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# Cost outcomes of pituitary adenoma resection: The use of a hybrid microscopic/endoscopic surgery

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## ABSTRACT

**Background:** The pathogenesis, surgical techniques, and outcomes of pituitary adenomas (PAs) remain variable. We compared our surgical techniques and perioperative/long-term PA outcomes to highlight the hybrid microscopic/endoscopic technique used to optimize efficiency, cost savings, and outcomes in PA surgery.

**Methods:** Consecutive PA cases performed from January 2017 through February 2020 were evaluated retrospectively. A cost analysis by surgical approach was performed combining this primarily microscopic series, with endoscopic visual assist, and a separate cohort of consecutive intra-institutional endoscopic-only PA resections.

**Results:** Among 160 patients included in the main cohort analysis (mean age 51.5 ± 16.2; 89 females [55.6%]), a microscope was used in 81.9% of cases, with endoscopic assistance (hybrid) or the endoscope alone used in the remaining cases. Surgical complications occurred in 5 cases (3.1%): postoperative diabetes insipidus in 3 (1.9%), electrolyte imbalances requiring additional drug treatment in 3 (1.9%), and syndrome of inappropriate anti-diuretic hormone release in 2 (1.2%). Thirty-three additional patients were included in the cost analysis (193 total). Patients treated with a microscopic-only approach had the lowest operating time (mean normalized operating room costs 1.00 [95% confidence interval (CI) 0.95, 1.04], $P < 0.001$; mean normalized total direct costs 5.00 [95%CI 4.69, 5.31], $P = 0.008$), with hybrid and endoscopic-only approaches having higher comparable operating times and costs.

**Conclusion:** PA surgery using a primarily microscopic approach (with endoscopic assistance for complex cases) remains a safe, efficient, and cost-effective strategy and results in shorter anesthesia time to reduce patient complications while maintaining excellent endocrinologic outcomes.

**Keywords:** Endoscope, Hybrid approach, Microscope, Pituitary adenoma, Transnasal surgery, Transsphenoidal surgery

## INTRODUCTION

Pituitary adenomas (PAs) have an estimated prevalence of 16% (14.4% in autopsy studies and 22.5% in radiologic studies).[22] Although data on histologic characterization, entity-specific treatment goals, and surgical techniques exist,[43,56,78] there remains a role for continued improvement in treatment outcomes.[47,55] The senior author, while becoming an early adopter of utilizing endoscopic visualization for optimal removal of complex and large PAs, also recognized the efficiency and simplicity of the uninaral microscopic approach, with the use of endoscopic visualization as an adjunct.

Following a multicenter study defining benchmark values for transsphenoidal surgery outcomes by Drexler *et al.*,[21] we, herein, expanded the data produced at our center to conduct a retrospective review of the clinical, radiographic, and endocrinologic outcomes after PA resection by the senior author over more than 3 years. We also compare operative times and costs by surgical strategy to assess the use of a primarily microscopic/endoscopic (hybrid) approach versus an endoscopic-only approach and reviewed these findings relative to published data.

## MATERIALS AND METHODS

This case series was conducted in accordance with local university Institutional Review Board approval, with a waiver of informed consent. This case series has been reported in line with the PROCESS Guideline.[3]

### Patient selection and data collection

Consecutive patients who underwent surgical treatment of PAs by a single surgeon at a high-volume hospital from January 2017 through February 2020 were identified on retrospective review. Data collected included demographic, clinical, tumor-related (previous hormone therapies/tumor treatments, presence of visual deficit, Knosp classification, and tumor extension), perioperative (visualization tool/surgical approach, operative time, tumor type, closure strategy, and surgical complications), postoperative (new hypopituitarism [requiring medications; excluding hypocortisolism in patients with corticotropic tumors], normalization of preoperatively altered hormones, neurologic/vision status, and length of stay [LOS]), and 6-month follow-up (readmissions, delayed endocrine/neurological deficits/normalization, delayed cerebrospinal fluid leak, and imaging outcome) details.

### Cost analysis

Cost data were collected on the above patient cohort (primarily microscopic or hybrid [microscope + endoscope], with some endoscopic-only) as well as on consecutive patients who underwent surgical treatment of PAs at the same center by other experienced surgeons (primarily endoscopic-only) from 1/2017 through 10/2022 (timeframe extended to gain additional endoscopic-only cases). The Value-Driven Outcomes database has been previously described to compare the relative costs of treatment for many medical conditions.[1,23,24,26,28,29,39-42,49,59,60,67,68,70-72,74-77] Cost data included operating room costs (inclusive of anesthesia, operating room time, and common supplies) and overall hospital-care cost for the procedure and recovery, compared by the operative technique utilized for PA removal (i.e., microscopic-alone, endoscopic-alone, or hybrid). Total direct costs were inclusive of operating room costs and postoperative hospitalized care through discharge. Professional payments, including those to the surgeon and anesthesiologist, and indirect costs, such as facility or equipment depreciation, were not included. Costs were adjusted for inflation based on monthly Consumer Price Index values per operation dates and normalized to the mean operating room costs for included cases. Patient demographics and tumor characteristics were compared between cohorts to assess for any differences.

