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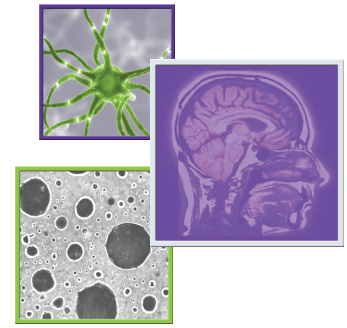

Pituitary adenomas: historical perspective, surgical management and future directions

Debebe Theodros[1], Mira Patel[1], Jacob Ruzevick[1], Michael Lim[1] & Chetan Bettegowda*[,1]

PRACTICE POINTS

- Patients with signs and symptoms of a pituitary neoplasm should undergo endocrine evaluation and imaging in order to fully appreciate disease quality.
- There are multiple approaches to resect pituitary adenomas including the transcranial, microscopic and endoscopic approaches.
- The transcranial approach may be used in cases of prominent extrasellar extension and questionable diagnosis, where further exposure may be necessary.
- The indications for microsurgical or trans-sphenoidal endoscopic surgery are similar, with the endonasal endoscopic approach being considered the gold-standard.
- The endoscopic approach has been associated with decreased morbidity, excellent rates of gross tumor resection and shorter hospital stays compared with other approaches.
- Patients should be monitored for complications related to endocrine function, as well as postoperative bleeding.

Pituitary adenomas are among the most common central nervous system tumors. They represent a diverse group of neoplasms that may or may not secrete hormones based on their cell of origin. Epidemiologic studies have documented the incidence of pituitary adenomas within the general population to be as high as 16.7%. A growing body of work has helped to elucidate the pathogenesis of these tumors. Each subtype has been shown to demonstrate unique cellular changes potentially leading to tumorigenesis. Surgical advancements over several decades have included microsurgery and the employment of the endoscope for surgical resection. These advancements increase the likelihood of gross-total resection and have resulted in decreased patient morbidity.

KEYWORDS

• microsurgery • pituitary adenomas • transsphenoidal surgery

Pituitary adenomas are a group of diverse neoplasms that typically arise from the hormone-secreting epithelial cells in the adenohypophysis of the pituitary gland and rarely metastasize [1–4]. Pituitary adenomas were classically categorized by their size and can vary dramatically with regards to their proliferative rate. Microadenomas are defined to be neoplasms <1 cm contained within the sella turcica, while macroadenomas are neoplasms ≥1 cm that may be contained within the sella turcica but often infiltrate into the superior, inferior and/or lateral extrasellar space [3,5,6]. Furthermore, pituitary neoplasms may be classified as functional or nonfunctional, where functional neoplasms present with clinical symptoms specific to increased hormonal secretion and activity. Nonfunctional pituitary adenomas commonly present due to mass effect or are identified incidentally on autopsy [6–8]. Prior to immunohistochemical analysis, adenomas were simply classified as acidophilic, which were

[1]The Johns Hopkins University School of Medicine, The Johns Hopkins University Department of Neurosurgery, The Johns Hopkins Hospital, Baltimore, MD, USA

*Author for correspondence: cbetteg1@jhmi.edu

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associated with acromegaly or gigantism; basophilic, which were associated with Cushing's disease; and chromophobic, which tended to be nonfunctional and present as a result of mass effect [9]. Development and use of immunohistochemical staining allows for further differentiation of pituitary neoplasms by *in vivo* hormone secretion, with the most common adenoma cell types being lactotrophic, gonadotrophic, somatotrophic, corticotrophic and less commonly, mammo-somatotrophic or thyrotrophic [3].

Epidemiology

Pituitary neoplasms represent an estimated 10–15% of all central nervous system (CNS) tumors and are the cause of approximately 25% of all surgical resections for CNS tumors [4,9,10]. Determination of the incidence and prevalence of pituitary neoplasms is challenging, as a subset of neoplasms are subclinical and discovered incidentally. Autopsy studies suggest pituitary neoplasms occur in approximately 1–35% of the general population [6,11–14]. Ezzat *et al.* performed a systematic review to evaluate the prevalence of pituitary tumors using imaging studies and determined the prevalence to be 22.5%, with a range between 1 and 40% in radiographic studies. In addition, the overall estimated prevalence of pituitary adenomas as assessed by imaging and autopsy studies was found to be 16.7% [6,12,13,15–22]. Symptomatic pituitary neoplasms may occur in up to 1 in 1064 people, with an overall population prevalence of approximately 80–90 per 100,000 [4,14,23–25].

Incidence appears to increase with age as approximately 3.5–8.5% of pituitary tumors are diagnosed prior to age 20, while an estimated 30% of individuals between the ages of 50 and 60 harbor incidentalomas [26]. Prolactinomas constitute the most commonly diagnosed secreting adenoma (35%) along with gonadotrophic adenomas (35%) followed by corticotrophic and somatotrophic adenomas (10–15% each), and thyrotrophic adenomas (2%) [3]. Pituitary neoplasms may actually represent a greater number of intracranial neoplasms as improved diagnostics continue to provide the ability to detect neoplasms at earlier stages of development [4,9,27].

Pathophysiology & clinical manifestations

The pathophysiology of pituitary adenomas is complex and varies between the different types of adenomas. Using X-chromosome inactivation, pituitary adenomas have been shown to be the result of monoclonal expansion of genetically altered adenohypophyseal cells [3,4,14,28–30]. The ensuing discussion relates to primary pituitary adenomas and excludes familial syndromes.

Disturbances in traditional oncogenic pathways have been implicated in the pathogenesis of sporadic pituitary adenomas. Constitutive expression of an isoform of the fibroblast FGFR4 has been implicated in the pathogenesis of nonfunctioning pituitary adenomas [31]. Additionally, upregulation of the phosphatidylinositol kinase/protein kinase B (Akt) pathway has been implicated in nonfunctioning as well as functional pituitary adenomas. Similarly, increased expression of pituitary tumor transforming gene (*PTTG*) has been observed in both functional and nonfunctional pituitary adenomas. Thus, it is plausible that increased expression of Akt1, Akt2 and *PTTG* may represent distinct mechanisms of formation [32–34]. Decreased expression of WIF1, sFRP2 and SFRP4 mRNA has been demonstrated in functional as well as nonfunctional pituitary adenomas and may implicate the WNT signaling pathway as another possible mechanism of formation [35,36]. Expression and activity of Protein Kinase C (PKC) was evaluated in patients who underwent resection and shown to be elevated, potentially implicating PKC in the pathogenesis of these neoplasms [37]. Additionally, chromatin remodeling via the zinc finger transcription factor, Ikaros, has been implicated in somatotrophic and lactotrophic neoplasm development [38].

