# Endoscopic Transsphenoidal Pituitary Surgery: Results and Complications

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## Introduction

Endoscopic transsphenoidal pituitary surgery (ETPS) is rapidly replacing both the open transcranial as well as the transsphenoidal microscope-based techniques for resection of pituitary adenomas. This change has resulted from technological advances in lens and camera resolution, minimally invasive surgical instrumentation, and neuronavigation systems, leading to an improved field of view as well as more extensive approaches to skull-base lesions accessed through small portals [46]. Angled endoscopes provide visualization of recesses inside the sella and direct visualization of the medial wall of the cavernous sinus, not accessible by the operating microscope. ETPS is also less invasive, with less postoperative pain, shorter hospitalization, and fewer postoperative complications than microscopic transsphenoidal surgery [40]. The disadvantages include lack of depth perception, the need for an assistant or endoscope holder, and increased incidence of postoperative epistaxis.

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There is also a steep learning curve, requiring an average of 25–50 operations to learn the techniques necessary to operate using the endoscope [11]. Most neurosurgeons typically work with an otorhinolaryngologist, which can also limit efficiency relating to scheduling challenges. Despite this, experiences with ETPS have largely been positive, with benefits outweighing the costs.

In this chapter, we look at the surgical outcomes of functional and nonfunctional pituitary adenomas and further discuss complications associated with ETPS in general.

## Nonfunctional Adenomas

Nonfunctional adenomas are by definition pituitary tumors that do not produce hormones. Their biologic latency makes them usually diagnosed at the stage of macro (>1 cm) and giant (>4 cm) adenomas. Their presence is revealed by symptoms related to mass effect on the pituitary gland and the surrounding structures. Visual field disturbance from compression on the optic chiasm is the most frequent chief complaint, in addition to headaches. As the main goal of surgery is safe visual tract decompression (with or without gross total resection), ETPS has been shown to be very effective at achieving this outcome [10, 35, 57, 59, 83, 88, 90].

Visual symptoms are present in around 67% of pituitary nonfunctioning adenomas. Loss of visual acuity and cranial nerve palsies from cavernous sinus invasion can amplify the visual disturbance associated with the classic visual field defect – a bitemporal hemianopia. In our review of recent literature [10, 35, 57, 59, 83, 88, 90], ETPS surgery allowed for improvement in visual outcome in almost 80% of the patients, while gross total resection (GTR) was attainable in around 70% of cases (Table 15.1). The volume of the tumor and the invasion of the cavernous sinus were the main obstacles for achieving GTR [26, 59].

Cavernous sinus extension of pituitary adenomas can be found in around 35% of patients. Overall, endoscopic GTR can still reach 30–35% in these patients. Tumors with Knosp Grade 0–2 (none to minimal cavernous sinus invasion) can be considered surgically curable. When ETPS was compared to microscopic resection for Knosp Grade 0–2 tumors, Jane et al. found no statistically significant difference in the extent of resection and endocrinological complications between the two cohorts [10]. The ETPS group did, however, have shorter hospitalizations, but also higher rates of CSF leaks. Failure to achieve GTR is usually associated with the lateral extension of tumor into the cavernous sinus (Knosp 3–4), with recent data suggesting a superiority of the endoscopic approach [35] for these tumors.

Evaluation of residual/recurrence rates can be complex; it depends primarily on the definition of extent of resection and the duration of follow-up. Zhan et al. reported in a series of 313 patients, a global recurrence rate of 11% after 32 months (mean) of follow-up, with an increased risk in younger patients (40–55 years) when compared with the older (>65 years) group (15% vs. 7%) [90]. Table 15.1 summarizes the GTR, visual outcome, and associated complications following ETPS for nonfunctioning adenomas in recently published papers.

