Complications associated with microscopic and endoscopic transsphenoidal pituitary surgery: experience of 1153 consecutive cases treated at a single tertiary care pituitary center

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OBJECTIVE Pituitary adenomas (PAs) are benign neoplasms that are frequently encountered during workup for endocrinopathy, headache, or visual loss. Transsphenoidal surgery remains the first-line approach for PA resection. The authors retrospectively assessed complication rates associated with transsphenoidal PA resection from an institutional database.

METHODS A retrospective analysis of 1153 consecutive transsphenoidal pituitary adenoma resections performed at the Keck Hospital of USC between November 1992 and March 2017 was conducted. Microscopic transsphenoidal resection was performed in 85.3% of cases, and endoscopic transsphenoidal resection was performed in 14.7%. Analysis of perioperative complications and patient and tumor risk factors was conducted.

RESULTS The overall median hospital stay was 3 days. There was 1 perioperative death (0.1%). Surgical complications included postoperative cerebrospinal fluid leak (2.6%), epistaxis (1.1%), postoperative hematoma (1.1%), meningitis (1.0%), cranial nerve paresis (0.8%), hydrocephalus (0.8%), vision loss (0.6%), stroke (0.3%), abdominal hematoma or infection (0.2%), carotid artery injury (0.1%), and vegetative state (0.2%). Perioperative medical complications included bacteremia/sepsis (0.5%), pneumonia (0.3%), myocardial infarction (0.3%), and deep venous thrombosis/pulmonary embolism (0.1%). Endocrine complications were the most frequent, including transient diabetes insipidus (4.3%), symptomatic hyponatremia (4.2%), new hypopituitarism (any axis) (3.6%), permanent diabetes insipidus (0.3%), and adrenal insufficiency (0.2%). There were no significant differences between microscopic and endoscopic approaches with regard to surgical complications (6.4% vs 8.8%, $p = 0.247$) or endocrine complications (11.4% vs 11.8%, $p = 0.888$). Risk factors for surgical complications included prior transsphenoidal surgery (11.4% vs 6.8%, $p = 0.025$), preoperative vision loss (10.3% vs 6.8%, $p = 0.002$), and presence of PA invasion on MRI (8.5% vs 4.4%, $p = 0.007$).

CONCLUSIONS In this single tertiary center study assessing complications associated with transsphenoidal PA resection, the rate of death or major disability was 0.26%. Risk factors for complications included prior surgical treatment and PA invasion. No differences in complication rates between endoscopic and microscopic surgery were observed. When performed at experienced pituitary centers, transsphenoidal surgery for PAs may be performed with a high degree of safety.

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KEYWORDS pituitary adenoma; transsphenoidal; complications; microsurgery; endoscopy; pituitary surgery

PITUITARY adenomas (PAs) are benign neoplasms and are the most common sellar masses. A recent cross-sectional study reported a prevalence of 77–94 cases per 100,000 individuals.¹⁵ In addition to hormonal dysfunction, PAs frequently compress surrounding struc-

tures or invade the cavernous sinus, leading to visual field deficits, decreased visual acuity, anterior pituitary dysfunction, and/or headaches.²⁹ Patients with hormone dysfunction, neurological deficits, or prolactinomas in whom medical management has failed are referred for surgery.

ABBREVIATIONS ACTH = adrenocorticotrophic hormone; DVT = deep venous thrombosis; GH = growth hormone; PA = pituitary adenoma; PE = pulmonary embolism.

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The transsphenoidal approach to the sellar region remains the mainstay of treatment for a majority of PAs requiring surgical intervention. The transsphenoidal approach was pioneered in 1907 by Hermann Schloffer and gained traction in the 1910s and 1920s under the leadership of Oskar Hirsch and Harvey Cushing, with Hirsch operating endonasally and Cushing operating sublabially.^{27,33} Despite significant drawbacks to the approach in the preantibiotic era, particularly with regard to limited visualization of the sella, Hirsch never stopped advocating for the endonasal transsphenoidal approach. In contrast, Cushing came to heavily favor transcranial surgery, believing that it achieved superior symptom resolution and decreased tumor recurrence. He abandoned the transsphenoidal approach altogether by 1929, and while his subfrontal and Hirsch's endonasal mortality rates were comparable at 4.5% and 5.4%, respectively, most contemporary neurosurgeons followed suit. Norman Dott, who spent a year with Cushing in 1923–1924, and Gerard Guiot, who observed Dott operate in 1956, were exceptions to this rule and continued operating transsphenoidally.^{19,26} However, it was not until Jules Hardy introduced the use of the operative microscope for transsphenoidal approaches in the 1960s that the microscopic transsphenoidal approach to the sella regained widespread favor.^{7,16,17,18,29}

