Pure endoscopic transsphenoidal surgery for treatment of acromegaly: results of 67 cases treated in a pituitary center

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Object. Acromegaly is a chronic disease related to the excess of growth hormone (GH) and insulin-like growth factor–I secretion, usually by pituitary adenomas. Traditional treatment of acromegaly consists of surgery, drug therapy, and eventually radiotherapy. The introduction of endoscopy as an additional tool for surgical treatment of pituitary adenomas and, therefore, acromegaly represents an important advance of pituitary surgery in the recent years. The aim of this retrospective study is to evaluate the results of pure transsphenoidal endoscopic surgery in a series of patients with acromegaly who were operated on by a pituitary specialist surgeon. The authors discuss the advantages, outcome, complications, and factors related to the success of the endoscopic approach in cases of GH-secreting adenomas.

Methods. The authors retrospectively analyzed data from cases involving patients with GH-secreting adenomas who underwent pure transsphenoidal endoscopic surgery at the Department of Neurosurgery of the General Hospital in Fortaleza, Brazil, between 2000 and 2009. Tumors were classified according to size as micro- or macroadenomas, and tumor extension was analyzed based on suprasellar/parasellar extension and sella floor destruction. All patients were followed up for at least 1 year. The criteria of disease control were GH levels < 1 ng/L after oral glucose tolerance test and normal insulin-like growth factor–I levels for age and sex.

Results. During the study period, 67 patients underwent pure endoscopic transsphenoidal surgery for treatment of acromegaly. Disease control was obtained in 50 cases (74.6%). The rate of treatment success was higher in patients with microadenomas (disease control achieved in 12 [85.7%] of 14 cases) than in those with larger lesions. Suprasellar/parasellar extension and high levels of sella floor erosion were associated with lower rates of disease control (p = 0.01 and p = 0.02, respectively). Complications related to the endoscopic surgery included epistaxis (6.0%), transitory diabetes insipidus (4.5%), and 1 case of seizure (1.5%).

Conclusions. Endoscopic transsphenoidal surgery represents an effective option for treatment of patients with acromegaly. High disease control rates and a small number of complications are some of the most important points related to the technique. Factors related to the success of the endoscopic surgery are lesion size, suprasellar/parasellar extension, and the degree of sella floor erosion. Although presenting important advantages, there is no conclusive evidence that endoscopy is superior to microsurgery in treatment of GH-secreting adenomas.

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Key Words • acromegaly • pituitary • adenoma • transphenoidal surgery • endoscopic surgery

Acromegaly was first described by Pierre Marie in 1886 as a syndrome characterized by the abnormal growth of extremities associated with the enlargement of the pituitary gland. Later on, it was described as associated not with a diffuse enlargement of the gland, but with the development of specific areas of hyperplasia of GH-secreting cells in the anterior lobe of the pituitary gland.

Clinically, acromegaly is characterized as a chronic disease related to high levels of GH and IGF-I. Its prevalence is estimated to be around 40–70 cases per million inhabitants, with an annual incidence of 3–4 new cases per million inhabitants. The main signs and symptoms are related to the somatic disfigurement secondary to hormonal imbalance, such as the abnormal growth of hands.

Abbreviations used in this paper: ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone; GH = growth hormone; IGF-I = insulin-like growth factor–I; LH = luteinizing hormone; TSH = thyroid-stimulating hormone.
and feet and facial alterations. Cardiovascular, metabolic, respiratory, and bone alterations are usually also present, which complicates management. Such alterations are related to the increased mortality observed in acromegalic patients, who have a 32% increased risk for all-cause mortality. According to previously published series, 60% of patients die of cardiovascular disease, 25% from respiratory complications, and 15% from cancer. High GH/IGF-I levels and heart disease are the main factors related to poor outcome in these patients.

Treatment options for acromegaly include surgery, medical therapy, and radiotherapy. The development of drug therapy for the control of acromegaly represents an important step toward hormonal control in patients with GH-secreting adenomas. Some of the options include the use of somatostatin analogs and pegvisomant, which are considered to represent useful options mainly for tumors that present characteristics associated with a small chance of surgical success. However, the costs of such treatment and the occurrence, in some cases, of major side effects, represent important limitations of the medical therapy.

Surgical treatment, which provides rapid control of GH/IGF-I levels and lower costs, remains, therefore, the first line of treatment for GH-secreting adenomas according to different neuroendocrinology societies and pituitary centers. Classically, transsphenoidal microsurgery has been considered the best surgical approach for most GH-secreting adenomas. However, in the last decade, the endoscopic approach to the treatment of sellar lesions has become an important option for resection of pituitary adenomas. Some of the advantages of such an approach include improved visualization, less nasal trauma, increased patient comfort, and, potentially, better results with respect to total tumor resection.