**Table 15.1** Results and complications of ETPS for nonfunctional pituitary macroadenomas

| | | # Pts | GTR | STR[a] | CS inv | Visual results | | | | Complications | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Author | Year | | | | | Preop VD | Postop VI | Unchanged | Worsened | CSF leak | Perm DI | Endo compl | Meningitis |
| Karppinen et al. [35] | 2015 | 41 | 23 | – | 20 | 31 | 30 | 0 | 1 | 1 | 1 | 2 | 0 |
| Zhan et al. [90] - older patients >65 | 2015 | 158 | 120 | 36 | 69 | 158 | 124 | 31 | 3 | 6 | 7 | 15 | 3 |
| Zhan et al. [90] - younger patients 40-55 yrs | 2015 | 155 | 119 | 34 | 67 | 155 | 126 | 27 | 2 | 6 | 5 | 13 | 2 |
| Yildirim et al. [88] | 2015 | 160 | 144 | 16 | – | 69 | 27 | – | – | 3 | 2 | 2 | 2 |
| Marenco et al. [50] | 2015 | 25 | 7 | 9 | 20 | 24 | 17 | 7 | 0 | 1 | 0 | 3 | 1 |
| Paluzzi et al. [59] | 2014 | 359 | 239 | 72 | 124 | 189 | 154 | 35 | 0 | 1 | – | 16 | 1 |
| Dallapiazza et al. [10] | 2014 | 56 | 54 | 0 | – | 22 | – | – | 2 | 4 | 0 | 3 | 1 |
| Nakao et al. [57] | 2011 | 43 | 20 | 23 | – | 43 | 42 | 1 | 0 | 4 | 1 | 3 | – |
| Total | | 997 | 726 | 190 | 300 | 691 | 520 | 94 | 8 | 26 | 16 | 55 | 10 |
| *Percentage* | | | *73%* | *27%* | *35%* | *69%* | *78%* | *20%* | *1%* | *3%* | *3%* | *6%* | *1%* |

*Pts* number of patients, *GTR* gross total resection, *STR* subtotal resection, *CS inv* cavernous sinus involvement, *Preop VD* preoperative visual disturbance, *Postop VI* postoperative visual improvement, *Perm DI* permanent diabetes insipidus, *Endo Compl* postoperative endocrinologic complications

[a]STR: Definition of subtotal resection is variable between studies

Preoperative pituitary dysfunction can be found in approximately 60% of patients. Reports of improvement of preoperative hypopituitarism after surgery are highly variable, ranging from 9 to 55% [15, 35, 50]. Given their large size, apoplexy in macro and giant nonfunctioning pituitary adenomas can represent a life-threatening complication. When diagnosed swiftly, ETPS has been shown to be effective in restoring cranial nerve palsies and visual deficits, while achieving GTR [91].

The main complications associated with ETPS for nonfunctional adenomas are as follows: Postop CSF leak rate of 3%, permanent DI rate of 3%, and meningitis 1% and other postop endocrinologic complication rate of 6%.

## Functional Adenomas

Given the nature of their secretions, treatment results for functional adenomas focus more on endocrinologic cure (EC) than gross total resection. Consensus is progressively being established over the remission criteria for the different subtypes [19, 39, 53, 77, 79]. The overall EC achieved by endoscopic endonasal surgery in recent literature is around 60–80% [20, 27, 51, 53, 59, 83]. Microadenomas are more inclined to biological remission, with EC usually superior to 80%, while macroadenoma are frequently harder to treat with EC percentages frequently lower than 60% [20, 24, 51, 53, 59]. Understandably, extension into the cavernous sinus reduces remission rates to less than 40% in most cases [24, 53, 59, 66] (Fig. 15.1a).

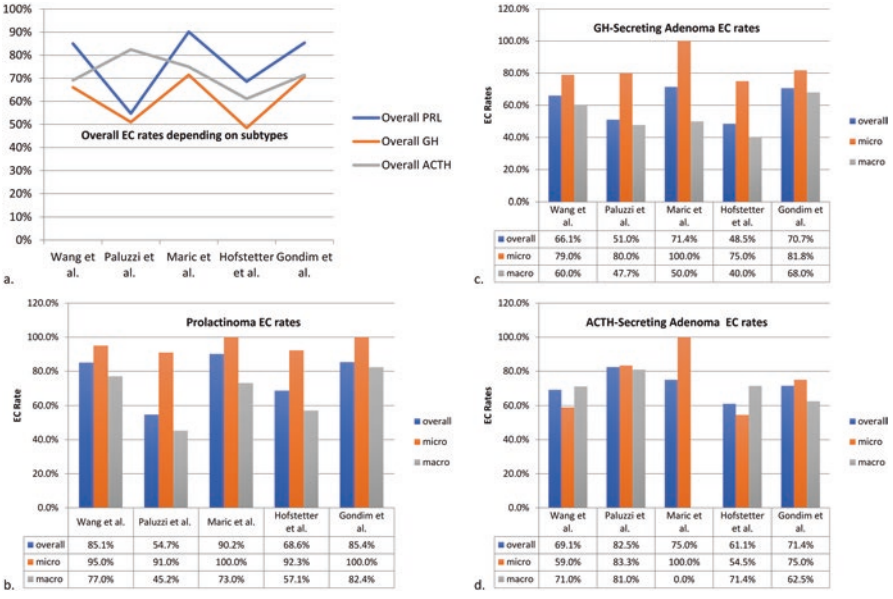


**Fig. 15.1** Results of ETPS functional pituitary adenomas (review of the recent literature [20, 27, 51, 59, 83]) (*EC* endocrinologic cure, *PRL* prolactin, *Micro* microadenomas, *Macro* macroadenomas)