Multiple studies of microscopic approaches have shown excellent endocrine outcomes with low rates of morbidity and mortality.^{6,7,34} Ciric et al. polled 3172 practicing neurosurgeons and based on 958 responses concluded that the most common complications (as assessed via questionnaire) included anterior pituitary insufficiency (19.4%), diabetes insipidus (17.8%), sinusitis (8.5%), septum perforation (6.7%), CSF leak (3.9%), epistaxis (3.4%), hemorrhage (2.9%), anesthetic complications (2.8%), loss of vision (1.8%), meningitis (1.5%), ophthalmoplegia (1.4%), CNS injury (1.3%), carotid artery injury (1.1%), and death (0.9%).⁷ This study also found that surgical experience was associated with fewer complications and lower mortality. However, with the endoscopic approach to the sella still in its infancy, Ciric and colleagues did not examine its safety profile when compared with the established microscopic approach. In fact, it was only in the mid-1990s that reports of fully endoscopic approaches to the sella were first published,^{16,24} beginning a gradual mainstream transition from fully microscopic to fully endoscopic approaches.³² Since that time, several studies have reported equivalent or improved rates of tumor resection or endocrine control with endoscopic approaches, including a large meta-analysis.¹¹ Multiple studies have shown shorter hospital stay for patients undergoing endoscopic procedures.^{5,11,17} Despite this shift toward endoscopic approaches, data comparing endoscopic versus microscopic approaches remain limited to small prospective studies,^{5,23} small institutional retrospective studies, and meta-analyses with conflicting results. With the exception of one large meta-analysis that showed an increased risk of vascular complications with endoscopic approaches¹ and one small retrospective study that showed a lower rate of major complications with endoscopic surgery,³⁷ most studies have not found significant differences in complication rates between the two procedures.^{10,25,36} This retrospective review of complications as-

sociated with transsphenoidal PA resection is the largest single-institution series to date, with a total of 1153 consecutive surgeries for PAs at a tertiary pituitary center.

Methods

A retrospective analysis of patients undergoing transsphenoidal surgery for PAs was conducted following approval from our institutional IRB. We identified 1153 consecutive patients who underwent transsphenoidal resection for pituitary adenomas at the Keck Hospital of USC between November 1992 and March 2017 (REDCap electronic data capture tool hosted at Keck Hospital of USC).²¹ Available data included demographic information (e.g., age, sex), preoperative clinical symptoms and tumor characteristics (e.g., diameter, consistency, invasion), length of stay, and complications of interest, which were identified and reconciled with those from previous studies, including those of Ciric et al.¹⁷ Surgical complications of interest included postoperative cerebrospinal fluid leak, epistaxis, hematoma, meningitis, cranial nerve paresis, hydrocephalus, vision loss, stroke, abdominal hematoma or infection, carotid artery injury, vegetative state, and death within 30 days of resection. Perioperative medical complications included bacteremia/sepsis, pneumonia, myocardial infarction, and deep venous thrombosis/pulmonary embolism (DVT/PE). Endocrine complications included diabetes insipidus, symptomatic hyponatremia, new hypopituitarism (any axis), and adrenal insufficiency.

Endocrine and Neuroimaging Assessment

Patients were evaluated in a multidisciplinary pituitary center by a team of neurosurgeons and pituitary endocrinologists. Each patient underwent baseline pituitary hormone testing that included prolactin, insulin-like growth factor-1, growth hormone (GH), testosterone, cortisol, adrenocorticotropic hormone (ACTH), thyroid hormone (TH), and thyroid-stimulating hormone (TSH). All patients underwent MRI with and without contrast with thin cuts through the sella. PAs were considered invasive if they had cavernous sinus invasion (Knosp grade 3 or 4) or clear clival invasion. Patients with prolactin-secreting macroadenomas were first given a trial of medical management and only referred for surgery if hormonal or compressive symptoms were not alleviated with medical therapy. Patients with Cushing's disease, acromegaly, visual symptoms, growing tumors, and pituitary apoplexy were referred for surgery.

Surgical Approach

Microscopic transsphenoidal operations were performed by an experienced senior pituitary surgeon (M.H.W.) between November 1992 and 2011 via the sublabial or endonasal approach.²⁰ Endoscopic transsphenoidal operations were performed by a fellowship-trained endoscopic neurosurgeon (G.Z.) beginning in October 2011. For extended endoscopic procedures, a 2-surgeon approach was used along with an otolaryngology colleague for exposure and development of a nasoseptal flap.²⁸ Ten patients in the endoscopic group underwent extended endoscopic approaches for PAs that extended outside the sel-

la. Intraoperative CSF leaks were typically repaired using a multilayered fascial apposition technique.⁹

Statistical Analysis

The Pearson chi-square test was used for the comparison of categorical variables, using Fisher’s exact test instead if any cell contained fewer than 5 patients. The Mann-Whitney U-test was used for comparison of continuous variables. Odds ratios with 95% confidence intervals were obtained for preoperative predictors of complications, including age, previous surgeries, tumor size, invasion, tumor consistency, and preoperative symptoms. Statistical significance was defined as $p < 0.05$. All analysis was performed using IBM SPSS (version 22.0, IBM Corp.).