In the current study, we aimed to describe the results of endoscopic transsphenoidal surgery for the treatment of acromegaly in our center from 2000 to 2009. We also analyze the current literature related to endoscopic treatment of acromegaly and the role of surgery in the management of such cases.

**Methods**

**Study Design**

We performed a retrospective analysis of data from 67 cases involving patients with GH-secreting adenomas who had been referred to the neuroendocrine department of Fortaleza General Hospital in Fortaleza, Brazil. All of the patients underwent transsphenoidal endoscopic adenomectomy for acromegaly between 2000 and 2009. The median duration of follow-up was 2 years (range 12 months–6 years). Earlier results were reported for a subset of these patients in a previous paper. The operations were all performed using the transsphenoidal endoscopic technique, and the aim of treatment was to remove the tumor in its totality without causing hypopituitarism. The study was performed under the authorization of the ethics committee of Fortaleza General Hospital, and all patients agreed with the proposed treatment after careful explanation of all options for the management of acromegaly.

**Patient Population**

The inclusion criteria used in the study were as follows: clinical diagnosis compatible with acromegaly (GH > 1 mU/L, IGF-I level greater than the normal age- and sex-adjusted level), presence of GH-secreting pituitary adenoma, tumor determined to be positive for GH marker through histological examination, no previous treatment, surgery performed by the senior author (J.A.G.), and at least 1 year of follow-up. Data were analyzed according to patient age and gender. Clinical outcome was defined according to the presence or absence of compressive signs and/or endocrinological control.

**Endocrinological Assessment**

The following pre- and postoperative endocrinological investigations were performed at our hospital: multiple measurements of plasma GH (normal value < 1 µg/L for adults) and IGF-I. The normal age- and sex-adjusted ranges for IGF-I are determined in our laboratory using in-house results obtained from healthy controls. Other endocrinological findings were assessed with respect to the following reference ranges: prolactin, 1.5–30 µg/L; ACTH, 30–60 pg/ml, and serum cortisol levels; TSH, 0.3–4 mU/ml; LH, 6–34 mU/ml; and FSH, 2–2.2 mU/ml. The evaluation of gonadal function was further evaluated based on menstrual history in female patients and on testosterone levels in male patients. Endocrinological evaluation was performed before surgery, 3 months after surgery, and every 6 months thereafter. Six patients (5 with macroadenomas and 1 with a microadenoma) had elevated prolactin levels (range 52–1000 µg/L). Five patients with macroadenomas had multiple hormone deficiency (ACTH, LH, and FSH deficiency in 2 cases; TSH, LH, and FSH in 2; and ACTH, TSH, FSH, and LH in 1). Four men had testosterone deficiencies. Immunohistochemical analysis of resected tumor tissue was performed in all cases.

**Neuroimaging Examination**

All patients underwent tumor evaluation by means of MR imaging. We used 1.5-T MR imaging with T1- and T2-weighted spin echo sequences obtained before and after administration of Gd-based contrast medium. Tumor size was classified according to maximum tumor diameter in 2 categories: microadenoma (≤ 10 mm) and macroadenomas (> 10 mm). Based on the Hardy classification, according to the suprasellar/parasellar extension of the tumor, pituitary adenomas were classified as: A, lesion limited to the sella; B, lesion with minimal suprasellar extension and no considerable optic nerve compression; C, lesion presenting important suprasellar extension and optic nerve compression; or D, lesion with considerable parasellar extension. According to the presence of sella floor erosion and tumor extension, the lesions were classified as: 1, no floor destruction; 2, minimal floor destruction with no sphenoid sinus invasion; 3, minimal sphenoid sinus invasion; or 4, diffuse destruction of the sella floor with sphenoid sinus invasion.

A facial CT scan was used in all patients to evaluate the parasellar sinuses (septal anatomy, sphenoidal, and maxillofacial anatomy) for surgical planning. Follow-up

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MR imaging studies were performed 3 months after surgery and every 6 months thereafter.

Tumor Removal

The success of tumor removal was determined on the basis of both the MR imaging findings obtained 3 months after surgery and the surgeon’s intraoperative observation. A tumor was considered to be totally removed when the surgeon’s observation and the MR imaging examination documented no residual tumor. Resection was considered subtotal when part of the tumor remained in situ.

