Operative Strategies to Minimize Complications Following Resection of Pituitary Macroadenomas

Jayesh P. Thawani^{1,2,*} Ashwin G. Ramayya^{1,*} Jared M. Pisapia¹ Kalil G. Abdullah¹ John Y-K. Lee¹
M. Sean Grady¹

¹Department of Neurosurgery, University of Pennsylvania, Philadelphia, Pennsylvania, United States

²School of Engineering and Applied Sciences, University of Pennsylvania, Philadelphia, Pennsylvania, United States

Address for correspondence Jayesh P. Thawani, MD, Department of Neurosurgery, University of Pennsylvania, 3400 Spruce Street, 3 Silverstein Pavilion, Philadelphia, PA 19104, United States (e-mail: jayesh.thawani@uphs.upenn.edu).

J Neurol Surg B 2017;78:184–190.

Abstract

Introduction We sought to identify factors associated with increased length of stay (LOS) and morbidity in patients undergoing resection of pituitary macroadenomas.

Methods We reviewed records of 203 consecutive patients who underwent endoscopic endonasal resection of a pituitary macroadenoma (mean age = 55.7 [16–88]) years, volume = 11.3 (1.0–134.3) cm³. Complete resection was possible in 60/29.6% patients. Mean follow-up was 575 days. Multivariate logistic regression was performed using MATLAB.

Results Mean LOS was 4.67 (1–66) days and was associated with CSF leak ($p = 0.025$), lumbar drain placement ($p = 0.041$; $n = 8/3.9\%$ intraoperative, $n = 20/9.9\%$ postoperative), and any infection ($p = 0.066$). Age, diabetes insipidus ($n = 17/8.37\%$), and syndrome of inappropriate antidiuretic hormone secretion ($n = 12/5.9\%$) were not associated with increased LOS ($p > 0.2$). Postoperative CSF leak in the hospital ($n = 21/10.3\%$) was associated with intraoperative CSF leak ($p = 0.002$; $n = 82/40.4\%$) and complete resection ($p = 0.012$). There was no significant association ($p > 0.1$) between postoperative CSF leak in the hospital following surgery and the use of a fat graft ($n = 61/30.1\%$), nasoseptal flap (155/76.4%), or perioperative lumbar drain placement ($n = 8/3.94\%$).

Keywords

- pituitary macroadenoma
- length of stay

Conclusion Complete resection is associated with increased risk of CSF leak and LOS. Operative strategies including placement of fat graft, nasoseptal flap, or intraoperative lumbar drain placement may have limited value in reducing the risk of postoperative CSF leak.

Introduction

Pituitary (> 1 cm) and giant macroadenomas (> 4 cm) represent an array of clinical phenotypes, manifesting most

often as cranial neuropathy or less commonly as an endocrine disturbance. Endoscopic techniques have served roles in improving the safe exposure of and surgical resection of these lesions.¹ Resection of large and giant pituitary macroadenomas is associated with complications including cerebrospinal fluid (CSF) leak, meningitis, postoperative fluid and

* Denotes equal contribution

electrolyte disorders including diabetes insipidus (DI), and local recurrence.^{1–3} The tumors involving the cavernous sinus and those with volumes greater than 10 cm³ are associated with a lower likelihood of complete resection and higher rates of morbidity following endoscopic endonasal surgery.⁴

Rates of complete radiographic resection with endoscopic endonasal techniques range between 24 and 66% in patients with giant and/or large pituitary macroadenomas and are generally lower than those reported in patients with microadenomas.^{5–7} These studies differ greatly in terms of patient characteristics, most notably in regards to size cutoffs in the “nongiant” macroadenoma groups with tumors less than 4 cm in largest dimension. Nevertheless, several authors have advocated a maximal-safe resection strategy in large tumors with surveillance, adjuvant chemotherapeutic, or radiotherapies following surgery.^{5,6} Length of stay (LOS) in patients undergoing endoscopic surgery for pituitary macroadenomas has been reported at 2.4 days in a group of 56 patients with tumors not encroaching on the carotid arteries or cavernous sinus.⁸ Given complications associated with larger tumors, we sought to first clearly define these, then work to identify risk factors associated with LOS and complications in a large cohort of patients undergoing endoscopic endonasal surgery for pituitary macroadenomas.

