Functional and Nonfunctional Pituitary Adenomas

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Ankush Chandra and Manish K. Aghi

4.1 Introduction

Pituitary adenomas are slow-growing, benign, monoclonal tumors that arise from the cells of the pituitary gland. Due to their low rate of recurrence and rare transformation to higher-grade tumors, pituitary adenomas are classified as WHO (World Health Organization) grade I tumors [1]. While pituitary adenomas were once considered a rare occurrence, recent studies have shown that their prevalence is much higher due to the advent of better diagnostic methods and increased utilization of imaging techniques. Pituitary adenomas account for 15–18% of all intracranial tumors and are the third most common primary brain tumor, following meningiomas and gliomas [2–6]. They are divided into two categories, namely, functional pituitary adenomas (FPAs) and nonfunctional pituitary adenomas (NFPAs).

4.2 Rationale

In general, the rationale for treatment of pituitary adenomas is alleviation of presenting symptoms and prevention of future symptoms. FPAs typically present with hypersecretion of one or more hormones of the pituitary gland detectable in the serum, leading to clinical syndromes whose symptoms are summarized in detail in Table 4.1. NFPAs are endocrine-inactive tumors and can be incidental findings on radiologic exams or can present with symptoms of mass effect (Table 4.1, Fig. 4.1) [23–26]. Due to physiologic effects of FPAs, they typically present at smaller sizes than NFPAs [26]. When treatment is indicated for symptomatic adenomas or incidentally found adenomas large enough to warrant preemptive treatment, surgical resection is the first-line treatment for most pituitary adenomas.

A. Chandra · M. K. Aghi (✉)
Department of Neurological Surgery, University of California San Francisco, CA, USA
e-mail: Manish.aghi@ucsf.edu

4.3 Patient Selection

Appropriate patient selection requires a complete diagnostic workup. If a pituitary adenoma is clinically suspected, radiological investigation should be performed. *Magnetic resonance imaging* (MRI) is the **gold standard** for imaging most sellar tumors (Fig. 4.2) [7, 27]. It is important to note that imaging is not only important for confirming a pituitary mass but also to differentially diagnose other sellar and extrasellar masses such as craniopharyngioma, Rathke's cleft cyst, pituitary abscess, epidermoid cyst, chordoma, meningioma, metastatic tumor, aneurysm, lymphocytic hypophysitis, arachnoid cyst, mucocele, lymphoma, or sarcoidosis [7].

In parallel, appropriate laboratory biochemical tests should be done. Routine endocrine evaluation of all anterior pituitary axes to assess for hypopituitarism is recommended because, beyond revealing a significant rate of deficits surpassing the level of clinical suspicion for all pituitary axes, the cutoff values to initiate thyroid and adrenal replacement might be different in a patient with panhypopituitarism versus isolated deficiencies [7, 28]. Such evaluation will also distinguish NFPAs from specific types of FPAs [7, 28]. Different pathologies associated with pituitary adenomas are summarized in Table 4.2.

Prolactinomas

According to the guidelines set by the Pituitary Society and the Endocrine Society, the diagnosis of prolactinoma requires both biochemical and radiographic evidences. A single measurement of serum prolactin is recommended. If serum prolactin levels are above 200 μg/L, a prolactinoma is almost certainly the underlying cause [8, 11, 12, 36]. However, if the serum prolactin levels are present between the upper limit of normal prolactin levels and 200 μg/L in a patient with imaging suggestive of pituitary adenoma, then stalk effect from a nonfunctional adenoma is a possible diagnosis rather than prolactinoma. Since prolactinomas are very responsive to

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Table 4.1 Symptoms associated with different types of pituitary adenomas. Shown are symptoms associated with different types of functional and nonfunctional pituitary adenomas

Type of pituitary adenoma	Associated symptoms
Prolactinoma	*High prolactin*: Amenorrhea (females), hypogonadism, chronic kidney disease, galactorrhea, infertility, osteoporosis, hirsutism [7] *Macroadenoma (mass effect)*: Headaches, visual impairments, and hypopituitarism [7, 8]
NFPA	*Symptoms of mass effect*: Chronic headache, visual impairments, and pituitary insufficiency [9, 10]
Somatotroph adenoma (acromegaly)	*Classical presentation*: Acral and soft tissue overgrowth, bony overgrowth, coarse facial appearance, skin thickening, macrognathia, enlarged hands and feet [11–14] *Uncontrolled acromegaly*: Carpel tunnel syndrome, metabolic dysregulation (diabetes mellitus, dyslipidemia, and insulin resistance), cardiovascular disorders (hypertension, cardiac hypertrophy, cardiac myopathy, and arrhythmias), and increased risk of colon polyps, colon cancer, and other tumors [12–18] *Macroadenomas (mass effect)*: Disordered sleep, hypopituitarism, headaches, and visual disturbances [13, 15, 16, 19, 20]
Corticotroph adenoma (Cushing's disease)	*Characteristic symptoms*: Central obesity, moon face, facial plethora, diabetes mellitus, hirsutism, easy bruising, proximal myopathy, and purple striae [21, 22] *Other symptoms*: Metabolic, neuropsychological, musculoskeletal, cardiovascular, dermatological, hormonal, and immunological abnormalities [21]

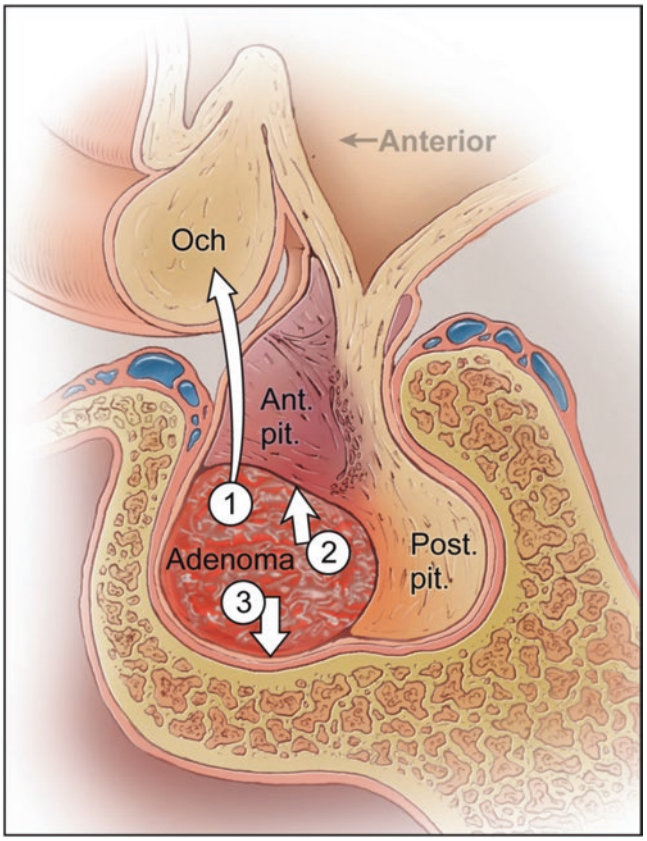

Fig. 4.1 Symptoms of mass effect from pituitary adenomas. These symptoms (headache, visual, or endocrine dysfunction) are classic symptoms of NFPAs and FPAs, with FPAs also having symptoms of hormonal hypersecretion that often predominate over these mass effect symptoms

