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Volumetry in the Assessment of Pituitary Adenoma Resection: Endoscopy versus Microscopy

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Abstract

Background Assessment of the extent of resection after surgical resection of pituitary adenomas is most commonly reported in terms of the presence or absence of residual tumor. A quantitative comparison of volumetric resection between endonasal endoscopy (EE) and microsurgery (MS) has rarely been done.

Methods A retrospective analysis was performed on a consecutive series of 154 patients with pituitary adenomas treated by the same surgeon at a single institution. We employed volumetric analysis pre- and postoperatively on two cohorts of pituitary adenoma patients treated through MS ($n = 37$) versus EE approach ($n = 117$).

Results Volumetric analysis revealed a higher incidence of complete resection (64.4 vs. 56.8%) and mean volume reduction in the EE cohort (92.7 vs. 88.4%), although not significant. Recurrence rates were significantly lower in the EE group (7.7% vs 24.3%, $p = 0.015$). Subgroup analysis identified that patients with preoperative tumor volumes >1 mL were less likely to recur through EE (7.8 vs. MS: 29.6%; $p = 0.0063$). A higher incidence of complete resection was also noted in patients with favorable Knosp grades (0–1) (EE: 87.8 vs. MS: 63.2%; $p = 0.036$). Postoperative complication rates were not significantly different between both techniques.

Conclusion Both microscopy and endoscopy are well-tolerated, effective approaches in the treatment of pituitary adenomas. Our series demonstrated that EE may be superior to MS in preventing tumor recurrence and achieving a complete resection in certain subsets of patients. EE provides a slight advantage in tumor control outcomes that may justify the paradigm shift to pure endoscopy at our center.

Keywords
- pituitary adenoma
- volumetry
- endoscopy
- microscopy

Introduction

The past 10 years have seen a rapid paradigm shift in pituitary adenoma surgery. The endonasal endoscopic approach has quickly supplanted the microsurgical approach due to a conglomeration of different factors. Advantages of the endonasal endoscopy (EE) approach include a lower risk of nasal septal perforation and a wider panoramic view of the posterior sphenoid sinus and sellar contents, with improved illumination. In experienced hands, either approach has been documented to yield high success rates, with excellent patient satisfaction and few complications.

Comparisons between microscopy and endoscopy have demonstrated few differences between the two techniques. Dehdashti et al showed no differences between the two approaches in 200 patients with pituitary adenomas.[1] EE

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appears to more readily demonstrate its advantages when treating larger tumors. Komotar, et al., found that in treating giant pituitary macroadenomas, EE yielded markedly better rates of gross total resection and visual improvement when compared with both the microscopic transsphenoidal approach and open craniotomy.[2] In an analysis of 99 Knosp grade 0 to 2 nonfunctioning pituitary adenomas, Dallapiazza et al found no differences in the extent of resection between microscopic resection (microsurgery [MS]) and EE.[3]

A clear advantage for either approach in the treatment of endocrinologically affected patients has yet to be demonstrated. Starke et al showed no differences in biochemical remission rates or perioperative complications between microscopy and EE in 113 acromegalics.[4] Lenzi et al, on the other hand, found a greater biochemical remission rate with EE in 37 acromegalics.[5] Cho and Liau analyzed results from 44 patients with prolactin-secreting pituitary adenomas and found no differences in the outcomes of these patients with either approach, although they did find a lower overall complication rate with EE.[6] D'Haens et al reported on 120 patients with biochemically active pituitary adenomas and found no differences in endocrinological outcomes, though they did experience more postoperative cerebrospinal fluid (CSF) leaks with EE.[7]

In this study, we analyze our pituitary adenoma patients, including those having had sublabial MS as well as those having undergone EE. To better define the features of both techniques, we used volumetric measurements to assess preoperative tumor characteristics and postoperative results. Recently, Zaidi et al have demonstrated the utility of volumetric analysis in assessing outcomes for pituitary surgery for different surgeons comparing endoscopic and microscopic techniques.[8] We plan on employing a similar methodology to help investigate whether microscopic or endoscopic resection of pituitary adenoma yields discernably different results for the same experienced surgeon.