### Surgical approach

A uninaral microscopic approach is used by the senior author for most PAs. Adjunctive or stand-alone endoscopy is reserved for more complex or invasive tumors (e.g., high Knosp grade, significant intraventricular extension, or sinus invasion). Neuronavigation is used to confirm bony anatomy. A submucosal dissection and nasal speculum are used to access the sella. Extracapsular tumor dissection is not typically performed to avoid inadvertent injury to the residual pituitary gland and stalk. For larger tumors (≥4 cm) with an intact diaphragma sellae, early central debulking is avoided by resecting the lateral and posterior aspects of the tumor first, promoting diaphragma descent in a posterior-to-anterior fashion to avoid leaving the tumor in the posterior or lateral gutters.[46] For closure, fat packing is used if a leak is encountered or if there is substantially exposed arachnoid[17,18] versus reapproximation of the nasal septum and mucosa.

Patients included in the comparative cost analysis underwent standard endoscopic-only PA resections [14] with a binaural, two-surgeon technique with rhinology assistance and a wide bilateral sphenoidotomy. Tumor removal was performed similarly. The closure was determined based on an intraoperative assessment of diaphragm integrity and included Gelfoam, a free mucosal graft, or a nasoseptal flap.

### Statistical analysis

Continuous variables are reported as mean ± standard deviation. For univariable analysis, independent samples $t$-tests and the Mann–Whitney U-test were used to compare continuous parametric and nonparametric variables, respectively. A Chi-square test was used to compare categorical variables. Multivariable logistic regression was performed for variables with $P < 0.10$ on univariable analysis. Stepwise models with both forward (0.15) and backward selection (0.20) were used. Age and sex were considered for inclusion in all stepwise models a priori. For analysis of rare outcomes, Firth logistic regression was used. Comparisons of cost and operative time by surgical approach (i.e., microscopic, hybrid, and endoscopic) were made through analysis of variance testing. $\alpha < 0.05$ was considered statistically significant. Statistical analysis was performed using Stata MP Version 14.1 (StataCorp LP) and Statistical Package for the Social Sciences v.28 (IBM Corp).

## RESULTS

### Baseline characteristics

A total of 160 patients with PAs treated by the senior author were included in the clinical outcomes analysis (mean age 51.6 ± 16.2 years; 89 females [55.6%]) [Table 1]. Of those patients, 57 (35.6%) were on preoperative hormone replacement; 82 (51.2%) had preoperative visual deficits; 31 (19.4%) had received earlier tumor treatments, including surgery, pharmacotherapy, and radiation; 143 (89.4%) had macroadenomas; and 66 (41.2%) had tumor extension beyond the sella. A Knosp score of 1 was the most common PA grade (57 patients; 35.6%).

### Treatment details and outcomes

Most tumors were silent/null cells (111/160, 69.4%) [Table 2]. The microscope was used alone in 81.9% of cases (14.4% hybrid and 3.8% endoscope-only). The mean operating time was 110.36 ± 31.48 min. Fat packing with a sling technique was used for closure in 61.3% of cases. Surgical complications occurred in 5 cases (3.1%), including reoperation for mass effect (1.2%), cerebrospinal fluid leak requiring intervention (1.2%), and meningitis, which was treated with no sequelae (0.6%). The rates of postoperative diabetes insipidus (DI), syndrome of inappropriate anti-diuretic hormone release, and electrolyte imbalances requiring additional drug treatment at the time of discharge were 1.9%, 1.2%, and 1.9%, respectively. Postoperative normalization of preoperatively altered hormone levels (excluding hypersecretion) was seen in 40 patients (25.0%), and 21 patients (13.1%) had new postoperative hypopituitarism requiring hormone replacement. The postoperative vision was stable or improved in 159/160 patients (99.3%), and no patients (0%) had new non-vision postoperative neurologic deficits. The median length of hospital stay was 4.0 days (interquartile range 3.0, 5.0).

