Pituitary Adenoma

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Introduction

Almost all pituitary adenomas are benign, but given the critical neurovascular structures around the sella, compression of neighboring structures can cause significant morbidity [1]. Pituitary adenomas are subdivided into microadenomas, less than 1 cm in size, and macroadenomas, greater than 1 cm. Another way to categorize pituitary adenomas is whether they secrete hormones or not, regarded as functional or nonfunctional, respectively. Invasion of pituitary adenomas into the cavernous sinus leads to difficulty removing these tumors and is an independent risk factor for subtotal resection and recurrence [2–7]. The residual pituitary adenoma in these cases requires multimodal treatment with medical and radiation therapies to achieve the goals of treatment while preserving critical neurovascular structures.

The cavernous sinus is a plexus of trabeculated venous channels separating the meningeal and periosteal layers of the dura just lateral to the sella in the coronal plane. The adjacent and intertwined neurovascular components make

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operating in this area complex. The lateral wall of the cavernous sinus contains the oculomotor nerve, the trochlear nerve, and the ophthalmic and sometimes maxillary division of the trigeminal nerve. The abducens nerve runs within the sinus just lateral to the cavernous internal carotid artery. The medial wall of the cavernous sinus is a distinct structure separating the pituitary gland from the cavernous sinus and is often invaded by pituitary adenomas [8].

Epidemiology

Pituitary adenomas are a common lesion of the skull base with a wide-ranging prevalence based on radiological and postmortem studies estimated to be 16.7–22.5% [1, 9]. The vast majority of pituitary adenomas are not clinically relevant and are asymptomatic. Pituitary tumors account for approximately 10% of all brain tumors [10]. Pituitary adenoma incidence has a slight female predominance of 3.84 cases per 100,000 per year versus 3.23 in males. There has been described a significantly higher incidence of pituitary tumors, including adenomas, among blacks compared to whites [11].

Pituitary adenomas most commonly present between the ages of 30–50, slightly earlier in females [10]. Pituitary tumors account for the highest proportion of tumors in the central nervous system of children, adolescents, and young adults [9]. Approximately 5% are related to familial syndromes such as familial isolate pituitary adenoma (FIPA) or multiple endocrine neoplasia type I [9, 11].

Pathology

Pituitary adenomas are thought to develop through clonal expansion of a single abnormal cell in the adenohypophysis due to somatic mutations or chromosomal abnormalities [11]. Approximately 65% of pituitary adenomas secrete endocrine hormones and are considered functional. All types of pituitary adenomas can invade the cavernous sinus, but the growth hormone-secreting adenomas invade the cavernous sinus at roughly twice the rate than the others [3].

Most pituitary adenomas do not grow after detection. Only 10% of microadenomas and 20% of macroadenomas grew over 2–8 years in a meta-analysis of 445 adenomas [12]. Local invasion occurs in approximately 5% of pituitary adenomas and may constitute a unique genetic subset of pituitary adenomas even though being similar on histology [13]. Pituitary carcinomas are rare metastatic lesions with a poor prognosis of approximately 66% survival at 1 year. These entities are typically invasive and secrete either ACTH or prolactin [14].

Diagnosis

Presentations of pituitary adenomas can be quite variable, ranging from endocrine abnormalities causing Cushing's disease, acromegaly, hyperthyroidism, amenorrhea/galactorrhea, and symptoms of mass effect such as headache, visual field loss, or diplopia. They can also present with apoplexy, causing severe headache and visual symptoms. Large macroadenomas can cause the underproduction of pituitary hormones through compression. Growth hormone is the most sensitive to compression and is typically first to become deficient, followed by gonadotropins, TSH, ACTH, and prolactin. Rarely, pituitary adenoma invasion into the sphenoid sinus can present with epistaxis or CSF leak. Pituitary adenomas are also often found incidentally, and many never require surgical intervention.