## Prolactinomas

The majority of prolactinomas are sensitive to dopamine antagonists, however, a nonnegligible amount of tumors still exhibit resistance to medical therapy, necessitating the resort to surgery. A consensus is not yet available, but usually resistance is defined by the failure to attain normoprolactinemia and/or to reach tumor shrinkage of more than 50% after 3 months of maximal medical treatment [55, 85]. Drug response usually correlates to the tumor size. Resistance to bromocriptine and cabergoline is respectively around 10% and 25% for microprolactinomas, and 25% and 30% for macroprolactinomas [55, 81, 82, 85]. Only 21% of patients with microprolactinomas, and 16% of patients with macroprolactinomas demonstrated cure (normal blood prolactin) after treatment withdrawal, underlining the burden of long-term medical treatment [64]. Drug intolerance might also direct patients toward surgical management. A randomized multicenter study of 459 patients found that side effects associated with cabergoline and bromocriptine provoked 3% and 12% of patients respectively to stop their medical treatment [84], leading to surgical management. In cases of apoplexy and acute visual deterioration, surgery should be attempted prior to any medical therapy.

The surgical EC rate of microprolactinomas is predictably high (>90%) (Fig. 15.1a, b). Based on the excellent curative results achieved with surgery, some reports advocate surgical treatment as a first-line treatment in microprolactinomas [8, 32, 73]. A good needed majority of prolactinomas are however discovered at the macroadenoma stage (~60%), and the subsequent EC rate of ETPS is lower at approximately 76% [20, 26, 51, 59, 83] (Fig. 15.1a, b). The cure rate is inversely correlated to tumor size and preoperative prolactin levels [1].

A recent systematic review of the literature failed to identify any strong evidence that preoperative dopamine agonists can have beneficial or harmful effects on surgical results [5]. In residual and recurrent tumors, medical treatment might regain efficacy [25, 59]. In medication-refractory tumors, stereotactic radiosurgery can be proposed. Although stereotactic radiosurgery can control tumor growth, it is still associated with multiple side effects including panhypopituitarism and CN palsies [54].

## GH-secreting Adenomas: Acromegaly

Guidelines for the definition of an EC have been updated recently, complicating any analysis of previous papers. Currently, EC is defined by the normalization of IGF-1, with GH levels <0.4 ng/mL after OGTT (oral glucose tolerance test) or GH levels <1 ng/mL when randomly tested [19]. Previously, under the Cortina criteria, a cure was defined as normalization of IGF-1 and GH levels <1.0 ng/mL after OGTT [18]. Unsurprisingly, these more stringent criteria negatively impact the attained EC rates of recent reports. Paluzzi et al. described a drop of EC rates from 65 to 51% when applying the new definition [59]. Interestingly, the drop of EC rates was even larger for cavernous sinus invading macroadenomas (47–15%) [59], underlining the prior underestimation of the invasiveness of these tumors.

GH-secreting adenomas are classically diagnosed at the stage of macroadenoma (~80%), with preoperative and perioperative examination reporting dural invasion of the cavernous sinus in over 50% of patients [25, 59]. This explains the lower rate of EC attained by surgical treatment alone in GH-secreting adenomas (~60%) when compared to other subtypes [20, 26, 51, 59, 83] (Fig. 15.1a, c). In addition to tumor size and invasion of the cavernous sinus as factors influencing postoperative remission [25], high preoperative GH levels have also been shown to be inversely correlated to postoperative remission rates [2]. While intraoperative GH levels are not clinically useful [80], early postoperative normalization of GH levels has been shown to be a good prognosticator of long-term outcome in acromegaly [34, 36].

Somatostatin analogue injections like octreotide and lanreotide, typically administered to patients on a monthly basis, suppress GH production in about 70% and cause tumor shrinkage in 30–50%. These are usually reserved for when first-line surgical treatment is impossible. Even though multiple reports emphasize a positive effect of preoperative medical treatment on short-term postoperative remission, an improvement of long-term ER is still under debate [16, 49, 67, 75]. Surgery still represents the first-choice treatment, since it offers a cost-effective and a safe cure to a good proportion of patients.