Methods

Imaging and medical records of all patients who underwent surgical intervention by the senior author (J. J. M.) through sublabial MS or EE from January 2003 through August 2012 were reviewed retrospectively. It is important to note that the senior author exclusively used the MS approach until 2007, then a hybrid approach on a few patients, and subsequently a purely endoscopic approach since 2007. The two compared groups are therefore temporally sequential and nonconcomitant. Adult patients with pituitary adenoma as the final pathological diagnosis were included. Pathological specimens were reviewed by institutional neuropathologists. In total, 281 patient records were reviewed. One patient was excluded at 17 years of age. A hybrid approach was used in 10 patients, who were excluded as well. Imaging adequate to perform volumetry and clinical records were available for 154 patients. Demographic data, magnetic resonance imaging (MRI), surgical records, and clinical presentation and outcome data were collected for each patient.

Volumetry was performed for each patient's available imaging (►**Fig. 1**). One neuroradiologist blinded to the method of treatment reviewed all available studies and performed the volumetry. Aquarius iNtuition Edition version 4.4.8 (TeraRecon, Foster City, California, United States) software was used to measure the volume of tumor, employing manual regions of interest drawn upon contrast-enhanced T1-weighted MRI. Coronal sequences were primarily used in this process, though, when available, fat-saturated contrast-enhanced T1-weighted MRI was preferred. Axial contrast-enhanced T1-weighted MRI was used in the rare cases when coronal views were not obtainable. Tumors were graded in terms of cavernous sinus involvement based on the original Knosp classification scheme.[9]

Standard descriptive statistics, analysis of continuous variables, and comparison of categorical data were performed using commercially available software (GraphPad Prism, La Jolla, California, United States). Statistical significance was set at $p < 0.05$. Comparison of means was performed between the MS and EE cohorts for age at surgery, length of follow-up, Knosp grade, preoperative tumor volume, initial postoperative tumor volume, initial absolute volume reduction, and percentage volume reduction, using the two-tailed Student's *t*-test (►**Fig. 2**). Comparison between the two cohorts was also performed for gender and for incidences of apoplectic presentation, postoperative diabetes insipidus, vision recovery, biochemical remission, residual tumor defined as measuring >0.01 cm^3 (100 mm^3),

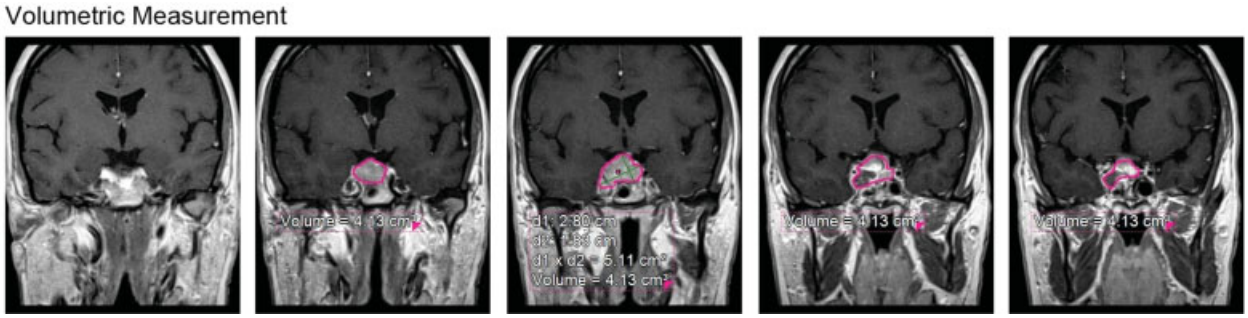

Fig. 1 Volumetry was performed for each patient by the same neuroradiologist blinded to the method of treatment. Aquarius iNtuition Edition version 4.4.8 (TeraRecon, Foster City, California, United States) software was used to measure the volume of tumor, employing manual regions of interest drawn upon contrast-enhanced T1-weighted coronal magnetic response imaging (MRI), where possible.