Methods

Data Collection

We reviewed records from 203 consecutive patients who underwent endoscopic endonasal resection of a pituitary macroadenoma at our institution during a 5-year interval (January 1, 2009 and January 1, 2014) at our health system. For each patient, we obtained information about demographics (►Table 1), prior treatment, presenting features and surgical outcomes (►Table 2), and complications and operative strategies aimed at reducing complications (►Table 3). Preoperative volumes of tumors were obtained based on radiology reports and measured in cubic centimeters (cm³). Neuroradiology defined degree of resection and anatomic details such as cavernous sinus involvement.

Statistical Analyses

We performed multivariate logistic regression analyses to identify factors that were predictive of the following categorical outcomes: gross total resection (GTR) as deemed by neuroradiology on postoperative day 1, symptom resolution,

Table 2 Prior treatment, presenting features, and surgical outcomes

Mean preoperative volume (range)	11.3 cm ³ (0.77–13.4)
Mean preoperative maximum dimension (range)	2.4 cm (1.1–6.7)
Prior surgery	<i>n</i> = 26 (12.8%)
Prior radiation	<i>n</i> = 9 (3.94%)
Pathology	
Null	<i>n</i> = 74 (36.5%)
Somatotroph	<i>n</i> = 21 (10.3%)
Corticotroph	<i>n</i> = 19 (9.95%)
Gonadotroph	<i>n</i> = 32 (15.7%)
Prolactinoma	<i>n</i> = 7 (3.45%)
Thyroid	<i>n</i> = 1 (0.05%)
Clinical symptoms	
Incidental	<i>n</i> = 67 (33.0%)
Headache	<i>n</i> = 77 (37.9%)
Visual fields	<i>n</i> = 96 (47.3%)
Acromegaly	<i>n</i> = 16 (7.88%)
Cushing disease	<i>n</i> = 7 (3.45%)
Surgical outcomes	
% GTR	<i>n</i> = 60 (29.6%)
% Cavernous sinus involved	<i>n</i> = 86 (42.4%)
Postoperative radiation	<i>n</i> = 28 (13.8%)

Abbreviation: GTR, gross total resection.

CSF leaks, and postsurgical DI. We also applied a multivariate linear regression model to identify factors related to hospital LOS (coded as a continuous variable). All independent variables were coded as categorical, except for age. For each regression model, we report the chi-square statistic and *p* value comparing the model's accuracy with a null model. For each significant independent variable, we report the odds ratio (OR), the *t* statistic, and the *p* value. We considered *p* < 0.05 to be statistically significant. We performed post-hoc univariate statistical tests on each independent variable that met statistical significance using a chi-square test or a one-way ANOVA (analysis of variance), as appropriate. All analyses were performed using MATLAB (MathWorks, Massachusetts, United States).

Operative Management and Endocrine Follow-up

We care for patients collaboratively with otorhinolaryngology and endocrinology. Our preference is to obtain as maximal an extent of resection as is safe. A bimanual approach is utilized through both nostrils. In patients undergoing transphenoidal surgery with macroadenomas, a nasoseptal flap is prepared by otorhinolaryngology. With evidence of a CSF leak intraoperatively, a direct repair with fat graft and/or fascia lata is attempted during the procedure. First, a fat graft (obtained from the superficial abdomen) is obtained and

Table 1 Demographic data

Total number	203
Age (mean ± SD)	55.7 (16–88)
Sex	
Female	<i>n</i> = 99 (48.7%)
Male	<i>n</i> = 104 (51.2%)
Mean days of follow-up	575 d

Abbreviation: SD, standard deviation.