When it is not curative, surgery can still allow for tumor debulking, which not only increases the postoperative response to medical treatment [7, 25, 56], but also improves the efficacy of stereotactic radiosurgery treatments, and reduces its side effects. In association with surgery, Paluzzi et al. reported that these adjuvant treatments increased the EC rate in cavernous sinus invading macroadenomas from 15 to 52% [59]. The recurrence rate after long-term EC in acromegaly tends to be lower than other adenomas, but still ranges between 3 and 10% at 5 years follow-up [56, 58]. Reoperation for recurrence can still achieve satisfying results, with 57% of patients reporting EC in a series by Yamada et al. [87].

## ACTH-secreting Adenomas: Cushing's Disease

No consensus is available over the biochemical definition of EC in ACTH-secreting adenomas. Differences in preoperative adjuvant medical treatments, postoperative hormonal replacement therapies, and perioperative hormone testing protocols, add to the complexity of any standardization. Current guidelines tend to suggest early hormonal testing while withholding treatment with glucocorticoids, or at least using low nonsuppressive doses [3, 47, 72]. Close monitoring is mandatory to diagnose early and treat any signs of hypoadrenalism [3]. Multiple reports suggest that morning serum cortisol level of <2 μg/dL, UFC (Urine Free Cortisol) of <20 μg/24 h, and ACTH serum level of <5 ρg/mL are highly predictive of long-term remission and low recurrence [3, 23]. Patients with a cortisol level between 2 and 5 μg/dL can still be considered in remission but should have closer hormonal monitoring [3]. Patients with higher cortisol levels are diagnosed with persistent disease.

The EC percentages achieved by surgery alone are usually around 70% [20, 26, 51, 59, 83]. In contrast to prolactin- and GH-secreting adenomas, where the EC rate

is inversely linked to tumor volume, the EC rate in ACTH-secreting adenomas is associated with the identification and resection of small tumors [20, 26, 51, 59, 83] (Fig. 15.1a, d). Even though usually discovered and treated as microadenomas (70%), ACTH-secreting adenomas still display a nonnegligible rate of dural invasion, as reported by Lonser et al. who identified 34% with histologically confirmed dural invasion, while preoperative MRI predicted it in only 4% of these cases [47]. Interestingly, the larger size of the ACTH-secreting adenomas as well as their location in the far lateral potion of the anterior lobe of the pituitary gland was associated with higher rates of dural invasion [47].

If the first surgery is ineffective in achieving EC, either because no tumor was seen on preoperative imaging or because no tumor could be identified intraoperatively, repeated surgery after inferior petrosal sinus sampling is an option. Hemihypophysectomy can be performed if the inferior petrosal sinus sampling localizes the tumor to one side [20]. Surgery is the mainstay of treatment for ACTH-secreting adenomas. Even for recurrent disease, a second surgery offers a reasonable possibility (61%) of immediate remission [63]. If the operation is not successful, other treatments, including pituitary radiation, medical therapy, and even bilateral adrenalectomy, may be required.

Multiple medical therapies are available as a complement to surgical treatment. Various pituitary-targeting drugs (pasireotide, cabergoline), steroidogenesis inhibitors (ketoconazole, metyrapone) and glucocorticoid receptor-blockers (mefeprostone) can be used as first-line medical therapy only when surgery is not an option, or if surgery has failed [9]. The substitutive treatment of postoperative panhypopituitarism can be less disturbing to the quality of life of these patients than some of these drugs.

As in other adenoma subtypes, radiosurgery can represent a useful option when the tumor is locally invasive [59, 83]. Sheehan et al. reported, in a retrospective study of 96 patients, a 70% remission rate after Gamma Knife surgery, with a median time to remission of 16 months [74].

## Complications

Complications of endoscopic transsphenoidal pituitary surgery (ETPS) can grossly be divided into the categories of sinonasal, neurologic, infectious, vascular, and endocrine.

In order to access the skull base through the endonasal approach, a significant amount of dissection must occur involving the nasal cavities and sinuses which may lead to postoperative sinonasal complications. Specifically adhesions, septal perforations, epistaxis, and acute and chronic rhinosinusitis may develop [45, 76]. Typically close follow-up by a rhinologist during the first postoperative year can help identify these adverse events and treat them appropriately, either with nasal drops, antibiotics, or more frequent surveillance. Sinonasal quality of life (QOL) following endoscopic pituitary surgery reaches a nadir at two to three weeks and recovers by three months postoperatively [44, 60]. Nasoseptal flap elevation does

not significantly affect QOL [30]. Subtotal resection of tumor negatively impacts postoperative QOL, in both secreting and nonsecreting pituitary adenomas [52].