Initial imaging obtained is often a noncontrasted head CT that reveals a sellar isohypoattenuation. Further evaluation of a patient with a suspected pituitary adenoma includes complete endocrine labs (24 h urinary-free cortisol, prolactin, thyroxine, thyrotropin, ACTH, growth hormone, luteinizing hormone, follicle-stimulating hormone, insulin-like growth hormone-1, testosterone for men, estradiol in women) along with detailed ophthalmological testing. Imaging evaluation includes MRI with and without gadolinium along with delayed

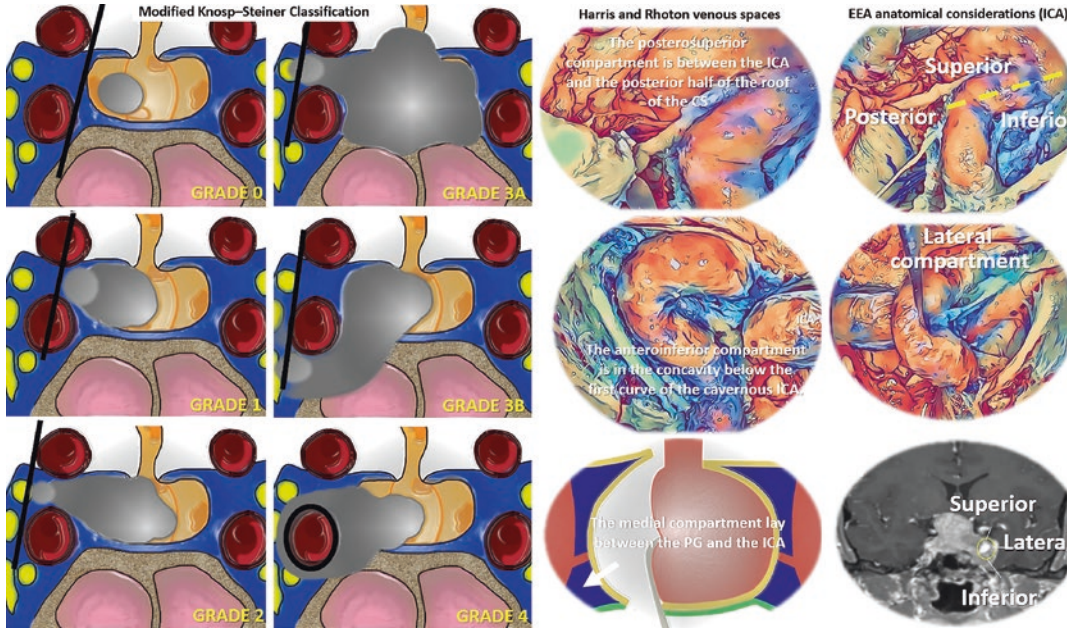

Fig. 24.1 Original artistic depiction showing the Knosp grade system and other used new/modified anatomy-based classifications for pituitary tumors with cavernous sinus invasion. The modified Knosp system grades the parasellar extension of the tumor toward the cavernous sinus concerning the intracavernous carotid artery. PG: pituitary gland; ICA: internal carotid artery; EEA: endoscopic endonasal approach

contrast-enhanced imaging of the sella, which demonstrates delayed enhancement of the pituitary adenoma. In addition, vascular imaging if the cavernous sinus is involved. Formal catheter angiography or a CT angiogram depending on the surgeon's preference; ours is usually a CT angiogram, which can then be fused with MRI in thin slices for neuronavigation. For patients with a history of significant facial trauma or sinus surgery, we have an endoscopic examination by our otolaryngology colleagues performed before surgery to assess the anatomy and viability of various reconstructive flap options.

Typically, MRI is used to detect and determine the severity of cavernous sinus invasion, although direct observation intraoperatively is considered the gold standard. The incidence of cavernous sinus invasion by pituitary adenomas is extremely variable, with rates from 9% to 63%, depending on the imaging and observational classification used [15]. The Knosp classification is the most widely used grading of cavernous sinus invasion. It is based on the relationship of the pituitary adenoma to tangential lines drawn in relation to the medial, midpoint, and lateral cavernous ICA and the supraclinoid ICA (Fig. 24.1). As such, the Knosp grade 0 does not encroach the medial carotid line. The Knosp grade 1 passes the medial tangential line of the carotids but not the intercarotid line, grade 2 passes the intercarotid line but not the line tangential to the lateral carotids, grade 3 passes the lateral border of the ICAs, and grade 4 encompasses the ICA circumferentially within the cavernous sinus. An updated grading system created subtypes 3a and 3b, which is when the pituitary adenoma passes the lateral ICA margin from above (3a) or below (3b) the cavernous ICA [5]. Knosp class 3 and 4 imaging classifications are predictive of cavernous sinus invasion: grade 3b is associated with intraoperative findings of cavernous sinus invasion in 70% of cases, and grade 4 is associated with a 100% rate of invasion [5]. The Knosp classification has been related to the histologically and surgically confirmed invasion of the cavernous sinus and the likelihood of gross total resection and endo-

crinologic remission [5, 16]. The rate of endocrinologic remission is inversely related to the Knosp classification. A study of growth hormone-secreting adenomas had 82.2% of Knosp class 1 and 2 achieving biochemical remission following surgery, 42.9% of class 3, and only 25% of class 4 [4]. Although the Knosp classification scale has been found to be overall reliable, the middle-grade interrater reliability is relatively weak. When dichotomized to two clinically useful categories unlikely to have cavernous sinus involvement and likely to have cavernous sinus involvement, the reliability was again strong [17].

