Endoscopic endonasal transsphenoidal approach to large and giant pituitary adenomas: institutional experience and predictors of extent of resection

Clinical article

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Object. While the use of endoscopic approaches has become increasingly accepted in the resection of pituitary adenomas, limited evidence exists regarding the success of this technique for patients with large and giant pituitary adenomas. This study reviews the outcomes of a large cohort of patients with large and giant pituitary adenomas who underwent endoscopic endonasal transsphenoidal surgery at the authors’ institution and focuses on identifying factors that can predict extent of resection and hence aid in developing guidelines and indications for the use of endoscopic endonasal transsphenoidal surgery versus open craniotomy approaches to large and giant pituitary adenomas.

Methods. The authors reviewed 487 patients who underwent endoscopic endonasal transsphenoidal resection of sellar masses. From this group, 73 consecutive patients with large and giant pituitary adenomas (defined as maximum diameter ≥ 3 cm and tumor volume ≥ 10 cm³) who underwent endoscopic endonasal transsphenoidal surgery between January 1, 2006, and June 6, 2012, were included in the study. Clinical presentation, radiological studies, laboratory investigations, tumor pathology data, clinical outcomes, extent of resection measured by volumetric analysis, and complications were analyzed.

Results. The mean preoperative tumor diameter in this series was 4.1 cm and the volume was 18 cm³. The average resection rate was 82.9%, corresponding with a mean residual volume of 3 cm³. Gross-total resection was achieved in 16 patients (24%), near-total in 11 (17%), subtotal in 24 (36%), and partial in 15 (23%). Seventy-three percent of patients experienced improvement in visual acuity, while 24% were unchanged. Visual fields were improved in 61.8% and unchanged in 5.5%. Overall, 27 patients (37%) experienced a total of 32 complications. The most common complications were sinusitis (14%) and CSF leak (10%). Six patients underwent subsequent radiation therapy because of aggressive tumor histopathology. No deaths occurred in this cohort of patients. Statistically significant predictors of extent of resection included highest Knosp grade (p = 0.001), preoperative tumor volume (p = 0.025), preoperative maximum tumor diameter (p = 0.002), hemorrhagic component (p = 0.027), posterior extension (p = 0.001), and sphenoid sinus invasion (p = 0.005).

Conclusions. Endoscopic endonasal transsphenoidal surgery is an effective treatment method for patients with large and giant pituitary adenomas, which results in high (>80%) rates of resection and improvement in visual function. It is not associated with high rates of major complications and is safe when performed by experienced surgeons. The preoperative Knosp grade, tumor volume, tumor diameter, hemorrhagic components on MRI, posterior extension, and sphenoid sinus invasion may allow a prediction of extent of resection and in these patients a staged operation may be required to maximize extent of resection.

Key Words • endoscopic • sellar • CSF leak • Knosp grade • cavernous sinus • pituitary surgery

Abbreviations used in this paper: FGFR4 = fibroblast growth factor receptor-4; GTR = gross-total resection; ICA = internal carotid artery; SIADH = syndrome of inappropriate antidiuretic hormone secretion.

Pituitary adenomas are the third most common intracranial neoplasm, accounting for 10%–25% of intracranial neoplasms with a prevalence of 16.9% in autopsy studies.6 A subgroup of these lesions that are particularly challenging to manage are those that can be classified as large or giant pituitary adenomas.2,3 Giant pituitary adenomas have classically been described as those ≥ 4 cm in maximum diameter, while large pituitary adenomas currently lack a consistent definition in existing literature.3,7,8,11,16,17 Regardless of particular size criteria, large pituitary adenomas that grow beyond the sella can
be challenging to manage surgically because of the limited space and proximity of key anatomical structures that are at risk depending on the surgical approach.\textsuperscript{2,3}

Traditionally, these large tumors have been managed by an open craniotomy approach that required brain retraction because microscopic approaches provided limited visualization beyond the sella.\textsuperscript{20} However, over the past 2 decades, the advent of endoscopic endonasal transsphenoidal surgery for the resection of pituitary adenomas has greatly increased the number of tumors being resected by a transsphenoidal approach because of the improved visualization granted by this technique.\textsuperscript{2,3}

