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Predictors of short-term outcomes following endoscopic pituitary surgery☆

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ABSTRACT

Objective: Refinement of endoscopic pituitary surgery requires an understanding of the impact of demographic and surgical variables on outcomes.
Methods: Multivariate logistic regression and ANOVA models were used to explore variables for association with outcomes in a consecutive series of 57 patients undergoing endoscopic pituitary surgery.
Results: The mean duration of surgery was 177 min and was longer in patients with larger tumor size ($p = 0.03$) and presentation with visual symptoms ($p = 0.02$) in univariate analyses. The median duration of hospitalization was 3 days and was longer in patients with larger tumors ($p = 0.0005$). Gross tumor removal was achieved in 89%. Tumor size correlated with extent of tumor removal with an almost 3-fold decrease in complete tumor removal for every 1 cm increase in tumor size ($p = 0.047$). High rates of hormonal control (90%) and improvement in visual symptoms (92%) were noted.
Conclusions: High rates of gross tumor removal, hormonal cure and visual field improvement were noted in this series. Markers including tumor size and visual symptoms may be used to stratify patients.
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1. Introduction

Endoscopic pituitary surgery has undergone significant evolution in the past decade. Initial descriptions of the technical aspects of the procedure have been followed by the favorable reporting of short-term outcomes from multiple institutional series [1–8]. As the popularity of the procedure expands, an evidenced based understanding of its indications, effectiveness and limitations becomes critical for further development. The theoretical advantages of the endoscopic approach include panoramic visualization of the surgical site throughout the procedure. This may improve the identification of the tumor, normal pituitary tissue and critical neurovascular structures resulting in the potential for improved tumor control and decreased complications [1–8]. Although, the cumulative literature to date is limited in the reporting of long-term tumor control, multiple prior reports have described short-term outcomes data including perioperative complications and early hormone/tumor control. The goal of the current manuscript is to analyze the impact of patient and surgical variables on the short-term outcomes of extent of tumor resection and hormone resolution following endoscopic pituitary surgery.

2. Methods

A prospective series of all patients undergoing endoscopic pituitary tumor surgery between January 2004 and May 2006 at our institution was analyzed following Institutional Review Board approval. All procedures were performed by the senior authors (V.K.A., T.H.S.) at a single tertiary care medical center. Included in this study were surgeries with purely endoscopic approaches for pituitary tumors. Pathologies other than pituitary tumors, non-endoscopic surgery and endoscopic assisted surgery were excluded from these analyses. The operative, hospital and office records were reviewed for the patient demographics, presenting symptoms, tumor variables, operative variables, extent of tumor resection, duration of hospital stay and postoperative outcomes at last follow up. Operative variables included duration of surgery and completeness of tumor resection on endoscopic inspection and 3 month postoperative MRI reviewed by neuroradiology. Postopera-

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tive hormone resolution was determined for patients with secreting adenomas.

2.1. Statistical analysis

Descriptive statistics for the study variables were entered onto a Microsoft Excel (Seattle, WA) spreadsheet. Chi-square and Fisher's exact test were used to explore possible predictors of extent of tumor removal. Potential predictors of duration of surgery (minutes) and hospital length of stay (days) were determined using Student's *t*-tests. Multivariate logistic regression and ANOVA models were used to further explore variables that were found to be associated at a 5% level with the extent of tumor removal, duration of surgery and hospital length of stay, respectively. Age, gender, history of prior surgery, location of the lesion (isolated to sella vs. suprasellar extension), adenoma type (secreting vs. non-secreting), surgery approach (isolated to sella vs. suprasellar extension), maximal tumor dimension and presenting symptoms were assessed as potential predictors of duration of surgery. In addition to the variables mentioned above, duration of surgery (per 10 min increase), was also considered as a potential predictor of extent of tumor removal. All potential predictors were further considered for possible associations with hospital length of stay. All analyses were performed using SAS for Windows version 9.1 (Carey, NC).

2.2. Surgical technique

Intraoperative image guidance based on preoperative CT or MRI based data sets is used routinely at our institution. Additionally, intraoperative fluorescein is used according to a standard protocol and with informed consent [9]. In patients with significant nasal septal deviation, a septoplasty is performed initially and the harvested vomer is set aside for reconstruction. The middle turbinates are gently lateralized but preserved to promote normal postoperative middle meatus physiology. Based on the anatomy of the sphenoid sinus, sella and tumor, either a unilateral or bilateral approach is incorporated. For small lesions with adequate sphenoid pneumatization, a unilateral approach may be appropriate. In patients with larger lesions or unfavorable sphenoid sinus pneumatization patterns (multiple septations), a bilateral approach affords significant improvement in exposure. In these cases, a limited posterior septectomy incorporating the vomer and sphenoid rostrum is performed. Visualization is initially performed with a 0° endoscope. Following tumor resection, both 0 and angled (30°, 45° and 70°) endoscopes are placed into the surgical cavity to explore for any residual tumor. In patients with significant suprasellar extension, the tumor dissection may be performed primarily with angled endoscopes. A multilayered reconstruction using autologous grafts and tissues sealant is used for repair of the sella [10]. Planned lumbar drainage was used in three patients (5%) who underwent surgery for macroadenomas early in our experience.