Table 3 Complications and operative strategies aimed at reducing complications

Mean LOS (d)	4.67 (1–26)
% CSF leak (intraoperative)	<i>n</i> = 82 (40.4%)
% CSF leak (postoperative)	<i>n</i> = 21 (10.3%)
% DI (in hospital)	<i>n</i> = 17 (8.37%)
% SIADH (in hospital)	<i>n</i> = 12 (5.91%)
% DI (at follow-up)	<i>n</i> = 9 (4.43%)
% Infection	<i>n</i> = 7 (3.45%)
Meningitis	<i>n</i> = 2 (0.99%)
UTI	<i>n</i> = 5 (2.46%)
% Visual field changes	<i>n</i> = 3 (1.48%)
% Stroke	<i>n</i> = 1 (0.005%)
% Deceased	<i>n</i> = 2 (0.99%)
<i>Operative strategies</i>	
% Nasoseptal flap	<i>n</i> = 155 (76.4%)
% Fat graft	<i>n</i> = 61 (30.1%)
% Fascia lata	<i>n</i> = 3 (1.48%)
% Lumbar drain (perioperative)	<i>n</i> = 8 (3.94%)
% Lumbar drain (postoperative)	<i>n</i> = 20 (9.85%)
Duration of lumbar drain (d)	4.62 (3–9)
Days to lumbar drain placement (postoperative only)	3.85 (1–22)
% Return to OR (with CSF rhinorrhea)	<i>n</i> = 7 (3.45%)

Abbreviations: CSF, cerebrospinal fluid; DI, diabetes insipidus; LOS, length of stay; OR, operating room; SIADH, syndrome of inappropriate antidiuretic hormone; UTI, urinary tract infection.

placed in the resection cavity. If leakage persists or occurs with Valsalva maneuver, a fascia lata graft obtained from the right leg is obtained. If there is persistent leakage, a lumbar drain will be placed. The nasoseptal flap is elevated and the bone is not replaced. With a postoperative leak, patients are taken back to the operating room for exploration and definitive closure. In this case, lumbar drains are placed at the surgeon's discretion. Our endocrinology team follows every patient undergoing surgery and manages electrolytes through the peri- and postoperative periods. The management of sodium changes during the postoperative period is based on standard clinical guidelines and recommendations of the consult service.

Results

Patients had a mean age of 55.7 years (range: 16–88), and 48.7% of them were female (*n* = 99), and patients had a mean follow-up of 577 days (►Table 1). The mean preoperative volume of tumors was 11.3 cm³ (1.0–134.3 cm³) with 42.4% of tumors (*n* = 86) involving the cavernous sinus (►Table 2). A subset of patients had prior surgery (12.8%, *n* = 26) or prior radiation (3.94%, *n* = 9). The most common tumor pathology was null cell adenoma (36.5%, *n* = 74), followed by gonadotroph (15.7%,

n = 32), somatotroph (10.3%, *n* = 21), and corticotroph (9.95%, *n* = 19) adenomas. The most common presenting features were visual field changes (47.3%, *n* = 96), headache (37.9%, *n* = 77), and incidental discovery (33.0%, *n* = 67). A subset of patients underwent postoperative radiation (13.8%, *n* = 28).

We separately performed subgroup analyses of tumors based on their endocrinologic function. We divided tumors into nonfunctional tumors (null cell adenoma) and functional tumors (somatotrophs, corticotrophs, thyroid, gonadotrophs, and rarely prolactinomas). We did not analyze each functional group independently because of limited power (*n* < 30 in each group). We found the following: a trend toward greater size (13.4 cm³) among nonfunctional tumors as compared with functional tumors (9.8 cm³, *p* = 0.12). We observed similar rates of GTR among the two groups (*p* = 0.22) and did not observe significant differences in the rate at which symptoms resolved (*p* = 0.41).

We observed a trend toward a longer LOS in functional tumors (4.95 days), as compared with nonfunctional tumors (4.25 days, *p* = 0.15). We did not observe differences in the rates of intraoperative leaks or those evolving into postoperative leaks among nonfunctional and functional tumors (*p* > 0.2). Finally, we observed more frequent infections among functional tumors (5.2%) as compared with nonfunctional tumors (0%, *p* = 0.04) but did not observe a significant difference in the rate of DI (*p* > 0.5).

GTR was obtained in 29.6% of patients (*n* = 60) as defined on postoperative day 1 magnetic resonance imaging (MRI) read by neuroradiology. GTR was less likely to occur with larger tumors (OR = 0.40, *t* = 2.35, *p* = 0.019) and trended toward being less likely with cavernous sinus involvement (OR = 0.99, *t* = 1.85, *p* = 0.064). Post-hoc tests revealed that GTR was more frequent when the cavernous sinus was not involved (38.5%) compared with when it was involved (17.4%; chi square = 10.52, *p* = 0.001, ►Fig. 1). Also, tumors that underwent GTR were smaller (mean = 1.29 cm³) than those that underwent subtotal resection (mean = 7.2 cm³; *p* = 0.012). Nonsignificant predictors of GTR included age and sex (*p* > 0.14). Complete symptom resolution was less likely when visual field deficit (OR = 0.16, *t* = 2.97, *p* = 0.003) and headache (OR = 0.30, *t* = 2.09, *p* = 0.035) were presenting factors. Nonsignificant predictors included age, sex, tumor size, GTR (*p* > 0.2).