Along with mutations affecting traditional oncogenic pathways, epigenetic changes have rapidly emerged as key components of the pathophysiologic changes that lead to pituitary adenoma formation [10,27,39–45]. Histone modification of DNA methyltransferase 3b (DNMT3b) has been implicated in such epigenetic changes [27]. These epigenetic changes result in silencing of multiple known tumor suppressor genes which are reviewed elsewhere [27,39,46–50]. Methylation or deletion of death associated protein kinase (DAPK), which serves the p19/p53 tumor suppressors, is associated with malignant tumors [51]. Finally, HMGA1b and HMGA2 have been shown *in vivo* to promote pituitary cell proliferation by increasing expression of PIT1, a transcription factor that aids in the normal development of the pituitary gland [52].

• Prolactinomas

Many potential mechanisms for the development of prolactinomas have been suggested.

TGF-α regulates multiple pituitary hormones, and increased expression has been shown to promote prolactinoma development in transgenic mice [10,53]. Additionally, EGF induces pituitary cells to release prolactin and increased expression of EGFR has been associated with more aggressive tumors [54,55]. Lastly, expression of FGF4 has been implicated in the development lactotrophic adenomas and prolactinomas [56].

Women suffering from prolactinomas typically present with oligomenorrhea or amenorrhea as well as galactorrhea secondary to hyperprolactinemia. Men suffering from macroadenomatous prolactinomas typically present with mass effect but can also present with impotence as well as decreased libido in the case of microadenomas. Patients suffering from mammo-somatotrophic may present with features consistent with acromegaly or gigantism with hyperprolactinemia [3,57].

• Gonadotrophic adenomas

The gonadotropin-releasing hormone (GnRH) is regulated via activin and inhibin, which increase and decrease GnRH levels, respectively. Gonadotrophic adenomas have been shown to express increased levels of activin receptors, which may lead to tumorigenesis [58]. Furthermore, a truncated activin receptor ActRIB (ALK4) isoform, which does not transduce growth arrest signals, has been demonstrated to be expressed exclusively by neoplastic cells [59].

Gonadotrophic adenomas may arise in patients with prolonged, untreated primary hypogonadism. Hormone secretion by these tumors is thought to be insignificant and they were previously characterized as nonfunctional adenomas [60,61]. As a result, patients with gonadotrophic adenomas generally present with symptoms secondary to mass effect such as diminished vision and headaches. Interestingly, symptoms related to excess hormone secretions are rare and occasionally manifest as increased LH levels. Men may present with increased testosterone, while females may present with increased levels of estradiol and endometrial hyperplasia [57].

• Corticotrophic adenomas

Corticotrophic hyperplasia secondary to primary adrenal failure may progress to adenoma formation [3,62]. A specific point mutation at the glucocorticoid receptor cDNA nucleotide 2054, valine to aspartic acid, has been shown to be associated with a threefold lower glucocorticoid receptor affinity [63]. Separately, a heterozygous missense mutation substituting isoleucine for asparagine at position 559 has been shown to result in glucocorticoid resistance by decrease binding sites by 50% *in vitro* [64].

Mutation of DKC1 has been associated with dysfunction and decreased expression of p27. Corticotroph tumors have also been shown to exhibit decreased Brg1 levels as well [65–67]. Additionally, altered expression of miRNA may also play a role in the development of these adenomas. Decreased expression of miRNA such as miR145, miR21, miR15a and miR16, and increased expression of miR122 and mi493 represent a potential mechanism by which these adenomas may form [68–70]. Corticotrophic adenomas typically present with Cushing's disease or symptoms suggestive of hypercortisolism [57].

• Somatotrophic adenomas

Somatotrophic adenomas have been characterized by gain of function mutations in the GNAS1 gene on chromosome 20q13 converting arginine to cysteine at residue position 201 and arginine replaced with glycine at residue position 227 in the Gs_{α} subunit. Vallar *et al.* posited these mutations may result in constitutive activation of the Gs_{α} subunit and thus represent one possible mechanism of increased secretion of growth hormone in somatotrophic adenomas [3,39,71–74]. Hayward *et al.* demonstrated that in 21 out of 22 adenomas, the mutations were in the maternal copy of the allele suggesting the GNAS1 gene may undergo monoallelic imprinting [39,71]. In addition, a substitution of histidine to leucine at codon 49 of the growth hormone receptor in some somatotrophic adenomas has been shown to result in defective hormonal autoregulation [75].

Patients with somatotrophic adenomas typically present with symptoms related to increased IGF-I levels. Patients harboring chronic somatotrophic adenomas present with acromegaly and gigantism in adult and pediatric patients, respectively [57].

• Thyrotrophic adenomas

Thyrotrophic adenomas may arise from chronic hypothyroidism [76]. In the setting of chronic hypothyroidism, prolonged secretion of thyrotropin-releasing hormone (TRH) from the hypothalamus leads to thyrotrophic hyperplasia followed by transition to neoplasia [10].

Additionally, deletion of thyroid releasing hormone (TRH) receptor exon 3 leads to decreased ligand binding [77]. Patients may develop thyroid hormone resistance and present as either euthyroid or slightly hypothyroid or patients may present with a goiter and mild hyperthyroidism [57].

Historical perspective

In 1889, Sir Victor Horsley, became one of the first surgeons to attempt a transcranial pituitary resection [78–84]. An Italian physician, Davide Giordano, developed what would eventually become the trans-sphenoidal approach for pituitary surgery at the turn of the 20th century [85]. Building upon the works of Giordano, Hermann Schloffer, an Austrian surgeon, performed the first trans-sphenoidal surgery in 1907 [86,87]. In 1910, both Hirsch and Halstead built upon the work of Schloffer and introduced what would be the precursor to the endonasal and sublabial approaches, respectively [88]. The complete endonasal transseptal transsphenoidal approach was performed for the first time by Oskar Hirsch, a Viennese otolaryngologist in 1910 [86,89–91]. Harvey Cushing was establishing a similar, albeit slightly different operation using a transnasal/submucosal approach [89]. Cushing transitioned from the trans-sphenoidal approach to the transcranial approach in the 1960s and as a result of his vast influence in the field of neurosurgery, the trans-sphenoidal approach was virtually abandoned [86,89,92]. Interestingly, his reported mortality rates between the trans-sphenoidal and transcranial approach were similar; however, a greater percentage of patients who underwent the transsphenoidal approach were discharged in improved conditions [93]. However, Norman Dott, a student of Cushing's preserved the trans-sphenoidal approach along with Hirsch in Boston [94].