Results

From a database of 1153 transsphenoidal operations for PAs, a total of 983 cases (85.3%) were performed microscopically, and 170 cases (14.7%) were performed endoscopically, including 10 extended endonasal approaches (Fig. 1). Fifty-three percent of patients (611) were female and 45.8% (528) were male. The mean tumor diameter was 21.4 mm and 56.8% of tumors were invasive (655 patients). Fifty-four percent of patients had nonfunctioning

TABLE 1. Overall patient demographics

	Value	%
No. of patients	1153	
Demographics		
Mean age in yrs (SD)	49.5 (16.4)	
Median hospital LOS (IQR) in days	3 (2–4)	
Male	528	45.8%
Female	611	53.0%
Tumor type		
Nonfunctioning adenoma	623	54.0%
GH adenoma	168	14.6%
Prolactinoma	163	14.1%
ACTH adenoma	141	12.2%
Other	58	5.0%
Age distribution in yrs		
0–14	10	0.9%
15–35	221	19.2%
36–55	491	42.6%
56–65	164	14.2%
≥66	205	17.8%

LOS = length of stay.
Presented as the number of patients unless stated otherwise.

FIG. 1. Identification of patients for study inclusion.

adenomas, with the remainder divided among secreting adenomas, including GH adenoma (14.6%), prolactinoma (14.1%), ACTH adenoma (12.2%), and other (5.0%). The mean age at operation was 49.5 years (SD 16.4). Males were older at the time of surgery (53.2 vs 46.4 years, $p < 0.001$) (Table 1). Patients undergoing microscopic surgery were younger on average than those undergoing endoscopic surgery (49.1 vs 53.3 years, $p = 0.008$) (Table 2).

Predictors of Overall Complications

Overall, 17.2% of patients experienced any type of complication, including surgical, medical, and/or endocrine (Table 3). While males had larger mean tumor diameters (25 vs 18 mm, $p < 0.001$), females had longer hospital lengths of stay (median 3 vs 2 days, $p < 0.001$); overall complication rates were not significantly different (16.5% vs 17.8%, $p = 0.544$). Patient characteristics associated with any complication included preoperative headache ($p < 0.001$), visual symptoms ($p < 0.001$), hyperprolactinemia

TABLE 2. Patient demographics by surgical approach

Variable	Endoscopic (n = 170; 14.7%)	Microscopic (n = 983; 85.3%)	p Value
Mean age in yrs (SD)	53.3 (13.6)	49.1 (16.6)	0.008
Median hospital LOS (IQR)	3 (2–4)	3 (2–4)	0.836
Macro-/microadenoma ratio	6.30:1	2.97:1	0.001

Boldface type indicates statistical significance.

TABLE 3. Frequency of complications

	No. of Complications	%
Total complications	198	17.2%
Surgical complication	78	6.8%
Postop CSF leak	30	2.6%
Epistaxis	13	1.1%
Hematoma	13	1.1%
Meningitis	12	1.0%
Cranial nerve paresis	9	0.8%
Hydrocephalus	9	0.8%
Visual loss or worsened vision	7	0.6%
Stroke	4	0.3%
Abdominal hematoma or infection	2	0.2%
Carotid artery injury	1	0.1%
Vegetative state	2	0.2%
Death	1	0.1%
Periop medical complication	14	1.2%
Bacteremia/sepsis	6	0.5%
Pneumonia	4	0.3%
MI/angina	4	0.3%
DVT/PE	1	0.1%
Endocrine complication	132	11.4%
DI—transient	50	4.3%
Hyponatremia	48	4.2%
New hypopituitarism	41	3.6%
DI—permanent	3	0.3%
Adrenal insufficiency	2	0.2%

DI = diabetes insipidus; MI = myocardial infarction.

($p = 0.001$), decreased libido ($p = 0.017$), galactorrhea ($p = 0.036$), and dizziness ($p = 0.045$) (Table 4). Tumor invasion was a highly significant risk factor for complications (22.0% vs 10.8%, $p < 0.001$), with all assessed patterns of extension associated with greater than 2-fold increases in complication rates (Table 5).

Surgical Complications

A total of 6.8% of patients in this series experienced surgical complications, including 1 perioperative death (0.1%) due to a large suprasellar hematoma with associated pneumocephalus. Two patients sustained neurological damage resulting in a persistent vegetative state (0.2%). The first patient had a subarachnoid hemorrhage from which he never recovered. The second patient underwent an uneventful transsphenoidal resection of a 4-cm macroadenoma. After initially awaking at his neurological baseline, he developed altered mental status in the intensive care unit. CT and CT angiography of the head and neck showed intraventricular hemorrhage and acute hydrocephalus. A ventriculostomy was placed, and the patient was returned to the operating room urgently for craniotomy for hematoma evacuation; however, postoperative imaging showed bilateral posterior cerebral artery strokes, and the patient remained in a vegetative state.

Postoperative CSF leaks were encountered in 4 of 160

direct cases and 2 of 10 extended cases (2.5% vs 20%, $p = 0.041$). Additional surgical complications included epistaxis (1.1%), postoperative hematoma (1.1%), meningitis (1.0%), cranial nerve paresis (0.8%), hydrocephalus (0.8%), vision loss (0.6%), stroke (0.3%), abdominal hematoma or infection (0.2%), and carotid artery injury (0.1%) (Table 3).

