Research Article

Pablo Ajler*, Alvaro Campero, Federico Landriel, Ezequiel Goldschmidt, Santiago Hem, Antonio Carrizo

Early Results of Microsurgical Treatment of Acromegaly

https://doi.org/10.1515/inj-2017-0004

Abstract: *Purpose*: Acromegaly is an unusual disorder caused by abnormal oversecretion of growth hormone by pituitary adenomas. Transsphenoidal surgery is frequently the first management option. The objective of this article is to establish the effectiveness of a transnasal transsphenoidal approach in the treatment of GH-producing adenomas, and to identify risk factors for disease persistence. *Methods*: We conducted a retrospective review of 81 patients treated for acromegaly with transsphenoidal microsurgery between 2006 and 2010. *Results*: Macroadenomas accounted for 66.7% of the cases, contrast-enhanced MRI revealing cavernous sinus invasion in 28.4% of the patients (23 subjects). Cure was achieved in 72.8% (59 of 82). All microadenomas (27 cases) were managed effectively with surgery whereas cure rates stood at 66.7% for macroadenomas. Monovariate analysis showed that disease persistence was statistically associated with three variables. Odds ratio for remission stood at 1.68 for microadenomas and 0.033 for cavernous sinus invasion ($p<0.001$). Preoperative GH values were statistically associated with cure during follow up ($p<0.05$). Multivariate logistic regression analysis showed that only cavernous sinus invasion continued to be significantly associated with disease persistence (OR 3.52, $p<0.05$). *Conclusion*: The transnasal approach proves effective in the treatment and cure of acromegaly. Cavernous sinus invasion is a major predictor of disease persistence.

Keywords: acromegaly, transsphenoidal approach, pituitary adenoma

1 Introduction

Acromegaly is an unusual chronic disorder caused by abnormal oversecretion of growth hormone (GH) secondary to pituitary adenomas [1], and is characterized by somatic changes (excess bone growth and soft tissue swelling of limbs and face), and systemic complications such as cardiovascular disease, diabetes, thyroid and gonadal dysfunction [2,3]. Colon polyps appear at higher incidence rates and may develop into colonic cancer [4]. The prevalence estimate for acromegaly is 60/1,000,000 [5].

In the liver, GH induces the secretion of insulin growth factor 1 (IGF-1), which accounts for most of the clinical manifestations of acromegaly. Diagnosis is based on abnormal GH and IGF-1 values according to age and gender, and non-suppression of GH below 1 ng/ml during oral glucose tolerance tests (OGTT) [6]. Treatment options include surgery, radiation and medical therapy. There is some consensus regarding which treatment should be administered in each case, surgery being usually the first option [2,3,7,8]. Since the early 1970s, the transsphenoidal approach has gained wide acceptance for the treatment of sellar region tumors, and

***Corresponding author: Pablo Ajler,** Department of Neurosurgery, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, E-mail: pablo.ajler@gmail.com

Federico Landriel, Ezequiel Goldschmidt, Santiago Hem, Antonio Carrizo, Department of Neurosurgery, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

Alvaro Campero, Department of Neurosurgery, Hospital Padilla, Tucumán, Argentina

currently almost all GH-secreting adenomas are managed in this way. Surgery objectives include to stop GH oversecretion by maintaining normal pituitary function, and to relieve local compression. In recent years, endoscopic neurosurgery has become a useful procedure to approach the sellar region. Probably this new technique is a step forward in approaching these tumors [9-14].

Here we present a series of 81 acromegalic patients treated with a transsphenoidal approach who have been operated on by experienced neurosurgeons with no endoscopic assistance. The objective of this study is to establish the effectiveness of transsphenoidal microsurgery in the treatment of acromegaly and to indentify risk factors that might predict the need of different surgical techniques or additional therapy. The present series along with previous publications may be taken to compare and contrast this procedure with newer techniques as they emerge, and contribute to clarify the effectiveness of surgery in the treatment of acromegaly.

2 Methods

2.1 Patients

We conducted a retrospective review of 81 patients treated with transsphenoidal microsurgery for GH-producing adenomas between 2006 and 2010. The diagnosis was established following the clinical and biochemical criteria of current guidelines that include abnormally increased IGF-1 for a given age and gender, and absence of GH suppression during OGTT (the cutoff value being >1 ng/ml at 120 minutes) [2]. The characteristic clinical signs of acromegaly were present in all patients. Contrast-enhanced MRI was performed preoperatively and tumors were classified according to Hardy-Knosp's grading standard with focus on tumor size and cavernous sinus invasion. Neuro-ophtalmological and full endocrinological assessments of the anterior pituitary axis were performed preoperatively. No radiation or pharmacological treatment preceded surgery in any patient. We compared cases cured after surgery with those having persistent disease, and conducted univariate and multivariate analyses to identify factors that could be predictive of the surgical outcome. Clinical data were obtained from the electronic medical records.