Once the skull base has been encountered, this site becomes the location of the most common complication of transsphenoidal surgery—a CSF leak. Initial reports of endonasal transsphenoidal surgeries had very high rates of CSF leaks, mostly a result of inadequate repair of the skull base upon completion of the surgery. Advances in vascularized flaps and various multilayer closure techniques have reduced the rate of CSF leak to less than 5% [22, 28, 33, 41, 48], with some centers developing case-specific protocols to drive down the postoperative CSF leak rate close to 0% [62]. Risk factors that predispose a patient to develop postoperative CSF leaks include large skull-base exposures, prior radiation, reoperations, and other intracranial factors which result in elevated intracranial pressures [29].

Usually clinically diagnosed, CSF leaks are characterized by high-volume clear fluid dripping from the nose, which may or may not be position dependent. Less obvious leaks may present more insidiously, with dripping in the back of the pharynx, salty taste or positional headaches which resolve with lying flat. The use of intrathecal fluorescein, usually administered via lumbar puncture or lumbar drain preoperatively, can help identify CSF leaks intraoperatively and in the immediate postoperative period, with a characteristic staining of CSF to a fluorescent yellow-green color [68, 70].

CSF leak also means that there is communication of the nasal cavity and the intracranial compartment, which can lead to pneumocephalus and meningitis. Pneumocephalus can result in mass effect similar to blood or other intracranial lesions. Tension pneumocephalus can be a fatal complication caused by entraining air through the skull-base defect without a release mechanism and should be considered a surgical emergency.[69, 89]. Placement of a lumbar drain should be avoided in this circumstance since it may promote downward herniation. Reoperation for repair of the leak is generally required.

Infection is another concern following endoscopic transsphenoidal surgeries. The rate of infection and CSF inoculation however, is relatively low, despite the fact that the nasal cavity, which is colonized by multiple organisms, is the primary passageway to the sterile intracranial environment. Postoperative meningitis is rare with a reported incidence ranging from 1.6 to 8% [6, 31]. Patients will typically present with meningeal signs including headaches, neck stiffness, and photophobia. Fevers and chills are frequently reported, and laboratory studies may demonstrate elevated WBC, ESR, and CRP. The most common risk factor for meningitis is a postoperative CSF leak. Meningitis without the existence of a leak is extremely rare.

The rate of intracranial abscess formation after endonasal skull-base surgery is quite low [43], as most patients often seek medical attention before the frank development of cerebritis or a walled off abscess. Lastly, as mentioned previously, rhinosinusitis can have less emergent consequences but is reported to occur in about 8% of patients undergoing endoscopic transsphenoidal procedures [6].

Vascular injury and cerebrovascular accidents are also rare but potentially catastrophic complications of transsphenoidal pituitary surgery. Minor bleeding is frequently encountered during these procedures, usually from the nasal mucosa,

sinonasal arteries, and bone bleeding, which can typically be controlled with cautery or bone wax. Once through the floor of the skull base, venous bleeding from the cavernous sinus may be encountered which can be tamponaded through packing or other hemostatic agents.

Injury to the internal carotid artery, though rare (<0.125%), is the gravest complication in any transsphenoidal surgery and can lead to exsanguination and stroke if not dealt with expeditiously [17, 37, 61, 71]. Long-term sequelae of internal carotid injury may also occur, including pseudoaneurysm carotid-cavernous fistula formation [17, 21]. Although several techniques have been proposed to control an arterial injury, the most reliable is packing and endovascular occlusion of the artery [71].

Lesions with suprasellar extension such as large pituitary adenomas, craniopharyngiomas, and meningiomas may be intimately involved with the circle of Willis and various perforating vessels. In these situations, large-territory strokes are exceedingly rare, but possible. Therefore, identification and careful preservation of the anterior and posterior cerebral arteries, recurrent arteries of Heubner, and anterior and posterior communicating arteries is of utmost importance. Arterial injury can often lead to subarachnoid hemorrhage, which can in turn lead to seizures and development of hydrocephalus.