Patients had a mean LOS of 4.7 days (range: 1–26; ►Table 3). Intraoperative CSF leaks were the most common complication (40.4%, *n* = 82), followed by postoperative CSF leaks (10.3%, *n* = 21) and DI (8.37%, *n* = 17). Postoperative CSF leaks were those that occurred during the hospitalization. Hospital LOS was increased following infection (OR = 12.18, *t* = 1.84, *p* = 0.066), CSF leak (OR = 3.38, *t* = 2.25, *p* = 0.025), and lumbar drain placement (OR = 4.92, *t* = 2.05, *p* = 0.041). Post-hoc analyses showed that LOS was increased during admissions with an infection (8 vs. 4.5 days, *p* = 0.011, ►Fig. 2), CSF leak (5.7 vs. 4 days, *p* = 0.002), and lumbar drain placement (6.89 vs. 4.32 days, *p* < 0.001), compared with admissions during which these resective complications did not occur. Nonsignificant predictors included age, sex, DI, and syndrome of inappropriate antidiuretic hormone (SIADH) secretion (*p* > 0.4). Postoperative infections occurred in seven patients (3.45%), most commonly urinary tract

Fig. 1 Factors predicting gross total resection (GTR). (a) GTR was more frequent when the cavernous sinus was not involved (38.5%) compared with when it was involved (17.4%). (b) Tumors that underwent GTR were smaller (mean = 1.29 cm³) than those that underwent subtotal resection (mean = 7.17 cm³). * indicates $p < 0.05$. Error bars indicate standard error of mean. See main text for statistics.

infections (UTIs; $n = 5$), followed by meningitis ($n = 2$). Rare occurrences of more severe complications such as new visual field deficits ($n = 3$, 1.48%), stroke ($n = 1$, < 1%), and death ($n = 2$, < 1%) were also observed. Deaths were attributable to systemic cardiac and pulmonary events. Regarding infections, nonsignificant predictors included age, sex, prior surgery, prior radiation, tumor size, CSF leak, and lumbar drain placement ($p > 0.14$).

We separately analyzed factors related to intra- and postoperative CSF leaks. Intraoperative CSF leak was more likely during resection of large tumors (OR = 3.6e-05, $t = 2.14$, $p = 0.032$). Nonsignificant predictors included age, sex, prior surgery, GTR, cavernous sinus involved, or prior radiation ($p > 0.18$). Postoperative CSF leak was more likely following intraoperative CSF leak (OR = 7.96, $t = 3.12$, $p = 0.002$) and GTR (OR = 5.18, $t = 2.49$, $p = 0.012$). Post-hoc analyses revealed that postoperative CSF leaks occurred more frequently when an intraoperative CSF leak was noted (20.9 vs. 3.31% when no intraoperative leak was observed; $p < 0.001$; ► Fig. 3). Also, we observed a trend

toward greater postoperative CSF leaks following GTR compared with subtotal resections (16.7 vs. 7.75%; $p = 0.057$). Nonsignificant predictors of postoperative leaks, included age, sex, tumor size, sex, tumor size, prior surgery, prior radiation, cavernous sinus involvement, and infection status. Additionally, fat graft, nasoseptal flap, and intraoperative lumbar drain placement were not significant predictors of postoperative leak ($p > 0.1$).

DI noted in the hospital was more likely in younger patients (OR = 0.96, $t = 1.91$, $p = 0.056$) and when patients also developed SIADH (OR = 7.98, $t = 2.84$, $p = 0.004$). Nonsignificant predictors included sex, GTR, tumor size, CSF leak, or lumbar drain placement ($p > 0.2$). DI at follow-up was more likely when patients developed SIADH (OR = 1.6e02, $t = 3.23$, $p = 0.001$) or DI (OR = 9.10, $t = 2.09$, $p = 0.036$) during their hospital stay. We observed trends in relation to female sex ($t = 1.83$, $p = 0.067$), and 7-day postoperative sodium measurements ($t = 1.67$, $p = 0.093$). Nonsignificant predictors included age, sex, GTR, tumor size, CSF leak, and lumbar drain placement ($p > 0.2$).