While the use of endoscopic approaches has become more popular in many large neurosurgical centers, limited data have been published on the safety and efficacy of resecting large and giant pituitary adenomas via an endoscopic transnasal transsphenoidal approach. Reports on endoscopic endonasal transsphenoidal surgery to achieve improved resection rates via transsphenoidal approaches for large and giant pituitary adenomas continue to show promising results.\textsuperscript{3,5} Komotar et al. recently published a systematic review comparing endoscopic, microscopic, and open transcranial resection of giant (>4 cm) pituitary macroadenomas and found that endoscopic approaches achieved a gross-total resection (GTR) rate of 47.2% combined with visual improvement in 91.1%.\textsuperscript{13} Cusimano and colleagues recently completed a large comparison of open craniotomy and microscopic and endoscopic approaches with large and giant pituitary adenomas at their institution.\textsuperscript{3} In their study, the authors developed a new definition for large and giant pituitary adenomas, where tumors with a volume of \( \geq 10 \text{ cm}^3 \) were defined as large or giant. Similarly, Hofstetter et al. have provided further evidence that in tumors with a maximum diameter \( \geq 3 \text{ cm} \), volume is a greater predictor of extent of resection than diameter, and also suggested a volume of \( \geq 10 \text{ cm}^3 \) as a modern definition of giant pituitary adenomas, as this volume along with cavernous sinus invasion predicted extent of resection.\textsuperscript{10} These criteria may provide a more sensitive measure of tumor bulk than maximum diameter criteria and thus a more sophisticated way of identifying cases that may be difficult to manage surgically because of extrascellar extension.

Here, we present a 73-patient institutional series of endoscopic resection of giant pituitary adenomas meeting these modern volumetric criteria, as well as an analysis of factors that predict extent of resection. The endoscope has revolutionized transsphenoidal surgery and thus indications for this approach are expanding, yet expectations regarding surgical outcomes need to be defined. An exploration of old and new indications and contraindications is necessary to aid surgical planning for large and giant pituitary tumors. In this paper we will analyze preoperative characteristics that can begin to set the stage for an updated set of indications for transsphenoidal surgery.

**Methods**

After obtaining research ethics board approval, a prospectively maintained database of endoscopic transsphenoidal surgery for pituitary adenomas at the Toronto Western Hospital was reviewed. Inclusion criteria were patients with a postoperative pathologically confirmed diagnosis of pituitary adenoma, maximum tumor diameter in any plane \( \geq 3 \text{ cm} \), and tumor volume \( \geq 10 \text{ cm}^3 \). Exclusion criteria were lack of suprasellar growth of the pituitary adenoma and patients without a preoperative MRI. A total of 487 patients underwent endoscopic transsphenoidal surgery at our institution between January 1, 2006, and June 6, 2012. The maximum diameter on preoperative MRI (either T1- or T2-weighted imaging; coronal, sagittal, or axial slices) was determined for each case. Tumors with a diameter \( \geq 3 \text{ cm} \) were included for further evaluation, while those with a diameter < 3 cm were removed from the study. Patient records were reviewed, and patients with a pathological diagnosis other than pituitary adenoma were removed from the study, as well as those who underwent combined microscopic/endoscopic surgery, and 4 patients with tumors that did not have any suprasellar growth of the pituitary adenoma, leaving 99 patients who had a volumetric analysis of their preoperative tumor size.

**Tumor Volume Measurement**

Volumetric analysis was performed by 1 author (K.J.) for all cases. Volumetric analysis was completed using ITK-Snap software (http://www.itksnap.org/) using the manual segmentation tool function. Preoperative volumetric analysis was performed on coronal gadolinium-enhanced T1-weighted images from the study closest to the date of the patient’s operation. When gadolinium-enhanced coronal sections were unavailable, axial sections were used. Nonenhanced images were used when the contrast-enhanced studies were unavailable. From the 99 patients, 73 were selected with a tumor volume \( \geq 10 \text{ cm}^3 \). Reliability of volume measurements was assessed by comparison with measurements performed by a blinded second observer (E.M.).