Wilson's system has been devised to classify the invasiveness of pituitary adenomas [18]. In Wilson's system, the extension is classified as (0) no extension, (A) into the suprasellar cistern, (B) into the anterior recess of the third ventricle, (C) displacement of the floor of the third ventricle, (D) parasellar extension intracranially, and (E) into or beneath the cavernous sinus. Invasion and spread are also classified as (I) sella normal or focally expanded, (II) sella enlarged, (III) localized perforation of the sellar floor, (IV) diffuse destruction of the sellar floor, and (V) distant spread through the CSF or blood.

Thus, some authors do not consider this radiologic-based classification useful for predicting the invasion of the medial wall of the cavernous sinus (MWCS). As such, Fernandez-Miranda et al. recently proposed a new anatomy-based classification of cavernous sinus invasion based on modifications of the previous three-compartment CS classification described by Harris and Rhoton in 1976 [19]. It divides the CS into four compartments based on their relationship with the cavernous ICA's horizontal segment, where the superior and inferior compartments, corresponding to grades 3a and 3b of the modified Knosp classification, are located above and below this level (horizontal cav-ICA). Likewise, the posterior compartment, not previously detailed by the Knosp classification, would be located posteriorly to the horizontal cavernous ICA, and the lateral compartment would be lateral to the anterior genu and horizontal segment of the ICA. This anatomy-based classification promises to be useful for identifying invaded compartments of the CS, both preoperatively and intraoperatively, complementing the current imaging-based classifications and anatomical studies of the CS from an endonasal perspective [20].

Furthermore, in an attempt to better understand and standardize the management for pituitary adenomas, several classifications were proposed, such as Hardy's classification based on radiological parameters, histological classifications of adenohypophyseal tumors proposed by WHO in 2004 and 2007, as well as size-based classifications for pituitary tumors, such as the threshold of 1 cm used for microadenomas or macroadenomas, as aforementioned, or the threshold of 4 cm for giant pituitary adenomas. Also, for these giant tumors, Goel established four-grade rating based on their anatomic extensions and the nature of their meningeal coverings [21]. These grades reflected an increasing order of invasiveness of adjacent dural and arachnoidal compartments in which a radical transsphenoidal resection would be indicated for pituitary tumor grades I–III. In contrast, for those transgressing the diaphragma sellae boundary and encasing the arteries of the Circle of Willis (grade IV), a radical resection would be difficult, and the surgical aim can be tumor biopsy followed by radiation therapy.

Management Strategies

Treatment options for pituitary adenomas include observation, medical therapy, open craniotomy, minimally invasive microsurgical or endoscopic endonasal transsphenoidal approaches, and radiation therapy. The goals of treatment should be clearly defined to decide the optimal treatment paradigm for each patient. Generally, the goal of pituitary adenoma treatment should be to resolve symptoms by achieving tumor control and induce biochemical remission (if functional adenoma) while preserving critical neurovascular structures and avoiding iatrogenic injury. Other considerations include obtaining tissue for diagnosis if the preoperative imaging and/or history are unclear

on the differential diagnosis of the tumor (such as a patient with known metastatic disease from another organ site). Also, pathological investigation of an adenoma will yield some information on the risk of recurrence via proliferative index. Debulking of a tumor considered unresectable based on preoperative imaging in preparation for radiation might also be considered [22].

The endoscopic endonasal transsphenoidal approach has been increasingly accepted as the mainstay of surgical treatment for pituitary adenomas with cavernous sinus invasion. The microsurgical endonasal approach had previously been restricted medially to the sella due to restrictions in hand freedom of movement as well as illumination and line of sight. However, the development of expanded coronal plane approaches and angled endoscopes has opened more lateral visualization and access into the cavernous sinus. Currently, the use of open craniotomy for pituitary adenomas with cavernous sinus invasion is only in the rare case when the tumor expands beyond the reaches of an endonasal approach, far laterally into the middle fossa. Compared to the prior use of the operative microscope, the use of the endoscope has also demonstrated a greater extent of resection and biochemical remission in functional pituitary adenomas [23, 24].