On follow-up, 7 patients (4.4%) had a delayed electrolyte imbalance needing drug treatment, and 2 patients (1.2%) had delayed new hypopituitarism requiring replacement. In patients with evidence of preoperative hypersecretion, 36/49 (73.5%) had termination of hypersecretion. No patients (0%) had new delayed neurologic deficits or cerebrospinal fluid leaks requiring intervention. No remnant or recurrent

**Table 1:** Baseline patient characteristics.

| Factor (*n*=160) | Value |
|---|---|
| Patient age, mean (SD) | 51.58 (16.18) |
| Female | 89 (55.6%) |
| BMI, mean (SD) | 32.37 (7.80) |
| ASA score (%) | |
| 1 | 3 (1.9) |
| 2 | 73 (45.6) |
| 3 | 80 (50.0) |
| 4 | 4 (2.5) |
| Preoperative hormone replacement (%) | |
| Thyroid replacement (levothyroxine) | 47 (29.4) |
| Steroid replacement (hydrocortisone) | 18 (11.2) |
| Other | 11 (6.8) |
| Preoperative visual deficit | 82 (51.2%) |
| Previous treatment (%) | |
| Surgery | 17 (10.6) |
| Pharmacologic | 17 (10.6) |
| Radiation | 2 (1.2) |
| Tumor size (%) | |
| Microadenoma | 17 (10.6) |
| Macroadenoma | 143 (89.4) |
| Knosp classification (%) | |
| 0 | 24 (15.0) |
| 1 | 57 (35.6) |
| 2 | 46 (28.7) |
| 3A | 11 (6.9) |
| 3B | 6 (3.8) |
| 4 | 16 (10.0) |
| Tumor extension (%) | |
| None | 94 (58.8) |
| Intraventricular | 3 (1.9) |
| Cavernous sinus | 57 (35.6) |
| Intraventricular+cavernous sinus | 6 (3.8) |

Values reported as number (%) or mean (SD). SD: Standard deviation, BMI: Body mass index, ASA: American Society of Anesthesiology

**Table 2:** Treatment details and outcomes.

| Factor (*n*=160) | Value |
|---|---|
| Perioperative | |
| Tumor type (%) | |
| Prolactinoma | 9 (5.6) |
| Somatotrophic | 22 (13.8) |
| Prolactinoma+somatotrophic | 5 (3.1) |
| Corticotrophic | 13 (8.1) |

*(Contd...)*

**Table 2:** *(Continued).*

| Factor (*n*=160) | Value |
|---|---|
| Silent/null cell | 111 (69.4) |
| Surgical approach (%) | |
| Endoscope | 6 (3.8) |
| Microscope | 131 (81.9) |
| Hybrid | 23 (14.4) |
| Operating duration (minutes), mean (SD) | 110.36 (31.48) |
| Fat packing for closure | 98 (61.3%) |
| Surgical complications | |
| Reoperation | 2 (1.2%) |
| CSF leak requiring intervention | 2 (1.2%) |
| Meningitis | 1 (0.6%) |
| Diabetes insipidus* | 3 (1.9%) |
| SIADH | 2 (1.2%) |
| Electrolyte imbalance requiring additional drug treatment | 3 (1.9%) |
| Normalization of preoperatively altered hormone levels | 40 (25.0%) |
| New hypopituitarism requiring hormone replacement† | 21 (13.1%) |
| New non-vision neurological deficit | 0 (0%) |
| Postoperative vision change | |
| None | 96 (60.0%) |
| Deterioration | 1 (0.6%) |
| Improvement | 63 (39.4%) |
| LOS after surgery (days), median (IQR) | 4.00 (3.00, 5.00) |
| Follow-up (%) | |
| Delayed readmission related to surgery | 10 (6.2) |
| Delayed electrolyte imbalance needing drug treatment | 7 (4.4) |
| Delayed new hypopituitarism requiring replacement† | 2 (1.2) |
| Delayed new neurological deficit | 0 (0) |
| Delayed CSF leak requiring intervention | 0 (0) |
| Termination of hypersecretion (%) | |
| No | 12 (24.5) |
| Yes | 36 (73.5) |
| Unknown | 1 (2.0) |
| Remnant/recurrence on 6-month MRI (%) | |
| No | 103 (64.4) |
| Yes | 32 (20.0) |
| Unknown | 25 (15.6) |

Values reported as number (%) or mean (SD). *Defined as needing desmopressin on hospital discharge. †Excluding new hypocortisolism in corticotrophic tumors. SD: Standard deviation, CSF: Cerebrospinal fluid, SIADH: Syndrome of inappropriate anti-diuretic hormone release, LOS: Length of stay, IQR: Interquartile range, MRI: Magnetic resonance imaging

tumor was seen in 103 patients (64.4%) on 6-month magnetic resonance imaging (MRI).

Logistic regression assessed for variables associated with selected clinical outcomes such as new postoperative hypopituitarism requiring hormone replacement, postoperative termination of hypersecretion, and presence of recurrent/residual tumor on 6-month MRI [Tables 3 and 4]. New postoperative hypopituitarism requiring hormone replacement was positively associated with age ≤38 years and longer operation duration; postoperative termination of hypersecretion was positively associated with corticotroph tumor type; and presence of recurrent/residual tumor on 6-month MRI was positively associated with age ≤38 years, previous surgery, and cavernous sinus extension and negatively associated with secretory tumors ($P < 0.05$).