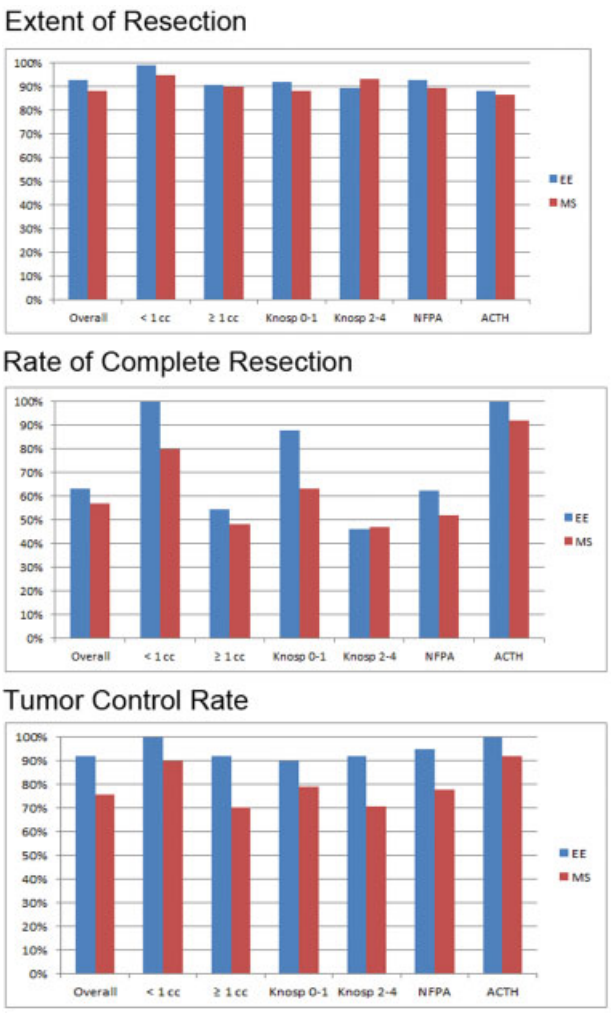

Fig. 2 Extent of resection, rate of complete resection, and tumor control rate are depicted graphically. ACTH, adrenocorticotropic hormone; EE, endonasal endoscopy; MS, microsurgery; NFPA, nonfunctioning pituitary adenoma.

Table 1 Baseline Characteristics of the 154 patients with pituitary adenomas

Patient characteristics	Endoscopy ($N = 117$)	Microscopy ($N = 37$)
Age (years)	50	52
Gender		
Male, *n* (%)	46.2%	27%
Apoplexy	7.7%	5.4%
Preoperative visual deficits	26.2%	18.9%
Pathology		
NSPA	70.1%	62.2%
Prolactin	6.6%	5.4%
ACTH	8.5%	29.7%
GH	14.5%	2.7%
Knosp grading		
Grade 0	16.2%	35.1%
Grade 1	24.8%	16.2%
Grade 2	15.4%	10.8%
Grade 3	25.6%	27%
Grade 4	15.4%	10.8%
Preoperative tumor volume (mL)	7.75	5.33
Follow-up (months)	31.9	21.6

Abbreviations: NSPA, nonsecretory pituitary adenoma; ACTH, adrenocorticotropic hormone; GH, growth hormone.

recurrence of tumor in setting of complete resection or growth of residual tumor (defined as tumor recurrence), postoperative CSF leak, epistaxis requiring operative intervention, stroke, and mortality, using Fisher's exact test. Tumor recurrence was defined as radiographic growth of tumor in patients who had either residual tumor or new tumor after complete resection. Similar subgroup analysis was performed in patients with Knosp grade 0 to 1 tumors, Knosp grade 2 to 4 tumors, nonsecretory pituitary adenomas (NSPAs), acromegaly, and Cushing's disease. Analysis was not performed in other biochemically active tumor types due to inadequate clinical follow-up data.

Results

Adequate imaging and clinical records were available for 154 patients. Of these, 37 patients were in the MS group and 117 in the EE group. Patient demographics are summarized in ►**Table 1**. There were no significant demographic differences, including mean age (52 vs. 50 years), gender proportions (10 males, 27 females vs. 54 males, 63 females), incidence of apoplectic presentation (5.4 vs. 7.7%), and average length of follow-up (21.6 vs. 31.9 months), between the microscopic and endoscopic cohorts, respectively. In terms of biochemical functionality, 62.2% of microscopy patients had NSPA, whereas 70.1% of EE patients had NSPA. Of the microscopy patients, 29.7% presented with Cushing's disease compared with 8.5% of EE patients. In terms of cavernous sinus involvement, 51.4% of microscopy patients were Knosp grade 0 to 1 compared with 41% of EE patients.