Postoperative volumetric analysis was performed to calculate the volume of residual tumor on first follow-up MRI, typically performed 3 months postoperatively at our institution. Time to follow-up MRI after operation varied between 1.5 and 14.4 months. Volumetric analysis was performed by one author (K.J.) and was validated by a second observer (B.L.G.). A comparison of pre- and postoperative tumor volumes was used to calculate the primary outcome of extent of resection.

Preoperative and postoperative volumes were also calculated for patients undergoing a reoperation. One patient who underwent a planned staged resection was considered to have undergone a single operation for the purposes of volumetric assessment.

**Patient Characteristics**

A chart review was performed to collect clinical data for each patient. Clinical characteristics analyzed included visual acuity, visual field deficit, ophthalmoplegia, pituitary hyper- and hypofunction syndromes, panhypopituitarism, diabetes insipidus, pituitary apoplexy, prior surgery, prior radiation, and prior medical management. Magnetic resonance imaging characteristics were
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obtained from preoperative radiology reports. Parameters collected were presence or absence of cystic component, hemorrhagic component, optic nerve compression, and hydrocephalus. Images were further assessed to determine where the tumor had suprasellar extension, anterior extension (over the planum sphenoidale), posterior extension (growth into the interpeduncular cistern/prepontine area and/or causing compression of the brainstem), suprasellar lateral extension (beyond the intracranial component of the internal carotid artery [ICA]), and Knosp grade. These assessments were done based on Hardy-Vezina and Knosp classification systems. Preoperative pituitary endocrine function laboratory data were collected, including follicle-stimulating hormone, thyroid-stimulating hormone, T3, T4, cortisol, adrenocorticotropic hormone, insulin-like growth factor–1, and prolactin levels. The surgeon performing the operation was noted. Pathological characteristics including cell type, functional status, MIB-1, p27, and fibroblast growth factor receptor–4 (FGFR4) were collected.

Postoperative characteristics were assessed, including change in visual acuity, visual fields, endocrine function, need for postoperative radiation, length of stay, postoperative panhypopituitarism, and permanent panhypopituitarism. Endocrine function is assessed in a multidisciplinary pituitary clinic with provocative or dynamic testing. The presence of postoperative complications including syndrome of inappropriate antidiuretic hormone secretion (SIADH), diabetes insipidus, cranial nerve palsy, ICA artery damage, CSF leak, CSF leak requiring a lumbar drain, headache, epistaxis, sinusitis, visual complications, deep venous thrombosis, pulmonary embolism, vasospasm, subdural hygroma, hematoma, seizure, hydrocephalus, meningitis, coma, and death were noted.

Surgical Approach

All patients in this study underwent transnasal transsphenoidal endoscopic resection of a pituitary adenoma with stereotactic image guidance and use of microvascular Doppler probes. The objective of surgery was to achieve maximum decompression of the optic apparatus, to achieve maximum resection with care not to injure sensitive neural and vascular structures, and to preserve or restore endocrine function. All procedures were carried out using a pure endoscopic approach primarily with the aid of a 0° 4-mm endoscope (Karl Storz GmbH & Co. KG) held mainly in the superior aspect of the right nasal cavity by an assistant. A right middle turbinectomy was undertaken before a unilateral, vascularized nasoseptal flap was raised on the sphenopalatine artery, to be used for skull base reconstruction after tumor removal. A posterior septectomy allowed for a 2-nostril bimanual technique. A posterior sphenoidotomy performed. The lateral limits were the medial part of each cavernous sinus, which allowed removal of the posterior part of the planum sphenoidale. The lateral limits within the region of the tuberculum sellae were the medial orbital walls, allowing for exposure of the optic nerves. Neuronavigation and Doppler ultrasound were used to identify the carotid arteries and guide the extent of the bony resection. A combination of microsurgical piecemeal and suction was used to debulk and reduce the tumor mass, followed by identification and meticulous bimanual dissection to separate the tumor from bordering neurovascular structures. Tumor arachnoid attachments superiorly and laterally along the optic chiasm and optic nerves are divided sharply to reduce the risk of thermocoagulation injury to these structures. Early in this series, 11 patients underwent a multilayered reconstruction to close the dural defect with autogenous fascia lata placed as an inlay (intradurally) and then as an outlay (extradurally). The remaining patients in this series had the defect repaired with a pedicled nasoseptal flap positioned so that its edges are in contact with exposed bone. Tissue glue (Tisseel, Baxter) is applied to the flap edges and is then covered with Surgicel (Ethicon) and collagen sponge. A nasal Foley catheter is used as packing to prevent graft migration.