Preoperative predictors of surgical complications included visual deficit (10.3%, $p = 0.002$), including visual field cut (11.1%, $p = 0.002$) and decreased visual acuity (17.5%, $p = 0.004$). Other risk factors for surgical complications included age older than 65 years (10.3% vs 6.8%, $p = 0.035$), prior transsphenoidal surgery (11.4% vs 6.8%, $p = 0.025$), and certain tumor characteristics, such as PA invasion (56/655, 8.5% vs 4.4%, $p = 0.007$) and a highly vascular tumor consistency (50.0% vs 6.6%, $p = 0.001$) (Tables 4 and 5).

Medical Complications

Perioperative medical complications included bacteremia/sepsis (0.5%), pneumonia (0.3%), myocardial infarction (0.3%), and DVT/PE (0.1%) (Table 3). Risk factors for medical complications included preoperative visual symptoms ($p = 0.032$), fatigue ($p = 0.035$), Cushing's disease ($p = 0.007$), and prior craniotomy ($p = 0.015$) or radiosurgery ($p = 0.048$) (Table 4).

Endocrine Complications

Endocrine complications were the most frequent and developed in 11.4% of patients, including transient diabetes insipidus (4.3%), symptomatic hyponatremia (4.2%), new hypopituitarism (3.6%), permanent diabetes insipidus (0.3%), and adrenal insufficiency (0.2%) (Table 3). Endocrine complications were more frequent in patients younger than 15 years (40.0% vs 11.4%, $p = 0.022$). Additional preoperative clinical predictors of endocrine complications included headache (16.7%, $p < 0.001$), vision loss (17.3%, $p < 0.001$), hyperprolactinemia (21.3%, $p < 0.001$), hypothyroidism (16.9%, $p = 0.029$), and galactorrhea (22.1%, $p = 0.005$) (Table 4).

Endoscopic Versus Microscopic Approaches

There was no statistically significant difference in median hospital length of stay in patients who underwent microscopic (3, IQR 2–4 days) versus endoscopic (3, IQR 2–4 days) approaches ($p = 0.836$). The ratio of macroadenomas to microadenomas was higher for endoscopic cases than for microscopic cases (6.3:1 vs 2.97:1, $p = 0.001$) (Table 2). There were no significant differences between microscopic and endoscopic approaches with regard to overall complications (16.7% vs 20.0%, $p = 0.290$), surgical complications (6.4% vs 8.8%, $p = 0.247$), perioperative medical complications (1.3% vs 0.6%, $p = 0.707$), or endocrine complications (11.4% vs 11.8%, $p = 0.888$). However, there was a significantly greater incidence of delayed postoperative epistaxis among endoscopic cases (2.9% vs 0.8%, $p = 0.031$) (Table 6).

Discussion

Transsphenoidal approaches to the sella have been the

TABLE 4. Patient characteristics associated with complications

	Total		Surgical Complication			Periop Medical Complication			Endocrine Complication			Overall Complications		
	No.	%	No.	%	p Value	No.	%	p Value	No.	%	p Value	No.	%	p Value
No. of patients	1153		78	6.8%		14	1.2%		132	11.4%		198	17.2%	
Age distribution in yrs														
0–14	10	0.9%	1	10.0%	0.513	0	0.0%	>0.99	4	40.0%	0.022	4	40.0%	0.082
15–35	221	19.2%	14	6.3%	0.707	3	1.4%	>0.99	25	11.3%	0.794	39	17.6%	0.996
36–55	491	42.6%	32	6.5%	0.645	5	1.0%	0.499	53	10.8%	0.345	81	16.5%	0.373
56–65	164	14.2%	7	4.3%	0.148	1	0.6%	0.707	22	13.4%	0.492	27	16.5%	0.669
≥66	204	17.7%	21	10.3%	0.035	5	2.5%	0.155	26	12.7%	0.650	42	20.6%	0.220
Preop symptoms														
Headache	323	28.0%	29	9.0%	0.062	5	1.5%	0.552	54	16.7%	<0.001	79	24.5%	<0.001
Vision loss	330	28.6%	34	10.3%	0.002	8	2.4%	0.032	57	17.3%	<0.001	83	25.2%	<0.001
Visual field cut	252	21.9%	28	11.1%	0.002	6	2.4%	0.094	46	18.3%	<0.001	64	25.4%	<0.001
Visual acuity loss	57	4.9%	10	17.5%	0.004	3	5.3%	0.028	14	24.6%	0.001	19	33.3%	0.001
Hyperprolactinemia	188	16.3%	10	5.3%	0.388	1	0.5%	0.713	40	21.3%	<0.001	48	25.5%	0.001
Fatigue	161	14.0%	9	5.6%	0.522	5	3.1%	0.035	22	13.7%	0.341	32	19.9%	0.327
Hypothyroidism	142	12.3%	11	7.7%	0.619	2	1.4%	0.687	24	16.9%	0.029	30	21.1%	0.182
Decreased libido	130	11.3%	14	10.8%	0.054	1	0.8%	>0.99	21	16.2%	0.074	32	24.6%	0.017
Amenorrhea/oligomenorrhea	126	10.9%	6	4.8%	0.343	2	1.6%	0.659	20	15.9%	0.098	26	20.6%	0.275
Acromegaly	128	11.1%	12	9.4%	0.212	4	3.1%	0.060	10	7.8%	0.171	20	15.6%	0.622
Low gonadotrope axis	108	9.4%	7	6.5%	0.902	1	0.9%	>0.99	18	16.7%	0.074	21	19.4%	0.511
Galactorrhea	68	5.9%	3	4.4%	0.618	0	0.0%	>0.99	15	22.1%	0.005	18	26.5%	0.036
Cushing's disease	69	6.0%	3	4.3%	0.619	4	5.8%	0.007	8	11.6%	0.969	15	21.7%	0.300
Dizziness	60	5.2%	9	15.0%	0.016	1	1.7%	0.529	11	18.3%	0.085	16	26.7%	0.045
Panhypopituitarism	55	4.8%	4	7.3%	0.784	1	1.8%	0.498	6	10.9%	0.898	10	18.2%	0.839
Low cortisol axis	52	4.5%	6	11.5%	0.157	2	3.8%	0.129	6	11.5%	0.983	11	21.2%	0.436
Hypopituitarism	51	4.4%	1	2.0%	0.250	1	2.0%	0.471	5	9.8%	0.706	6	11.8%	0.295
Cranial nerve palsy	30	2.6%	0	0.0%	0.258	1	3.3%	0.310	5	16.7%	0.377	7	23.3%	0.365
Altered mental status	26	2.3%	3	11.5%	0.414	0	0.0%	>0.99	1	3.8%	0.349	5	19.2%	0.792
Apoplexy	28	2.4%	2	7.1%	0.714	0	0.0%	>0.99	5	17.9%	0.359	7	25.0%	0.306
Low GH axis	13	1.1%	0	0.0%	>0.99	0	0.0%	>0.99	4	30.8%	0.052	4	30.8%	0.255
Hyperthyroidism	10	0.9%	1	10.0%	0.505	0	0.0%	>0.99	1	10.0%	>0.99	2	20.0%	0.685
DI	6	0.5%	0	0.0%	>0.99	0	0.0%	>0.99	1	16.7%	0.519	1	16.7%	>0.99
Prior treatment														
Prior transsphenoidal surgery	132	11.4%	15	11.4%	0.025	4	3.0%	0.066	18	13.6%	0.401	28	21.2%	0.191
Prior craniotomy	16	1.4%	3	18.8%	0.088	2	12.5%	0.015	3	18.8%	0.415	5	31.3%	0.172
Prior radiosurgery	4	0.3%	1	25.0%	0.245	1	25.0%	0.048	0	0.0%	1.000	2	50.0%	0.139