### Operating time and cost analysis

For the operating time and costs analysis, data from 193 patients undergoing PA removal by one of three techniques (i.e., endoscopic-only, microscopic-only, and hybrid) were assessed (160 patients from the above cohort plus a second consecutive endoscopic-only cohort of 33 patients). No differences were seen in patient demographics and general PA characteristics across cohorts [Table 5]. A microscopic-only approach had lower operative time ($P < 0.001$), normalized mean operating costs ($P < 0.001$), and normalized mean total direct hospital costs ($P = 0.008$) [Table 6]. The hybrid approach was comparable with an endoscopic-only approach in all three categories.

## DISCUSSION

In this study, the senior author's primarily microscopic approach to PA resection is supported by low procedural complication/new pituitary dysfunction rates, high rates of gross total resection (GTR)/normalization of hypersecretion, and optimized surgical time and cost efficiency. These data further define benchmarks for outcomes in pituitary surgery at high-volume centers.[21]

### Microscopic versus endoscopic approaches

The uninaral microscopic approach is favored by the senior author and was the predominant technique used in this study (modified from Griffith and Veerapen[31]). This approach involves a single linear incision in the mucosa at the interface of the perpendicular plate of the ethmoid bone with the rostrum of the sphenoid sinus. The septum is displaced contralaterally, and the remainder of the approach is performed in a submucosal fashion, preserving the mucosa of the nasal cavity. The sphenoid mucosa is removed sparingly but enough to remove the tumor. The

**Table 3:** Factors associated with postoperative outcomes.

| Variable | Univariable OR (95% CI) | *P*-value | Multivariable OR (95% CI) | *P*-value |
|---|---|---|---|---|
| New postoperative hypopituitarism requiring hormone replacement^ | | | | |
| Age | | | | |
| 11–38 years | 7.889 (1.335,46.630) | 0.023 | 9.981 (1.429,69.696) | 0.020 |
| 41–52 years | 3.667 (0.568,23.657) | 0.172 | 3.880 (0.554,27.201) | 0.172 |
| 53–66 years | 3.381 (0.525,21.764) | 0.200 | 3.882 (0.559,26.963) | 0.170 |
| 67–85 years (Ref) | 1 (1.000,1.000) | – | 1 (1.000,1.000) | – |
| Operation duration | 1.015 (1.002,1.029) | 0.023 | 1.023 (1.007,1.040) | 0.006 |
| Postoperative termination of hypersecretion | | | | |
| Tumor type | | | | |
| Prolactinoma (Ref) | 1 | – | 1 | – |
| Prolactinoma+somatotroph | 0.833 (0.090,7.675) | 0.872 | 0.638 (0.063,6.410) | 0.703 |
| Somatotroph | 7.5 (1.246,45.15) | 0.028 | 6.087 (0.955,38.79) | 0.056 |
| Corticotroph | 15 (1.325,169.87) | 0.029 | 18.11 (1.444, 227.22) | 0.025 |
| Presence of remnant/recurrent tumor on 6-month MRI* | | | | |
| Age | | | | |
| 11–38 years (Ref) | 1.045 (0.350,3.120) | 0.936 | 7.631 (1.237,47.094) | 0.029 |
| 40–52 years | 0.786 (0.260,2.375) | 0.670 | 1.250 (0.246,6.338) | 0.788 |
| 53–66 years | 0.479 (0.150,1.534) | 0.215 | 0.670 (0.125,3.598) | 0.640 |
| 67–85 years | 1 (1.000,1.000) | – | 1 (1.000,1.000) | – |
| Previous surgery | 5.366 (1.809,15.921) | 0.002 | 12.24 (2.235,67.037) | 0.004 |
| Cavernous sinus extension | 13.78 (4.839,39.235) | <0.001 | 7.055 (1.972,25.232) | 0.003 |
| Secretory tumor | 0.177 (0.050,0.620) | 0.007 | 0.121 (0.016,0.903) | 0.039 |

*Previous radiation and tumor size dropped from the logistic regression model. ^Firth logistic regression used. OR: Odds ratio, CI: Confidence interval, MRI: Magnetic resonance imaging