Surgical Procedure

After induction of general anesthesia, the patient is placed in the supine position on the operating table with the back elevated 30° and the head tilted back 20° and toward the left shoulder 25°. The surgeon is positioned on the right side of the patient. Normally, the left nostril is used, but the choice is based on nasal anatomy. A 30°, or less frequently 45° or 70°, rigid endoscope (180/4 mm) is used. The nasosphenoidal phase of the procedure is performed holding the endoscope with the nondominant hand. The endoscope is navigated into the nasal cavity. The floor of the sella is located approximately 1 cm above the inferior margin of the middle turbinate. The space between the middle turbinate and the nasal septum is gently widened, and a large opening is made in the anterior wall of the sphenoid sinus. Inside the sphenoid sinus, the sella is then localized, the endoscope is fixed, the anterior wall of the sella and the dura mater are opened widely with a high-speed drill or Kerrison rongeur, and the tumor is removed. For the reconstruction of the sellar region, we used a combination of fascia lata, abdominal fat, mucope-riosteum, and fibrin sealants.

Disease Control

The aim of treatment was to remove the tumor in its entirety without causing hypopituitarism. The success of tumor removal was based on the surgeon’s intraoperative observations as well as contrast-enhanced MR images obtained 3 months after surgery. The tumor was considered to be totally removed when the surgeon’s intraoperative report and the MR imaging examination documented an absence of residual tumor. The criteria used for acromegaly control were the current internationally accepted criteria for biochemical “cure” of the disease: the nadir GH level after oral glucose administration should be less than 1 ng/ml, and the IGF-I level should correspond to the appropriate age- and sex-adjusted reference values.

Results

Between 2000 and 2009, 367 patients underwent endoscopic transsphenoidal surgery for treatment of skull base lesions at the Department of Neurosurgery of the Fortaleza General Hospital. Pituitary adenomas were the most common lesions treated, representing 82% of the 367 cases. In the group of functioning pituitary adenomas, the most common subtype was GH-secreting adenomas.

During the study period, 67 GH-secreting pituitary adenomas were treated by pure transphenoidal endoscopic surgery in Fortaleza General Hospital of Fortaleza by the senior author (J.A.G.). The mean age (± SD) of the 67 patients was 44.8 ± 12.4 years (range 20–76 years); 32 (47.8%) of the patients were male, and 35 (52.2%) were female.

Five patients with macroadenomas had multiple hormone deficiencies preoperatively. These patients were being treated with hormone replacement therapy—3 of them with glucocorticoids (20–30 mg hydrocortisone), 3 with levothyroxine (0.1–0.15 mg/day), and 4 men with depot testosterone (200–300 mg, intramuscularly, per 3–4 weeks); no patient was receiving desmopressin treatment. A total of 6 patients (5 with macroadenomas and 1 with a microadenoma) had elevated prolactin levels at the preoperative evaluation: in 3 of these patients (2 with macroadenomas and 1 with a microadenoma), the prolactin levels normalized after surgery; in the 3 others (all of whom had macroadenomas) the prolactin levels were stabilized with the use of dopamine agonists.

All pituitary adenomas were anatomically analyzed based on MR imaging findings. The mean size of the lesions was 21.5 ± 10.1 mm (range 8–49 mm). All lesions were classified as micro- or macroadenomas (Table 1). Microadenomas were present in the minority of cases, representing only 20.9% of the cases (14 patients). Macroadenomas, therefore, were responsible for the symptoms of the patients in most of the cases (53 patients [79.1%]). Extension of the tumor, usually considered an important factor related to the success of resection, was analyzed based on the degree of suprasellar and parasellar extension, according to the Hardy classification. Based on this variable, 27 (40.3%) of the lesions were classified as Class A, 18 (26.9%) as Class B, 10 (14.9%) as Class C, and 12 (17.9%) as Class D. Based on sella floor erosion and tumor extension, tumors were classified as Grades I–IV, as follows: 10 lesions (14.9%) were classified as Grade I pituitary adenomas, 45 (67.1%) as Grade 2, 7 (10.4%) as Grade 3, and 5 (7.5%) cases as Grade 4. Most of the pitu

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itary adenomas were completely solid (60 cases, 89.6%). Cystic areas, therefore, were present only in a minority of cases (7 patients [10.4%]).

Complications associated with endoscopic pituitary surgery and, therefore, surgical treatment for acromegaly include CSF leak, diabetes insipidus, meningitis, pituitary dysfunction, nasal lesions, and death.\(^2\,13,24\) In the current study, 8 patients (11.9%) had minor complications related to the surgical procedure. Epistaxis was observed in 4 cases (6.0%), transitory diabetes insipidus in 3 cases (4.5%), and 1 case (1.5%) of seizures in the immediate postoperative time. No major complications related to the procedure, such as meningitis, CSF leaks or carotid lesions were observed in our study. There was no case of death related to the surgical approach. Thyroid hormone deficiency was observed in 5 patients who underwent endoscopic surgery for treatment of macroadenomas. These patients were treated with levothyroxine.