Boldface type indicates statistical significance.

mainstay of treatment for pituitary adenomas for decades. Since the first series of purely endoscopic cases was reported in the 1990s, there has been a nationwide shift from microscopic approaches toward pure endoscopic approaches.³² Many academic centers have transitioned to endoscopic approaches, producing a generation of surgeons who are trained exclusively in endoscopy. Despite the increasing adoption of endoscopic methods for tumor resection, data supporting this transition have been limited to small prospective studies with fewer than 50 patients, small retrospective studies, and meta-analyses of available studies in the literature. Although two groups have per-

formed randomized controlled studies comparing microscopic to endoscopic surgeries,^{5,22} with 10 and 22 patients per group, respectively, the studies were underpowered to detect differences in rates of complications between the two surgical groups. Larger retrospective studies comparing microscopic to endoscopic cases have been similarly limited by smaller numbers of patients, while meta-analyses are limited by center-to-center variability and difference in eras of treatment in the two groups, including potential variation in the definition of complications.^{11,17}

We report a large, single-center tertiary pituitary center experience with 1153 surgical cases performed over 2

TABLE 5. Tumor characteristics associated with complications

	Total		Surgical Complication						Overall Complications					
	No.	% of Total	No.	%	p Value	OR	95% CI		No.	%	p Value	OR	95% CI	
							Lower	Upper					Lower	Upper
No. of patients	1153		78	6.8%					198	17.2%				
Tumor size														
Microadenoma (ref)	232	20.1%	12	5.2%					38	16.4%				
Macroadenoma	766	66.4%	64	8.4%	0.113	1.671	0.886	3.154	158	20.6%	0.155	1.327	0.900	1.958
Invasion or extension														
No invasion (ref)	498	43.2%	22	4.4%					54	10.8%				
Invasion	655	56.8%	56	8.5%	0.007	2.023	1.218	3.361	144	22.0%	<0.001	2.317	1.653	3.248
Suprasellar	511	44.3%	44	8.6%	0.008	2.039	1.203	3.455	119	23.3%	<0.001	2.496	1.761	3.534
Cavernous sinus	417	36.2%	38	9.1%	0.005	2.169	1.262	3.731	91	21.8%	<0.001	2.295	1.592	3.309
Infrasellar sinus	117	10.1%	13	11.1%	0.007	2.705	1.319	5.544	29	24.8%	<0.001	2.701	1.634	4.494
Infrasellar clivus	38	3.3%	5	13.2%	0.024	3.278	1.167	9.212	12	31.6%	<0.001	3.795	1.811	7.954
Ventricle	17	1.5%	4	23.5%	0.002	6.657	2.006	22.090	8	47.1%	<0.001	7.309	2.707	19.736
Frontal lobe	6	0.5%	3	50.0%	<0.001	21.636	4.129	113.387	4	66.7%	0.001	16.444	2.942	91.904

Boldface type indicates statistical significance.

decades. Rates of major neurological morbidity and mortality were low, with a 0.1% rate of internal carotid artery injury, 0.2% rate of vegetative state, and postoperative death occurring in only 1 patient (0.1%). Rates of common complications were low, with an incidence rate of postoperative CSF rhinorrhea of 2.6%. Risk factors for surgical complications associated with transsphenoidal surgery for PAs included prior surgery and PA invasion into surrounding structures. Taken together, when performed at high-volume centers, transsphenoidal surgery for PAs is safe, with a very low rate of major and minor complications.