medical treatment, surgery is reserved for those prolactinomas that have a definitive surgical indication (acute hemorrhage, cystic components, or resistance to or intolerance of dopamine agonists) or for patients who make an informed choice to pursue surgery after seeing both an endocrinologist to discuss medical therapy and a neurosurgeon with extensive experience with pituitary tumor surgery. Figures 4.3b and 4.4a, b show the histology of prolactinomas.

Acromegaly

According to the clinical practice guidelines set by the Endocrine Society, once the physician identifies clinical features of acromegaly, biochemical screening should be performed for confirmed diagnosis [13, 37]. Serum IGF-1, the preferred screening tool over random GH level, is measured and matched to age and sex of the patient [11, 13]. If IGF-1 levels are discordant with normal range, an oral glucose tolerance test (OGTT) with 75 g of glucose is performed: a lack of fall of serum GH levels below 1 ug/L within 2 h would confirm acromegaly [13, 15, 38]. First-line therapy for acromegaly is transsphenoidal surgery (details of which are described below) [13, 37]. In cases where there is residual tumor following surgery, repeat surgery should be performed to achieve full resection if the residual mass is surgically accessible [13]. If residual tumor is not surgically accessible, radiation therapy or radiosurgery, or medical therapy with somatostatin analogues or the GH receptor antagonist, pegvisomant, should be implemented. Figures 4.3a and 4.5a, b show the histology of these tumors.

Cushing's Disease

The Endocrine Society recommends exclusion of exogenous glucocorticoid use prior to performing any laboratory test to evaluate for suspected Cushing's disease [39, 40]. For initial diagnosis, one of the four tests should be used for patients with low index of suspicion, and two tests should be done for patients with high index of suspicion: (1) urine free cortisol

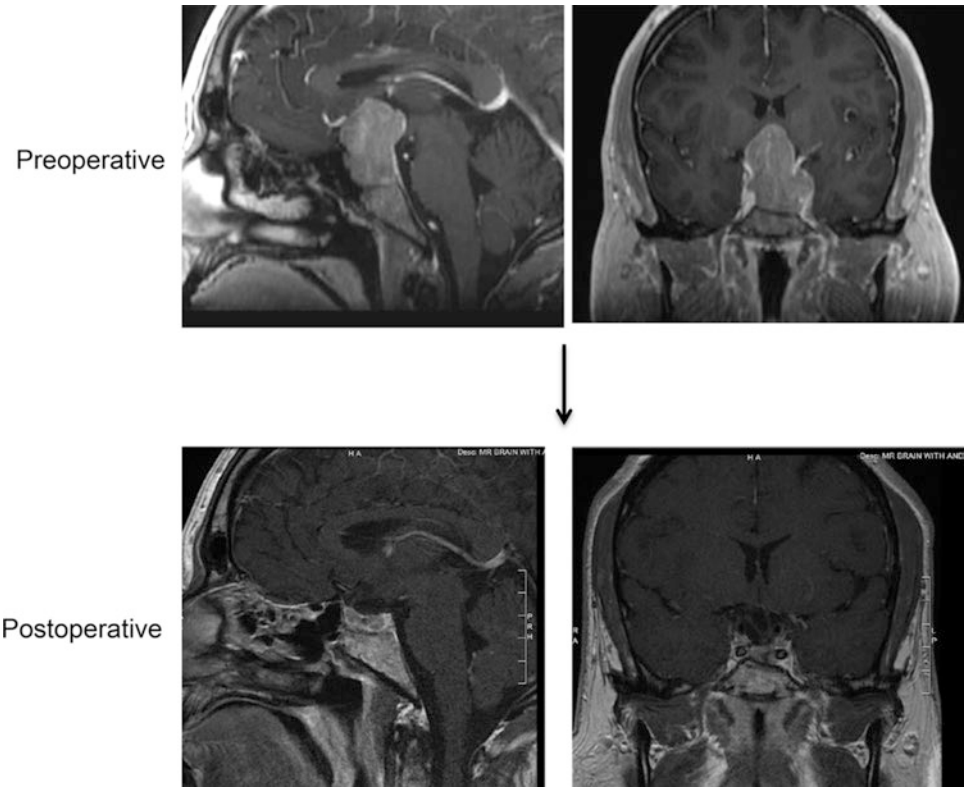

Fig. 4.2 MRI images of pituitary adenoma. Shown are sagittal (*left*) and coronal (*right*) T1 post-gadolinium images of a newly diagnosed giant (larger than 4 cm in maximal diameter) nonfunctional pituitary adenoma with the *upper images* representing preoperative images and *lower images* representing postoperative images after endoscopic endonasal resection with no residual tumor seen on postoperative imaging

Table 4.2 Summary of different pathologic types of pituitary adenomas and their prevalence. Shown are the prevalence, common age groups, and gender predilections of nonfunctional pituitary adenomas (NFPAs) and four types of functional adenomas

Type of lesion	Prevalence (%)	Common age group	Most prevalent gender
Prolactinoma	50[a]	20–50 years old[b]	Females > males[c]
NFPA (endocrine-silent)	25–35[a]	>40 years old[b]	Males > females[c]
Somatotroph adenoma (acromegaly)	10–15[a]	Bimodal: ~20 years old and 50–65 years old[b]	Males > females[c]
Corticotroph adenoma (Cushing's disease)	10–15[a]	<30 years old (M)[b] >37 years old (F)[b]	Females > males[c]
TSH-releasing adenoma	0.5–3[a]	50–60 years old[b]	Females > males[c]

[a]Refs. [29–31]
[b]Refs. [29, 32–34]
[c]Ref. [35]