Extended approaches were used selectively in this series in cases in which the primary surgeon felt that additional bone removal would increase the extent of resection. For the purposes of this study, an extended approach was defined as bone removal over the planum or tuberculum sellae. In addition, extended approaches were routinely used in patients who underwent reoperation, unless the trajectory of the extended anterior approach clearly would not lead to additional tumor debulking.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics software (version 20, IBM). Baseline characteristics were assessed using the descriptive statistics function. Predictors of extent of resection were calculated using the nonparametric independent samples tool for ordinal and nominal independent variables, using Mann-Whitney U-test and Kruskal-Wallis test. Linear regression was used to assess the relationship between extent of resection and continuous independent predictor variables. A p value < 0.05 was considered statistically significant.

Results

Baseline Characteristics

Endoscopic resection of large and giant pituitary adenomas was performed in 73 patients at our institution between January 1, 2006, and June 6, 2012. Of these patients, 66 had available preoperative and postoperative MRI studies (Fig. 1), in addition to complete clinical assessment, available for volumetric analysis. Baseline characteristics are summarized in Table 1. The average age of the study population was 54.5 years, and the study population had a high male/female ratio (1.0.46; 68.5% male, 31.5% female). The average tumor diameter for the series was 4.09 cm (range 3.0–7.9 cm), and the average preoperative tumor volume was 18.44 cm³ (range 10.05–73.73 cm³).

The majority of patients in this series presented with visual acuity (57.5%) and/or visual field (45.2%) deficits. Forty-seven patients (64.4%) were found to have endocrine dysfunction prior to surgery. Prior to surgery, 9.6% experienced ophthalmoplegia and 8.2% had apoplexy (defined by clinical presentation and confirmed by radiographic and
intraoperative findings); 16.4% of patients had prior surgery, 4.1% had received prior radiation, and 15.1% received some form of medical management related to their adenoma prior to surgery. Cabergoline (2.7%) and bromocriptine (1.4%) were used to try to induce tumor remission.

Extended endoscopic approaches were used for 22 patients (30.1%). Of patients with radiographic evidence of cavernous sinus invasion (Knosp grade ≥ 2), 23.8% underwent surgical exploration of the cavernous sinus component.

Prior to surgery, MRI demonstrated a cystic component in 30.1% of tumors, a hemorrhagic component in 24.7%, sphenoid sinus invasion in 35.6%, anterior extension in 16.4%, posterior extension in 31.5%, suprasellar lateral extension in 26.0%, optic nerve compression in 94.5%, and hydrocephalus in 5.5% (Table 2). The Knosp grade was determined to assess cavernous sinus invasion. On preoperative imaging, the highest Knosp grade was 0 for 6.8% of tumors, 1 for 27.4%, 2 for 19.2%, 3 for 31.5%, and 4 for 15.1%.