The different options and techniques for the endonasal endoscopic approach are based on how much lateral access is needed and if the ICA needs to be transposed. For most pituitary adenomas with lower Knosp grades (1 or 2), a standard transsphenoidal approach is usually sufficient, with or without resection of the middle turbinate depending on individual patient anatomy. The more lateral access that is needed with higher Knosp grades (3 or 4) may necessitate the use of a proper expanded endoscopic endonasal approach with middle turbinate resection, the sacrifice of the ipsilateral nasoseptal pedicle, and adoption of an expanded transpterygoid exposure with mobilization and/or sacrifice of the Vidian nerve, as needed, to improve the exposure and working angles within the cavernous sinus.

In addition, patient outcomes are expected to be good if gross total resection is achieved safely. In one series of 50 pituitary adenomas Knosp class 1–3, there was 100% gross total resection, no radiographic recurrence, and only one biochemical recurrence 2 years postoperatively [25]. There were no deaths or ICA injuries, only once CSF leak. There were four (8%) new cranial nerve palsies that resolved by 3 months. Although the generalizability of these results may be limited due to the fact that this series coming from a high-volume skull base center with an experienced team. Experts have suggested that only experienced surgeons should perform resections into the cavernous sinus due to the risks of devastating neurovascular complications [25, 26]. A meta-analysis of pituitary adenomas with cavernous sinus invasion reports ICA injuries from 0% to 5% and new cranial nerve deficits up to 27% [15].

There are many considerations in weighing the benefits of an aggressive gross total resection against the risk of injuring the critical structures within the cavernous sinus. In our practice, we favor an aggressive resection for functional adenomas as a gross total resection is the best opportunity for biochemical remission [6] and a less aggressive approach to nonfunctioning adenomas as their symptoms can often be controlled with decompression and the majority do not recur or grow. Less aggressive options could include leaving residual tumor behind with the intention of treating with stereotactic radiosurgery upon tumor progression. Instead of resecting the medial wall of the cavernous sinus that is invaded by the tumor, it could be coagulated and shrunken. In case gross total resection is not achievable, there is evidence that subtotal resection remains beneficial. Subtotal resection of GH secreting tumors can improve hormonal control with somatostatins or radiation [27, 28].

Functional pituitary adenomas should be treated with the assistance of an endocrinology team (Chap. 19). Many patients can achieve hormonal and symptomatic control medically either before surgery in the case of prolactinomas or after surgery due to residual or recurrence from growth hormone-secreting or ACTH-secreting adenomas. Up to 90% of patients with prolactinomas can achieve hormonal control with dopamine agonists such as bromocriptine or cabergoline. With growth hormone-secreting

tumors, somatostatin analogs can achieve near 40% hormonal control and up to 90% control with pegvisomant, a growth hormone receptor blocker. The cortisol blocker mifepristone can achieve symptomatic control in up to 87% of those with ACTH-secreting adenomas [29]. Radiation therapy techniques allowing focused delivery can also be harnessed for the treatment of pituitary adenomas. Stereotactic radiosurgery (SRS) has traditionally been reserved for patients not able to tolerate surgery or for those with residual tumors after surgery since it is not often able to provide a "cure." Nevertheless, SRS is effective: nonfunctioning pituitary adenomas with the residual disease have up to a 96% control rate with SRS [30]. Prolactinomas had 27–50% biochemical remission with SRS [31, 32]. Growth hormone-releasing tumors had an even greater response, with up to 82% having biochemical control after SRS, although this effect is often delayed for 6–18 months after radiation delivery [33]. Although considered safe and often less morbid than surgery, there remains a 30% risk of hypopituitarism after radiation to the sella, as well as rare side effects such as radiation-induced optic neuritis [33].

Along with SRS, there are many treatment options to consider for pituitary adenomas that recur. In patients who are older or asymptomatic, observation is a reasonable approach. Reoperation using the same approach or a different approach can be considered as well. Reoperation has been shown to be as successful as primary operations for growth hormone-secreting tumors [2]. Although, when the cavernous sinus is involved, reoperation is less successful. A multimodal combination of surgery, SRS, medical treatment, and reoperation maybe what is needed to produce the best results for some patients. With ACTH secreting macroadenomas with cavernous sinus invasion, remission increased from 20% to 40% after reoperation, SRS, and medical treatment. Similar results were seen with remission for macro-prolactinomas going from 17.6% to 47%. Growth hormone-secreting macroadenomas up to 52.6% remission with SRS and somatostatins used in combination with surgery compared to just 15.8% with surgery alone [7].