Disease control was achieved in most of the cases (50 patients [74.62%]); however, in 17 cases (25.4%) surgical treatment did not provide adequate control of acromegaly. Adequate postoperative disease control was achieved in 12 (85.7%) of the 14 patients who had microadenomas. In the group of patients with macroadenomas the rate of adequate disease control obtained with surgery was somewhat lower, with success achieved in 38 cases (71.7%). With respect to the correlation of suprasellar/parasellar tumor extension and sella floor erosion grades with the success of treatment, pituitary adenomas with higher levels of extrasellar extension and sella floor destruction were associated with a lower disease control index (p = 0.01 and p = 0.02, respectively) (Figs. 1 and 2). There was no significant difference in the outcome of patients that presented lesions with cystic areas (adequate control was achieved in 6 of 7 patients with cystic adenomas and in 44 of 60 patients with noncystic adenomas, p = 0.31). Four patients underwent a second operation after presenting with residual tumors considered to be easily resected by the transsphenoidal endoscopic technique. All of those patients had a favorable outcome (adequate endocrinological control) after the second procedure.

**Discussion**

Transsphenoidal surgery for treatment of acromegaly

**Fig. 1.** Disease control in patients with acromegaly according to the degree of suprasellar/parasellar extension of the lesion. Based on the Hardy classification, extension was classified as follows: A, lesion limited to the sella; B, lesion with minimal suprasellar extension and no considerable optic nerve compression; C, lesion presenting important suprasellar extension and optic nerve compression; or D, lesion with considerable parasellar extension.

**Fig. 2.** Disease control in patients with acromegaly according to the degree of sella floor erosion and pituitary tumor extension. Lesions were classified as follows: 1, no floor destruction; 2, minimal floor destruction with no sphenoid sinus invasion; 3, minimal sphenoid sinus invasion; or 4, diffuse destruction of the sella floor with sphenoid sinus invasion.

has been used since the initial work of Schloffer\(^7\) and Cushing.\(^2\) Characterized by lower morbidity and mortality rates than with the transcranial approach, transsphenoidal microscopic surgery (either sublabial or endonasal) has been considered the gold standard surgical treatment for acromegaly in recent decades. However, this type of approach presents considerable limitations, including: limited visual field during surgery, nasal lesions associated to the septum dissection, and important cosmetic limitations if a sublabial approach is used.\(^7\,13,22\)

The introduction of endoscopy represents one of the most important advances in pituitary surgery in recent years. In 1970, Messerklinger\(^21\) developed the endoscopic technique. Thereafter, surgeons started to use the endoscope in skull base surgery and in procedures involving the sellar and parasellar region.\(^2\,13\) In 1992, Jankowski et al.\(^15\) introduced the endoscope in the pituitary surgery field, describing the use of the endonasal transsphenoidal endoscopic technique for removal of 3 pituitary adenomas. Transsphenoidal endoscopically guided pituitary surgery was standardized in actual clinical practice by Jho and Carrau\(^16\) and by Cappabianca et al.\(^3\) The development of neuroendoscopy and the popularization of transsphenoidal endoscopically guided pituitary surgery have been associated with better tumor resection results, which are often related to better visualization of the sella, less nasal dissection, and improvement in the resection of suprasellar and parasellar components of the adenoma.\(^10,13\) Although endoscopic surgery provides better illumination and visualization of the lesions, no report has definitively proved the superiority of endoscopic surgery over microsurgery in the surgical treatment of pituitary lesions so far.

The success of endoscopic transsphenoidal surgery in the treatment of acromegaly has been studied by different authors.\(^7\,13,24\) According to our review, the current study presents the largest series of GH-secreting adenomas surgically treated by a single neurosurgeon using the pure endoscopic approach. In our center, all cases of GH-secreting adenomas are initially treated with endoscopic surgery, unless large cavernous sinus invasion is observed in the preoperative MR imaging or the patient has clinical comorbidities that do not allow for surgery. In those cases, medical therapy based on the use of somatostatin analogs is usually attempted.

Microadenomas represented 20.9% of the cases treated by our team. Lesion size, which usually has been considered an important factor related to disease control, was a major variable regarding to the success of the treatment.
with small lesions presenting a trend toward higher levels of disease control. The difference between the outcome in patients with microadenomas and those with macroadenomas, however, was not great enough to be considered statistically significant (85.7% control rate for microadenomas vs 71.7% for macroadenomas, \( p = 0.284 \)). The overall rate of surgical success in our study (74.6%), is comparable to the rates presented in recent papers, which vary from 52% to 85%.