(at least two measurements); (2) nocturnal salivary cortisol (two measurements); (3) 1-mg overnight dexamethasone suppression test (DST); and (4) longer low-dose DST (2 mg/d for 48 h) [40]. While these tests are sensitive to elevated levels of glucocorticoids, they are not specific [41]. If the results from the initial tests are positive, then additional tests need to be done to differentiate between Cushing's syndrome and pseudo-Cushing's syndrome, which can be achieved by dexamethasone-corticotrophin releasing hormone (CRH) test [11]. Furthermore, if ACTH is elevated, a combination of CRH/desmopressin tests, high-dose dexamethasone test, and pituitary MRI may be used to confirm pituitary source [11]. In order to distinguish from an ectopic ACTH tumor, inferior petrosal sinus sampling (IPSS) using desmopressin or CRH is the single most important test [39, 42, 43]. The first-line treatment for Cushing's disease is microscopic or endoscopic transsphenoidal adenomectomy [44, 45] by an experienced surgeon as it is associated with a complete remission rate of 65–90% for microadenomas and 65% for macroadenomas [39, 46–52]. In the event there is incomplete resection of the tumor, a repeat transsphenoidal surgery is recommended provided there is radiological evidence of the tumor [47, 53]. Should transsphenoidal surgery fail to achieve biochemical remission, additional treatment should be pursued either with radiosurgery or medical management with agents inhibiting ACTH release

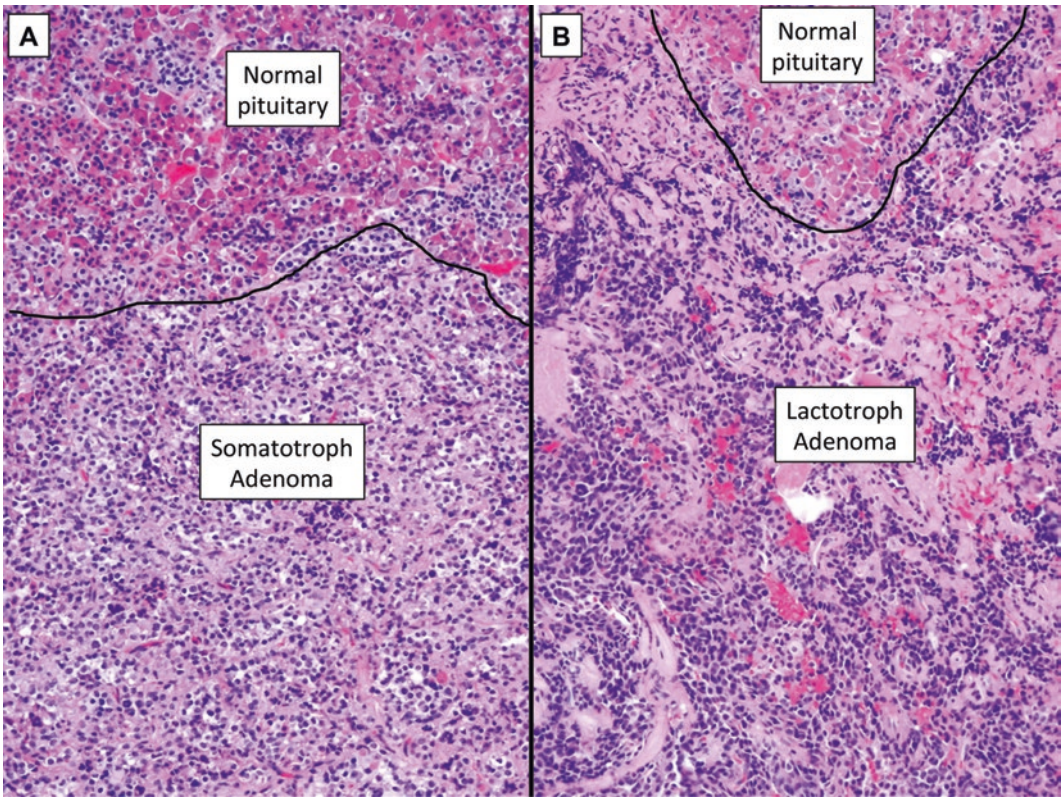

Fig. 4.3 (**a**, **b**) **Histological appearance of gland-tumor interface**. Shown are hematoxylin and eosin stains of (**a**) somatotroph and (**b**) lactotroph adenomas resected from a single patient with two microadenomas. A sharp gland-tumor interface is seen with both adenomas

in the pituitary gland, agents targeting steroid biosynthesis in the adrenal glands, or agents targeting the cortisol receptor in target tissues.

Nonfunctional Pituitary Adenomas

Due to their lack of hormone production and insidious growth pattern, NFPAs (Figs. 4.2a, b) are diagnosed either incidentally on unrelated radiologic evaluations or due to symptoms of mass effect of the lesion on surrounding structures [23–26]. According to the recent guidelines established by the Congress of Neurological Surgeons, high-resolution MRI is recommended for radiologic assessment of NFPA, while routine endocrine evaluation of all anterior pituitary axes for hypothyroidism, prolactin testing for high levels, and high levels of IGF-1 to rule out growth hormone hypersecretion, are recommended [28, 54]. Ophthalmological tests, such as automated static perimetry and visual evoked potentials, are used to determine early visual deficits and optic nerve functioning, respectively [55]. First-line treatment for NPFA is surgical resection by microsurgical or endoscopic transsphenoidal surgery, with the endoscopic approach providing greater visualization of the surgical field [56]. In invasive NFPA cases, where there is significant suprasellar, temporal, and frontal extension, a combined transcranial and transsphenoidal surgical technique can be used [56]. In the event of residual or recurrent NFPA, radiosurgery or radiation therapy is recommended to lower the risk of tumor progression. In cases where there is no residual or only small residual adenoma postoperatively, observation through serial imaging can be followed [57].

4.4 Surgical Anatomy

In general, treatment options include observation through serial imaging for smaller asymptomatic NFPAs, medical management with dopamine agonists for prolactinomas, or surgical resection through a transsphenoidal approach followed by medical management or radiation for residual tumor as needed based on whether the tumor is an NFPA or FPA. Medical treatment options are reviewed elsewhere [7, 8, 13, 37, 39, 47, 58–64]. Before understanding the nuances of transsphenoidal surgery, pertinent surgical anatomy of the transsphenoidal corridor must be understood.