**Table 4:** Logistic regression results of factors associated with postoperative outcomes.

| Variable | Univariable OR (95% CI) | *P*-value | Multivariable OR (95% CI) | *P*-value |
|---|---|---|---|---|
| New postoperative hypopituitarism requiring hormone replacement* | | | | |
| Age | | | | |
| 11–38 years | 7.889 (1.335, 46.630) | **0.023** | 9.981 (1.429, 69.696) | **0.020** |
| 41–52 years | 3.667 (0.568, 23.657) | 0.172 | 3.880 (0.554, 27.201) | 0.172 |
| 53–66 years | 3.381 (0.525, 21.764) | 0.200 | 3.882 (0.559, 26.963) | 0.170 |
| 67–85 years (Ref) | 1 (1.000, 1.000) | – | 1 (1.000, 1.000) | – |
| Female | 1.652 (0.644, 4.237) | 0.297 | 2.201 (0.809, 5.994) | 0.123 |
| Knosp>0[§] | 1.494 (0.371, 6.007) | 0.572 | – | – |
| Tumor type | | | | |
| Prolactinoma | 3.621 (0.882, 14.855) | 0.074 | 3.227 (0.605, 17.219) | 0.170 |
| Somatotroph | 1.207 (0.341, 4.274) | 0.771 | 0.876 (0.219, 3.512) | 0.852 |
| Prolactinoma+somatotroph | 2.241 (0.326, 15.418) | 0.412 | 2.190 (0.292, 16.436) | 0.446 |
| Corticotroph | 0.249 (0.014, 4.419) | 0.343 | 0.0826 (0.003, 1.957) | 0.123 |
| Silent/null cell (Ref) | 1 (1.000, 1.000) | – | 1 (1.000, 1.000) | – |
| Operation duration | 1.015 (1.002, 1.029) | **0.023** | 1.023 (1.007, 1.040) | **0.006** |

*(Contd...)*

**Table 4:** *(Continued)*.

| Variable | Univariable OR (95% CI) | *P*-value | Multivariable OR (95% CI) | *P*-value |
|---|---|---|---|---|
| Postoperative improvement in vision† | | | | |
| Age$ | 1.003 (0.969, 1.038) | 0.876 | – | – |
| Female$ | 1.612 (0.572, 4.546) | 0.367 | – | – |
| Fat packing for closure | 3.438 (1.123, 10.528) | **0.031** | 3.171 (0.983, 10.225) | 00.053 |
| Operation duration$ | 1.016 (0.999, 1.034) | 0.069 | – | – |
| Postoperative termination of hypersecretion | | | | |
| Age | 1.034 (0.987, 1.085) | 0.160 | 1.047 (0.984, 1.115) | 0.149 |
| Female$ | 3.64 (0.934, 14.18) | 0.063 | – | – |
| Prior pharmacologic treatment$ | 0.226 (0.051, 0.998) | 0.050 | – | – |
| Tumor type | | | | |
| Prolactinoma (Ref) | 1 | – | 1 | – |
| Prolactinoma+somatotroph | 0.833 (0.090, 7.675) | 0.872 | 0.638 (0.063, 6.410) | 0.703 |
| Somatotroph | 7.5 (1.246, 45.15) | **0.028** | 6.087 (0.955, 38.79) | 0.056 |
| Corticotroph | 15 1.325, 169.87) | **0.029** | 18.11 (1.444, 227.22) | **0.025** |
| Presence of recurrent/residual tumor on 6-month MRI# | | | | |
| Age | | | | |
| 11–38 years (Ref) | 1.045 (0.350, 3.120) | 0.936 | 7.631 (1.237, 47.094) | **0.029** |
| 40–52 years | 0.786 (0.260, 2.375) | 0.670 | 1.250 (0.246, 6.338) | 0.788 |
| 53–66 years | 0.479 (0.150, 1.534) | 0.215 | 0.670 (0.125, 3.598) | 0.640 |
| 67–85 years | 1 (1.000, 1.000) | – | 1 (1.000, 1.000) | – |
| Female$ | 0.839 (0.379, 1.857) | 0.665 | – | – |
| Preoperative hormone replacement$ | 2.892 (1.278, 6.542) | **0.011** | – | – |
| Levothyroxine | 3.120 (1.365, 7.130) | **0.007** | – | – |
| Hydrocortisone | 4.647 (1.617, 13.354) | **0.004** | – | – |
| Preoperative visual deficit | 5.811 (2.203, 15.324) | **<0.001** | 3.463 (0.753, 15.936) | 0.111 |
| Previous surgery | 5.366 (1.809, 15.921) | **0.002** | 12.24 (2.235, 67.037) | **0.004** |
| Cavernous sinus extension | 13.78 (4.839, 39.235) | **<0.001** | 7.055 (1.972, 25.232) | **0.003** |
| Secretory tumor | 0.177 (0.050, 0.620) | **0.007** | 0.121 (0.016, 0.903) | **0.039** |
| Surgical approach$ | | | | |
| Microscope (Ref) | 1 | – | – | – |
| Endoscope | 9.778 (1.663, 57.489) | **0.012** | – | – |
| Hybrid | 3.761 (1.429, 9.899) | **0.007** | – | – |
| Operation duration$ | 1.015 (1.002, 1.029) | **0.022** | – | – |