Guiot, a French neurosurgeon and a student of Dott's, implemented the approach in his native France and combined intraoperative fluoroscopy as a means of providing improved visualization [94–96]. In 1965, Guiot introduced his fluoroscopy-guided trans-sphenoidal approach to Jules Hardy, a Canadian surgeon. Hardy further refined the use of fluoroscopy and incorporated the operating microscope [78,97]. The Hardy approach, along with modifications, has continued to be performed by neurosurgeons to this day [78,96].

The endoscope was invented in 1806 by Philipp Bozzini allowing for paranasal approaches to the pituitary [98]. In 1961, Guiot became the first neurosurgeon to use the endoscope for pituitary adenoma resection, but soon abandoned the endoscope due to unacceptable visualization of anatomical structures [95]. However, the endoscopic trans-sphenoidal procedure was not lost and would be reintroduced in the early 1990s [95]. Janokowski would become the first neurosurgeon to pursue the endoscopic endonasal approach to resect a pituitary adenoma [95,99–101].

Surgical management

• Preoperative considerations

Patients presenting with signs and symptoms of a pituitary neoplasm should undergo formal visual field evaluation, as well as endocrine evaluation focused on pituitary function as patients may require preoperative treatment. Patients should also undergo T1-weighted MRI with and without gadolinium contrast in order to appreciate tumor size and identify anatomical landmarks for surgery [102,103]. Additionally, T2-weighted MRI may provide information related to the fibrotic nature of each individual patient's adenoma and thus, the complexity of the case [102]. In cases of suprasellar extension, MRI is able to identify patients with a 'prefixed chiasm' where suprasellar extension shifts the optic chiasm superior and rostrally, which decreases surgical accessibility [102,103]. Patients unable to undergo MRI can undergo computed tomography (CT); however, this is a less favorable option.

The indications for microscopic or endoscopic trans-sphenoidal surgery are virtually the same. Patients with nonfunctional adenomas undergo surgery when these adenomas begin to exert mass effect upon surrounding structures (optic chiasm, parenchyma) with resultant headaches, or lead to hypopituitarism. Conversely, patients presenting with hormonal syndromes, such as acromegaly or Cushing's disease may proceed directly to trans-sphenoidal surgical resection. The exception is in the case of prolactinomas,where patients undergo surgical resection if they have failed to respond to dopaminergic medications, experienced severe side effects or experience mass effect and elect to undergo surgery. Additionally, patients with suprasellar extension may be better candidates for trans-sphenoidal versus microscopic surgery due to the enhanced visualization. The indications for transcranial surgery are primarily for patients harboring adenomas with prominent extrasellar extension, adenomas with extensive

fibrosis, failed trans-sphenoidal surgery, inadequate decompression and uncertain diagnosis. In addition, the presence of ectatic carotid arteries, severe sinus infection, or aneurysms warrants open craniotomy [102].

• Transcranial approach

The most commonly used transcranial approach is the frontosphenotemporal. A curvilinear incision is made from just inferior of the zygomatic arch to the contralateral midpupillary line. The scalp is dissected away and the fascia of the superficial temporalis muscle and artery are preserved. Another curvilinear incision is made into the fascia of the superficial temporalis muscle, exposing the frontalis nerve. The superficial temporal fat pad and fascia are elevated and reflected back along the skin flap. The temporalis muscle is elevated and subperiosteal dissection is performed to elevate the muscle flap anteriorly and inferiorly. The muscle flap is stabilized with fish hooks.

Craniotomy can be performed via a number of methods. One method is to create two burr holes and employ use of the pneumatic drill. After freeing the bone flap, a Penfield #3 dissector is used to free the flap from the dura. The frontal and temporal dura are dissected away from the sphenoid bone using a Penfield #1 dissector. The bone is smoothed with the pneumatic drill and use of a diamond bit and generous irrigation. Cottonoids are used to gently remove blood from the field prior to dura incision. The dural incision is semicircular and care is taken to avoid the bridging veins. Sutures keep the dural flap attached to the previously deployed fish hooks, which are under tension and prevent the dural flaps from entering the operative field.

A Nauta knife can be used to split the lateral sulcus, or self-retractors with tefla strips can retract the frontal and temporal lobes. The tumor is removed in a piece-meal fashion with constant visualization of critical anatomical structures. Titanium burr-hole covers and plates are used to attach the bone flap to the skull, and bone cement is used to cover and gap defects. The temporalis muscle is then reattached and the skin is closed [102].

• Microsurgical trans-sphenoidal approach

The trans-sphenoidal approach, as developed by Jules Hardy, continues to be used, with modifications. Initially, the patient is intubated, placed on prophylactic antibiotics and large gauze is packed into the oropharyngeal cavity to prevent bronchial aspirations. In addition, a lumbar spinal catheter may be inserted to allow injected air to push the suprasellar components of the tumors into the surgical field. The patient is positioned supine in order to bring the microscope in from above and the patient's head is on a horseshoe head holder with a C-arm portable image intensifier [104–107]. Historically, the sublabial approach was utilized, which involved a horizontal sublabial incision that extended from canine to canine and deep through to the periosteum of the premaxilla. Elevation of the periosteum and blunt dissection revealed the anterior septal cartilage perichondrium, which was incised. Identification of the subperichondrial space allowed the formation of a superior tunnel, which was allowed to communicate with the inferior tunnel with dissection, bilaterally. Excision of the bony septum ultimately revealed the anterior wall of the sphenoid septum [108]. The contemporary approach involves access to the sphenoid sinus via the trans-sphenoidal approach. Dissection posteriorly toward the rostrum of the sphenoid sinus is guided by intraoperative fluoroscopy. A Hardy speculum is inserted and access to the sphenoid sinus is achieved by removal of the vomer with a Middleton Rongeur, and the opening is widened with small Kerrison Rongeurs. Removal of the mucosa of the sphenoid sinus is performed to reduce intraoperative bleeding. Intraoperative fluoroscopy is utilized to confirm landmarks and the intraoperative microscope is used to approach the sella, providing superior visualization. The dura is exposed via bipolar coagulation and an H-shaped #11 scalpel blade and resection of the tumor begins inferiorly, taking care not to disturb the bilateral cavernous sinus and carotid arteries. Resection of the tumor is aided by blunt ring currettes. If CSF is encountered, a layer of gel foam and Surgicel is placed as a seal. Once resection is satisfactory, fascia lata harvested from the lateral thigh as well as muscle is placed in the pituitary fossa to prevent herniation of the suprasellar contents. A piece of bone from the sphenoid sinus is used to reconstruct the opening within the anterior sella. A fat graft, also obtained from the lateral thigh, is placed in the sphenoid sinus as additional support. Vaseline/Bacitracin gauze is inserted into each nostril and the sublabial incision is closed. The oropharyngeal cavity is suctioned, the large gauze packing is removed and the patient is extubated [104–107].