The pituitary gland sits in the sella turcica of the sphenoid bone, which is present in the center of skull base in the

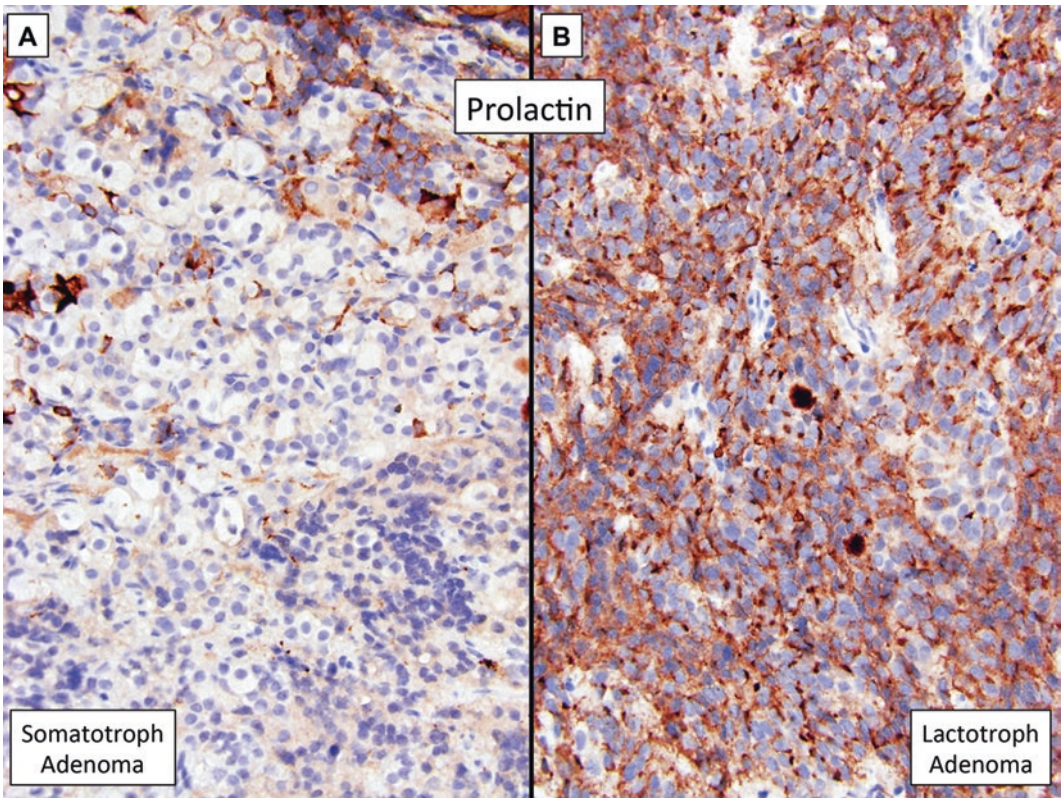

Fig. 4.4 (**a**, **b**) **Histological appearance of prolactin-staining of pituitary adenomas**. Shown is peroxidase-based prolactin immunostaining of (**a**) somatotroph and (**b**) lactotroph adenomas resected from a single patient with two microadenomas (same patient as in Fig. 4.3a, b). *Brown stain* represents areas of prolactin immunostaining. Note that there is prolactin immunostaining in the normal gland, but the density of this staining is higher in the prolactinoma

middle cranial fossa [65–67]. Gaining neurosurgical access to the sella requires understanding the vital anatomical structures surrounding the sella superiorly, posteriorly, and laterally [68–70]. Superior to the sella, the diaphragm sellae separates the pituitary gland from the CSF of the suprasellar cistern, which contains the optic nerves and chiasm. Posterior to the sella, the bony dorsum sella, and the inferior extension of the posterior clinoid processes, separates the pituitary gland from the dura overlying the prepontine cistern, which contains the basilar artery anterior to the brain stem. The cavernous sinus and internal carotid arteries are lateral to the sella. These anatomic constraints, superior, posterior, and lateral to the sella, make the endonasal route through the sphenoid sinus the preferred surgical route to access pathologies in the pituitary gland.

Sellar tumors often extend upward into the suprasellar region, leading to clinical consequences as a result of compression of the optic chiasm. If the optic chiasm is prefixed and located more anteriorly over the bony tuberculum sellae, a variant occurring in 10% of cadaveric specimens, a growing pituitary tumor can cause mass effect on the retrochiasmatic optic tracts. If the chiasm is postfixed and located more posteriorly over the bony dorsum sellae, a variant occurring in 10% of cadaveric specimens, a growing pituitary tumor can exert mass effect on the prechiasmatic optic nerves (Fig. 4.6) [70].

The suprasellar compartment houses the anterior incisural space, which is located between the free edges of the tentorium and the front of the midbrain [65, 71]. This area is clinically significant because the infundibulum crosses this region to reach the diaphragma sellae. The optic nerve and chiasm, anterior part of the optic tract, oculomotor nerve, and the posterior part of the olfactory tracts also pass through the suprasellar region. Arterial structures in the suprasellar region include the Circle of Willis, basilar, and internal carotid arteries. Specifically, the posterior portion of the Circle of Willis and the apex of the basilar artery are present in the anterior incisural space below the floor of the third ventricle, while the anterior and posterior cerebral arteries and the perforating branches from the internal carotid, anterior choroidal, anterior and posterior cerebral, and anterior and posterior communicating arteries send branches to the walls of the third ventricle and anterior incisural space. A suprasellar lesion or suprasellar extension of a pituitary adenoma can