Boldface *P*-values are statistically significant. *Firth logistic regression used. †Only patients with baseline abnormal vision were included in the analysis. $Dropped during stepwise regression modeling due to non-significance. #Prior radiation and tumor size dropped from the logistic regression model. OR: Odds ratio, CI: Confidence interval, MRI: Magnetic resonance imaging

primary advantages of this approach include: (1) minimal nasal mucosal disruption as compared with an endoscopic approach (including preservation of the nasal mucosa over the sphenoid sinus and turbinates, with reduction of the septum at the end of the procedure); (2) bimanual dissection technique for tumor removal; and (3) a nasal retractor largely reduces intraoperative bleeding. This is the major determinant of efficiency and time saving as compared with the endoscope. The endoscope is then used as necessary for enhanced visualization in the suprasellar region and laterally within the cavernous sinus. Thus, the advantages of both techniques are achieved in this hybrid approach. Tumors purely within the sella seldom require further visualization for their removal.

This differs from recent moves toward greater use of purely endoscopic transsphenoidal approaches for pituitary tumor surgery of all complexities (e.g., with or without sinus invasion, high or low Knosp grade) despite inconclusive

**Table 5:** Comparison of patient and tumor characteristics between primarily microscopic and endoscopic patient cohorts.

| Variable | Cohort 1 (*n*=160)* | Cohort 2 (*n*=33)* | *P*-value |
|---|---|---|---|
| Patient age, mean (SD) | 51.58 (16.18) | 56.06 (14.76) | 0.153 |
| Female, *n* (%) | 89 (55.6) | 13 (39.4) | 0.089 |
| BMI, mean (SD) | 32.37 (7.82) | 29.67 (5.77) | 0.112 |
| Tumor size (%) | | | |
| Microadenoma | 17 (10.6) | 2 (6.1) | 0.423 |
| Macroadenoma | 143 (89.4) | 31 (93.9) | |
| ASA score, mean (SD) | 2.53 (0.58) | 2.66 (0.70) | 0.335 |
| Knosp classification grade 1+, *n* (%) | 136 (85.0) | 23 (82.1) | 0.699 |
| Preoperative hormone replacement, *n* (%) | 57 (35.6) | 7 (21.2) | 0.109 |
| Preoperative visual deficit, *n* (%) | 82 (51.2) | 23 (69.7) | 0.053 |
| Previous treatment (surgery, pharmacologic, or radiation), *n* (%) | 75 (46.9) | 11 (33.3) | 0.154 |
| Cavernous sinus tumor extension, *n* (%) | 63 (39.4) | 14 (45.2) | 0.548 |

*Cohort 1 from the senior author using a primarily microscopic approach, with endoscopic assistance as needed. Cohort 2 from other surgeons using an endoscopic-only approach. SD: Standard deviation, ASA: American Society of anesthesiologists, BMI: Body mass index

**Table 6:** Time and normalized cost analysis (adjusted for inflation) by operative technique.

| Variable | Microscopic-only | Hybrid | Endoscopic-only | *P*-value |
|---|---|---|---|---|
| Operative time (minutes) | 178.1 (171.4, 184.7) | 213.2 (195.7, 230.7) | 218.97 (202.47, 235.48) | <0.001 |
| Operating room cost* | 1.00 (0.95, 1.04) | 1.24 (1.12, 1.36) | 1.19 (1.10, 1.28) | <0.001 |
| Total direct cost* | 5.00 (4.69, 5.31) | 5.86 (4.99, 6.72) | 6.28 (5.03, 7.53) | 0.008 |

*Costs normalized to mean operating room cost during the baseline period for comparison. Analysis of variance tests performed. Mean with 95% confidence interval shown

evidence for its adoption.[27,63] For example, a 2020 meta-analysis of 29 case–control studies by Chen *et al.*[15] did not find a statistically significant difference in the rates of GTR, correction of hypersecretion, or visual improvement with endoscopic versus microscopic pituitary tumor resection. Broersen *et al.*[13] also found no clear advantage of either technique based on surgical outcomes and complications in patients with pituitary tumors causing Cushing disease. Without a clear advantage in outcomes, the choice of endoscopic versus microscopic technique is thus commonly left to individual surgeon preference. Although endoscopic pituitary surgery can offer better visualization and surgical field illumination, this is potentially offset by a relatively steep learning curve and instrument crowding that can limit two-handed surgical technique.[61] Anecdotally, the enhanced visualization provided by the endoscope can also lead to more aggressive manipulation of the tumor-gland interface and risk new postoperative hypopituitarism when compared with the two-handed microsurgical technique and the relatively limited surgical footprint offered by a microscopic approach in experienced hands.