Results from our analysis are summarized in ►**Table 2**. Overall, complete resection was found in 56.8% through MS and 64.4% through EE ($p = 0.44$). Percent volume reduction was 88.4% through MS and 92.7% through EE ($p = 0.29$). Recurrent tumor growth was seen in 24.3% of MS patients and in 7.7% of EE patients ($p = 0.015$), a statistically significant difference. An annual risk of recurrence was 13.5 and 2.9% per year for MS and EE subgroups, respectively ($p < 0.01$). There were no significant differences seen in postoperative diabetes insipidus, vision recovery, biochemical remission, or complication rates (►**Table 1**). No patients in our series had worsening vision after surgical resection of their tumor. Complications and postoperative endocrinopathies are reported in ►**Table 3**. Endocrinopathy was defined

Table 2 Extent of resection and outcomes for pituitary adenomas

	Endoscopy	Microscopy	*p*-Value
Extent of resection			
Overall	92.7%	88.4%	0.147
< 1 mL	99%	94.8%	0.133
≥ 1 mL	91%	89.7%	0.712
Knosp 0–1	91.9%	88.4%	0.292
Knosp 2–4	89.7%	93.4%	0.339
NFPA	92.8%	89.3%	0.327
ACTH	88.2%	86.6%	0.902
Complete resection			
Overall	63.4%	56.8%	0.439
< 1 mL	100%	80%	0.0676
≥ 1 mL	54.4%	48.1%	0.662
Knosp 0–1	87.8%	63.2%	0.0361
Knosp 2–4	46.2%	47.1%	1
NFPA	62.2%	52%	0.472
ACTH	100%	92%	0.587
Radiographic tumor control			
Overall	92%	75.7%	0.0150
< 1 mL	100%	90%	1
≥ 1 mL	92.2%	70.4%	0.00630
Knosp 0–1	90%	78.9%	0.128
Knosp 2–4	92%	70.6%	0.0282
NFPA	95.1%	78%	0.0228
ACTH	100%	92%	0.476
Biochemical remission			
Overall	62.5%	57.1%	0.42
ACTH	50%	60%	0.87
GH	66.7%	50%	0.73

Abbreviations: NFPA, nonfunctioning pituitary adenoma; ACTH, adrenocorticotropic hormone; GH, growth hormone.

Table 3 Complications

	Endoscopy	Microscopy
Total complications	8.3% (5)	4.2%(1)
CSF leak (*n*)	1.7% (1)	0%
Meningitis (*n*)	3.3% (2)	0%
Epistaxis (*n*)	3.3% (2)	0%
Subarachnoid hemorrhage (*n*)	0%	1.7% (1)
Endocrinopathy	43.3% (26)	25% (6)

Abbreviation: CSF, cerebrospinal fluid.

as the need for long-term hormone replacement after surgery.

To compare a more uniform group of tumors, we compared results in patients with NSPA, which yielded similar results. Complete resection was found in 52.2% through MS and 62.2% through EE ($p = 0.47$). Percent volume reduction was 89.3% through MS and 92.8% through EE ($p = 0.33$). Recurrent tumor growth was seen in 21.7% of MS patients and in 4.9% of EE patients ($p = 0.023$), a statistically significant difference. Again, no significant differences were seen in postoperative diabetes insipidus, vision recovery, biochemical remission, or complication rates.

Of our patients presenting with Cushing's disease, 11 underwent MS and 10 underwent EE. No significant differences were found when comparing approaches in this group of patients. Complete resection was found in 72.7% through MS and 90% through EE ($p = 0.59$). Percent volume reduction was 86.6% through MS and 88.2% through EE ($p = 0.90$). Recurrent tumor growth was seen in 18.2% of MS patients and in 0% of EE patients ($p = 0.48$). No significant differences were seen in postoperative diabetes insipidus, vision recovery, biochemical remission, or complication rates.