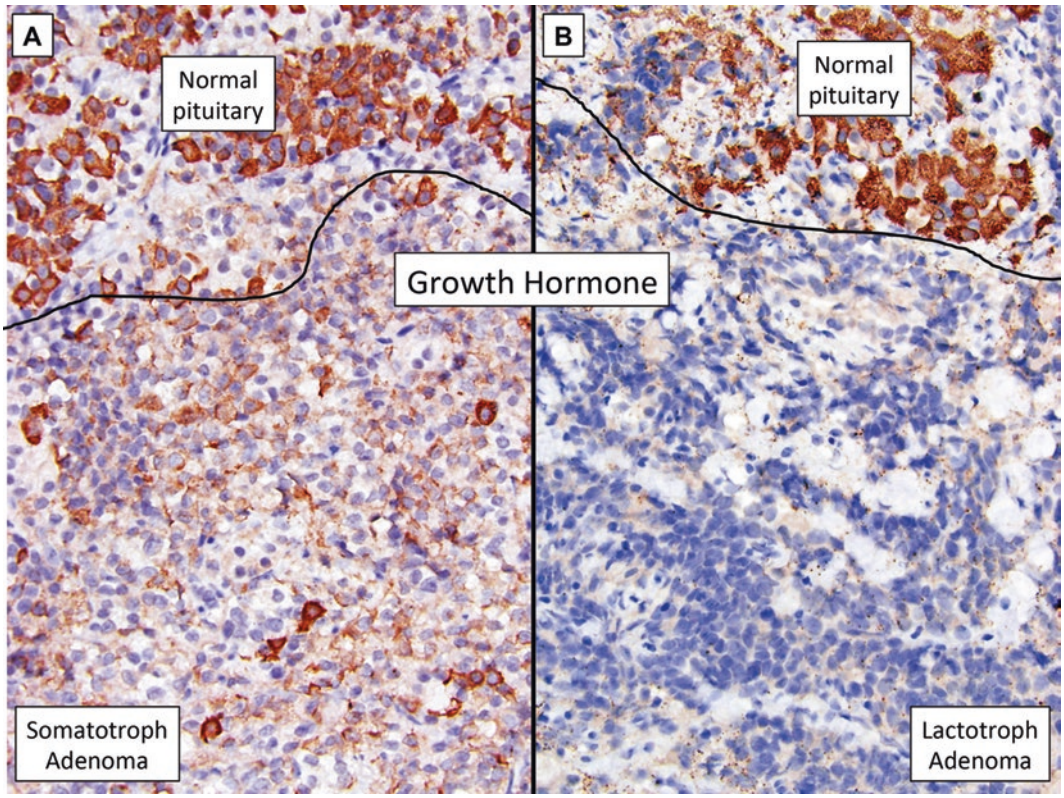

Fig. 4.5 (**a**, **b**) **Histological appearance of growth hormone (GH) staining of pituitary adenomas.** Shown is peroxidase-based GH immunostaining of (**a**) somatotroph and (**b**) lactotroph adenomas resected from a single patient with two microadenomas (same case as shown in Fig. 4.3a, b). *Brown stain* represents areas of GH immunostaining. Note that there is GH immunostaining in the normal gland, but the density of this staining is higher in the somatotroph adenoma

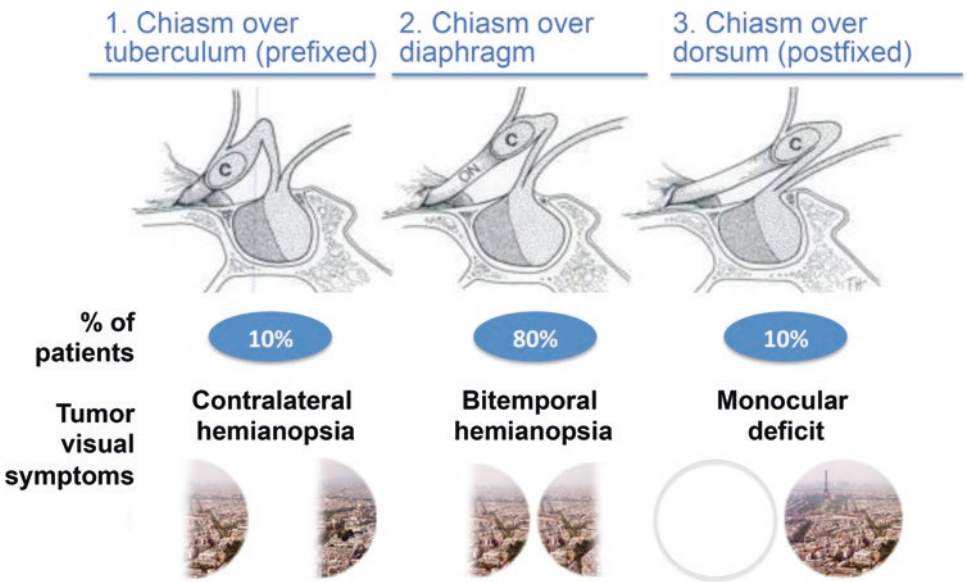

Fig. 4.6 **Three possible optic chiasm locations in patients.** Shown are three potential locations of the optic chiasm in the midsagittal plane: an anterior location for a prefixed chiasm over the bony tuberculum sellae, a central location over the diaphragm sellae, and a posterior location for a postfixed chiasm over the bony dorsum sellae. This impacts the potential visual field deficits that arise from a growing adenoma – an adenoma growing in a patient with a prefixed chiasm will exert mass effect on the retrochiasmatic fibers and could therefore cause a contralateral hemianopsia; an adenoma growing in a patient with a central chiasm will exert mass effect on the chiasm and could cause a bitemporal hemianopsia; and an adenoma growing in a patient with a postfixed chiasm will exert mass effect on the prechiasmatic optic nerve fibers and could therefore cause a monocular deficit

distort or encase these arteries and their perforating branches, making it vital to review preoperative imaging for these vessels before surgery [71–76].

4.5 Surgical Technique

Endoscopic transsphenoidal surgery is a versatile approach for resection of both FPA and NFPAs, combining the minimal invasiveness of endonasal approaches with the superior panoramic visualization offered by the endoscope relative to the microscope [13, 36, 37, 47, 56]. While many studies have reported similar to no difference in the effectiveness of endoscopic versus microsurgical transsphenoidal surgery, a recent extensive meta-analysis comparing the outcomes of endoscopic transsphenoidal and microsurgical technique found the endoscopic approach to be superior with higher safety and efficacy as well as higher gross total resection of the tumor, lower rate of postoperative septal perforation, and shorter postoperative hospital stays [77–79].

Operative Setup

Endoscopic endonasal pituitary surgery can be done by a neurosurgeon working alone or by a neurosurgeon working in partnership with an otolaryngologist. Prior to the operation, a surgical plan should be made, including decisions about whether to place a lumbar drain preoperatively, whether a fat graft will be harvested, and understanding of the tumor's involvement of vascular structures. Considerations specific to the patient such as airway issues that might arise with acromegaly, including the potential need for awake fiber-optic intubation in patients with excessive oropharyngeal soft tissue, and blood pressure and electrolyte issues that can arise with Cushing's disease patients should be discussed with the anesthesiologist before proceeding with surgery. Once the patient is under general anesthesia, an orotracheal intubation is performed. An antibiotic to cover nasal flora and stress-dose steroids are typically given. Many institutions give stress-dose steroids for all patients regardless of the size of the pituitary tumor, even when the tumor is causing preoperative hypopituitarism. For surgery, the patient is positioned supine with the trunk elevated to 10–20° and the head turned toward the surgeon with their head fixed in a Mayfield headrest or in a three-pin head-fixation system, with neuronavigation as a useful tool [80–82]. Special care should be taken to avoid obstruction of the jugular outflow and/or stretch injury to the brachial plexus. Depending on the anatomy of the lesion, the vertical position of the patient's head is manipulated. If the lesion is present in the clivus, sphenoid sinus, or is a microadenoma, the head is slightly flexed such that the bridge of the nose is parallel to the floor of the operating room. If the lesion extends into the suprasellar region or is a macroadenoma, the head is inclined toward the floor of the operating room. Next, the nasal cavity and surrounding facial region are disinfected with a 5% povidone-iodine solution [83].