As expected, the majority of the tumors in this series were nonfunctioning pituitary adenomas (89.0%) (Table 3). Gonadotrophic adenomas were the most common cell type (60.3%), followed by null cell adenomas (16.4%), corticotrophs (8.2%), unknown (8.2%), somatotroph (4.1%), lactotroph (1.4%), and oncocytic (1.4%). MIB-1 staining was ≥ 3% in 50.7%, < 3% in 45.2%, and unknown in 4.1%. Positive staining for p27 was 47.9%, 37.0% had weak staining, and 4.1% were negative; p27 staining was not performed in 11% of patients. Overall, 50.7% of tumors stained positive for FGFR4, while 15.1% had weak staining, 16.4% had negative staining, and staining was not performed in 17.8% of tumors.

Outcomes

The outcomes assessed in this series included extent of resection, visual changes, endocrine function, and complications. In the 66 patients with preoperative and postoperative MRI studies available for volumetric analysis, an average resection rate of 82.9% ± 16.5% was achieved (range 37.0%–100%). Complete resection according to postoperative MRI was achieved in 16 patients (24.2%). Near-total (≥ 90%) resection was achieved in an additional 11 patients (16.7%), subtotal (70%–89.9%) in...
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24 patients (36.4%), and partial (<70%) in 15 patients (22.7%). The mean postoperative tumor volume was 3.66 ± 5.35 cm³ (range 0–34.62 cm³).

Postoperative visual acuity status was available for 63 patients and is summarized in Table 4. Forty-six patients (73.0%) experienced improvement in their visual acuity, while 3 (4.8%) worsened. Four patients (6.3%) experienced no change, and the remaining 10 patients (15.9%) did not have a visual acuity deficit pre- or postoperatively. Postoperative visual fields were available for 55 patients, of whom 34 (61.8%) experienced improvement. Eighteen patients (32.7%) had normal visual fields pre- and postoperatively, and 3 (5.5%) experienced no change. No patient experienced worsening visual fields following surgery. A statistically significant relationship was found between postoperative visual acuity and extent of resection (p = 0.01). Patients with unchanged visual acuity deficits had a smaller extent of resection (71.5%), while those with the greatest extent of resection (89.9%) had worsening visual symptoms. Extent of resection was 83.4% in those who had visual acuity improvement and 80.2% with normal visual acuity pre- and postoperatively. Of the 7 patients with preoperative ophthalmoplegia symptoms, 5 experienced improvement, 1 experienced worsening of symptoms, and 1 experienced no change.

Only 4 patients (5.5%) had new onset of postoperative panhypopituitarism on provocative testing. Of the 10 patients who had evidence of panhypopituitarism preoperatively, only 1 patient experienced improvement and no longer required hormone replacement.

In this study, 27 patients (37.0%) experienced 32 complications (Table 5). The most common complications experienced were sinusitis (13.7%) and CSF leak (9.6%). Cerebrospinal fluid leaks were resolved using a lumbar drain and did not require surgical revision. Other complications included SIADH (4.1%), worsening headache (2.7%), epistaxis (2.7%), meningitis (2.7%), and hydrocephalus requiring a ventriculoperitoneal shunt (2.7%). No patients were documented to have had new postoperative seizures, subdural hygromas, hematomas into the tumor bed requiring evacuation, vasospasm, deep venous thrombosis, pulmonary embolism, carotid artery damage, cranial nerve damage, coma, or death. One patient experienced brisk epistaxis in the postoperative period, and a bleeding artery in the nasal mucosa was identified and coagulated upon reexploration in the operating suite.

The mean length of stay was 10.1 days; however, the median and mode lengths of stay were 4 days. The maximum length of stay was 122 days in a patient who required prolonged hospitalization for multiple comorbidities. Delayed reoperation was performed in 7 patients (9.6%) for regrowth of residual tumor. Postoperative radiation therapy was administered to 6 patients (8.2%) after discussion at a multidisciplinary tumor board. All patients had locally aggressive tumors that were refractory to medical and surgical treatment. Pathology was gonadotroph adenoma in 3 patients and the remaining were null cell, corticotroph, and so...
somatotroph. Five of the 6 patients were treated with 50-Gy fractionated radiotherapy at our institution; the remaining patient (corticotroph) was treated at her home institution with intensity-modulated radiation therapy.