This single-center retrospective analysis also provides robust data to complement the benchmark transsphenoidal surgery complication questionnaire pertaining to perioperative complications reported by Ciric et al. in 1997.⁷ The study by Ciric et al. reported similar rates of major morbidity in 1%–2% of cases and postoperative CSF leaks in 3.9% of cases, with even lower rates among the most experienced surgeons.² Although we noted lower rates of endocrine complications, the combined rates of CSF leak (2.6%), cranial nerve palsy (0.8%), internal carotid artery injury (0.1%), vegetative state (0.2%), and death (0.1%) for our 2 surgeons are comparable to self-reported rates of surgeons with more than 500 lifetime cases of transsphenoidal surgery cited in the study of Ciric et al. In particular, our observed rate of transient diabetes insipidus was < 5% and permanent diabetes insipidus was 0.3%. Of note, the data of Ciric et al. cannot be genuinely compared directly with our series, as the results were limited to microscopic approaches and encompassed all pituitary pathology, including highly morbid tumors such as craniopharyngioma. In addition, their study was questionnaire based, which may have lent itself to response and/or recall bias. Thus, this series of combined outcomes, spanning more than 20 years at a single, high-volume pituitary center, complements the existing literature and provides a new benchmark for complications associated with transsphenoidal PA surgery in experienced hands.

Our study identified important risk factors for complications. Patients with visual deficits and tumors with invasion into any surrounding structures were at higher risk of complication, likely a reflection of more severe underlying disease. Revision surgeries for prior transsphenoidal surgery, craniotomy, and radiosurgery were also at higher risk for complications, likely due to scarring and adhesions that make the surgical environment more challenging.¹⁴ Of note, care should be taken to correct any hormonal dysfunction prior to surgery, as patients with Cushing's disease and hypothyroidism exhibited an elevated risk of medical complications during their hospitalization. Previous studies have demonstrated an effect of tumor size on extent of resection, as well as a relationship with various outcome variables, such as surgery duration, hospital length of stay, and some complications.^{13,22,35} Although not statistically significant in our study, we found a trend toward increased complications for patients with macroadenomas.

Limitations of the Study

This single-institution retrospective series is subject to the typical limitations of all retrospective studies, such as the inability to determine causation, only association. We also employed a univariate analysis but did not assess for relationships between variables. Additionally, while we compared complication rates between microadenomas and macroadenomas, we did not distinguish between macroadenomas of different sizes, precluding a comparison of complications as well as resection rates for very large macroadenomas. As it relates to parasellar extension, we also did not distinguish between Knosp grades 3 and 4, which are regularly grouped together when classifying tumors as invasive.¹² This allowed a proper comparison with the existing literature despite a recent study demonstrating a significant difference in surgically observed invasion between grade 3 and 4 adenomas.³⁰ Our analysis also did not distinguish between revision transsphenoidal surgery

TABLE 6. Complications by surgical approach

	Endoscopic		Microscopic		p Value
	No.	%	No.	%	
No. of patients	170	14.7%	983	85.3%	
Total no. of complications	34	20.0%	164	16.7%	0.290
Surgical complication	15	8.8%	63	6.4%	0.247
CSF leak	6	3.5%	24	2.4%	0.431
Epistaxis	5	2.9%	8	0.8%	0.031
Hematoma	2	1.2%	11	1.1%	>0.99
Meningitis	2	1.2%	10	1.0%	0.694
Cranial nerve palsy	0	0.0%	9	0.9%	0.371
Hydrocephalus	1	0.6%	8	0.8%	>0.99
Visual loss or worsened vision	0	0.0%	7	0.7%	0.602
Stroke	1	0.6%	3	0.3%	0.472
Abdominal hematoma or infection	1	0.6%	1	0.1%	0.273
Carotid artery injury	0	0.0%	1	0.1%	>0.99
Vegetative state	1	0.6%	1	0.1%	0.273
Death	0	0.0%	1	0.1%	>0.99
Periop medical complication	1	0.6%	13	1.3%	0.707
Bacteremia/sepsis	0	0.0%	6	0.6%	0.600
Pneumonia	1	0.6%	3	0.3%	0.472
MI/angina	0	0.0%	4	0.4%	>0.99
DVT/PE	0	0.0%	1	0.1%	>0.99
Endocrine complication	20	11.8%	112	11.4%	0.888
DI—transient	7	4.1%	43	4.4%	0.879
Hyponatremia	11	6.5%	37	3.8%	0.103
New hypopituitarism	6	3.5%	35	3.6%	0.984
DI—permanent	1	0.6%	2	0.2%	0.381
Adrenal insufficiency	1	0.6%	1	0.1%	0.273

Boldface type indicates statistical significance.

for previous microscopic and endoscopic cases. This could have confounded the positive association that we found between revision surgery and complication rates, as we know that revision surgeries are more frequently necessary following microsurgery, which offers inferior visualization of critical neurovascular structures and lower rates of gross-total resection.^{13,14} Finally, microscopic and endoscopic cases reported in this series were only partly overlapping, with microscopic cases representing the latter cases of an experienced senior pituitary surgeon and endoscopic cases representing the first cases of a fellowship-trained junior faculty surgeon at the start of his career. Despite reports of a steep learning curve for endoscopic approaches to the sella,^{3,4,31} we were unable to detect a significant difference in the rates of complications for the 2 approaches.