Surgery Described

Surgical Technique: Expanded Endoscopic Endonasal Approach to Cavernous Sinus

The patient is placed in rigid head fixation with the head turned toward the operator. We utilize neuromonitoring via somatosensory-evoked potentials (SSEPs) and extraocular muscle electromyography (EMG) for tumors that invade the cavernous sinus. Preoperatively, antibiotics are administered. We strongly believe in a team approach for endoscopic skull base surgery consisting of a neurosurgeon and an otolaryngologist head and neck surgeon, each with subspecialty training in endoscopic endonasal surgery. Endoscopic endonasal approaches to the cavernous sinus are detailed in Chap. 22. Figure 24.2 illustrates our endoscopic technique through step-by-step intraoperative photos detailing the expanded endoscopic approach to remove an extensive pituitary adenoma with cavernous sinus invasion. Broad exposure of the sphenoid sinus is performed, and mucosal flaps are preserved for later reconstruction. If a full transpterygoid approach is necessary, a nasoseptal flap pedicled on the contralateral side is fashioned, and the ipsilateral side pedicle is coagulated and cut to allow for the lateral transpterygoid corridor to be opened. A medial maxillary opening is widened, and the contents of the pterygopalatine fossa can be exposed after removal of the posterior wall of the maxillary sinus. Nevertheless, we tend to lateralize the periosteum covering the pterygopalatine contents, thus avoiding damage to neurovascular structures inside the fossa. However, the Vidian nerve can at times be exposed and lateralized but often will be sacrificed if dealing with malignancies. As such, most of the time this nerve is used to map the ICA. Tracing the Vidian canal back to the carotid level allows for safe identification of the carotid level as it turns from the petrous to the clival segment. The sella is drilled with a high-speed drill, and the dura is wide opened. A micro Doppler is used to confirm and map the ICA; neuronavigation can be helpful but should not be relied on

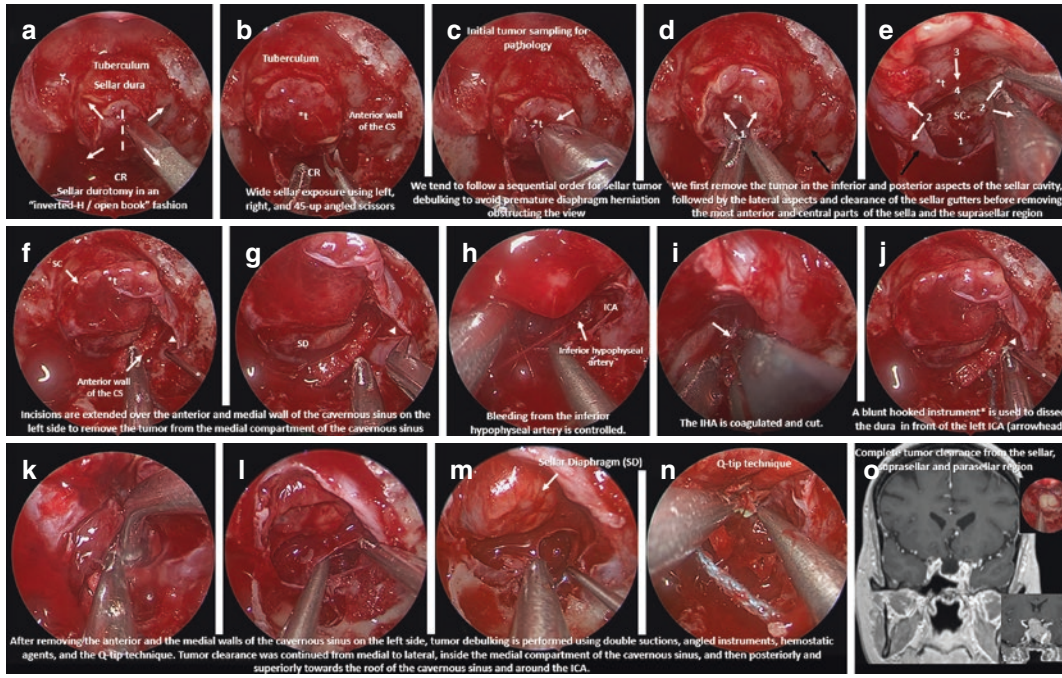

Fig. 24.2 Step-by-step intraoperative photos show the tumor debulking technique during the expanded sellar/parasellar EEA during the removal of an extensive pituitary adenoma with suprasellar extension and left-sided cavernous sinus invasion (**a**–**n**). Comparative pre- and postoperative coronal MRI can be seen in **o**, demonstrating a near-total resection and adequate skull base reconstruction. CS: cavernous sinus; CR: cavernous recess; *t: tumor; SC: sellar cavity; SD: sellar diaphragm; IHA: inferior hypophyseal artery