In patients with preoperative tumor volume <1 mL, no significant differences were found when comparing approaches in this group of patients. Complete resection was found in 80% through MS and 100% through EE ($p = 0.068$), which approached statistical significance. Percent volume reduction was 94.8% through MS and 99% through EE ($p = 0.13$). Recurrent tumor growth was seen in 10% of MS patients and in 0% of EE patients ($p = 1$). No significant differences were seen in postoperative diabetes insipidus, vision recovery, biochemical remission, or complication rates.

In patients with preoperative tumor volume ≥ 1 mL, complete resection was found in 48.1% through MS and 54.4% through EE ($p = 0.66$). Percent volume reduction was 89.7% through MS and 91% through EE ($p = 0.71$). Recurrent tumor growth was seen in 29.6% of MS patients and in 7.8% of EE patients ($p = 0.0063$), a statistically significant difference. No significant differences were seen in postoperative diabetes insipidus, vision recovery, biochemical remission, or complication rates.

To assess the value of each particular approach for cavernous sinus involvement, we grouped our patients into Knosp grade 0 to 1 and Knosp grade 2 to 4. In the Knosp grade 0 to 1 patients, we found a statistically significant superiority in terms of the extent of resection with EE. Complete resection was found in 63.2% through MS and 87.8% through EE ($p = 0.036$). Percent volume reduction was 88.4% through MS and 91.9% through EE ($p = 0.29$). Recurrent tumor growth was seen in 21.1% of MS patients and in 10% of EE patients ($p = 0.13$). No significant differences were seen in postoperative diabetes insipidus, vision recovery, biochemical remission, or complication rates.

In the Knosp grade 2 to 4 patients, our findings were similar to our other results. Complete resection was found in 47.1% through MS and 46.2% through EE ($p = 1$). Percent volume reduction was 93% through MS and 90% through EE

($p = 0.34$). Recurrent tumor growth was seen in 29.4%% of MS patients and in 8% of EE patients ($p = 0.48$). No significant differences were seen in postoperative diabetes insipidus, vision recovery, biochemical remission, or complication rates.

Discussion

In the late 19th century, Horsley and Paul unsuccessfully attempted the first surgery for a suspected pituitary tumor through a transcranial subtemporal approach.[10–12] Despite their failures, Cushing, by 1910, adopted the techniques of other neurosurgeons such as Schoffler to develop a sublabial, transseptal, transsphenoidal approach, which was later popularized by A. E. Halstead.[13–15] These fundamental steps were galvanized by the adoption of the operative microscope in the 1960s, building on through the sequential contributions of Dott, Guiot, and Hardy.[11,16] Guiot was quite visionary in describing and performing purely endoscopic resections of pituitary adenomas in the early 1960s, yet for nearly three decades, the sublabial and endonasal microsurgical transsphenoidal approaches remained the mainstay of pituitary surgery. Over the last two decades, a shift toward EE has ensued, though the quantitative benefit of this approach has not been clarified. The paradigm shift, particularly among younger neurosurgeons, may be explained by perceived benefits and biases in training. With our series, we attempt to elucidate any advantages of either approach from a quantitative standpoint through volumetric analysis of the tumor resections. In short, is the paradigm shift justified? Is EE superior to MS, or at least not inferior?

For pituitary adenomas, the objective of treatment is primarily a maximal safe resection with/without radiation depending on the size, extent of resection, and recurrence. Although a microscopic gross total resection may not always be possible, maximizing the extent of resection remains a mainstay of treatment in preventing recurrence and symptomatic progression. Our series demonstrated that EE may be superior to MS in preventing tumor recurrence and achieving a complete resection in certain subsets of patients (tumor volume > 1 mL, favorable Knosp scores). Several studies are in accordance with our results, demonstrating a higher rate of gross total resection in the EE cohorts.[4,17–19] To substantiate the volumetric analysis, our postoperative MRIs (within 48 hours) were validated by the study neuroradiologist with a second MRI approximately 3 months after resection.