Although we cannot rule out the contribution of improvements in technology and improved medical care over the course of our series, particularly with regard to imaging, the implementation of image-guided surgeries, and the evolution of the nascent field of endoscopy, our series supports the conclusion that endoscopic transsphenoidal approaches can be achieved with a comparable

safety profile in high-volume centers. In the absence of a large, multicenter randomized clinical trial comparing the 2 methods directly, available data support the conclusion that in high-volume centers, both approaches have similar complication rates.

Conclusions

In one of the largest studies assessing medical and surgical complications associated with microscopic and endoscopic transsphenoidal PA resections, the rate of death or major disability was 0.26%. Risk factors for complications included prior surgical or radiation-based treatment, endocrinopathies, and invasive PA disease. No differences in complication rates between endoscopic and microscopic surgery were observed. When performed at experienced pituitary centers, safety rates for patients undergoing transsphenoidal PA resection are extremely high.

References

1. Ammirati M, Wei L, Ciric I: Short-term outcome of endoscopic versus microscopic pituitary adenoma surgery: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* **84**:843–849, 2013
2. Barker FG II, Klibanski A, Swearingen B: Transsphenoidal surgery for pituitary tumors in the United States, 1996–2000: mortality, morbidity, and the effects of hospital and surgeon volume. *J Clin Endocrinol Metab* **88**:4709–4719, 2003
3. Cappabianca P, Cavallo LM, Colao A, de Divitiis E: Surgical complications associated with the endoscopic endonasal transsphenoidal approach for pituitary adenomas. *J Neurosurg* **97**:293–298, 2002
4. Chi F, Wang Y, Lin Y, Ge J, Qiu Y, Guo L: A learning curve of endoscopic transsphenoidal surgery for pituitary adenoma. *J Craniofac Surg* **24**:2064–2067, 2013
5. Cho DY, Liao WR: Comparison of endonasal endoscopic surgery and sublabial microsurgery for prolactinomas. *Surg Neurol* **58**:371–376, 2002
6. Ciric I, Mikhael M, Stafford T, Lawson L, Garces R: Transsphenoidal microsurgery of pituitary macroadenomas with long-term follow-up results. *J Neurosurg* **59**:395–401, 1983
7. Ciric I, Ragin A, Baumgartner C, Pierce D: Complications of transsphenoidal surgery: results of a national survey, review of the literature, and personal experience. *Neurosurgery* **40**:225–237, 1997
8. Cohen-Gadol AA, Laws ER, Spencer DD, De Salles AAF: The evolution of Harvey Cushing's surgical approach to pituitary tumors from transsphenoidal to transfrontal. *J Neurosurg* **103**:372–377, 2005
9. Couldwell WT, Kan P, Weiss MH: Simple closure following transsphenoidal surgery. Technical note. *Neurosurg Focus* **20**(3):E11, 2006
10. Dallapiazza R, Bond AE, Grober Y, Louis RG, Payne SC, Oldfield EH, et al: Retrospective analysis of a concurrent series of microscopic versus endoscopic transsphenoidal surgeries for Knosp Grades 0–2 nonfunctioning pituitary macroadenomas at a single institution. *J Neurosurg* **121**:511–517, 2014
11. DeKlotz TR, Chia SH, Lu W, Makambi KH, Aulisi E, Deeb Z: Meta-analysis of endoscopic versus sublabial pituitary surgery. *Laryngoscope* **122**:511–518, 2012
12. Dhandapani S, Singh H, Negm HM, Cohen S, Anand VK, Schwartz TH: Cavernous sinus invasion in pituitary adenomas: systematic review and pooled data meta-analysis of radiologic criteria and comparison of endoscopic and microscopic surgery. *World Neurosurg* **96**:36–46, 2016