without Doppler confirmation when incising the lateral dura to expose tumor within the cavernous sinus. Venous bleeding is controlled with hemostatic agents; cavernous sinus invasion may lead to significant preoperative thrombosis and a relatively dry cavernous sinus due to the mass effect of the tumor. Brisk bleeding may herald the completion of the resection, "unplugging" the remaining sinus. Dissection of the pituitary adenoma is performed circumferentially, preferably extracapsular, although this is often impossible with cavernous invasion, and so debulking is performed as needed. Compared to many pathologies found within the cavernous sinus, many pituitary adenomas are relatively soft, and so, angled dissectors and suction tips may allow for additional resection beyond what boundaries straight dissectors reach. Maximal safe resection is done working from medial to lateral while preserving cranial nerves and the ICA. Alternatively, the medial wall of the cavernous sinus can be resected initially to gain early control of cavernous sinus bleeding [8, 25]. Stimulation with EMG probes here can be helpful in identifying the abducens nerve. Relevant surgical anatomy is demonstrated in Fig. 24.3. After maximal safe resection, the reconstruction is performed with Duragen© matrix inlay/onlay and a vascularized nasoseptal flap, as needed.

Case Illustration

A 57-year-old female presented with a history of gradual onset of bilateral blurry vision and tooth pain. Upon examination, the patient was neurologically intact, except for bilateral peripheral vision loss. MRI with contrast was obtained. It demonstrated a large sellar/parasellar mass with a superior suprasellar extension and significant displacement of the optic chiasm, and invasion of all compartments of the cavernous sinus on the left side. After blood samples and multidisciplinary team evaluation, in the setting

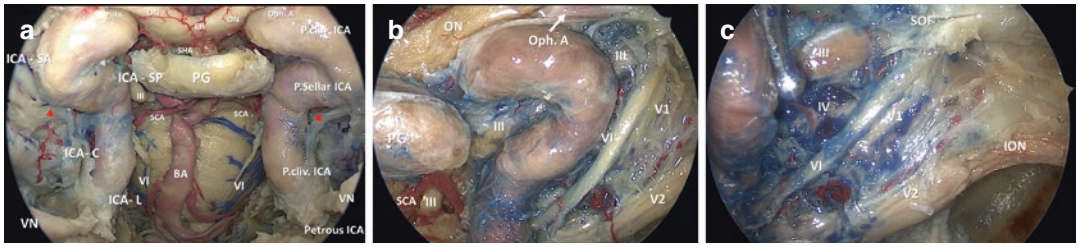

Fig. 24.3 Original stepwise cadaveric dissection images showing the anatomical landmarks of the expanded sellar and parasellar approaches to remove pituitary tumors with cavernous sinus invasion. The cavernous sinus and its neurovascular relations are exposed on both sides after bone and dural opening (**a–c**). III: oculomotor nerve; V1: ophthalmic nerve; V2: maxillary nerve; V3: mandibular nerve; VI: abducens nerve; C: clivus; BA: basilar artery; SCA: superior cerebellar artery; ICA-Sa: anterior bend of the internal carotid artery–parasellar segment; ICA-Sp: posterior bend of the internal carotid artery–parasellar segment; ICA-C: paraclival segment of the internal carotid artery; ICA-L: lacerum segment of the internal carotid artery; ICA-P: petrous segment of the internal carotid artery; PG: pituitary gland; VN: Vidian nerve

of the normal pituitary panel, and a young patient with progressive visual deterioration due to a sizeable nonfunctional macroadenoma, surgery was indicated. The patient underwent an expanded endoscopic endonasal transsphenoidal sellar/parasellar approaches with left-sided transpterygoid, transcavernous exposures. A step-by-step approach is depicted in Fig. 24.2. There were no intra- or postoperative complications, and the pathology was positive for LH/gonadotropin tumor (Ki-67 index of 1–2%). The patient remains stable after surgery with no postoperative deficits. Pre-and postoperative MRI can be seen in Figs. 24.2 and 24.4. It demonstrates a near-total resection of the tumor with a minimal residual in the lower aspect of the left cavernous sinus only observed during follow-up.