Our data support the efficiency of a microscope-first approach to most PAs, with the microscopic-only cases being faster and less costly than hybrid or endoscopic-only cases. Moreover, the hybrid approach for more complex cases was comparable in operative time and costs with an endoscopic-only approach (used primarily for non-selected PAs as part of the time and cost analysis in this work). These data suggest that the use of a primarily microscopic approach to PAs, with a hybrid approach used in selected complex cases, can decrease both operating room time and costs compared with the use of an endoscope alone. Asemota *et al.*[6] similarly found that endoscopic-only approaches had higher overall total and hospital/facility costs than microscopic approaches for transsphenoidal pituitary surgery despite a similar postoperative LOS. Although costs were not addressed in the recent multicenter study by Findlay *et al.*[25] that similarly reported shorter operative times with microscopic versus endoscopic surgery, they also found that microscopic surgery was associated with longer hospital stays, with the association between LOS and costs well documented.[6] The median 4-day LOS in the current series is nonetheless lower than the LOS in either the endoscopic or the microscopic cohort in that study, suggesting that cost savings by approach may vary based on individual surgeon metrics. Cost-effectiveness modeling studies further highlight the link between surgical outcomes and overall treatment costs,[4,64] although such projections are highly dependent on the input variables used. For example, in a work by Rudmik *et al.*,[64] although endoscopic versus microscopic surgery was projected to have lower overall treatment costs, this was largely driven by relatively high rates of permanent DI not seen in the current work.

**Endocrinologic outcomes**

***Postoperative pituitary dysfunction***

Providing important context for the surgical and cost efficiency seen with the senior author's approach to PAs, endocrinologic and tumor control outcomes were excellent in this series. In our study, 13.1% of patients had immediate new postoperative hypopituitarism requiring hormone replacement therapy, and 2 patients (1.2%) had delayed new hypopituitarism requiring hormone replacement. In the recent TRANSSPHER study that examined the results of microscopic versus endoscopic surgery for the treatment of nonfunctioning adenomas, Little *et al.*[43] found that new postoperative hormone deficiencies were present in 28.4% (19/67) of patients undergoing microscopic surgery versus 9.7% (14/145) of patients undergoing endoscopic surgery. They suggested that the lower rate of new postoperative pituitary dysfunction seen with the endoscope may be a result of enhanced visualization of the pituitary gland and surrounding tumor. Their study excluded functioning adenomas (which, although not borne out in the current work, may have a higher risk of postoperative gland dysfunction due to a more aggressive resection goal) and determined dysfunction at 6-month follow-up rather than within the immediate postoperative period (meaning that shorter-term pituitary dysfunction was likely not captured). Other studies report variable rates of postoperative hypopituitarism (0–14%) using the endoscope and/or microscope.[2,69] A summary of these, and other hormonal comparisons between this series and the literature, are detailed in Table 7,[2,5,7,9-13,15,16,19,30,32,33,36-38,43-45,50,53,62,65,66,69,73] with the outcomes herein on the lower end of those documented for new postoperative hypopituitarism. Among the variables associated with new hypopituitarism identified on multivariate analysis in this work, longer operative time is likely a proxy for tumor complexity and a potentially greater chance of manipulating or injuring the gland. We hypothesize that the increased risk of gland dysfunction seen in younger patients may be from a greater sensitivity of younger glands to manipulation.

***Postoperative DI and normalization of hypersecretion***

In our series, 1.9% of patients experienced long-standing DI that required hormone replacement after discharge. These results compare favorably with those of other published works, for example, in a meta-analysis by Goudakos *et al*[30] 806 patients demonstrated long-term DI rates of 10% and 2% with microscopic and endoscopic approaches, respectively. Larger meta-analysis data from Chen *et al.*[15] (7774 patients) reported even higher DI rates of 8.2% and 7.1% with the microscope and endoscope, respectively, but there was no delineation between transient and longer-term DI.

In addition, 49/160 (30.6%) of PAs herein were hormone-secreting tumors, and postoperative termination of hypersecretion was achieved in 73.5% (36/49) of cases on follow-up. This compares favorably with the data from the large meta-analysis by Chen *et al.*,[15], which reported rates of hypersecretion normalization of 61.8% and 62.4% with the microscope and endoscope, respectively. A broader review of the literature nonetheless reveals variability (61–98%) in postoperative rates of hypersecretion normalization [15,20,30,33,36] with outcomes affected by tumor histology and size.[35,66] Similarly, in our multivariate analysis, adrenocorticotropic hormone (ACTH)-secreting tumors (relative to prolactinomas) were associated with greater odds of termination of hypersecretion (Odds ratio [OR] = 18.1). This may result from a propensity to diagnose ACTH-secreting tumors when they are small – due to the profound effects of excess cortisol – combined with an aggressive surgical approach that commonly involves partial gland resection and/or alcohol sclerosis.