• Endoscopic endonasal approach

The patient is intubated, placed under general anesthesia and positioned in a supine matter such that the trunk is slightly elevated and the head rotated towards the surgeon and may or may not be secured by a pin fixation device. Intraoperative clindamycin is used and delivered via the endoscope's irrigation system and patients generally receive 2 g of cefazolin pre- and postoperatively. Decongestion of the nasal mucosa and with diluted adrenaline (1:100,000) or xylometazoline hydrochloride soaked cotton pads was historically used as there was decreased intraoperative bleeding; however, postoperative bleeding increases, thus, careful hemostasis using monopolar coagulation intraoperatively is used to prevent the incidence of postoperative bleeding [109]. Access to the sphenoid sinus can be gained via a variety of different ways which include endonasal or transnasal, one or two nostrils and with or without an endoscope holder or nasal speculum [99,101,110–118]. The endoscope, commonly a rigid 4 mm in diameter, 18 cm in length, 0-degree lens, is advanced through the floor of the nasal cavity of choice along the midline [119].

Lateralization or resection of the middle turbinate reveals the sphenoid ostia. An anterior sphenoidotomy is performed after visualization of the sphenoid sinus rostrum with either a power-drill or rongeur-assisted fracture. Drilling of the vomer occurs first with complete exposure of the bilateral rostrum portion of the sphenoid sinus achieved by submucosal dissection of the contralateral rostrum. Finally, Kurze scissors are used to penetrate the sphenoid sinus mucosa with resultant visualization of the sella, cavernous sinus and clivus. On the other hand, Kerrison rongeurs may be used to fracture rostral nasal septum, which is displaced contralaterally. The thick vomer is fractured using the septal breaker. At this point, bilateral dissection of the sphenoid sinus mucosa and removal of the anterior wall of the sphenoid sinus with ronguers provides adequate endoscopic view of the relevant anatomy [109]. Complete removal of the sphenoid septum is often warranted and exposes important anatomic findings within the sphenoid cavity, including the planum, clivus, medial and lateral opticocarotid recesses, sellar and clival carotid prominences. Image guidance in conjunction with micro-Doppler probe allows visualization of the carotid arteries and the dura is opened along the medial and superior cavernous sinus to avoid damage to critical structures [120]. A fixed endoscope is positioned within the nasal cavity allowing the surgeon to place two instruments under the endoscope. The sellar floor is opened using bone punches or a microdrill with the size of the opening dictated by the pathology. An incision into the dura in a midline position is made taking care of intercavernous entities.

Removal of macroadenomas is accomplished in stages, with removal of the inferior or posterior portion first, then lateral, and finally the superior aspect as gravity may cause this portion to fall into the newly created surgical cavity [109]. This approach serves to preserve the operative field. Extension into the medial wall can be resected using curved suction cannulas. Ring curettes in conjunction with suction cannulas are used to remove the tumor, which is often soften and white as compared with the more firm, orange-yellow or white anterior and posterior pituitary, respectively. Microadenomas may be encased by the pituitary with access obtained using the Jannetta 45-degree microdissector. Ring currettes are used in the dissection of these tumors, with a thin rim of normal pituitary removed using the Jannetta 45-degree microdissector to increase cure-rates. Macroadenomas may present themselves with incision of the dura mater. Care must be taken to not suction valuable specimens for pathology, emploring the use of the ring currettes initially. Once enough specimen is obtained, cannula suction of the tumor is performed to achieve total surgical resection or adequate deubulking. With fibrotic adenomas, suction cannula serves to hold the adenoma steady as ring curettes gently remove the adenoma to prevent traction. Debulking of the central portion is first achieved with 45-degree angled curettes, followed by 90-degree angled curette for tumor tissue along the sellar floor. The lateral portions of the tumor are removed ultimately revealing the medial walls of the cavernous sinus. The rostral tumor is removed with care to preserve normal pituitary tissue, with circumferential removal upon identification of the diaphragm. As aforementioned, the superior adenoma descends with adequate debulking and is removed. In the event that the tumor is fibrotic and the superior portion does not descend, further exposure of the bone at the planum sphenoidale or tuberculum sella, or use of a 30-degree lens endoscope may improve exposure. With large resections, the normal pituitary tissue may be stretched to resemble a

thin piece of transparent membrane. In order to prevent postoperative CSF leak, an abdominal fat graft or piece of Gelfoam sponge is used to support the pituitary tissue [109].

After adequate or complete removal of the lesion, repair of the sella using synthetic or resorbable materials or fat is performed as aforementioned. This serves to create a protective barrier, decrease dead space and prevent descent of the chiasm into the empty sellar space. Finally, hemostasis is achieved and irrigation along with removal of the endoscope occurs.

Pituitary adenoma considerations

Many factors play a role in determining if complete tumor resection for patients harboring pituitary adenomas using a trans-sphenoidal approach is possible. Subtotal resection of pituitary tumors, in rare cases can lead to serious complications such as postoperative bleeding, edema and mass effect. Physical characteristics of the tumor can play a substantial role in determining the surgical intervention. A large tumor diameter has been shown to be an independent predictor of subtotal resection and higher postoperative complication rates. Despite large tumor size, the trans-sphenoidal approach is often utilized; however, a transcranial approach may be used in conjunction in order to attain greater tumor resection [121–126]. In addition, tumors that demonstrate marked fibrosis represent dissection challenges when utilizing the trans-sphenoidal approach. An analogous situation may arise in patients treated with radiation therapy, as there can be significant development of scar tissue and adhesions [127–130]. The use of nasal packing as a means of controlling hemostasis in endoscopically performed operations is considered no longer significant, as careful dissection of the sphenoid sinus mcuosa, meticulous hemostasis have lead to a significant decrease in postoperative bleeding [109]. Furthermore, it is now believed that vasoconstrictors ironically lead to increase postoperative bleeding via a rebound vasodilatory effect [109]. Invasive tumors with evidence of vasogenic edema may represent degradation of the tumor pseudcapsule. A subtotal resection can lead to intracapsular hemorrhage and further exacerbation surrounding brain parenchyma warranting an open craniotomy [131]. Zada *et al.* reviewed 13 cases representative of complex sellar region tumors that underwent a trans-sphenoidal-based approach and reported subtotal resection in 12 of those cases. Of the 13 cases, 8 demonstrated suprasellar extension, 3 demonstrated retrosellar extension and 9 demonstrated intracranial vessel involvement [131].