Summary Algorithm for Management

At diagnosis, endocrine and ophthalmological evaluations are needed to assess for subtle abnormalities. If the pituitary adenoma is a prolactinoma, then primary treatment is with a dopamine agonist and serial imaging to ensure stability or regression. If a prolactinoma is resistant to dopamine agonists and symptoms persist or tumor size increases on imaging, or if the patient cannot tolerate the side effects, then we pursue surgery. If the pituitary adenoma is not a prolactinoma and is symptomatic with either endocrine or mass effect, then the primary treatment is surgery. If asymptomatic and incidentally discovered, then observation is safe with serial MRIs. One caveat in our practice is if a patient is younger (generally, under age 65) and a pituitary adenoma is abutting or displacing the optic chiasm or prechiasmatic nerve, we offer upfront surgical resection instead of observation to prophylactically decompress and prevent future vision loss. This is a nuanced discussion to have with the patients, and if they choose further observation knowing the risk of future vision loss, that is a viable strategy as well.

When pursuing surgery, we prefer the endoscopic endonasal approach unless the pituitary adenoma is expanding outside the sellar region, past the lateral aspect of the cavernous sinus into the temporal fossa. In that case, an open craniotomy or combined or staged endonasal and craniotomy is considered. If an endonasal endoscopic approach is utilized, then evaluating the Knosp grade helps determine the degree of exposure needed. For Knosp grade 1 or 2 tumors, a midline standard endonasal approach should suffice. For Knosp grade 3 or 4 tumors, an attempt is made at gross total resection, then a middle turbinate resection with lateral transpterygoid extension is used; the degree of lateral exposure can be tailored to the lesion. For tumors classified as Knosp grade 4, a full transpterygoid approach

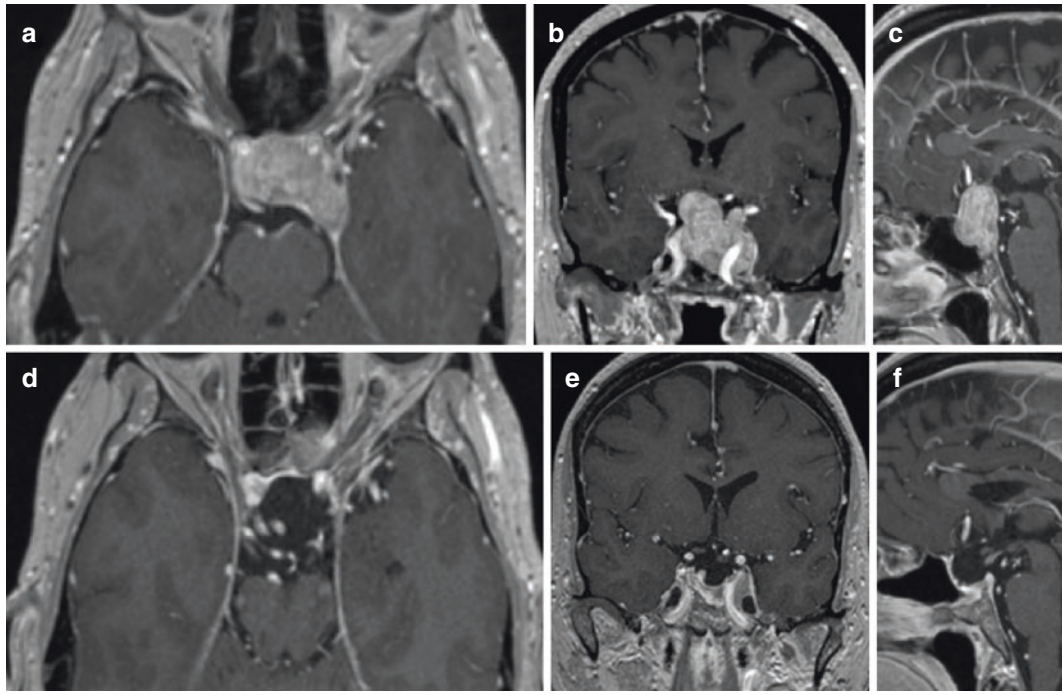

Fig. 24.4 Pre- (**a**–**c**) and postoperative (**d**–**f**) MRI with contrast of the patient whose procedure is described in case 1 can be seen. It demonstrates a near-total resection and adequate skull base reconstruction

with skeletonization and the ICA mobilization can be performed depending on how aggressive resection is planned.