Instrumentation

There are six components that enable visualization during endoscopic pituitary surgery: the light source, the endoscope, fiber-optic cable, camera, monitor, and video recording equipment [80]. Most endoscopes are rigid with 4 mm diameter, 18 or 30 cm length, and a 0°, 30°, or 45° lens [80]. For children or patients with very narrow nasal passages, smaller endoscopes ranging from 1.9 to 2.7 mm diameter are available. In order to enable the endoscope to be brought in and out of the nasal passages with minimal accumulation of debris on the lens, the endoscope is inserted through a sheath connected to an irrigation system for clearing the lens during the procedure [82]. When the procedure is being performed by a surgeon working alone, an endoscope holder can be used to provide stability to the endoscope for a fixed image of the surgical field and to free the surgeon's hand.

The endoscope is connected to the light source by a high-quality fiber-optic cable. The light source commonly used is a Xenon cold light as this light source has a color temperature similar to that of solar light and provides lower heat dispersion with greater illumination in contrast to halogen lights [80, 81].

Surgical tools used in endoscopic transsphenoidal surgery are distinct from those used in microsurgical techniques, which require bayonet-shaped tools. Instead, straight tools are used in the endoscopic technique as they can be inserted close to the endoscope along its axis and can be equipped with different angled tips to manage all areas of the surgical site. Several surgical tools are available in the market and are used variably by surgeons [84, 85].

The endoscopic light source, monitor, video camera, and recorder are placed behind the head of the patient and in front of the operator. The lead surgeon is on the right of the patient, while the scrub nurse and assisting surgeon is to the left of the patient. The anesthesiologist with his equipment is usually at the level of the patient's legs (Fig. 4.7).

Technique

The endoscopic endonasal transsphenoidal surgical technique can be divided into three phases: *nasal phase*, *sphenoid phase*, and *sellar phase* [80, 84]. During the nasal phase, three clinically significant goals are met: exposure of nasal cavity anatomy, formation of a surgical pathway for tools and navigation, and gaining access to the sphenoid

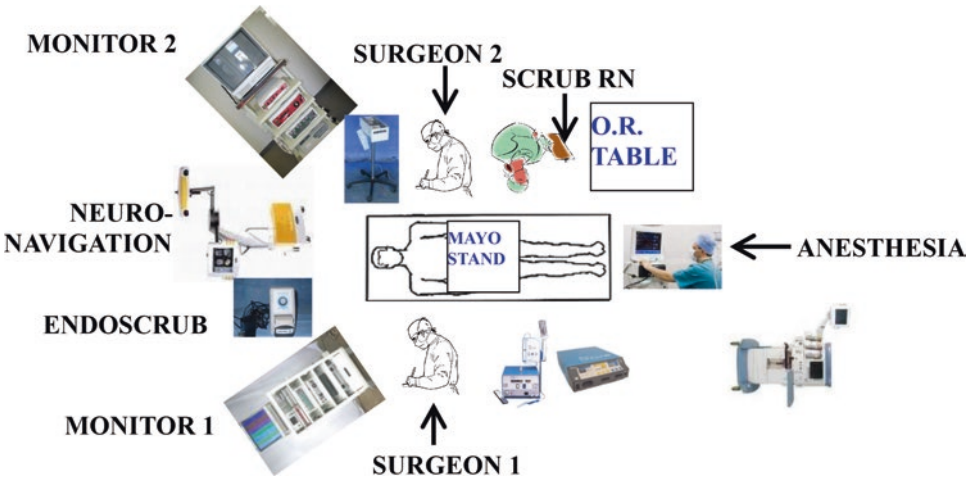

Fig. 4.7 Operating room setup for endoscopic endonasal pituitary surgery. Shown is a diagram of a typical operating room setup for endoscopic endonasal pituitary surgery. The anesthesiologist is at the foot of the bed with an extended endotracheal tube secured to the patient's side and running to the ventilator. Endoscopic monitors are placed at 45° angles to the left and right of the patient allowing surgeons working on each side of the patient to visualize the monitors. The *photo* shows surgeons operating across from each other, but they can also both operate on the patient's right side, with the otolaryngologist in front of the neurosurgeon

sinus. A 0- or 30º endoscope with 4 mm diameter is inserted into one nostril. Typically, the right nostril is preferred as a surgical route because of easy access to the surgeon standing to the right of the patient. But in certain scenarios, the left nostril may be used due to narrowing of the right nostril as a result of scarring, hypertrophy of turbinates (e.g., in acromegaly), septal deviation, and synechiae due to prior sinonasal surgery [82]. The first structure to be identified is the inferior turbinate laterally and the nasal septum medially. At the level of the head of the middle turbinate, cottonoids soaked in epinephrine (1:100,000) are placed between the nasal septum and middle turbinate to vasoconstrict the area and widen the nasal space [80, 83]. To further widen the nasal space for an adequate surgical route, the head of the middle turbinate is dislocated laterally where, if needed, it can be protected by gauze or a cottonoid to prevent abrasive injury during the procedure. As the endoscope is moved along the floor of the nasal cavity, it reaches the choana, an orifice which communicates with the nasopharynx. The medial margin of the choana is the vomer, which also marks the midline of the approach. At this point the endoscope is angled upward along the roof of the choana, and the sphenoethmoidal recess until the sphenoid ostium (usually 1.5 cm above the roof of choana) is reached to access the sphenoid sinus.

The sphenoid phase involves anterior sphenoidotomy for accessing the sella and pituitary gland. In order to prevent bleeding from the septal branches of the sphenopalatine artery, once the endoscope reaches the sphenoid cavity, the septal mucosa is coagulated, beginning 0.5 cm from the top of choana to the superior border of the nasal cavity [80, 82]. Next, the septal mucosa is incised and mobilized to the side with a microdissector following which the nasal septum is broken at the sphenoid rostrum to achieve wide exposure of the sphenoid floor [86]. Anterior sphenoidotomy can be performed using either Kerrison rongeurs or a microdrill by proceeding in a circumferential direction. Next, the sphenoid rostrum is removed in fragments and not en bloc to prevent any laceration and bleeding in the nasal mucosa during retraction from the nasal cavity [80, 82]. In order to ensure surgical tools reach the sella within the visible field of the endoscope, it is necessary to make sure the removal of the anterior wall is wide. Caution must be taken in the inferolateral direction to prevent injury to the sphenopalatine artery or its branches as discussed in "Surgical Anatomy." One or more septa can be seen inside the sphenoid sinus, and special care must be taken when removing septa implanted over carotid prominences. Septa are removed using nasal forceps or cutting bone punches without detaching the sphenoidal mucosa, except when mucosa is too prominent or adenomatous infiltration is seen or suspected [80, 81]. Following removal of the septa, the posterior and lateral walls of the sphenoid sinus are endoscopically visible, with the sellar floor at the center, planum sphenoidale above it, clival indentation below it, and bony prominences of the intracavernous carotid artery and optic nerve lateral [80, 81].