Mass effect as characterized by compression of the optic chiasm and involvement of the optic nerve by pituitary adenomas is common. The relationship of the tumor to the optic chiasm, the level of involvement of the optic nerves and the degree of extension into the optic foramina must be considered and are often assessed on coronal T1-weighted MRI [131,132]. Direct visualization of these structures intraoperatively is often warranted and can be best appreciated via the transcranial approach [131,132]. Also, proper identification of the relationship of the tumor to arteries of the circle of Willis is critical. There is risk of damage to vessels directly involved with the tumor, commonly those of the internal carotid arteries (ICA), anterior cerebral arteries (ACA) as well as vessels outside of the surgical field of view, but adherent to the tumor capsule [131]. Failure to appreciate the tumor-vessel relationships may result in vasospasm and hemorrhage during or after trans-sphenoidal resection [133–136].

Extension of pituitary adenomas can occur in a suprasellar, retrosellar, or lateral fashion. Suprasellar extension of macroadenomas is the most common direction of extension and can result in penetration of the floor of the third ventricle and hypothalamus [131,137,138]. Suprasellar extension may be associated with ventricular infiltration and hydrocephalus as a result of obstruction of the aqueduct of Sylvius [139,140]. Displacement of the hypothalamus, and/or involvement of branches of the ICA and ACA can also occur in the setting of suprasellar extension. Macroadenomas with suprasellar extension may warrant a staged approach, such as initial trans-sphenoidal approach followed by interhemispheric-transcallosal approach, in order to enhance tumor resection and minimize potential complications as a result of tumor extension or involvement of cerebral vasculature [121,123,125,131,141]. Following resection, hemorrhage within the tumor cavity may necessitate a subsequent craniotomy. If reoperation is necessary, an interhemispheric-transcallosal craniotomy and subsequent transsylvian approach may be warranted [131].

Lateral extension into the cavernous sinus is less common and decreases the likelihood of gross total resection, especially when there is involvement of the cranial nerves, ICA and

adventitia [131,142–145]. In addition, lateral extension of pituitary adenomas is not limited to the cavernous sinus, but can also invade the middle cranial fossa [131]. Often, a multimodality approach consisting of an initial trans-sphenoidal approach followed by a transcranial operation, or incorporation of postoperative adjunctive treatment with medical therapy to decrease tumor burden prior to stereotactic radiosurgery, may be used to optimize resection [131,146–148]. Knosp *et al.* described radiologic criteria that would correlate with pituitary adenoma growth with cavernous sinus involvement intraoperatively [149]. According to their grading scale, Grade 0 was characterized as normal, Grade 1 demonstrates extension up to the intercarotid line, Grade 2 demonstrates tumor extension past the intercarotid line but no further than a line tangent to the intra- and supracavernous ICA, Grade 3 demonstrates extension past the tangent described in Grade 2 and Grade 4 is defined as total encasement of the intracavernous carotid artery [149].

Retrosellar extension of pituitary adenomas represent challenging cases related to access. A trans-sphenoidal-transclival approach in adenomas free of the vessels of posterior circulation can result in gross total resection [130,150–152]. Involvement of the optic tracts, pituitary stalk and/or posterior circulation, as well as the possibility of scar tissue and adhesions from previous operations decreases the likelihood of gross total resection using a purely trans-sphenoidal approach. As a result, staged operations or a trans-sphenoidal-transpetrosal approach can be considered in the hopes of achieving complete resection [153,154].

Complications

As with any surgical procedure, the transcranial approach is not without potential risks. The most common complication is frontal lobe damage, more often than not, due to excessive retraction. As aforementioned, gentle retraction, placement of tefla or cotton strips and/or separation of the sylvian fissure may reduce the risk of frontal lobe damage. Frontal lobe damage manifestation may appear as early as intraoperatively, in the form of blue brain parenchyma representing hemorrhagic infarction, which should be removed before closure. Postoperatively, frontal lobe damage may be subtle, but is indicated in patients reporting changes in memory, judgment, concentration, personality and anosmia [102].

A significant risk of optic nerve damage is possible when utilizing the transcranial approach, specifically of the ipsilateral optic nerve. The tumor should be debulked before the portions of tumor adjacent to the optic nerves are manipulated. Additionally, it is important to preserve blood supply to the nerves and chiasm as well. Patients may develop postoperative visual deterioration as a result of hematoma development within the tumor cavity, herniation of the chiasm into the pituitary fossa and ischemia. A feared complication is damage to the internal carotid artery; however, proper identification from the middle cerebral artery can help mitigate this risk [102].

Hypothalamic damage is rare, but may result in excessive excision and is devastating, as patients present with decrease thirst and hunger regulation. More common is damage to the anterior pituitary gland. The tumor commonly pushes the diaphragm superiorly which is ultimately cut and removed in the transcranial approach. Hormone replacement may mitigate decrease hormonal production; however, patients may never be the same. Another feared complication is diabetes insipidus (DI). Plasma osmolality greater than 295 mOsm/kg and urine osmolality less than 295 mOsm/kg in a patient with a urinary output of 200 ml/h for 3 h postoperatively is suggestive of DI and patients should receive desmopression and repeat plasma and urine osmolality measurements 24 h later. Salt-wasting syndrome may arise 1–2 weeks postoperatively with patients presenting with headache, coma and low plasma sodium. Damage to the pituitary gland may lead the syndrome of inappropriate antidiuretic hormone release and subsequent low plasma sodiums. Central venous line can determine if the etiology is based on low sodium or volume overload and patients can be treated with fluid and salt or fluid restricted depending on the etiology. Regardless, it is highly advisable to avoid rapid sodium correction for fear of central pontine myelinosis [102].

The indications for the endoscopic versus microsurgical trans-sphenoidal approach for resection of pituitary adenomas are essentially the same [119]. As a result, similar complications can arise, albeit for a variety of reasons. Tumor characteristics, such as size and extension, should be carefully evaluated and are often a cause of complications. Other causes of complications generally relate to surgical approach, surgical manipulation of the pituitary gland, hypothalamus and optic apparatus [155].

In the immediate postoperative period, patients should be monitored for hormonal dysfunction. Corresponding hormones for the pituitary subtype resected should be evaluated. Additionally, serum electrolytes should be monitored in the immediate postoperative period, 1 day later and 1 week later. Fluid intake and output is monitored, along with urine specific gravity and signs of DI, such as polyuria, polydipsia, dilute urine and increased serum osmolality/sodium. Barring serious complications, patients will typically be discharged after 1 hospital day.