The functional status of a pituitary adenoma is taken into account when deciding how aggressive to be with resection. For a functional pituitary adenoma, symptomatic relief is usually only achieved with a gross total resection as lack of biochemical remission is associated in functional adenomas with poor quality-of-life outcomes [34]. Our team thus prefers a more aggressive resection for functional tumors. If the pituitary adenoma is nonfunctioning and symptoms are related to mass effect, symptom control can be achieved with subtotal resection. The goal remains in nonfunctioning tumors to resect as much tumor as safely possible, but typically less aggressively than functional tumors. The residual tumor can be observed or treated with radiation therapy. Functional tumors with residual should be treated with SRS. This treatment algorithm is summarized in Fig. 24.5. There are a variety of options on how to treat residual tumor or recurrence, including the same surgical approach, a different surgical approach, radiation therapy, or observation. The treatment should be tailored to the individual patient with an experienced multidisciplinary team.

Conclusion

The mainstay of surgical treatment for pituitary adenomas with cavernous sinus invasion is an endoscopic endonasal approach for resection, sometimes with extended approaches, radiation, medical treatment, or open craniotomies. As such, excellent knowledge of surgical anatomy and nuances to remove the natural barriers preventing full access to the paramedian skull base, determines the ease of using the expanded sellar/parasellar approaches as the main gateway for all the coronal modules during endoscopic endonasal access (EEA) to pituitary tumors with cavernous sinus (CS) invasion. Meticulous utilization of operative landmarks and strategies can help avoid and mitigate surgical complications.

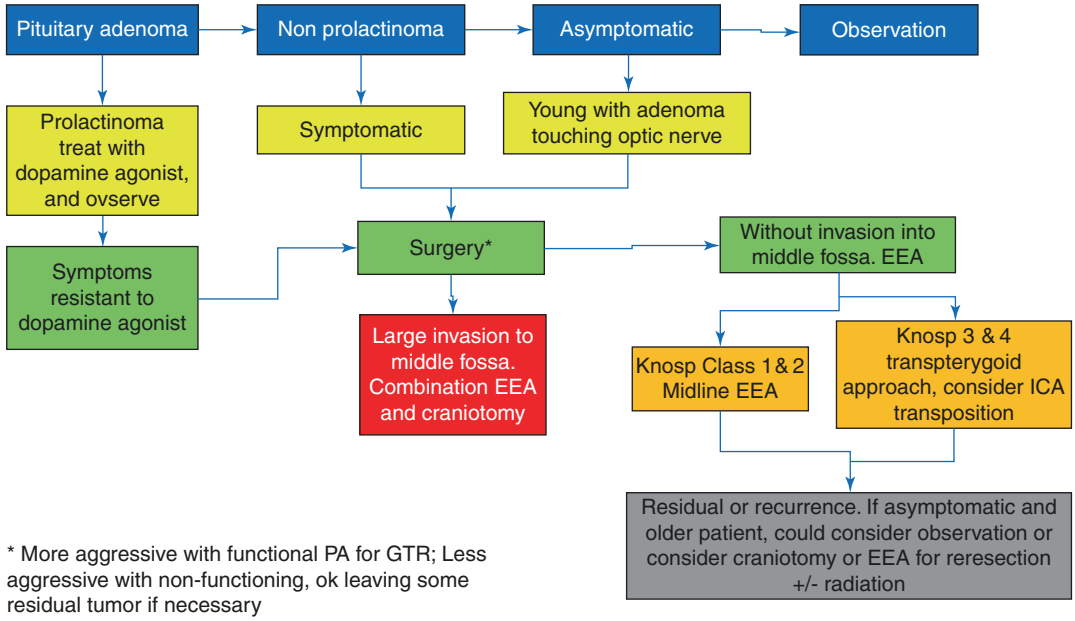

Fig. 24.5 Flow sheet of a treatment algorithm for pituitary adenomas with invasion into the cavernous sinus

Compliance with Ethical Standards

Funding
No funding was received for this research.

Ethical Approval
All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ohio State University Wexner Medical Center institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent
Informed consent was obtained from all individual participants included in this study.

Conflict of Interest Photographs in this chapter were taken at ALT-VISION at The Ohio State University. This laboratory receives educational support from the following companies: Carl Zeiss Microscopy, Intuitive Surgical Corp., KLS Martin Corp., Karl Storz Endoscopy, Leica Microsystems, Medtronic Corp., Stryker Corp., and Vycor Medical. Dr. Prevedello is a consultant for Stryker Corp., Medtronic Corp., and Integra; he has received an honorarium from Mizuho and royalties from KLS- Martin. Ricardo L. Carrau is a consultant for Medtronic Corp.

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