The sellar phase involves exposing and resecting the lesion (Fig. 4.8a–d). Once the sphenoid sinus roof is completely cleared and visible, a longer endoscope (4 mm in diameter, 0º angled lens, 30 cm length) is used and, if desired, can be stabilized by fixing it to an adjustable endoscope holder to free both hands of the surgeon. In the case of most macroadenomas, the sellar floor can be opened using a dissector and enlarged with a rongeur [81]. However, if the sellar floor is very thick, as is often the case for microadenomas,

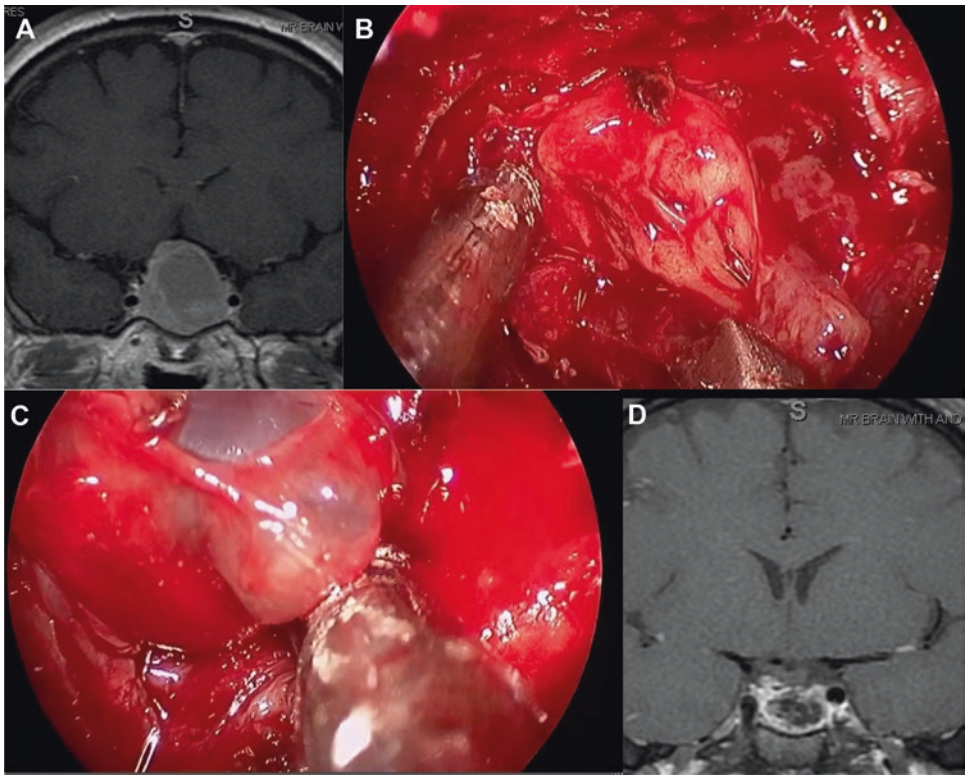

Fig. 4.8 (**a**–**d**) **View through the endoscope of a pituitary adenoma being resected.** Shown are MRI images and endoscopic view from a particular case of (**a**) nonfunctional pituitary macroadenoma with internal blood products in the tumor in a patient with vision loss with tumor to the left and some normal gland to the right as seen on a coronal T1 post-gadolinium MRI; (**b**) view through a zero degree endoscope during endoscopic transsphenoidal resection of the yellow hemorrhagic tumor being resected from the sella; (**c**) view through a zero degree endoscope of the last bit of adenoma being removed with the translucent diaphragma sellae prolapsing down into the sella; and (**d**) postoperative MRI showing no residual adenoma

a high-speed microdrill or bone punchers are used. In either case, the opening in the sellar bone is enlarged according to the pathology of the lesion. Next, the exposed dura is incised in a cruciate fashion or in a linear rectangle [80, 81, 86]. In the case of macroadenomas, the dural incision is often bloodless due to the compression and obliteration of superior and inferior intercavernous sinuses, while, in the case of microadenomas and specifically in Cushing's disease, the entire sellar dura may be covered by one or two venous channels and can lead to dural bleeding on incision [80, 82]. To circumvent this problem, the intercavernous sinuses can be cauterized or secured and sealed using surgical clips around them [80, 82]. Extra caution must be taken when incising dura in microadenomas because sometimes an ectatic carotid artery may also be located within the sella in acromegalic patients [87, 88].

Endoscopic tumor resection uses techniques identical to those of conventional microsurgical endonasal approaches, specifically internal debulking, capsular mobilization, and extracapsular dissection of neurovascular structures, along with coagulation and capsule resection [83]. Using various curettes, suction, and grasping forceps, the lesion is removed in fractions. Following removal of the lesion, the 0º endoscope can be replaced with a 30 or 45º endoscope if needed to visualize the lateral surgical borders to ensure maximal extent of resection. If an intraoperative CSF leak occurs during the resection, repair can be done using a variety of techniques, including autologous devascularized tissue graft such as a periumbilical fat graft or fascia lata, as well as autologous vascularized tissue graft such as a nasoseptal flap [81, 89–92]. The sellar and sphenoid floor can be reconstructed with bone pieces, although the importance of such repair remains subject to debate. At the end of the procedure, hemostasis is obtained and the middle turbinate is restored gently to its normal anatomical position. The amount of packing to place in the nares is subject to the discretion of the surgeon, with a septal splint sutured to the site of nasoseptal flap harvest offering value in preventing postoperative nasal crusting and bioresorbable nasal dressing such as NasoPore™ (Stryker Instruments) providing some tamponade to support the healing of the surgical site.

Special points of emphasis for larger tumors are discussed below:

1. **Macroadenomas**: Resection of macroadenomas is accomplished sequentially with the inferior and lateral regions of the lesion removed first followed by the superior aspect [80]. Following removal of visible tumor, if the diaphragma sellae does not descend, the surgeon can ask the anesthesia team to perform a Valsalva maneuver to force the diaphragma downward and any remaining unresected tumor to protrude into the sellar cavity [80, 81]. A thorough inspection of the sellar cavity and suprasellar cistern, if it was explored, must be done after resection of all visible tumor, and an angled endoscope can be used for this step, if needed. If the adenoma invades the

medial wall of the cavernous sinus, the endoscopic approach can allow chasing of the tumor through the focus of invasion or through a more lateral transethmoid-transpterygoid path through the bulla ethmoidalis of the middle turbinate followed by ethmoidectomy of the anterior and posterior ethmoid cells [84]. For such a lateral approach, the use of intraoperative Doppler probe is necessary to prevent carotid artery injury in the cavernous sinuses. Resection of tumor in the cavernous sinus requires considerable experience and judgment and may be more appropriate for functional adenomas where biochemical remission will require complete tumor resection or where maximizing extent of resection can improve the efficacy of any necessary postoperative medical therapy.