Deviation from a midline and vertical approach and superior dissection may result in damage to the cribriform plate leading to anosmia and cerebrospinal fluid (CSF) leak in patients undergoing a trans-sphenoidal approach [97,156,157]. As aforementioned, small CSF leaks may be repaired with fat grafts; however, more robust methods of repair are required with larger defects. Vascularized flaps (including the nasoseptal flap) have demonstrated excellent success in repairs of large CSF leaks in the setting of endoscopic skull base operations. Thorp *et al.* describe their institutions experiences in a 151 patient series of 152 vascularized flaps, reporting three perioperative defects and five perioperative CSF leaks in total [158].

Temporary anesthesia of the upper lip and anterior maxillary teeth may arise after a sublabial incision [159–161]. In addition, saddle nose may arise with removal of the cartilaginous septum [156,157,160,162]. Nasal septum perforation may also occur and arises as a result of the development of opposing bimucosal tears. Certain measures decrease the likelihood of perforation and include submucosal injection of a local anesthetic and creation of a single flap with a superior–inferior tunnel on one side and a posterior submucosal tunnel on the other side followed by removal of the nasal cartilage [160,163,164]. Additionally, sinusitis may develop postoperatively and can be avoided with antibiotic use for 7–10 days and removal of nasal packing at the earliest possible time, postoperatively [155].

The sphenoid sinus contains critical structures including cranial nerves and the internal carotid arteries. Access to the sphenoid sinus can result in damage to the sphenopalatine artery, which may cause prolonged postoperative epistaxis [165–167]. Additionally, another notable complication of the endoscopic approach is hemorrhage as a result of damage to the septal branches of the sphenopalatine artery during sphenoidotomy or damage to the internal carotid artery during tumor removal [88]. Advancement of the speculum inferiorly may fracture the sphenoid body and structures contained within the sphenoid sinus [157,168]. Anatomical considerations are also important to understand in order to avoid complications. Some individuals exhibit a thin or absent bony plate shielding the optic nerves. Surgical manipulation and monopolar coagulation should be avoided within the sinus in order to minimize the risk of damage to the optic nerves [169]. Additionally, it is important to note that as many as 4% of individuals may not have bone overlying the anterior loop of the carotid artery, resulting in direct contact between the spenoid sinus mucosa and adventitia of the artery [169–171].

Intrasellar complications are potentially devastating. Preoperative localization of the carotid arteries is crucial as the distance between the arteries may span as little as 4 mm [159,169,172,173]. Damage to either ICA within the sellar region may result in vasospasm, vascular occlusion, carotid cavernous fistulas, or death [159,167,172,174–180].

Pituitary adenomas are confined to the extra-arachnoid space and the ability of the trans-sphenoidal approach to preserve the subarachnoid space contributes to its relatively benign surgical status [155]. However, penetration into the subarachnoid space is possible and not without complications. Particular structures that may be compromised include the optic nerves and chiasm, vasculature and hypothalamus [163]. Visual loss as a result of surgical trauma, vascular compromise or development of a hematoma may also occur in patients undergoing trans-sphenoidal surgeries [166–168,181]. Prolapse of the optic nerve or chiasm into an empty sella after removal of a macroadenoma may occur months to years later and represents another mechanism of visual loss [157]. Surgical manipulation of the suprasellar component of the tumor may also result in hemorrhage or swelling of residual tissue, visual deficits, hydrocephalus, altered mental status and death [137,156,165,166]. Finally, closure of the sella performed inadequately may result in CSF leak [155].

Postoperatively, deep-vein thrombosis (DVT) and pulmonary emboli can occur in patients who undergo trans-sphenoidal surgery [165,167]. As a result, DVT prophylaxis is a key component of the surgical and perioperative management in these patients.

Endocrine abnormalities are a frequent complication in trans-sphenoidal surgery. Anterior pituitary insufficiency may result, with McLanahan *et al.* reporting decreased anterior pituitary function in 12.5% of patients [182–184]. Anterior pituitary insufficiency is more likely to occur in macroadenomas and preservation of normal anterior pituitary tissue can be sufficient to maintain pituitary function [155,183,185]. Pituitary stalk manipulation during resection of microadenomas may result in temporary diabetes insipidus (DI) postoperatively in as many as 1.6–60% of trans-sphenoidal cases. However, permanent DI occurs in only 1.8–3.0% of cases [156,165,181,186]. Development of SIADH may occur, where sudden release of ADH as a result of necrosis of the neurohypophysis has been suggested as a potential mechanism [155].

Use of the endoscope provides a panoramic, wider working angle view of the sphenoid sinus allowing critical anatomical structures not previously visualized using the microscope to be identified. Enhanced visualization within the sinus and sella turcica allows for more delicate resection of adenomas [187]. In the hands of experienced operators, direct visualization of these structures has led to decreased rates of complications associated with damage of these structures, such as the hypothalamus, carotid arteries and optic nerves and chiasm compared with microsurgery [169,187]. Greater resection of recurrent or residual pituitary adenomas with fibrosis or scar tissues can be achieved using the endoscope relative to the microscope [188,189]. As experience accumulates, the endoscope has been shown to lead to lower complication rates, decreased functional disabilities and lower cosmetic disabilities as compared with transcranial and other trans-sphenoidal approaches [119,190]. In addition, use of the endoscope significantly decreases the incidence of upper lip, nasal complications, alveolar numbness and saddle nose deformities [88,189].

As a result of the close proximity of the endoscope with the operative field, excessive bleeding can obscure the lens of the endoscope and thus the surgeon's view of the operating field. Cleansing of the lens during the early endoscopic era consisted of extraction of the endoscope and manual removal of blood and debris from the lens. These disturbances to the operation can increase the length of the operation when performed by inexperienced surgeons [88]. Contemporary lens cleaning tools are incorporated into endoscopes and provide the surgeon with irrigation and suction capabilities along with the advantages conferred by the endoscope itself [187]. However, patients may present with significant delayed epistaxis up to 2 weeks after surgery. Damage to the internal carotid resulting in pseudoaneurysm formation may occur; however, hemorrhage from the posterior septal artery is the most common cause, and can be stabilized via endoscopic electrocoagulation [109].

Endoscopic approaches also present new challenges for the neurosurgeon. The endoscope provides a 2D view as opposed to the 3D view provided by the operating microscope. Depth perception is more difficult to appreciate with the endoscope, as the neurosurgeon must drive the endoscope in and out of the surgical field to appreciate the depth of the field. As compared with the microscope, the zoom and focusing capabilities of the endoscope are limited [88]. These disadvantages may increase the risk of damage to the posterior pituitary, cavernous sinus, or diaphragm leading to CSF leaks and DI [88]. A nasal speculum or retractor is rarely used in endoscopic procedures, and as a result, instruments enter the operative field out of the line of sight of the endoscope, potentially damaging the nasal mucosa and medial wall of the middle turbinate [88]. The greater view of the surgical field and visualization of anatomic landmarks helps to mitigate the depth concern [187,189]. Technological advances such as stereoscopic endoscopes are now available which restores depth perception to the surgeon, potentially decreasing complications associated with 2D vision [187]. Additionally, while the complication rate of endoscopic pituitary surgery may be high in inexperienced hands, recent studies have shown that a learning curve exists for the endoscopic approach that may be overcome with specialization [191,192].