Neurologic complications encountered postoperatively are primarily attributed to cranial neuropathies. While many patients with pituitary tumors may present with varying degrees of visual field deficits and ophthalmoplegia, the incidence of these developing postoperatively is still relatively low, on the order of 1–2% [6, 65]. Even when surgery is performed in the cavernous sinus, the rate of permanent cranial neuropathy is nearly 0% with a rate of transient neuropathy of 5.6% [86]. The abducens nerve is the most medially oriented cranial nerve within the cavernous sinus and, therefore, can be injured leading to a lateral gaze palsy. Inadvertent breaches through the lamina papyracea can injure the medial rectus muscle leading to weakness of ipsilateral medial gaze and diplopia [4].

The optic nerves and chiasm may be intimately involved with larger pituitary tumors and require careful dissection to prevent any injury. In addition to careful preservation of the nerves themselves, the tenuous blood supply to these nerves must be respected as inadvertent thermal injury can lead to ischemic complications and permanent visual defects. The same holds for the ophthalmic artery, which branches from the ICA after it emerges from the cavernous sinus. Injury to this vessel can also lead to unilateral blindness, though robust collateral circulation can circumvent this complication in some cases [42, 78].

Orbital/retro-orbital hematomas occur in less than 1% of endoscopic transsphenoidal surgeries and can present with any combination of unilateral or bilateral ophthalmoplegias. This complication is time sensitive and the rate of neurologic recovery is proportional to the time of decompression. Any unexplained postoperative ophthalmoplegia, visual acuity decline, or progressive proptosis should be immediately investigated with imaging.

Endocrinopathies may present postoperatively as a result of manipulation of the pituitary gland and stalk or disruption of blood supply to the organ. Preoperative endocrine labs should be assessed on all patients to establish a baseline. The frequencies of

postoperative anterior pituitary insufficiency is highly variable between reports. The average is approximately 6% (Table 15.1), but rates seem to get lower in specialized high-volume centers at around 2–3% [13, 25, 59]. Postoperative anterior hypopituitarism is also correlated to the tumor size, particularly when the adenoma is larger than 20 mm [12, 14]. Giant adenomas are even at a higher risk with around 5–9% of postoperative deficiencies [33, 38, 57]. Frequently more than one axis is impaired. The corticotropic axis seems to be the most frequently damaged, followed by the thyrotrophic [59]; this observed propensity is probably skewed due to the important functional role of these axes in adults.

Diabetes insipidus (DI) is the most frequently encountered endocrinopathy in transsphenoidal pituitary surgery. About 4–20% of individuals may experience transient DI whereas 1–5% experience permanent DI [77]. This occurs from disruption of the posterior pituitary gland, pituitary stalk, or other fibers arising from the hypothalamus which leads to dysregulation of antidiuretic hormone (ADH). This results in disruption of water balance regulation leading to dehydration and hypernatremia. Postoperative net fluid balance, urine specific gravity, hourly urine output, and frequent sodium levels should be carefully monitored, and appropriate treatment with desmopressin instituted. Giant adenoma appears to be associated with an increased risk for developing postoperative permanent DI with incidence rates stretching to 10% [12, 38, 57].

The second most frequent endocrinopathy following transsphenoidal surgery is hypocortisolemia. Decreased release of ACTH from the pituitary axis results in low levels of circulating cortisol, which is best assessed in the morning hours of postoperative days 1 and 2. Hypocortisolemia can result in mild gastrointestinal symptoms, dizziness, fatigue, and headaches, but can progress to severe hypotension without treatment. For those patients who become hypocortisolemic postoperatively, steroid replacement therapy should be initiated, typically with hydrocortisone twice daily.

## Conclusion

As advances in lens technology and extended instrumentation have evolved over the past two decades, endoscopic transsphenoidal surgery, for pathologies of the sellar and suprasellar region, has become a valuable commodity to the skull-base surgeon. This approach allows for excellent visualization and safe resection with relatively few complications compared to traditional open microneurosurgical approaches.

Endoscopic transsphenoidal pituitary surgery (ETPS) has excellent outcomes, with gross total resection (GTR) rates upward of 70% for nonfunctioning macroadenomas, and endocrinologic cure rates of 60–80% for functional tumors. The GTR rates are higher for smaller tumors and those without cavernous sinus invasion. For tumors invading the cavernous sinus, the outcomes for ETPS are superior to that of microscopic transsphenoidal pituitary surgery. With further refinement in endoscopic technology (3D endoscopes) and endoscopic instrumentation, along with increased operator proficiency, outcomes for ETPS will continue to improve with time.

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