Fig. 2 Factors predicting length of stay (LOS). LOS was increased during admissions associated with an infection (a, 8 vs. 4.5 days), cerebrospinal fluid (CSF) leak (b, 5.7 vs. 4 days), and lumbar drain placement (c, 6.89 vs. 4.32 days). * indicates $p < 0.05$. See main text for statistics.

Fig. 3 Factors predicting postoperative cerebrospinal fluid (CSF) leak. (a) Postoperative CSF leaks occurred more frequently when an intraoperative CSF leak was noted (20.9%), compared with when no intraoperative leak was observed (3.31%). (b) We observed a trend toward greater postoperative CSF leaks following GTR compared with subtotal resections (16.7 vs. 7.75%). * indicates $p < 0.05$. See main text for statistics.

Macroadenomas can vary in their operative morbidity based on their size and location. To further explore these relations, we performed two subanalyses. First, to assess whether tumor size has a nonlinear relation with operative morbidity, we divided tumors into quartiles based on tumor size and assessed complication rates in each category (quartile 1, 0.77–3.2 cm³; quartile 2, 3.2–7.18 cm³; quartile 3, 7.2–14 cm³; quartile 4, 14–134.3 cm³, ► **Fig. 4**). We observed the following: GTR was more frequent in the smallest quartile of tumors (>50%) and as compared with the other three quartiles (15–25%, $p < 0.001$). LOS, the rates of infection, and DI did not vary among these groups ($p > 0.5$)

The rate of intraoperative leaks did not vary by tumor size ($p > 0.2$). Thus, the relation between tumor size and the rate of intraoperative CSF leak was only apparent when using multivar-

iate analyses. We observed an inverse relation between tumor size and the risk that an intraoperative CSF leak would evolve into a postoperative leak. Specifically, an intraoperative CSF leak associated with the smallest tumors more frequently evolved into postoperative leak (57%) as compared with intraoperative leaks associated with tumors in the other three quartiles (5–20%, $p = 0.002$, ► **Fig. 4b**). These results suggest that mass effect from relatively large tumors may prevent intraoperative leaks from evolving into postoperative leaks by providing a tamponading effect to counteract CSF pulsations. In contrast, small tumors may not provide such a counteractive force. Alternatively, intraoperative CSF leaks occurring in association with smaller tumors may have been less aggressively treated. However, even when only considering the smallest quartile of tumors, the rates of nasoseptal flap placement, fat grafts, or intraoperative lumbar

Fig. 4 Relation between tumor size and the risk of an intraoperative leak evolving into a postoperative leak. (a) We divided tumors into quartiles based on their preoperative volume. Here we show the mean volume for tumors in each quartile (error bars represent S.E.M.). (b) We computed the percentage of intraoperative CSF leaks that evolved into postoperative leaks separately for each quartile. We found that an intraoperative leak was more likely to evolve into a postoperative leak for the smallest quartile of tumors. * indicates $p < 0.05$. See main text for statistics.

drain placement did not differ when comparing intraoperative CSF leaks that evolved into postoperative leaks and those that did not ($p > 0.2$).

We separately analyzed tumors that were associated with clinically significant intracranial invasion (either lateral or suprasellar, presenting with headaches, visual changes, or any cranial nerve deficit) and tumors that were predominantly contained within the sphenoid sinus (and did not present with any of the aforementioned symptoms). We observed the following: tumors associated with intracranial invasion were larger (13.7 cm^3) and less frequently associated with GTR (23%) as compared with those that were contained in the sphenoid (6.7 cm^3 and 40%, respectively, $p < 0.017$, **Fig. 5**).

LOS was increased for tumors with clinically significant intracranial invasion (5.2 days) compared with those predominantly contained within the sphenoid (3.7 days, $p = 0.003$, **Fig. 5**). LOS, the rates of infection, and DI did not vary among these groups ($p > 0.5$). Intraoperative CSF leaks occurred at similar rates for tumors with and without intracranial invasion ($p = 0.45$) and we did not observe a significant difference in the likelihood of an intraoperative leak evolving into a postoperative leak in these groups ($p = 0.17$).

