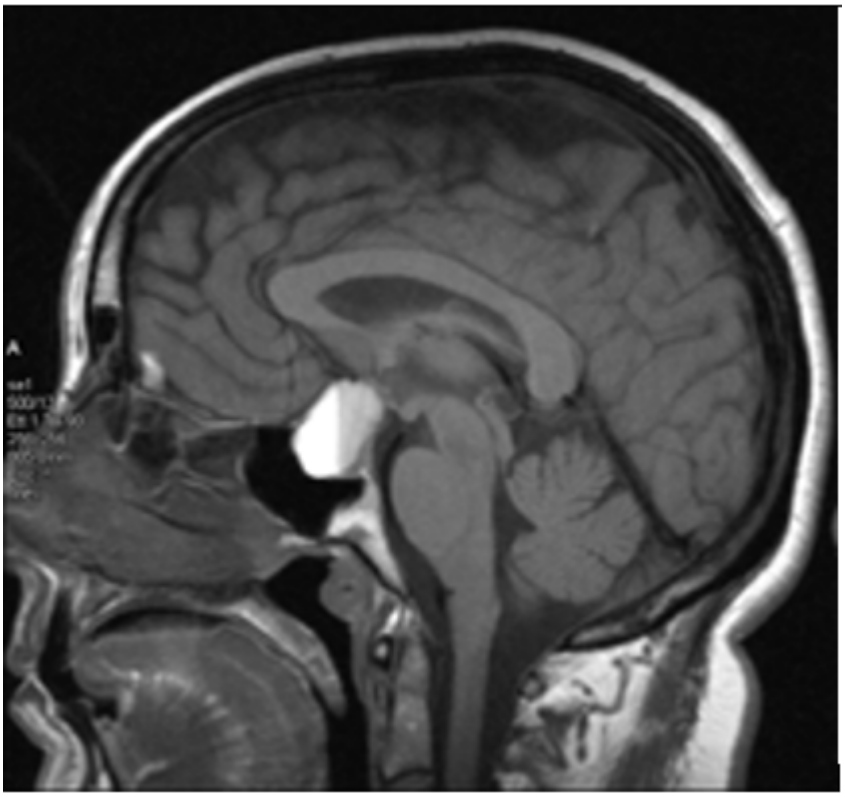

Figure 3. Pituitary tumor apoplexy. Sagittal T1 weighted MRI without contrast in a patient presenting with pituitary tumor apoplexy. Note the fluid-fluid level within the tumor indicative of the apoplectic tumor.

Neurological Dysfunction

Neurologic signs and symptoms develop as adenomas grow beyond the confines of the sella turcica and exert pressure upon adjacent brain structures. As tumors enlarge, they compress the optic nerves and optic chiasm, and patients experience visual deficits and diminished visual acuity. Classically this causes a bitemporal hemianopia, i.e., visual loss in the temporal fields of each eye. Tumor growth may also affect other nerves (such as the 3rd, 4th, 5th, or 6th cranial nerves) and cause facial pain and/or double vision or drooping of the eyelid. Headache, although a non-specific complaint, can occur when a tumor stretches the dural sac that surrounds the pituitary gland. Headache from pituitary lesions is usually frontal or retro-orbital – it may be bitemporal or radiate to the occipito-cervical region. Many patients will have been previously diagnosed with “migraine”, or “tension-headache” (33).

DIAGNOSIS

A panel of endocrinological tests can often confirm the clinical diagnosis of pituitary adenoma. Serum GH and IGF-1 levels screen for acromegaly. Failure

to suppress GH levels after an oral glucose load (oral glucose tolerance test (OGTT)) can further confirm the diagnosis. Although any macroadenoma may cause moderate increases in serum PRL, levels greater than 200 ng/ml (3600 mU/L) are highly suggestive of a prolactin secreting adenoma. Dilution of the samples for assay may be necessary to avoid the "hook effect" related to macroprolactinemia.