3. Results

Fifty seven patients underwent endoscopic pituitary surgery at our institution between January 2004 and May 2006. The patient and tumor demographics, and short-term outcome measures are shown in Table 1. The mean follow up for this study was 186 days. Patients undergoing surgery for secreting tumors had failed medical therapy. Based on endoscopic examination of the tumor cavity and 3 month post-operative MRI, gross tumor removal was achieved in 89% of cases ($n = 51$). Sub-total tumor resection (11%) occurred because of cavernous sinus extension in five patients (9%) and hemorrhage in one patient. The latter involved intra-operative bleeding from a branch of the ophthalmic artery in a patient with a non-secreting, macroadenoma with significant suprasellar extension. This was successfully embolized without sequela. Of the 24 patients with visual symptoms prior to surgery, 22 (92%) reported either complete resolution or significant improvement after the procedure. No patients experienced worsened visual acuity, visual fields or new onset diplopia. Two patients (3.5%) experienced postoperative diabetes insipidus at last follow up. There were no CSF leaks requiring revision surgery. There were no perioperative deaths in this series.

The only significant predictor of extent of tumor removal was maximum tumor size, being smaller tumors more likely to have been totally removed than larger tumors (mean maximal tumor dimension 2.1 cm (SD = 0.9 cm) and 3.1 cm (SD = 1.4 cm) for gross-total removal vs. sub-total removal, respectively, $p = 0.03$). In logistic regression analysis, we found that for every 1 cm increase in the size of the tumor, there was an almost 3-fold decrease in the likelihood totally removing the tumor (OR = 2.96, 95% confidence interval (CI) = (1.02, 8.62), $p = 0.047$). There was an indication that tumors confined to the sella were more likely to be totally removed (46/50, 92%) than those with extra-sellar extension (5/7, 71%); tumors confined to the sella were smaller on average than

Table 1
Demographics, perioperative variables and short-term outcomes.

Characteristic[a]	Patients ($N = 57$[b])
Female sex	28 (49%)
Age (years)	
Mean (SD)	48 (16)
Median (min, max)	48 (12, 77)
Patient with prior pituitary surgery	8 (14%)
Presenting symptoms	
Headaches	15 (26%)
Hormonal	25 (44%)
Visual problems	24 (42%)
Incidental finding on an imaging study	5 (9%)
Non-specific neurological	4 (7%)
Surveillance for a prior history of pituitary tumors	1 (2%)
Seizures	1 (2%)
Adenoma type	
Secreting	21 (37%)
Non-secreting	36 (63%)
Lesion site	
Confined to the sella	50 (88%)
Extra-sellar extension	7 (12%)
Maximum tumor dimension (cm) on preoperative MRI	
Mean (SD)	2.15 (0.94)
Median (min, max)	2 (0.4, 4.6)
Surgical dissection site	
Confined to the sella	50 (88%)
Extended to the tuberculum sella and planum sella	5 (9%)
Extended to the cribriform plate and fovea ethmoidalis	2 (3%)
Gross tumor removal	51 (89%)
Hormone resolution (for secreting adenomas)	19/21 (90%)
ACTH	3/4 (75%)
GH	5/6 (83%)
Prolactin	11/11 (100%)
Duration of surgery (min)	
Mean (SD)	177 (64)
Median (min, max)	177 (78, 330)
Hospital length of stay (days)	
Mean (SD)	4 (2.5)
Median (min, max)	3 (2, 15)

SD = standard deviation, min = minimum, max = maximum.

[a] *N* (%) unless otherwise indicated.

[b] Number of missing records for the following characteristics: prior pituitary surgery = 1, duration of surgery = 2, maximum tumor dimension = 6.

those that extended beyond the sella (mean maximal tumor dimension 2 cm (SD = 0.8 cm) and 3.3 cm (SD = 1.1 cm) for tumors confined to the sella vs. tumors extending beyond the sella, respectively, $p = 0.001$), but this difference was not statistically significant ($p = 0.13$). Although only two patients developed permanent diabetes insipidus, these patients spent on average 74 extra minutes in surgery than those patients who did not developed the complication (mean duration of surgery 248 min, SD = 39 min for patients with permanent diabetes insipidus vs. 174 min, SD = 63 min for patients with no permanent diabetes insipidus, $p = 0.11$). Results from a logistic regression indicate that for every 10 extra minutes in the duration of the surgery, patients were 18% more likely to develop diabetes insipidus (OR = 1.18, 95% CI = (0.95, 1.48)), even if the association is not significant ($p = 0.14$).