Discussion

Pituitary and giant macroadenomas involving the cavernous sinus and adjacent cranial nerves make a safe and complete resection additionally challenging in patients via an endoscopic, endonasal approach alone.^{3–5} As it has been previously described, involvement of the cavernous sinus serves as a risk factor for incomplete resection and recurrence.⁹ Repeat surgery has been associated with complications including postoperative DI, meningitis, and CSF leaks requiring repair.^{9–11}

Our data demonstrate that our approach to resect macroadenomas (see Methods) can be associated with complications and does not necessarily relate to a reduced LOS. Our mean LOS was 4.7 days and most closely correlated with the

presence of infection, both intra- and extraoperative CSF leak, and a need for lumbar drain placement.

CSF leaks represent a potential preventable event associated with surgery that relates to increased LOS. Predictably, surgical resection of large tumors was associated with CSF leak. However, we did not find that age, prior surgery, prior radiation, or cavernous sinus involvement related to CSF leak—both intra- or postoperatively. As expected, a postoperative CSF leak was more likely seen in the case of an intraoperative leak and with GTR. Placement of a fat graft, harvesting of a nasoseptal flap, and placement of a lumbar drain were not predictive of a postoperative CSF leak. Based on these results, the intraoperative maneuvers to repair CSF leak deserve further study in a prospective manner, as the benefits may not be as clearly appreciated. The aforementioned maneuvers increase operative time and may contribute to morbidity such as anosmia, surgical pain, and infection.¹²

Antibiotics are administered at the time of surgery (prior to incision and at two doses postoperatively) but not in a prophylactic manner (e.g., with CSF leak). The majority of infections in our series related to UTIs. All patients undergo placement of a urinary catheter for surgery. The urinary catheter is typically removed on the first postoperative day unless the patient has a fluid or electrolyte disorder identified. Two patients developed meningitis and both had known CSF rhinorrhea—a factor that has been closely associated with the development of meningitis following transsphenoidal surgery.^{13,14}

DI and SIADH represent well-known endocrinologic complications following transsphenoidal surgery. Large tumors, GTR, and CSF leak were not associated with the development of DI while in the hospital. A diagnosis of SIADH was closely related to the development of DI, however, suggesting that these clinical entities go hand in hand as part of a triphasic response following resection of macroadenomas.¹⁵ Interestingly, complications such as DI and SIADH, as noted in the hospital following surgery, were not associated with increased LOS. This may reflect the adequate management of these issues

Fig. 5 Separating tumors based on intracranial invasion. (a) Tumors that were associated with clinically significant intracranial invasion were larger in size (a) and involved an increased length of stay (LOS) (b) than tumors that were predominantly contained within the sphenoid (see main text for details). * indicates $p < 0.05$. See main text for statistics.

by our endocrinology team, who serve as consultants for all patients undergoing pituitary surgery.

The results of this study may help guide clinical practice by identifying factors that contribute to increased LOS. Compared with the sublabial approach, the endoscopic endonasal approach is associated with a lower LOS based on a meta-analysis (3.3 vs. 5.9 days).¹⁶ Our mean LOS was 4.7 days for a population of patients with large and technically difficult tumors to resect. In a recently published series, Yoshor et al described a protocol for early discharge following transsphenoidal operations for sellar pathology. In this series, lumbar drains were avoided, nasal packings were not placed, and intensive care unit (ICU) admissions were avoided when possible. By implementing an early and frequent patient education scheme, the authors were able to address most issues as they arose. Although several patients (16% or 8/50) developed early DI, they were able to manage these cases effectively (2% or 1/50 had persistent DI).¹² Shortcomings of the present study include its retrospective nature and those inherent in multivariate regression analyses, although our sample size is relatively large.

Conclusion

During endoscopic endonasal resection of pituitary macroadenomas, aggressive surgical resection resulting in GTR increases the chance of developing a CSF leak and increased LOS. The most appropriate surgical strategy (aggressive vs. conservative) must be evaluated on a case-by-case basis. Operative strategies including placement of fat graft, nasoseptal flap, or intraoperative lumbar drain placement may have limited value in reducing the risk of postoperative CSF leak.