Endocrinologic studies that suggest Cushing's disease includes an elevated ACTH and late night salivary or elevated 24-hour urine free cortisol (UFC), loss of the normal diurnal variation in cortisol levels, and suppression of serum cortisol levels after high dose dexamethasone but failure to suppress after low dose dexamethasone. Inferior petrosal vein sampling after corticotropin-releasing hormone (CRH) stimulation (i.e., Inferior Petrosal Sinus Sampling; IPSS) may be required to confirm and localize the pituitary source. At times, prior to diagnosing Cushing's disease, other ectopic sources of excess ACTH, such as bronchogenic or pancreatic carcinoma and pulmonary carcinoid tumors, must be excluded. This can often be accomplished with a CT scan or MRI of the chest and abdomen and with novel nuclear imaging tests (34, 35). Obesity, alcoholism, and depression also elevate serum cortisol levels, and the diagnosis of Cushing's disease should be made with caution in these "pseudo-Cushing's" settings (36).

TREATMENT

Although some incidentally-discovered microadenomas that do not cause symptoms may be followed clinically and with repeated MRI, patients with macroadenomas generally need medical or surgical intervention. Therapeutic goals include improved quality of life and survival; elimination of mass effect and reversal of related signs and symptoms, normalization of hormonal hypersecretion; preservation or recovery of normal pituitary function, and prevention of recurrence of the pituitary tumor.

MEDICAL THERAPY

Medical therapy is available for most hypersecretory tumors (37-40). The majority of prolactin-secreting adenomas are effectively treated with dopamine agonists (bromocriptine and cabergoline). Cabergoline is generally preferred as a result of a better side-effect profile, and between 80-90% of patients can achieve hormonal control (37). Surgical intervention is ordinarily reserved for those who are intolerant of medical therapy because of multiple side effects (e.g., nausea, headache, impulsive or compulsive behavior), whose prolactin levels remain elevated, or whose tumors continue to grow despite maximal medical treatment.

Medical treatment using somatostatin analogues (octreotide, lanreotide, and pasireotide) and dopamine agonists (cabergoline) have varying degrees of efficacy for treating GH adenomas. The growth hormone receptor antagonist, pegvisamont, can be used in combination with other agents (41-43), and hormonal control can generally be achieved in about 60-90% of patients (37). Although medical therapy is most often reserved for those patients' awaiting surgery or those with persistent disease postoperatively, some advocate primary medical therapy, particularly for invasive tumors (44, 45). There is some conflicting evidence that pre-surgical medical therapy may improve surgical outcome (46).

Ketoconazole and/or metyrapone therapy can normalize serum cortisol levels in patients with Cushing's disease preoperatively 50-75% of the time. Metyrapone and ketoconazole inhibit enzymes in the adrenal gland required for steroid synthesis. A new and safer formulation, levoketoconazole is now available. Along with acromegaly, surgery remains the first-line therapy for ACTH secreting tumors and Cushing disease. Clinical trials have also demonstrated some role for medical therapy with cabergoline or pasireotide, and with mifepristone

(cortisol receptor blocker) in selected cases (47, 48).A new agent, osilodrostat, is under development.

The disadvantage of medical treatment of hypersecretory syndromes is that it is usually suppressive in nature and not fully cytotoxic. Tumors often recur when medications are discontinued, or they become resistant to therapy. Potential new targets are being explored, but have not yet reached clinical practice (49-51).

RADIATION THERAPY

Radiotherapy is most often employed in conjunction with medical or surgical therapy. Fractionated external beam radiation therapy can reduce excessive hormone production and can reduce the incidence of tumor recurrence (52); however, it can be replaced by stereotactic radiotherapy with focal conformal fractionated delivery. Gamma knife, Cyberknife, proton beam or linear accelerator stereotactic radiosurgery is increasingly considered as adjunctive therapy for pituitary tumors, and can be effective in normalizing hormonal hypersecretion and preventing recurrence (53-55). Whether by fractionated external beam or radiosurgery, the effects of radiotherapy are delayed. Patients require continued suppressive medical therapy during the period between treatment and effect. There is also a significant incidence of radiation-induced delayed hypopituitarism (52). There is no evidence to date that one of these various modalities is superior to another in efficacy, risks of complications, recurrence rates, or incidence of hypopituitarism. For more information on radiotherapy for pituitary tumors, see the corresponding chapter in Endotext.