***Tumor remnant/recurrence***

In our study, remnant/recurrent tumors on 6-month MRI were present in 32/160 patients (20.0%, with an additional 15% lost to follow-up) and were associated with previous surgery and cavernous sinus extension on multivariate analysis. Comparisons with other studies are provided in Table 5, with these rates similar to the only other study[53] with a comparable timeframe. These factors pose considerable challenges to achieving a GTR due to scarring in re-do cases and the complex neurovasculature of the cavernous sinus that limits safe tumor resection from this space.[8,45,48,51,57] Tumor secretion was also found to be negatively associated with remnant/recurrence, potentially because secreting tumors are found when smaller (from symptoms of secretion) and a more aggressive surgical strategy is used. Finally, remnant/recurrent tumor was also associated with younger age (18–38 years) (OR = 7.63). Although some studies have found no link between age and remnant/recurrence,[34,54,62] others have similarly suggested an association between younger age and adenoma return.[44,45,52,58,73] A more aggressive approach to resection may be warranted in younger patients, although this must be weighed against risks of postoperative gland dysfunction from additional manipulation.

**Table 7:** Comparison of endocrinologic data versus cited literature.

| Variable | Study | Rate (%) | Surgical approach |
|---|---|---|---|
| New postoperative hypopituitarism | Ciric *et al.*, 1997[16] | 19.4 | Both |
| | Tabaee *et al.*, 2009[69] | 5–22 | Endoscopic |
| | Roelfsema *et al.*, 2012[62] | 7–25 | Endoscopic |
| | Juraschka *et al.*, 2014[37] | 5 | Endoscopic |
| | Sampedro-Nuñez *et al.*, 2016[65] | 28.4 | Microscopic |
| | Asemota *et al.*, 2017[5] | 17 | Both |
| | Agam *et al.*, 2019[2] | 3.6 | Both |
| | Little *et al.*, 2019[43] | 28.4 | Microscopic |
| | | 9.7 | Endoscopic |
| | Chen *et al.*, 2020[15] | 5.7 | Microscopic |
| | | 7.0 | Endoscopic |
| | Biamonte *et al.*, 2021[9] | 12.2 | Endoscopic |
| | Current study | 13.1 | Microscopic |
| Long-term diabetes insipidus | Black *et al.*, 1987[10] | 0.4 | Microscopic |
| | Goudakos *et al.*, 2011[30] | 10.0 | Microscopic |
| | | 2.0 | Endoscopic |
| | Nayak *et al.*, 2018[50] | 4.0 | Endoscopic |
| | Agam *et al.*, 2019[2] | 0.3 | Both |
| | Current study | 1.9 | Microscopic |
| Termination/normalization of hypersecretion | Santoro *et al.*, 2007[66] | 65 | Unspecified |
| | Hofmann *et al.*, 2008[33] | 75.9 | Microscopic |
| | D'Haens *et al.*, 2009[19] | 50.0 | Microscopic |
| | | 63.0 | Endoscopic |
| | Goudakos *et al.*, 2011[30] | 60.0 | Microscopic |
| | | 66.0 | Endoscopic |
| | Chen *et al.*, 2020[15] | 61.8 | Microscopic |
| | | 62.4 | Endoscopic |
| | Current study | 73.5 | Microscopic |
| Tumor remnant/recurrence | Jane *et al.*, 2001[36] | 1.3–16 | Microscopic |
| | Patil *et al.*, 2008[53]* | 17.4 | Unspecified |
| | Losa *et al.*, 2008[45] | 19 | Unspecified |
| | Brochier *et al.*, 2010[12] | 24–47 | Unspecified |
| | Heringer *et al.*, 2016[32] | 56.5 | Microscopic |
| | | 54.9 | Endoscopic |
| | Karki *et al.*, 2017[38] | 15.6 | Microscopic |
| | Watts *et al.*, 2017[73] | 29 | Both |
| | Azab *et al.*, 2019[7] | 4.4 | Microscopic |
| | Broersen *et al.*, 2019[13] | 11.0 | Microscopic |
| | Liu *et al.*, 2019[44] | 13.0 | Endoscopic |
| | Braun *et al.*, 2020[11] | 13 | Endoscopic |
| | Current study* | 20.0 | Microscopic |

*Assessed within 6 months of surgery.

### Limitations

Limitations include those inherent to retrospective and single-center/surgeon studies: selection bias, potential demographic homogeneity, and low technique variability, which may dampen the study's generalizability. Varying levels of surgeon experience within the time and cost comparison may also have influenced operative times and surgical outcomes, although consecutive patient cohorts with comparable baseline characteristics were used to minimize other potential confounding variables.

## CONCLUSION

A primarily microscopic approach can minimize PA operative time and costs while maintaining excellent clinical outcomes.

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