Endoscopic versus microscopic trans-sphenoidal surgery

A comparison between endoscopic and microscopic trans-sphenoidal approaches suggests the endoscopic approach results in more favorable outcomes with regards to a variety of measurable outcomes. The length of surgery is significantly reduced in patients undergoing endoscopic versus microscopic surgery. Higgins *et al.* reported the total time patients were in the operating room was significantly reduced (187 vs 229 min) for the endoscopic as compared with microscopic techniques [193]. Additionally, Cho *et al.* reported a significantly shorter operative time of 1.0–3.0

Table 1. Studies comparing the endoscopic endonasal and microsurgical approaches to pituitary adenoma resection.

Study	Study type	n	Complications (%)		Overall remission rate (%)		Post-op CSF leak (%)	
			E	M	E	M	E	M
Frank *et al.*	CS	381	–	–	–	–	1.2	–
D'Haens *et al.*	CS	120	11.7	5	63	50	10	1.7
Kabil *et al.*	CS	300	12.4	–	90	–	1.7	–
Starke *et al.*	CS	113	–	–	70.8	68.3	2.8	2.4
Razak *et al.*	CS	80	22.5	55	94	57	10	15
Cheng *et al.*	CS	127	25	28.8	71	49.2	4.4	3.4
Cho *et al.*	CS	44	4.5	27	–	–	–	–
Zada *et al.*	CS	100	7*	–	–	–	3	–

†Major surgical complications only.
CS: Case series; E: Endoscopic approach; M Microsurgical approach.
Data taken from [194,207,208,210,215–217,219].

h compared with 1.5–4.0 h for endoscopic and microscopic techniques, respectively [194].

The hospital stay of patients undergoing endoscopic versus microscopic trans-sphenoidal surgery is also significantly reduced. The mean hospitalization ranged from 3.2 to 3.7 days and 5.3 to 8.3 days for patients who underwent an endonasal endoscopic approach versus a sublabial transseptal approach, respectively [194–196]. Furthermore, Dusick *et al.* reported 86% of patients who underwent endoscopic resection were discharged no later than day 4, whereas only 36% of patients who underwent the sublabial microscopic approach were discharged by day 4 [197]. The rate of DI between the endoscopic and microscopic approaches have been found to be different; yet, statistically insignificant [193,196]. Neal *et al.* reported 33% of patients who underwent the sublabial approach experienced DI versus 7 and 5% of patients who underwent transnasal microscopic and endonasal endoscopic resection, respectively [195]. Endoscopic trans-sphenoidal approaches are considered minimally invasive and have also been shown to result in a significantly lower rate of rhinotologic complications. White *et al.* reported decreased postoperative epistaxis and septal deviations in the endoscopic approach versus the microscopic approach, which were found to be statistically significant [196]. Finally, endoscopic trans-sphenoidal procedures demonstrate lower rates of postoperative pain and discomfort as opposed to a microsurgical approach. Casler *et al.* found 66.7% of patients who underwent endoscopic resection were pain free within the first postoperative day compared with only 13.3% of patients who underwent the microscopic approach [198,199]. Strychowsky *et al.* performed a systematic review and found less blood loss, shorter hospital durations and operative times, and fewer nasal complications with endoscopic surgery; however, they noted a higher incidence of postoperative CSF leak [200].

Goudakos *et al.* performed a systematic review of the literature and meta-analysis evaluating the efficacy and safety of endoscopic versus microscopic approaches. Eleven studies were included and there was no statistically significant difference found related to remission rates of functional adenomas, complete tumor removal and CSF leak [201]. However, they found increased DI ($p = 0.003$) and intracranial complications ($p < 0.05$) in patients undergoing microscopic resection, and further confirmed a significantly shorter hospital stay for patients undergoing endoscopic resection (3.7–4.4 days vs 5.4–5.7 days; $p < 0.00001$) [201].

Similarly, Zhu *et al.* performed a systematic review and meta-analysis of the literature focused on short- and long-term complications in patients undergoing either microsurgery or endoscopic trans-sphenoidal surgery. They found significantly shorter follow-up among patients undergoing endoscopic surgery ($p = 0.02$), lower rate of DI ($p < 0.0001$) and fewer complications ($p = 0.0008$), less blood loss ($p = 0.03$), higher rates of complete tumor resection ($p = 0.03$) and shorter hospitalization ($p < 0.00001$) [202].

Open craniotomy versus microsurgical versus endoscopic endonasal approach

Microscopic trans-sphenoidal surgery is the current gold standard for pituitary adenoma resection, but a number of retrospective cohort and case controlled studies, as well as meta-analyses, and systematic reviews have provided evidence for the endoscopic approach as an alternative to the microscope (Table 1).

Elliot *et al.* performed a meta-analysis comparing transcranial and trans-sphenoidal approaches in pediatric patients undergoing resection for craniopharyngiomas. There were differences in baseline characteristics, with patients undergoing transcranial resection demonstrating less visual loss, increased hydrocephalus rates and higher rates of increased cerebral pressure (ICP; all $p < 0.0001$) [203]. During the postoperative period, patients undergoing a transcranial approach experienced lower rates of total resection ($p < 0.0003$), higher rates of recurrence ($p < 0.0005$), increased neurologic morbidity, DI and vision loss (all $p < 0.0001$) compared with patients who underwent a trans-sphenoidal approach [203].

The endoscopic approach to pituitary adenoma resection has obvious advantages regarding invasiveness compared with the open approach, but studies have shown that the endoscopic approach is equivalent or better than the open approach for other measureable outcomes. Graham *et al.* compared 122 open pituitary surgeries to 71 endoscopic procedures, and they found a lower mean follow-up time (18.8 vs 49.3 months), lower recurrence rate (18.2 vs 28.4%, $p = 0.219$), shorter mean hospital stay (4.1 vs 6.0 days, $p < 0.001$) and lower complication rate (33.3 vs 43.4%) in the endoscopic group compared with the open surgery group [204]. Zada and colleagues discussed 13 cases of complex sellar region tumors and suggest that those tumors with suprasellar, retrosellar and lateral extension beyond the cavernous sinus are more amenable to open craniotomy because of the involvement of nearby critical structures such as the internal carotid and arteries and inherent limitations to complete tumor resection with an endoscopic approach [131]. In addition, fibrotic tumors, those that have invaded the brain parenchyma or create cerebral edema, those that have had previous surgery or radiation, those that invade the cerebral arteries or the optic nerve apparatus may be better served by an open approach to minimize risk to the patient and improve the likelihood of complete tumor resection [131]. Studies in surgical approaches to tuberculum sellae meningiomas hesitantly endorse the potential use of the endoscopic technique, but note that skull base bone and dural defects are difficult to repair endoscopically compared with transcranially, and therefore are at increased risk for postoperative CSF leak with the endoscopic approach [205].