SURGERY

Indications for Surgery

For most pituitary tumors, surgery remains the first-line treatment of symptomatic pituitary adenomas. Large or invasive asymptomatic tumors may also warrant surgical consideration. It is sometime possible to estimate a tumor's invasiveness on an MRI using the Knosp grading system (56). Asymptomatic tumors with evidence of radiographic invasion or displacement of the optic apparatus may benefit from surgery to prevent neurological deficits and progressive pituitary dysfunction. Surgery is also chosen secondarily when medical treatment fails for the treatment of prolactinoma. Regardless of the tumor type, surgery provides prompt relief from excess hormone secretion and mass effect. There is evidence to suggest that debulking of medically refractory prolactinomas and GH adenomas can return these tumors to a responsive state (57, 58). Rarely is surgery recommended as first line therapy for prolactinomas (59). Surgery may be indicated in pituitary apoplexy with acute vision loss $\leq$ 72 hours as a result of mass effect on the optic chiasm from hematoma formation. Studies have shown that some patients with pituitary apoplexy can be successfully treated without operative intervention, but they are often confounded by selection bias, and the ideal patient has not been conclusively established for operative versus non-operative treatment (60-62).

Peri-Operative Management

A major component of the surgical management of patients with pituitary tumors actually occurs in the peri-operative period. Detailed information on peri-operative management of pituitary tumors can be found elsewhere (63). Briefly, pre-operative planning is very important in order to avoid complications and achieve optimal outcomes. It is obligatory to note any prior nasal surgery, review prior imaging, and obtain adequate pre-operative imaging for integration with neuronavigational systems. Typically, a high resolution T1 post contrast MRI is adequate for neuronavigational registration. The authors advocate additional imaging that includes (1) coronal and

sagittal T1-weighted pre and post contrast images with at least 3mm slice thickness through the parasellar region for identification of the tumor, pituitary gland/stalk, cavernous sinus, and vasculature, (2) axial T2-weighted images of the sella to measure intercarotid distance, and (3) a coronal and sagittal strong T2-weighted Constructive Interface in Steady State (i.e., CISS, also known as FIESTA) through the parasellar region to identify midline structures and the optic chiasm. For revision surgery, a CT scan of the sinuses can be helpful to identify abnormal osseous anatomy. The imaging should be reviewed to identify normal gland and pituitary stalk, look for cavernous sinus invasion, identify arachnoid diverticula, and verify anatomical landmarks. Finally, it is critical to assess pre-operative pituitary function and replete necessary hormones (especially cortisol and thyroid hormones) prior to surgery. Remember to replete cortisol before thyroid hormone to avoid precipitating an adrenal crisis. For more information on the evaluation and management of pituitary hormone deficiency, see corresponding chapters in *Endotext*.

Post-operative management varies from routine to very complicated depending on the lesion size and extent of the operation and post-operative pituitary function. Patients with complete removal of intrasellar non-functioning tumors and intraoperative preservation of the normal pituitary gland without a cerebrospinal fluid (CSF) leak can have a relatively benign post-operative course. It is important to monitor closely for diabetes insipidus (DI), check a fasting morning cortisol to rule out secondary adrenal insufficiency, and restrict fluids as appropriate to prevent the syndrome of inappropriate anti-diuretic hormone (SIADH) (64). Patients with larger suprasellar or invasive tumors and/or those with CSF leaks requiring more extensive skull base reconstructions may require ICU care (65, 66). For information on the management of endocrine dysfunction and post-operative care in Cushing's disease and Acromegaly, please see the corresponding chapters in *Endotext*.

Surgical Technique

The minimally invasive transsphenoidal approach can be used effectively for 95% of pituitary tumors. Exceptions are those large tumors with significant temporal or anterior cranial fossa extension. In such circumstances, transcranial approaches are often more appropriate. Occasionally, combined transsphenoidal and transcranial approaches are used. Nevertheless, some surgeons extend the basic transsphenoidal exposure in order to remove some of these tumors and avoid a craniotomy (Fig. 4) (67-70).

The transsphenoidal approach is a versatile method for treating pituitary tumors (Table 4). Endoscopic approaches may be used in isolation or as an adjunct to the other transsphenoidal approaches (Fig. 4) (71-78). Computer-guided neuronavigational techniques are nearly ubiquitous at major pituitary centers in lieu of traditional fluoroscopic guidance (79, 80). The role of neuronavigation is most pertinent in recurrent adenomas in which the midline anatomy has been distorted by previous transsphenoidal surgery. Intraoperative MRI is increasingly available and appears to be most applicable for large tumors (81). There are three basic variations of the transsphenoidal approach.