Most of the patients in our study had large macroadenomas (53 cases [79.1%]), lesions that have been associated with poor disease control in some series.\(^2\)\(^4\) We believe the variable of size is not the only factor related to the poor clinical control found in cases of larger lesions. Therefore, we analyzed the tumor extension according to suprasellar/parasellar extension and the extension of sella floor erosion, based on the Hardy scale. According to our data, the presence of higher levels of suprasellar and parasellar extension were related to a lower chance of disease control (\( p = 0.01 \)). Major limitation was associated with lesions with parasellar extension in close relation with the internal carotid artery and the cavernous sinus (Class D, with only a 50% rate of clinical control after surgery). In cases in which surgery did not provide adequate control, somatostatin agonists were prescribed to achieve lower levels of GH/IGF-I. In one patient who presented with major cavernous sinus invasion, radiotherapy was attempted secondarily, but no hormonal control has been obtained to date. Considering specifically the variable of sella floor erosion, pituitary adenomas with greater extent of sellar destruction were associated with poor clinical control (\( p = 0.02 \)). Tumors associated with large erosions had more extensive posterior, inferior, and anterior components, which require an overall larger opening of the skull base. Such procedures are more complex since the surgeon usually has to deal with regions situated peripherally to the sella—such as the clivus and the anterior fossa—and their neurovascular structures, which could justify, at least in part, the lower chances of clinical control in those cases. The presence of cystic areas inside the lesion was not an important factor related to disease control (\( p = 0.31 \)). However, in cases with large/predominant cystic areas, we believe resection might be easier to accomplish because the resection of cystic lesions is usually simpler than the resection of solid masses. We believe a larger study, with more cases of cystic lesions, is needed to demonstrate such an association.

Different management options exist for GH-secreting adenomas that do not respond to surgery as a first-line treatment,\(^2\)\(^0\) including a second surgical procedure, radiotherapy, and medical therapy. In 17 patients (25.4%) in our series, surgery did not result in clinical control. Most of these patients (12 cases) were treated with somatostatin analogs postoperatively to obtain reduction of GH/IGF-I levels. One patient was treated with radiotherapy after unsuccessful resection. Four patients underwent a second endoscopic surgery because they were considered to have residual tumor that could be easily removed by a new approach.

Economically, the endoscopic transsphenoidal procedure also represents an interesting option for management of acromegaly. As described previously,\(^1\)\(^2\) a center with experience in the surgical treatment of patients with acromegaly will result in considerable cost savings to the health system. Moreover, treating uncomplicated acromegaly by means of transsphenoidal surgery has been reported to be less expensive than medical treatment or a course of radiotherapy.\(^2\)\(^3\)\(^2\)\(^5\) In the hands of an experienced pituitary surgeon, transsphenoidal surgery is associated with a high cure rate with few postoperative complications and a low recurrence rate.\(^1\)\(^3\)\(^13\)\(^2\)\(^5\)

**Conclusions**

Acromegaly is a chronic clinical condition related to high levels of GH and IGF-I. Endoscopic transsphe- noidal surgery represents one of the most effective options for treatment of acromegalic patients. Presenting an improved panoramic visualization of the surgical field, superior close-up views of the anatomy, and different working angles for resection of the lesion, endoscopy has become an important tool for pituitary adenoma resection in recent years. High disease control rates and low rates of complications are some of the most important points related to the technique. Some of the factors related to the success of endoscopic surgery are lesion size, suprasellar/parasellar extension, and the degree of sella floor erosion. The cost of surgical treatment for acromegaly is usually lower than that of medical therapy and/or radiotherapy. Therefore, if an experienced pituitary surgeon is available, we advocate the use of endoscopic transsphenoidal surgery as the first-line treatment for GH-secreting adenomas that do not demonstrate major cavernous sinus invasion. So far, however, there is no definitive evidence that endoscopy is superior to microsurgery for treatment of acromegaly or any other pituitary adenoma.

**Disclosure**

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

Author contributions to the study and manuscript preparation include the following. Conception and design: Almeida, Gondim, Albuquerque, Gomes, Ferraz. Acquisition of data: Almeida, Gondim, Albuquerque, Gomes, Schops. Analysis and interpretation of data: Almeida, Gondim, Gomes, Ferraz. Drafting the article: Almeida, Gondim, Albuquerque, Schops. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Almeida, Gondim. Administrative/technical/material support: Gondim. Study supervision: Gondim, Gomes, Schops, Ferraz.

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