**Predictors of Extent of Resection**

Preoperative patient clinical and radiological characteristics were analyzed to determine the ability to predict extent of resection achieved and are outlined in Table 6. Statistically significant predictors of decreased extent of resection included maximum tumor diameter ($R = 0.367$, $R^2 = 0.135$, $p = 0.002$), preoperative tumor volume ($R = 0.275$, $R^2 = 0.076$, $p = 0.025$), sphenoid sinus invasion ($p = 0.001$), and Knosp grade ($p = 0.001$). Hemorrhagic tumor component ($p = 0.027$) was a statistically significant predictor of increased extent of resection. When tumors were grouped by diameter of 3–4 cm ($n = 24$), 4–4.9 cm ($n = 35$), and ≥5 cm, there was a statistically significant difference between extent of resection (89%, 80.6%, and 73.4% respectively) (Table 6).

In regard to tumor volume, in post hoc analysis, statistical significance in resection was only reached when tumor volume is $\leq 24$ cm$^3$ ($p = 0.023$, mean difference 12.23% [95% CI 1.70–22.75%]). Suprasellar lateral intracranial extension approached statistical significance ($p = 0.053$). Sex, preoperative visual acuity, visual fields, ophthalmoplegia, endocrine functional status, apoplexy, prior surgery, prior radiation therapy, prior medical therapy, cystic tumor component, hydrocephalus, anterior extension, optic nerve compression, surgeon, cell type, cell functional status, MIB-1, $p27$, and FGFR4 markers were not statistically significant predictors of extent of resection.

**Discussion**

Mounting evidence, including the results of this se-
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**TABLE 6: Outcomes: significant predictors of extent of resection**

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Mean Resection</th>
<th>Pearson’s R</th>
<th>p Value</th>
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<tr>
<td>diameter (cm)</td>
<td>0.367</td>
<td>0.002</td>
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</tr>
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<td>grouped diameters</td>
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<tr>
<td>&lt;4 (24)</td>
<td>89.02%</td>
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<tr>
<td>4–4.9 (35)</td>
<td>80.60%</td>
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<tr>
<td>≥5 (7)</td>
<td>73.38%</td>
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<tr>
<td>preop vol (cm³)</td>
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<tr>
<td>individual vols</td>
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<td>25–29.9 (3)</td>
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<td>≥40 (2)</td>
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<tr>
<td>grouped vols</td>
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<td>&gt;24</td>
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<tr>
<td>0–1 (21)</td>
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<tr>
<td>2–4 (45)</td>
<td>79.12%</td>
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<tr>
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<td>0 (5)</td>
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<tr>
<td>1 (16)</td>
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<td>2 (14)</td>
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<td>3 (20)</td>
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<td>4 (11)</td>
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<td>posterior extension</td>
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<td>80.86%</td>
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<tr>
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</tr>
<tr>
<td>no (43)</td>
<td>87.00%</td>
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* Values in parentheses indicate the number of tumors.

ries, suggest the use of endoscopic transsphenoidal surgery as a first-line treatment for properly selected patients with large and giant pituitary adenomas, other than prolactinomas.3,4,15–18 To our knowledge, this report of 73 patients with giant pituitary adenomas defined by these size criteria is the largest in the literature to date, although significant heterogeneity in inclusion criteria exists, particularly with respect to tumor size, in the literature in this field.3,8,11,15–18 In this study, size criteria were developed based on first analyzing measured volumes of giant pituitary adenomas (≥ 4 cm). Then, using the minimum volume of this set (10.0 cm³) pituitary adenomas with a diameter ≥ 3 cm and volume ≥ 10.0 cm³ were included in this study. These criteria have also been independently derived and published by Cusimano et al.3 and Hofstetter et al.10 These criteria allow for a more sophisticated selection of pituitary adenomas that tend to be surgically challenging because of the extent of disease in an area of the skull that is challenging to access regardless of the approach. Further dialogue to standardize these criteria should be a priority for pituitary surgeons to enhance the ability to compare future studies in this field.