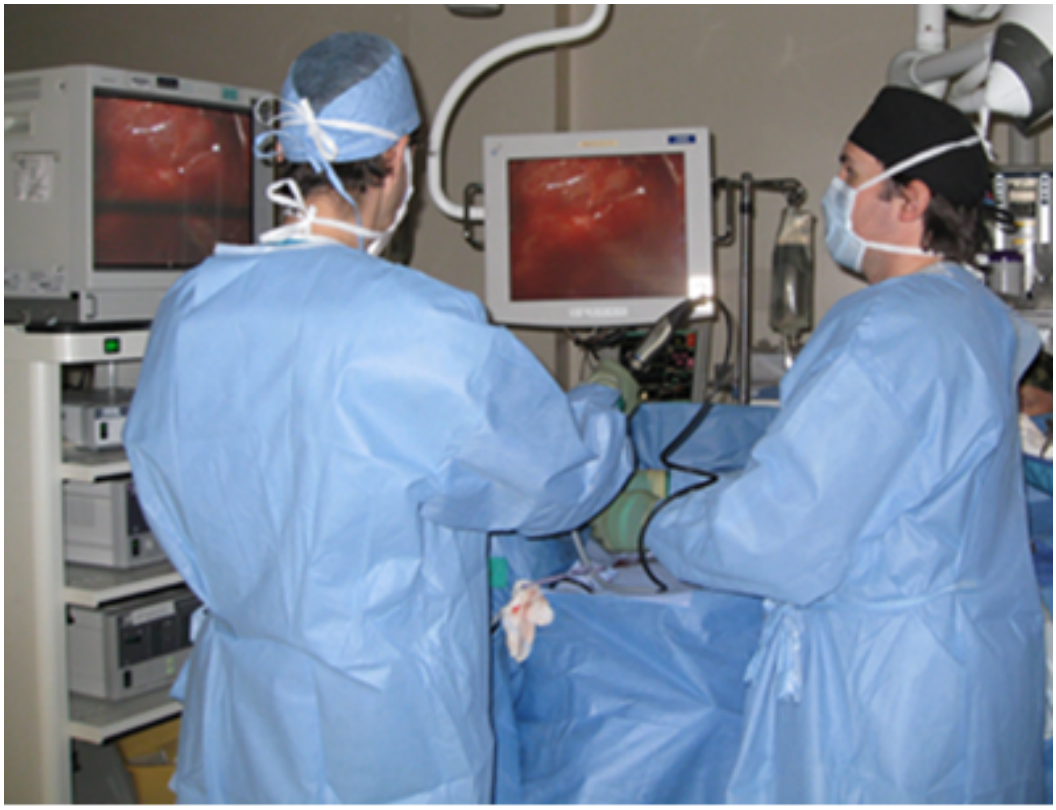

Figure 4. Endoscopic approach. Intra-operative photograph of one surgeon (left) driving the endoscope while the main surgeon (right) resects the tumor.

Table 4. Transsphenoidal Surgery for Pituitary Adenomas: Personal Summary of 3744 Cases over a 36 year period	
Type of Adenoma	**Number of Patients (%)**
Functioning adenomas	
GH adenoma (Acromegaly)	662 (17.7)
PRL adenoma	975 (26.0)
ACTH adenoma (Cushing's disease)	680 (18.2)
TSH adenoma	45 (1.2)
Non-functioning adenomas	1382 (36.9)

SUBMUCOSAL TRANSSEPTAL APPROACH

The patient is placed in a lawn-chair position and a hemi-transfixion incision is made just inside the nostril so that the scar cannot be seen after surgery (Fig. 5). Most often the entire procedure can be accomplished endonasally. Conversion to a sublabial approach may be necessary for large macroadenomas and children in whom the exposure through one nostril is sometimes inadequate. A submucosal plane is developed along the nasal septum back to the level of the sphenoid sinus. Bone of the septum can be harvested for use later in the operation. The bone in front of the pituitary gland is also removed, the dura opened, and tumor is extracted in fragments (Fig. 6). Afterwards the saved bone, cartilage, or artificial material can be used to refashion the normal housing of the pituitary gland. Closure is rapid and consists of several interrupted absorbable sutures in the nasal mucosa and temporary nasal packing to promote healing of the mucosa.