2. **Giant pituitary adenomas**: While the endoscopic endonasal transsphenoidal surgical technique has allowed resection of large adenomas [93–96], a transsphenoidal approach will leave significant enough residual for some giant adenomas (adenomas larger than 40 mm in diameter) to warrant a craniotomy either after initial transsphenoidal surgery (Fig. 4.9) or instead of transsphenoidal surgery [97, 98]. For staged approaches, it is important to minimize the time gap between the initial transsphenoidal surgery and the craniotomy due to the risk of apoplectic events occurring in residual tumor after the first surgery. For select tumors where the amount of residual adenoma is small enough to not require a second stage craniotomy, follow-up MRI in 4–6 weeks may be done to evaluate the residual tumor burden and reveal its collapse into the sella, in which case repeat transsphenoidal surgery can be considered.

4.6 Postoperative Care and Complications

Postoperative pain and discomfort has been reported to be minimal and patients rarely need analgesics [82, 86]. Due to potential occurrence of diabetes insipidus, patients are kept in the hospital at least for overnight observation [86, 99]. Serum sodium and urine output are measured the night after surgery as well as the following morning. For hypersecreting adenomas, the levels of the hypersecreted hormone can be checked postoperatively to assess for biochemical remission, recognizing that IGF-1 takes up to 6 months to normalize after surgery for acromegaly; immediate prolactin normalization typically occurs after prolactinoma resection; and cortisol sub-normalization is anticipated to occur with biochemical remission of Cushing's disease [100]. At discharge, patients are encouraged to engage in copious irrigation of the nasal vestibule and cavity three times a day for 1 week [80]. Irrigation of the nasal cavities serves to protect from infections, wash out small clots in the nasal cavities, and prevent possible endonasal synechiae. Patients are discharged on maintenance dexamethasone if there is preoperative evidence of adrenal insufficiency [82, 86]. At 12 weeks, in addition to clinical evaluation, an MRI is done to evaluate the extent of

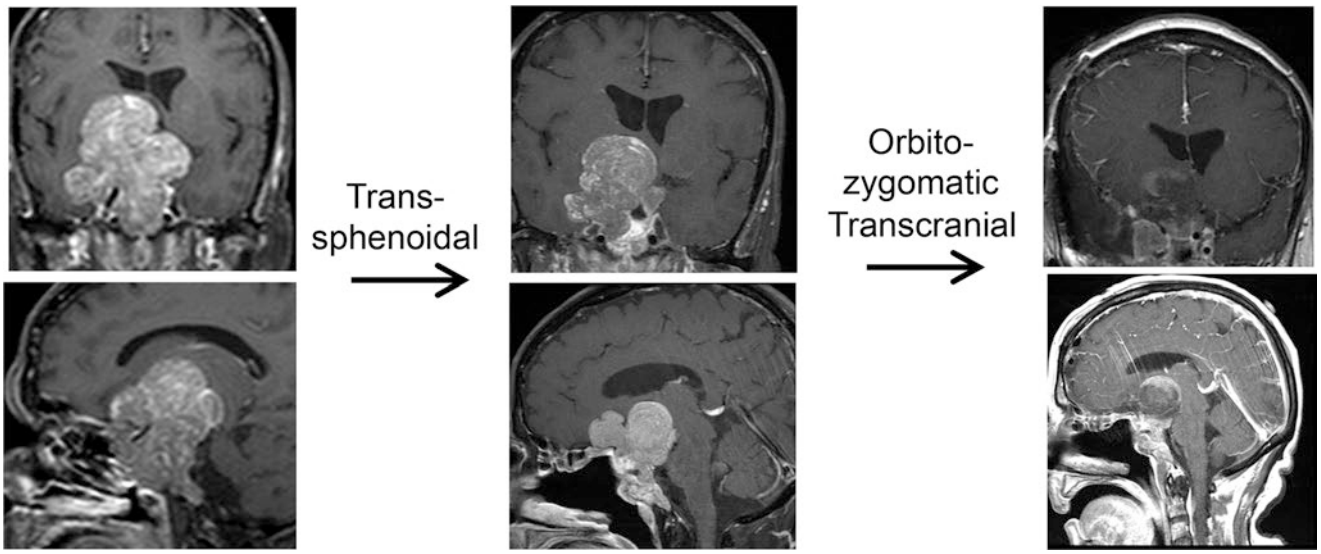

Fig. 4.9 Example of a giant pituitary adenoma requiring a two-staged approach. Shown is an example of a giant nonfunctional pituitary macroadenoma in a patient with two decades of vision loss. MRI revealed tumor eroding into the right Sylvian fissure with significant inferior extension into the sphenoid sinus. A staged approach was performed, with an endoscopic transsphenoidal resection of the sphenoid sinus and sellar components of the tumor done first, with intraoperative pathologic analysis confirming the diagnosis of pituitary adenoma. The next morning, the patient was brought back to the operating room where a right orbitozygomatic craniotomy was performed for resection of remaining tumor

surgical resection. For functional adenomas, the hormone being hypersecreted is also assessed at the 12-week follow-up [8, 13, 47, 53, 57, 60, 101, 102].

Complications of endoscopic transsphenoidal surgery, albeit uncommon, arise as a result of tumor characteristics (size and extension) and surgical approach and manipulation of the pituitary gland and surrounding structures [100, 103]. Complications associated with the endoscopic approach may be divided into four groups based on the anatomic location from which the complication arises: (1) nasofacial, (2) sphenoid sinus, (3) parasellar, and (4) endocrine [104]. Nasofacial complications primarily include epistaxis due to damage to vessels in the nasal cavity such as sphenopalatine artery and its branches [100]. Sphenoid sinus complications involve sphenoid sinusitis occurring in reaction to the transnasal portion of the procedure [104]. Parasellar complications include CSF rhinorrhea, swelling or infarction of residual tumor, meningitis, hematoma in the resection cavity, visual defects and transient CN VI palsy due to postoperative edema, and carotid artery injury [100, 104–106]. Endocrine complications include diabetes insipidus and new postoperative hypopituitarism [97, 104].

4.7 Surgical Pearls

- For newer neurosurgeons or those new to endoscopic transsphenoidal techniques, it is best to start with smaller cases before applying the approach to larger, riskier cases.
- Collaborating with an experienced otolaryngologist with skull base training can allow a two-surgeon teamwork concept to be applied to endoscopic endonasal pituitary surgery, which can reduce operative time and improve outcomes.
- It is important for the neurosurgeon operating on pituitary tumors to understand the delicate aspects of neuroendocrine surgery, such as identifying and preserving the normal gland by defining the gland-tumor interface and using an extracapsular dissection whenever possible.

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