Treatment of these tumors is frequently multimodal because of the complex anatomy and physiology of the region.2 Medical management of hormonal symptoms, as well as emerging therapies to initiate tumor remission, will continue to be mainstays of treatment. However, because of the significant morbidity caused by mass effect of these large tumors and the acute nature with which they tend to present, surgical decompression will continue to be an essential and unavoidable first-line treatment. Evidence suggests the continued innovation of surgical techniques to access the skull base has increased the safety and efficacy of surgery in this region.3,8,15

Traditionally, many tumor factors, such as fibrous adenomas, dumbbell configuration, tumors with large suprasellar components that do not descend, or simply larger adenomas have been a contraindication for transsphenoidal resection.3 These tumors would instead be operated on using open frontal or frontotemporal approaches, which have been demonstrated to be associated with higher rates of morbidity and mortality than endoscopic approaches.3 Recently, the use of endoscopes in transsphenoidal surgery, combined with new extended and expanded approaches, has prompted skull base surgeons to reconsider these classic limitations of transsphenoidal approaches. Endoscopes allow for a more panoramic as well as a tailored view of the surgical field using angled endoscopes. Furthermore, improvements in image guidance, specialized transsphenoidal instrumentation, the use of Doppler probes, and other neurophysiological monitoring techniques combined with endoscopic approaches have enhanced the efficacy of this technique.15

**Outcomes of Case Series**

Complete resection of large and giant pituitary tumors is notoriously difficult and often untenable because of the extent of disease and invasion of structures that are not currently accessible surgically.3,15 However, whether complete resection is possible, adequate resection that provides patients with decompression, visual symptom reversal, and control of disease is the principal goal of surgery. The results of this series, combined with emerging evidence in recent trials, have demonstrated that endoscopic approaches are replacing open craniotomy as a first-line approach to most large sellar lesions.3,15

In this study, GTR, as assessed by no evidence of any residual lesion on postoperative MRI, was achieved in 24.2% of patients. An additional 16.7% of patients had resection rates ≥ 90%. Additionally, the average resection rate for the entire series was 82.9%, representing a relatively consistent ability for endoscopic surgery to provide significant debulking and decompression. These rates...
of resection correlate well with some other recent studies on endoscopic transsphenoidal surgery, such as that by Cusimano’s group, who reported a 20.7% GTR rate and 90.6% average resection rate, and Koutrourious and colleagues, who achieved a 20.4% GTR rate. However, other recent studies, such as those by Gondim et al., who recently reported GTR in 38% of a series of 50 patients with pituitary adenomas ≥ 4 cm in maximum diameter, and Komotar et al., who reported a GTR rate of 47.2% in a systematic review of endoscopic transsphenoidal surgery for giant (≥ 4 cm) pituitary adenomas, have achieved even greater GTR rates. Thus, there is some discrepancy reported rates of GTR for large and giant pituitary adenomas (20.4%–47.2%). Given the relatively small sample size of all of these studies and varying inclusion criteria, this is not necessarily surprising. Regional variation in use of extended approaches and cavernous sinus exploration could contribute to achieved rates of resection. Furthermore, when subject to rigorous volumetric analysis, small amounts of residual tumor may be identified that decrease the reported GTR rate without meaningful difference in clinical outcome. Volumetric analysis also provides a more accurate measurement of extent of resection than ellipsoidal volume calculation, making rates of resection in studies using different calculations difficult to compare. Lastly, our study population included 12 patients (16.4%) who previously had undergone a nonendoscopic approach to their pituitary adenomas. We have previously reported how these challenging cases represent an important population that contemporary pituitary surgeons face in revising patients with recurrent tumor after debulking by an alternate modality. However, including these patients with previous incompletely debulked tumor may have increased the difficulty of surgery in this study’s population, which may account for the differences between this study and reports of greater GTR and extent of resection. Surgical debulking was accompanied by a satisfactory rate of improvement of patients’ visual symptoms. Of the 53 patients with postoperative visual acuity assessment (excluding those without pre- or postoperative visual acuity deficit), 46 (86.8%) experienced improvement, while only 3 (5.7%) worsened and 4 (7.5%) experienced no change. Similarly, of the 37 patients with either pre- or postoperative visual field deficit, 34 (91.9%) had improvement in their visual fields, while the remaining 3 (8.1%) remained unchanged. Overall, of the patients with documented postoperative visual assessment (with a deficit preoperatively), 62% experienced improvement in their visual function (either acuity or fields). This is consistent with previously reported visual outcomes in endoscopic pituitary surgery. Only 6 patients (8.2%) underwent adjuvant postoperative radiation therapy. The indications for postoperative radiation and modality of choice are controversial. In this series, patients underwent radiotherapy if there was evidence of continued postoperative growth of residual tumor and/or concerning histological features such as MIB-1 index greater than 5% or silent corticotroph or invasive null cell tumor subtype. The use of postoperative radiation in pituitary adenomas in the literature ranges from 20% to 73%. However, in the context of large and giant adenomas, the series from the Pittsburgh group reported that 11 patients (20.4%) required radiation therapy, whereas the series by Cusimano and colleagues reported that 8 patients (28%) required radiation therapy. Further studies are warranted for the selection of modality, timing, and follow-up for adjuvant radiation therapy.