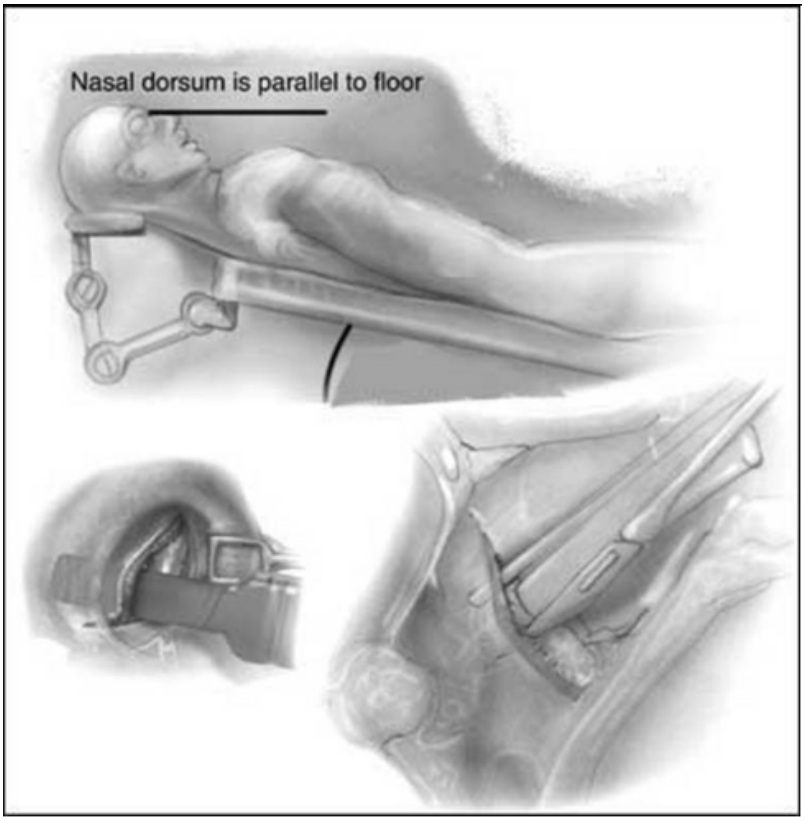

Figure 5. Standard positioning for the endonasal approach (above). Below left, endonasal hemitransfixion incision; below right, direct sphenoidotomy technique.

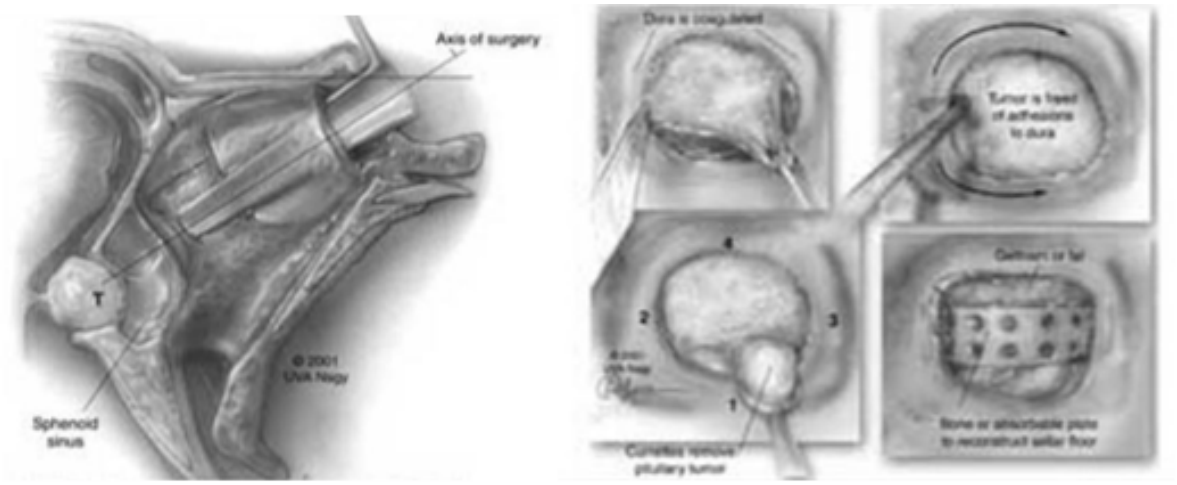

Figure 6. Left, standard endonasal approach showing the trajectory to sella in sagittal view; Right, sequential steps used in tumor removal and repair of the sellar floor common to all techniques.