13. Do H, Kshetty VR, Siu A, Belinsky I, Farrell CJ, Nyquist G, et al: Extent of resection, visual, and endocrinologic outcomes for endoscopic endonasal surgery for recurrent pituitary adenomas. **World Neurosurg** **102**:35–41, 2017
14. Esquenazi Y, Essayed WI, Singh H, Mauer E, Ahmed M, Christos PJ, et al: Endoscopic endonasal versus microscopic transsphenoidal surgery for recurrent and/or residual pituitary adenomas. **World Neurosurg** **101**:186–195, 2017
15. Fernandez A, Karavitaki N, Wass JAH: Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). **Clin Endocrinol (Oxf)** **72**:377–382, 2010
16. Gamea A, Fathi M, el-Guindy A: The use of the rigid endoscope in trans-sphenoidal pituitary surgery. **J Laryngol Otol** **108**:19–22, 1994
17. Goudakos JK, Markou KD, Georgalas C: Endoscopic versus microscopic trans-sphenoidal pituitary surgery: a systematic review and meta-analysis. **Clin Otolaryngol** **36**:212–220, 2011
18. Hardy J: [Excision of pituitary adenomas by trans-sphenoidal approach.] **Union Med Can** **91**:933–945, 1962 (Fr)
19. Hardy J: Transsphenoidal hypophysectomy. **J Neurosurg** **34**:582–594, 1971
20. Hardy J: Transsphenoidal microsurgery of the normal and pathological pituitary. **Clin Neurosurg** **16**:185–217, 1969
21. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG: Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. **J Biomed Inform** **42**:377–381, 2009
22. Jain AK, Gupta AK, Pathak A, Bhansali A, Bapuraj JR: Endonasal transsphenoidal pituitary surgery: is tumor volume a key factor in determining outcome? **Am J Otolaryngol** **29**:48–50, 2008
23. Jain AK, Gupta AK, Pathak A, Bhansali A, Bapuraj JR: Excision of pituitary adenomas: randomized comparison of surgical modalities. **Br J Neurosurg** **21**:328–331, 2007
24. Jho HD, Carrau RL, Ko Y, Daly MA: Endoscopic pituitary surgery: an early experience. **Surg Neurol** **47**:213–223, 1997
25. Karppinen A, Kivipelto L, Vehkavaara S, Ritvonen E, Tikkanen E, Kivisaari R, et al: transition from microscopic to endoscopic transsphenoidal surgery for nonfunctional pituitary adenomas. **World Neurosurg** **84**:48–57, 2015
26. Lanzino G, Laws ER Jr: Pioneers in the development of transsphenoidal surgery: Theodor Kocher, Oskar Hirsch, and Norman Dott. **J Neurosurg** **95**:1097–1103, 2001
27. Liu JK, Cohen-Gadol AA, Laws ER Jr, Cole CD, Kan P, Couldwell WT: Harvey Cushing and Oskar Hirsch: early forefathers of modern transsphenoidal surgery. **J Neurosurg** **103**:1096–1104, 2005
28. Lucas JW, Zada G: Endoscopic surgery for pituitary tumors. **Neurosurg Clin N Am** **23**:555–569, 2012
29. Marazuela M, Astigarraga B, Vicente A, Estrada J, Cuerda C, García-Uría J, et al: Recovery of visual and endocrine function following transsphenoidal surgery of large nonfunctioning pituitary adenomas. **J Endocrinol Invest** **17**:703–707, 1994
30. Micko ASG, Wöhrer A, Wolfsberger S, Knosp E: Invasion of the cavernous sinus space in pituitary adenomas: endoscopic verification and its correlation with an MRI-based classification. **J Neurosurg** **122**:803–811, 2015
31. Qureshi T, Chaus F, Fogg L, Dasgupta M, Straus D, Byrne RW: Learning curve for the transsphenoidal endoscopic endonasal approach to pituitary tumors. **Br J Neurosurg** **30**:637–642, 2016
32. Rolston JD, Han SJ, Aghi MK: Nationwide shift from microscopic to endoscopic transsphenoidal pituitary surgery. **Pituitary** **19**:248–250, 2016
33. Schmidt RF, Choudhry OJ, Takkellapati R, Eloy JA, Couldwell WT, Liu JK: Hermann Schloffer and the origin of transsphenoidal pituitary surgery. **Neurosurg Focus** **33**(2):E5, 2012
34. Semple PL, Laws ER Jr: Complications in a contemporary series of patients who underwent transsphenoidal surgery for Cushing's disease. **J Neurosurg** **91**:175–179, 1999
35. Tabaei A, Anand VK, Barrón Y, Hiltzik DH, Brown SM, Kacker A, et al: Predictors of short-term outcomes following endoscopic pituitary surgery. **Clin Neurol Neurosurg** **111**:119–122, 2009
36. Wang F, Zhou T, Wei S, Meng X, Zhang J, Hou Y, et al: Endoscopic endonasal transsphenoidal surgery of 1,166 pituitary adenomas. **Surg Endosc** **29**:1270–1280, 2015
37. Zaidi HA, Awad AW, Bohl MA, Chapple K, Knecht L, Jahnke H, et al: Comparison of outcomes between a less experienced surgeon using a fully endoscopic technique and a very experienced surgeon using a microscopic transsphenoidal technique for pituitary adenoma. **J Neurosurg** **124**:596–604, 2016

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Zada, Agam, Wrobel, Weiss, Carmichael. Acquisition of data: Zada, Agam, Wrobel, Weiss, Carmichael. Analysis and interpretation of data: Zada, Agam, Wedemeyer, Carmichael. Drafting the article: Agam, Wedemeyer. Critically revising the article: Zada, Agam, Wedemeyer, Carmichael. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Zada. Statistical analysis: Agam. Administrative/technical/material support: Weiss. Study supervision: Zada, Carmichael.

Supplemental Information

Previous Presentations

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