At the least, the endoscopic approach provides outcomes similar to the transcranial approach, aside from increased risk of CSF leak [130]. Rigorous evidence-based outcomes assessment can help guide surgeons toward the appropriate surgical approach on a case-by-case basis [206]. Improvements in complication rates and follow-up with the endoscopic approach should not be overlooked; however, and at this time it has become a suitable alternative to the open surgical approach.

Frank *et al.* report that in 381 patients who received endoscopic endonasal surgery, complication rates were similar or less than the complication rates of microscopic pituitary surgery reported in the literature, and tumor removal was superior for endosellar lesions with endoscopic surgery [207]. Regarding endocrinologic outcomes, in one study comparing the two techniques in two series of patients operated upon by the same surgeon, the hypersecretion remission rate, or cure rate, for the endonasal approach was 63% compared with 50% with microsurgery, and the cure rate difference was most notable in grade II tumors (78% endoscopic vs 43% microsurgical) [208]. Similarly, Kabil and colleagues reported a 90% cure rate overall in their retrospective review of 300 patients who received endoscopic endonasal pituitary tumor resection compared with a microsurgical cure rate of 66–82% in the literature [209–214]. The same group reported a complication rate for the endoscopic approach of 12.4% compared with 67.3% with the microsurgical approach as reported in the literature due to enhanced visualization and increased total resection. Razak *et al.* have reported similar results in their retrospective comparison of 40 patients receiving the endoscopic approach and 40 patients receiving microsurgical resection; they found significantly higher tumor remission rates with the endoscopic approach (94 vs 57%) and a significantly lower postoperative residual tumor volume (6.6 vs 24.6%). They also report lower complication rates with the endoscopic approach (22.5 vs 55%) [215].

Other retrospective cohort studies did not find significant differences in perioperative complications, but did find that the endoscopic approach was significantly more efficient than the microsurgical approach, resulting in less blood loss, lumbar drain usage, shorter operative time and postoperative hospital stay [193]. Similarly, Starke *et al.* did not find statistically

significant differences in remission rate (70.8 vs 68.3%) nor were their complication rates, including CSF leak (2.8 vs 2.4%) statistically significant between endoscopic and microsurgical groups [216]. While Cheng *et al.* did find a statistically significant difference in disease control rate of macroadenomas in favor of the endoscopic technique (64.9 vs 27.3%), they did not find a significant difference in postoperative complications between the two techniques (25.0 vs 28.8%) [217]. Other groups have also found significant differences in operative efficiency between the two techniques; Cho and colleagues report that the endoscopic technique resulted in a hospital stay that was 2.1 days shorter than the microsurgical technique and an operative time that was 1 h shorter in the endoscopic group [194].

Olfactory disturbances are an important complication of pituitary tumor resection. Kahilogullari *et al.* found that the endoscopic approach resulted in significantly less olfactory disturbance ($p < 0.05$), with 2 cases of hyposmia and no anosmia in the endoscopic group, and 13 cases of hyposmia and 5 cases of anosmia in the microsurgical group [218]. Zada and colleagues quantified patient complaints postoperatively, and found that nasal packing (39%), removal of packing (36%) and breathing from the mouth (35%) were the most common complaints [219]. Additional comparative studies are needed to evaluate differences in patient experience between the endoscopic endonasal and microsurgical techniques with regards to olfactory disturbance.

Systematic reviews and meta-analyses corroborate the selected results discussed above [200,201,220,221]. The endoscopic approach has been found to be associated with reduced mean blood loss, shorter operative times, fewer nasal complications, shorter hospital stays, trends toward greater gross total resection and fewer incidences of diabetes insipidus; however, the endoscopic approach is associated with higher rates of postoperative CSF leak in some studies and similar rates or lower rates compared with microsurgery in others [200,201,220]. Conversely, Ammirati *et al.* in a meta-analysis did not find any significant differences between the two approaches, except that the endoscopic approach resulted in a significantly higher rate of vascular complications [222]. Komotar *et al.* compared the endoscopic endonasal approach with the microsurgical and open transcranial approaches; they found superior outcomes in gross total resection (47.2% endoscopic vs 30.9% microsurgery vs 9.6% open) with the endoscopic approach compared with both the open and microsurgical approaches, and a higher rate of mortality with the open approach compared with trans-sphenoidal approaches ($p = 0.004$) [223].

While retrospective cohort studies and meta-analyses generally favor the endoscopic endonasal approach for pituitary adenoma resection, conflicting data and limited populations in these studies make it difficult to definitively assess the differences between the endoscopic, microsurgical and open approaches.

Conclusion & future considerations

Pituitary adenomas are among the most common central nervous system tumors. Work related to the pathogenesis of the various types of pituitary adenomas has provided greater insight as to the molecular mechanisms through which these cells transform into adenomas. Advances in surgical procedures including the endoscopic trans-sphenoidal approach, as well as advances in surgical instrumentation have afforded surgeons greater ability to resect these lesions while decreasing patient morbidity. Lastly, new imaging systems along with stereotactic radiosurgery may provide new techniques to ensure tumor control while maintaining patient's quality of life.

Future directions for transphenoidal surgery aim to attain complete surgical resection. As a result, increased visualization of microadenomas and residual adenomas is of paramount importance. The use of high-field and ultra high-field intraoperative magnetic resonance imaging (iMRI) provides enhanced spatial resolution and increased rates of complete tumor resection and decreased recurrence rates [224]. Another paradigm is 5-ALA enhanced visualization of residual adenomas using an optical biopsy system and endoscopic fluorescence detection system. Eljamel *et al.* highlighted the potential benefit of such imaging systems by demonstrating the sensitivity of the optical biopsy system and endoscopic fluorescence detection system to be 95.5 and 80.8%, respectively [225]. Finally, stereotactic radiosurgery may play a role in patients who do not wish to undergo repeat surgical treatment for residual or recurrent adenomas and/or are medically unstable [226].

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•• **Provides an excellent comparison of the three approaches discussed in this review.**

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