SEPTAL PUSHOVER/DIRECT SPHENOIDOTOMY

This approach uses incisions deeper within the nasal cavity (Fig 6, lower right. The incision for the septal pushover technique is made at the junction of the cartilaginous and bony septum. Submucosal tunnels are developed on either side of the bony septum until the sphenoid sinus is reached. Another option to reach the sphenoid sinus is by performing a direct sphenoidotomy. Using this method, no incision is made in the septum. Instead, the posterior part of septum just in front of the sphenoid sinus is deflected laterally and the sphenoid sinus is entered directly. There are several advantages to these techniques. Because there is no submucosal dissection of the cartilaginous septum, the risk of an anterior nasal septal perforation is eliminated. In addition, there is less need for nasal packing postoperatively, a frequent cause of postoperative pain and discomfort. The main drawback of these more direct approaches is that the exposure is not as wide as can be achieved by the standard endonasal transseptal approach in which the cartilaginous septum can be more extensively mobilized.

PURE ENDOSCOPIC APPROACH

The pure endoscopic approach has much appeal and is becoming the procedure of choice at many pituitary centers (82, 83). Surgery begins at the sphenoid rostrum where a direct anterior sphenoidotomy is performed after identifying the natural sphenoid os within the sphenoidoethmoidal recess. Some surgeons prefer to perform the surgery using a single nostril. A binostril approach, however, provides more maneuverability and two-handed microdissection. To achieve an adequate exposure for the binostril approach, the middle and superior turbinates are lateralized and the bony septum just in front of the sphenoid sinus is removed. The sphenoidotomy is widened from the midline inferior vomer to the ethmoid air cells superiorly and then laterally until the carotid arteries are easily visualized (Fig 7-A). This allows instruments to be used in both nostrils simultaneously. Although a specialized endoscope holder may be used during tumor removal, the “3-hand” technique is advocated by many surgeons. The “3-hand” or “4-hand” technique requires two surgeons; one surgeon maneuvers the endoscope while another has both hands free to remove the tumor using microsurgical techniques. The surgical

team is typically a neurosurgeon and otolaryngologist with experience in skull base surgery. Extended approaches are more commonly performed by teams rather than individuals (80, 84). The endoscope provides panoramic magnified views of the sellar anatomy during both the approach to and resection of tumors (Fig 7 – A, B). The option of using angled endoscopes allows surgeons to inspect for residual tumor, particularly along the cavernous sinus walls and the suprasellar region (85) (Fig 7 – C, D). No nasal packing is required as the procedure is performed posterior to the septum. The main disadvantages are the procedure's learning curve and that the depth of field may problematic for some surgeons. There are 3D endoscopes and continued development of High Defintion (HD) imaging that may help to alleviate this potential problem. A recent international survey showed that about 7% of surgeons report using the 3D endoscope for transsphenoidal surgery. Advances in patient specific anatomical modeling is increasingly available for integration with the neuronavigation in the form of "augmented reality" which helps the surgeon visualize otherwise hidden anatomical structures (86). Finally, given the importance of vision preservation during endonasal surgery, especially with extended approaches, new developments in visual evoked potential monitoring are being studied (87). The clinical benefit of these new technologies is promising but still uncertain.