Seven patients required reoperation. Six of these patients required reoperation because of regrowth with optic apparatus involvement accompanied by visual dysfunction. Reoperations were all performed between 1 and 4 years of the initial endoscopic operation. The remaining patient had a significant residual (47%) from the first surgery due to carotid and cavernous sinus involvement that grew substantially requiring repeat surgical intervention.

Predictors of Extent of Resection

In establishing endoscopic approaches as first-line treatments for large and giant pituitary adenomas, classic contraindications for transsphenoidal approaches are being questioned. Thus, an important aspect of future studies in this field is to define new limitations or relative contraindications to this procedure. In this study, a broad analysis of the ability of several preoperative parameters to predict extent of resection was performed to help establish what the limitations of endoscopic transsphenoidal approaches may be. Our experience shows that when tumor volume is ≤ 24 cm³, a significantly greater extent of resection can be achieved.

Limitations

The study has several limitations, largely related to its retrospective design that must be considered when interpreting the results. The operations performed in this series were also chiefly performed by specialized skull base surgeons; thus, the applicability of these results to centers with lower volume and experience performing endoscopic operations on giant pituitary tumors may be limited.

Conclusions

While analyzing factors that might predict limited resection by an endoscopic approach, this is essentially a surrogate end point. Ultimately, the goal of surgery is surgical decompression of neural structures, specifically decompression of the optic apparatus, and control of disease progression. While GTR without recurrence achieves this outcome, subtotal resection may be equally satisfactory in terms of clinical outcomes.

As endoscopic transsphenoidal surgery has emerged as the standard treatment of pituitary adenomas, particularly in experienced tertiary care centers, surgeon comfort and experience with this technique has expanded the indications for transsphenoidal approaches to pituitary adenomas. Emerging evidence, including the results of this study, demonstrates that endoscopic resection of large and giant pituitary adenomas provides reasonable resection rates, favorable clinical outcomes, and acceptably low complication rates compared with alternative approaches. Certain preoperative factors, including Knosp grade, tu-
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mor volume, tumor diameter, hemorrhagic components on MRI, posterior extension, and sphenoid sinus invasion may represent tumor characteristics that decrease the likelihood of successful and complete endoscopic transsphenoidal surgery. In such instances, it is important to consider changing the approach to the tumor so that it is understood that near-total resection can be achieved through staged surgery. Alternatively, redefining the goals and expectation of outcomes following surgery is important, such that partial resection with decompression of the optic apparatus is the expected surgical outcome and presence of residual is an accepted result, in particular in patients with comorbidities or older age where progression of residual tumor is not clinically concerning. Further reports of institutional experiences, longer follow-up, and investigations are needed to validate our results. Extending our endoscopic approach with innovative approaches to overcome current limitations of the endoscopic approach is also important.

Disclosure

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

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