A higher rate of volumetric resection may be explained by a variety of reasons. Mainly, the field of view during endoscopic endonasal approaches is significantly brighter and wider than in microscopic approaches. The lateral visualization provided by the angled endoscopes is simply nonexistent during monoaxial MS.[20] Elhadi et al demonstrated that a binostril EE provided a greater degree of surgical freedom compared with other transsphenoidal approaches including the microscopic approach. In addition to a narrower field, a large operative distance to the tumor also encumbers a gross total resection for the sublabial approach.[6]

Achieving a gross total resection theoretically provides a higher rate of endocrinological control, though our data are inadequate to truly assess for such a difference. D'Haens et al suggested that endocrinological control was increased by 13% using EE when compared with MS. Although our study did not address postoperative endocrinological control, a future study directly assessing this may be useful in the future.

Tumor recurrence in our series was significantly lower in our EE group compared with our microscopy group, in spite of a slightly longer postop follow-up period for the EE group. This may be directly related to the higher rates of gross total resection in the EE group. Additionally, for larger macroadenomas, chances of tumor recurrence remained higher using a microscopic approach, as a significant portion of the lesion may be outside the surgical field. EE might offer some advantages in capturing the lateral extent of these lesions with the help of angled endoscopes and a wider operative corridor.

Complications

Complications seen in both techniques remain similar. In our series, there was no demonstrable increase in the risk of worsening vision, CSF leak, diabetes insipidus, or other major morbidities with EE compared with MS. Our series seems to corroborate the data of other studies, suggesting that the incidence of CSF leakage may not be directly related to the surgical approach.[3,21,22] Rates of postoperative CSF leaks have been suggested to correlate with certain tumor types (nonadenomatous), tumor consistency (fibrous), previous surgeries, and flow rate of intraoperative CSF leak.[23,24] Therefore, careful judgment is still the most important aspect of CSF leak prevention.

Similarly, EE has been associated with a higher rate of vascular complications. Ammirati et al attribute higher vascular injury rates to lack of depth perception during endoscopy and overly aggressive lateral exposure near the opticocarotid recesses. Therefore, surgeons must exercise great caution when performing EE in areas where there is poor visualization and around the opticocarotid recesses.[25]

The sublabial approach has also been associated with longer hospital stays, postoperative lip edema, more uncomfortable hospital stay, poor cosmesis, and increased blood loss.[26] In experienced hands, however, the microscopic approaches have been shown to be both safe and effective. Complication rates have not generally been useful in determining whether endoscopy is preferable to microscopy.

Limitations

A few aspects of our study should be qualified while interpreting the results. First and foremost, the retrospective nature of our study did not permit us to obtain all of the data points for every patient. For example, several patients, particularly a large number of the earlier MS patients, were excluded from our analysis because a preoperative MRI was not available for volumetric analysis due to lack of electronic imaging systems at that time. As such, our study was potentially subject to selection bias (only patients with

adequate records and radiographic data were included in the analysis). Although the same neurosurgeon (J. J. M.) was the operator in both groups, it may be argued that the more recent EE group (compared with the slightly older MS group) might have benefitted from his increased surgical experience and biased the EE results toward the more favorable. We doubt that is a real issue, given that the MS patients were operated after 8 years into his clinical practice; therefore, the bias in surgical experience may favor the microscopic group. In fact, the EE cohort captures the learning curve of our team, which previously had minimal experience with endoscopic techniques. The complication rates in our study were also limited by the small size of patients in the MS group. Therefore, an absence of statistical difference between complication rates in these two groups may be a type II error.

Additionally, our study was not able to capture a complete dataset for the analysis of endocrinological results due to data lost in transition to an electronic medical record as well as due to patients not followed by endocrinologists within our health system; however, endocrinological results were presented when available. Furthermore, volumetry in this subset of functioning adenomas may be limited since the presence of endocrinological recurrence is more valuable than radiological recurrence in these patients. Lastly, our results may be subject to a publication bias as our results come from a purely retrospective cohort.

Conclusion

Both microscopy and endoscopy are well-tolerated, effective approaches in the treatment of pituitary adenomas. In our experience, a slight advantage in tumor control outcomes is associated with EE, at least as performed at our center with the assistance of experienced rhinologists. Additionally, in comparison to MS, EE may be superior in obtaining an improved extent of resection. We feel that this justifies the paradigm shift to pure endoscopy at our center. These results may certainly not be generalizable to all centers. Patients should expect excellent results with either approach, when performed by a skilled and experienced surgeon.

Disclosures

The authors have no financial or personal conflicts of interest.

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