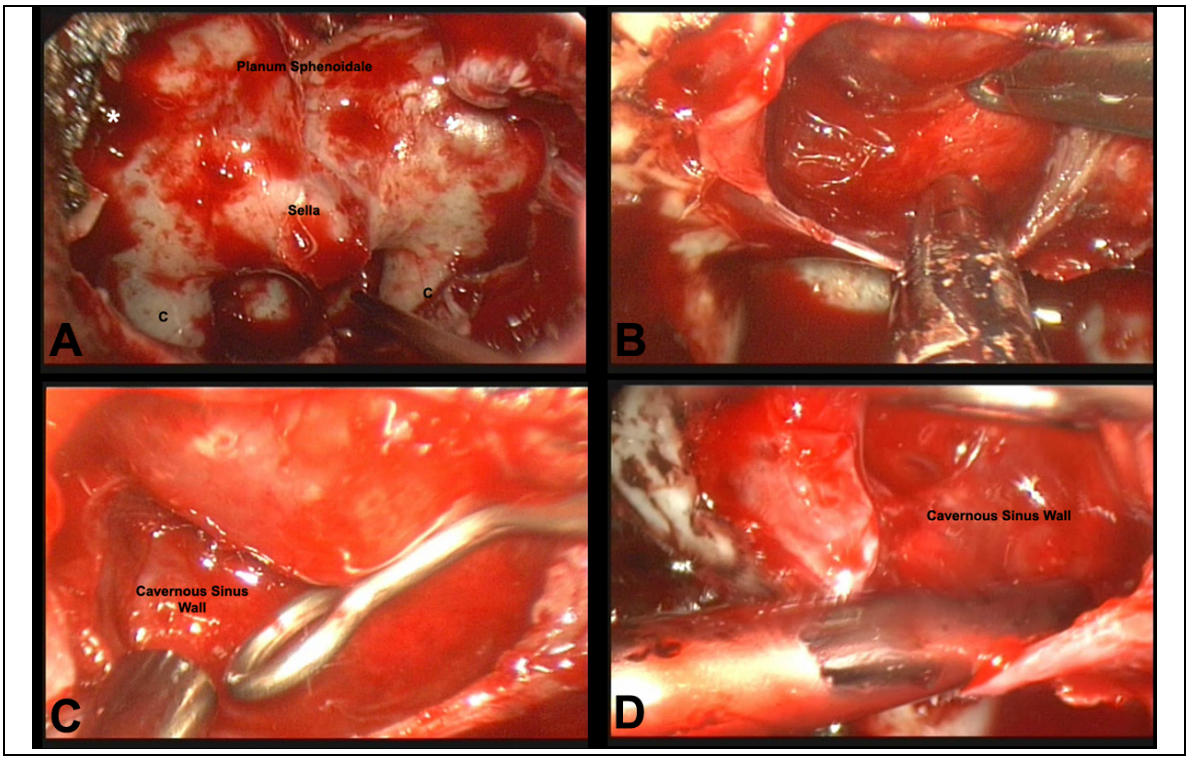

Figure 7. Endoscopic views. A. After the anterior wall of the sphenoid sinus is opened, the endoscope provides a panoramic view of the sella and surrounding anatomy. B. Endoscopic view of the tumor bed after resection. C. Endoscopic view of the right cavernous sinus wall using the 0 degree endoscope. D. Note the dramatically improved view of the right cavernous sinus wall in the same patient using the 45 degree endoscope. (arrowhead= carotid artery)

Outcome

Surgical outcomes after surgery for pituitary adenomas can be divided into functional outcomes and oncologic outcomes. Functional goals include the relief of symptoms and improvement or preservation of pituitary and visual function, along with improved quality of life (88-90). Visual deficits in patients with non-functioning pituitary adenomas are improved in approximately 80-90%. Some visual deterioration may occur in 0-4%. Most patients with intact pituitary function preoperatively retain their normal function. Those with preoperative pituitary deficiency regain function in 27% of the cases. The remaining patients are managed with hormone replacement therapy. Oncologic outcomes relate to tumor resection, recurrence, and biochemical remission from hormonal excess. Ten-year recurrence rates are approximately 16%, although only 6% require additional treatment (Table 5). On long-term follow-up, 83% of patients are alive and well without evidence of disease.

Table 5. Results of Transsphenoidal Surgery, Personal Summary of 3093 Cases over a 28 year period. Proportions (%) represent cumulative incidence.

Tumor	Remission	10-year Recurrence
Non-functioning adenoma	Not applicable*	16%
GH adenoma		
Microadenoma	88%	1.3%
Macroadenoma	65%	
PRL adenoma		
Microadenoma	87%	13%
Macroadenoma	56%	
ACTH adenoma		
Microadenoma	91%	12% (Adults)
Macroadenoma	65%	42% (Pediatric)
*Visual improvement occurs in 87% of those with preoperative visual loss.		