Funding Sources

None.

Acknowledgments

None.

References

- Komotar RJ, Starke RM, Raper DMS, Anand VK, Schwartz TH. Endoscopic endonasal compared with microscopic transsphenoidal and open transcranial resection of giant pituitary adenomas. *Pituitary* 2012;15(2):150–159. <http://www.ncbi.nlm.nih.gov/pubmed/22038033>. Accessed January 1, 2016
- Goel A. Challenge of giant pituitary tumors. *World Neurosurg* 2014;82:e121–e124. <http://www.ncbi.nlm.nih.gov/pubmed/24121298>. Accessed January 1, 2016
- Gondim JA, Almeida JPC, Albuquerque LAF, et al. Endoscopic endonasal approach for pituitary adenoma: surgical complications in 301 patients. *Pituitary* 2011;14(2):174–183
- Hofstetter CP, Nanaszko MJ, Mubita LL, Tsiouris J, Anand VK, Schwartz TH. Volumetric classification of pituitary macroadenomas predicts outcome and morbidity following endoscopic endonasal transsphenoidal surgery. *Pituitary* 2012;15(3):450–463
- Gondim JA, Almeida JPC, Albuquerque LAF, Gomes EF, Schops M. Giant pituitary adenomas: surgical outcomes of 50 cases operated on by the endonasal endoscopic approach. *World Neurosurg* 2014; 82:e281–e290. <http://www.ncbi.nlm.nih.gov/pubmed/23994073>. Accessed January 1, 2016
- Juraschka K, Khan OH, Godoy BL, et al. Endoscopic endonasal transsphenoidal approach to large and giant pituitary adenomas: institutional experience and predictors of extent of resection. *J Neurosurg* 2014;121(1):75–83
- Koutourousiou M, Gardner PA, Fernandez-Miranda JC, Paluzzi A, Wang EW, Snyderman CH. Endoscopic endonasal surgery for giant pituitary adenomas: advantages and limitations. *J Neurosurg* 2013;118(3):621–631. <http://www.ncbi.nlm.nih.gov/pubmed/23289816>. Accessed January 1, 2016
- Dallapiazza R, Bond AE, Grober Y, 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* 2014;121(3):511–517
- Cavallo LM, Solari D, Tasiou A, et al. Endoscopic endonasal transsphenoidal removal of recurrent and regrowing pituitary adenomas: experience on a 59-patient series. *World Neurosurg* 2015; 80:342–350. <http://www.ncbi.nlm.nih.gov/pubmed/23046913>. Accessed March 24, 2016
- Chabot JD, Chakraborty S, Imbarrato G, Dehdashti AR. Evaluation of outcomes after endoscopic endonasal surgery for large and giant pituitary macroadenoma: a retrospective review of 39 consecutive patients. *World Neurosurg* 2015;84(4):978–988
- Jahangiri A, Wagner J, Han SW, et al. Morbidity of repeat transsphenoidal surgery assessed in more than 1000 operations. *J Neurosurg* 2014;121(1):67–74
- Thomas JG, Gadgil N, Samson SL, Takashima M, Yoshor D. Prospective trial of a short hospital stay protocol after endoscopic endonasal pituitary adenoma surgery. *World Neurosurg* 2014;81(3–4):576–583
- Daudia A, Biswas D, Jones NS. Risk of meningitis with cerebrospinal fluid rhinorrhea. *Ann Otol Rhinol Laryngol* 2007;116(12):902–905
- Robert FSptzler, Charles B. Wilson: management of recurrent CSF rhinorrhea of the middle and posterior fossa. 2009 <http://thejns.org/doi/abs/10.3171/jns.1978.49.3.0393>. Accessed March 24, 2016
- Finken MJJ, Zwaveling-Soonawala N, Walenkamp MJE, Vulsma T, van Trotsenburg ASP, Rottevel J. Frequent occurrence of the triphasic response (diabetes insipidus/hyponatremia/diabetes insipidus) after surgery for craniopharyngioma in childhood. *Horm Res Paediatr* 2011;76(1):22–26
- DeKlotz TR, Chia SH, Lu W, Makambi KH, Aulisi E, Deeb Z. Meta-analysis of endoscopic versus sublabial pituitary surgery. *Laryngoscope* 2012;122(3):511–518