Larger tumor size and presentation with visual symptoms were both associated with longer durations of surgery in univariate analyses. For each centimeter increase in tumor size, duration of surgery increased on average 23 min (SD = 10 min, $p = 0.03$). An average 40 min increase in duration of surgery was noted in patients presenting with visual symptoms when compared to those with other presentations (SD = 17 min, $p = 0.02$). However, when looked in a multivariate model, neither condition was independently associated with duration of surgery. This is likely related to the presence of larger tumors in patients presenting with visual symptoms vs. those with other presentations (2.6 cm, SD = 0.7 cm vs. 1.8 cm, SD = 0.9 cm, respectively, $p = 0.002$). Finally, the hospital length of stay was longer in patients with larger tumors. Results for a multivariate model show that a patient spent 1 extra day in the hospital (SD = 0.3 days, $p = 0.0005$) for each extra centimeter in the size of the removed tumor.

Comparison between female and male patients revealed statistically significant younger age at surgery (mean 42 vs. 53 years, $p = 0.006$), fewer patients with a prior history of pituitary surgery (4% vs. 24%, $p = 0.03$), higher incidence of secreting adenomas (53% vs. 21%, $p = 0.01$), higher incidence of lesions confined to the sella (100% vs. 76%, $p = 0.006$) and smaller maximal tumor size (mean 1.8 cm vs. 2.5 cm, $p = 0.01$). However, there were no differences in perioperative outcomes including perioperative variables, gross tumor removal or complications based on gender.

4. Discussion

The theoretical advantages of the endoscopic approach are based on improved visualization and decreased tissue manipulation. In contrast to the conical view afforded by the operating microscope, the endoscope provides panoramic visualization throughout the procedure. The incorporation of both straight and angled endoscopes allow for greater degrees of freedom in terms of angles of trajectory. Additionally, passage of the endoscope directly into the tumor cavity allows for examination of the entire surgical field. This may allow for identification of areas of residual tumor and critical neurovascular structures, theoretically improving extent of tumor removal and incidence of complications. Finally, avoiding a sub-labial incision and Hardy retractor may decrease sinonasal trauma and facilitate postoperative recovery. As the field continues to evolve, further refinement of the technique requires a description of the impact of various patient and surgical variables on outcomes.

Several authors have reported favorable short-term outcomes following endoscopic pituitary surgery including gross tumor removal rates of 62–93% [1,3,4,7] and visual field improvement rates of 62–100% in symptomatic patients [3,8]. The reported range of hormonal cure following endoscopic pituitary surgery is 71–85% for GH secreting tumors [4,7,8], 64–100% for prolactin secreting tumors [3,4,7,8] and 69–86% for ACTH secreting tumors [4,7]. These studies and the current report compare favorably to the reported rates of tumor control [11,12] and hormonal resolution following microscopic surgery which range from 70–86% for ACTH secreting tumors [13,14], 52–85% for GH secreting tumors [15–17], and 54–86% for prolactinomas [18–20]. The challenges associated with transsphenoidal surgery for pituitary macroadenoma including the goals of surgery and potential for increased complications have also been described [21,22]. Comparable descriptions of endoscopic surgery for extensive macroadenoma are currently limited.

The results of the current study similarly support the positive short-term effectiveness of endoscopic pituitary surgery. We were able to achieve a high rate of gross-total tumor removal, symptomatic improvement and hormonal control. Analysis of our results demonstrated a statistically significant lower rate of gross-total tumor removal for larger tumors. This is an expected finding given the propensity for larger tumors to adhere to critical neurovascular structures and extend into the cavernous sinus. Similarly, the correlation between tumor size, duration of surgery, hospital length of stay and complications highlights the challenges associated with these tumors.

The correlation between larger tumor size, length of surgery, duration of hospital stay and diabetes insipidus is not surprising. Patients with giant macroadenomas require longer surgical procedures often requiring removal of the planum spehnoidale and tuberculum sellae [5]. The normal gland, including the neurohypophysis is markedly compressed and more difficult to preserve. Medical management of the ensuing diabetes insipidus then requires a longer hospital stay until the appropriate doses of DDAVP are determined. Likewise, a large arachnoid breech is common following complete removal of giant macroadenomas which may necessitate lumbar drainage and longer length of stay. No patients in this series required reoperation to repair a CSF leak.

The favorable short-term outcomes associated with this study support the further development of this approach. However, several limitations are identified including the non-randomized, single institutional study design. Additionally, this series represents the early experience of the senior authors and likely involves some degree of a learning curve. A larger series may yield improved overall outcomes as the level of experience increases. Finally, the lack of long-term follow up limits our ability to define the rate of long-term tumor control following endoscopic pituitary surgery.

5. Conclusion

The development of endonasal, endoscopic pituitary surgery requires a robust description of the short- and long-term outcomes of the procedure. Although multiple theoretical advantages have been described, direct comparison of outcomes to published microscopic series is necessary prior to its widespread adoption. The results of the current series support the favorable short-term outcomes of endoscopic pituitary surgery including gross tumor removal and hormonal control. A decreased rate of gross-total tumor removal, increased length of stay and permanent diabetes insipidus was noted for larger tumors, highlighting the challenges associated with large macroadenomas and cavernous sinus extension.

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