Currently, using strict criteria for remission and in expert hands, transsphenoidal surgery obtains remission in 85-90% of patients with acromegaly with microadenomas and 65% of those harboring macroadenomas. For functional tumors, remission rates vary by tumor size and tumor type (91). Microadenomas typically have higher biochemical remission rates and remission rates are highest for microprolactinomas (92.3%) and lowest for somatotroph macroadenomas (40%). Currently, acromegalic symptoms are improved in 95% and recurrence is less than 2 percent at ten years. Ninety seven percent of patients have preserved normal pituitary function (92). Modern criteria for remission include normal IGF-1 levels and either GH suppression to less than 0.4 ng/ml with oral glucose tolerance test or fasting GH less than 1.0 ng/ml. Using these criteria, surgical biochemical remission is over 60% (93). Both repeat surgery and medical therapy are options for those with residual disease and/or biochemical recurrence (37, 94).

Patients with prolactinomas who present for surgery are most often those who have failed medical management. Endonasal surgery for prolactinomas is associated with additional risks resulting from tumor fibrosis after dopamine agonist therapy but remission rates are still quite good. Prolactin levels are normalized in about 87% of microadenomas and 56% of macroadenomas (Table 5). The recurrence rate among those patients who are normalized after a transsphenoidal operation is 13% at ten years. Preserved pituitary function occurs in all but 3%.

Surgical management of Cushing's disease achieves a 91% remission rate for microadenomas, but falls to 65% for those with macroadenomas. Some 10-20% of adults experience recurrence after ten years. Postoperative stereotactic radiosurgery has achieved remission in approximately 60-70% of patients whose disease either did not remit following surgery or recurred (95).

Pituitary surgeons, with all health care professionals, strive for excellence in the care of our patients, it is becoming clear that criteria must be developed in order optimize surgical outcomes. Recently, a consensus statement on Pituitary Tumor Centers of Excellence (PTCOE) was released (96). In brief, PTCOE should be independent non-for-profit organizations, widely recognized by endocrinologist and pituitary surgeons, aimed at the advancement of pituitary science and the highest quality of patient care. They should also be recognized by external societies and act as resident training centers.

Complications of Transsphenoidal Surgery

Complication avoidance is central to transsphenoidal surgery given the close proximity of major neurologic and vascular structures (97, 98). Recently, surgical checklists for endonasal transsphenoidal surgery have been developed in order to optimize surgical outcomes and avoid complications (99). The overall mortality rate for transsphenoidal surgery is less than 0.5% (Table 6). Major morbidity (cerebrospinal fluid leak, meningitis, stroke, intracranial hemorrhage, and visual loss) occurs in between 1 and 3% of cases. Less serious complications (sinus disease, nasal septal perforations, and wound issues) occur in approximately 1-7%. Larger invasive tumors and giant adenomas are associated with a higher morbidity. In the modern era, more aggressive extended approaches to large invasive tumors has led to a higher incidence of CSF leak, but the use of the pedicled nasoseptal flap has been largely successful in preventing recurrent leaks with a success rate of up to 98.6% (100). The nasoseptal flap can also be used again in certain revision cases with good results (101).

Table 6. Complications of Transsphenoidal Surgery (1972-2017). Personal historical series and a modern results covering a 45 year period and 4,246 cases.

Outcome Measure	**Cumulative Incidence (%)**	
	1972-2000	1992-2017 (102)
Mortality	<0.5%	<0.3%
Major complication: (CSF leak, meningitis, ischemic stroke, intracranial hemorrhage, vascular injury, visual loss)	1.5%	CSF leak 2.6% Other 3.2%
Minor complication: (sinus disease, septal perforations, epistaxis, wound	6.5%	1.3%

Table 6. Complications of Transsphenoidal Surgery (1972-2017). Personal historical series and a modern results covering a 45 year period and 4,246 cases.		
Outcome Measure	**Cumulative Incidence (%)**	
	1972-2000	1992-2017 (102)
infections and hematomas)		

CONCLUSIONS

Pituitary adenomas are a complex set of benign tumors that present with characteristic hypersecretory syndromes and mass effect. Although medical and radiotherapy offer effective treatment for particular functional tumors in specific situations, transsphenoidal surgery continues to provide optimal outcomes for non-prolactin secreting adenomas with a low incidence of major morbidity.

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