2.2 Treatment

A multidisciplinary approach was used. In all cases, surgery was the first line of therapy. In brief, patients were placed in the semi-sitting position, with the head turned 45° to the right; the sphenoidal ostium was reached through the homolateral nostril; then the rostrum was excised along with the mucosa, and the sella floor was opened. Durotomy was performed and the tumor, removed. The opening was closed with fibrin glue and the sella floor was reconstructed by inserting a bone graft from the septum or rostrum [15-18]. Typically, the patients were discharged three days after surgery. Decisions regarding adjuvant pharmacological or radiation therapy when laboratory or clinical abnormalities persisted were made following current practice guidelines by the endocrinologist monitoring the patient.

2.3 Evaluation and follow-up

Following discharge, patients were evaluated subsequently at months 3 and 6 after surgery. The first evaluation was used to define cure and included clinical assessment as well as random IGF-1 and GH level measurements following OGTT. A new MRI scan was obtained at this time. Biochemical control was defined as normal IGF-1 according to age and gender, and GH <1.0 ng/ml during OGTT. In month 6 evaluation, patients were assessed for hormone deficits and the need of hormone replacement therapy. This criterion was used to define endocrine deficit. A visual field test was performed at this time for assessing visual improvement.

2.4 Statistical analysis

Variables are described as mean and standard deviation, or median and interquartile range according to the distribution observed. Categorical variables are described as proportions. Confidence intervals were reported for each case. Univariate analysis was conducted as per Chi-square for categorical variables, and a multivariate logistic regression analysis was performed to identify potential confounders. Statistical significance was considered for probabilities > 5%. The analysis was performed as per the Statistical Package for the Social Sciences (SPSS) v.17.0.

3 Results

A total of 81 acromegalic patients were treated with transnasal microsurgery between January 2005 and June 2010. The age mean was 41.52 years (range 12-75), and 56.8 % of the subjects were males. They represented 21% of all transsphenoidal microsurgeries conducted to treat sellar adenomas (81 out of 380). The media±interqantile ranges of preoperative GH and IGF-1 baseline values were 9.8±10.3 and 834±417, respectively. Two patients had a recent surgery in another center but because of persistent disease and a visible remanent of the adenoma on the MRI scan we reoperated on them and considered surgery as the primary treatment.

3.1 Tumor characteristics

Macroadenomas accounted for 66.7 % of the cases, contrast-enhanced MRI revealing cavernous sinus invasion in 28.4% of the patients (23 subjects), whereas 65.4% had a mixed component (89.65% positive prolactin cells and 10.35% positive LH cells) based on pathological analysis. Optic chiasm compression with visual field impairment (unilateral or bitemporal hemianopsia) was detected in 25.9% of the patients as a consequence of macroadenomas.

3.2 Cure after transsphenoidal surgery

Cure—as defined according to the above criteria—was achieved in 72.8% of the patients (59 out of 81): all microadenomas (27 cases) were managed effectively with surgery whereas cure rates stood at 66.7% for macroadenomas. Two patients had already been operated on for macroadenomas, one of whom achieved remission after the second procedure. Mixed tumors had the same outcome than GH adenomas. Pure GH secreting tumors had a remission rate of 71.7% whereas mixed tumors of 75%, the difference was not statistically different (p=0.8, Fisher exact test). Nineteen of the twenty-one patients with visual impairment (i. e. 90% of the cases) showed improvement as measured through the visual field tests performed 6 months after surgery. Patients with persistent abnormal hormonal values were treated in accordance with the MRI scan results, those with a positive image were treated by a new transsphenoidal approach or with radiosurgery, patients without abnormal findings were medically treated.

3.3 Remission and persistence predictors

Monovariate analysis showed that disease persistence was statistically associated with three variables. Odds ratio for cure stood at 1.68 for microadenomas and 0.033 for cavernous sinus invasion ($p<0.001$). Preoperative GH values, but no serum IGF-1 values, were statistically associated with cure ($p<0.05$) (Table 1). Multivariate logistic regression analysis including age, tumor size, cavernous sinus invasion and preoperative lab values was performed to individualize potential confounders. Only cavernous sinus invasion continued

to be significantly associated with disease persistence (OR 3.52, p<0.05) when multivariate analysis was performed, as opposed to preoperative GH concentration and tumor size, which were not associated in a statistically significant manner. (Figure 1, 2)

Table 1: Comparison of preoperative characteristics between patients cured after surgery and patients with persistent disease

	Biochemical control	**Persistent disease**	
Females+	26/59 (44%)	8/14 (57%)	P=0,39[c]
Age*	43,03±16,2	36,68±9,42	P=0,24[a]
Cavernouse sinus invasión	6/59 (10%)	17/22(77%)	p<0,001[c]
Microadenoma	28/59 (47%)	0/22 (0%)	p<0,001[c]
Preoperative GH[o](mU/ml)[+]	18,35±16,2	8,5±6,8	P<0,05[b]
Preoperative IGF-1[o](ng/ml)[+]	842±277	805±460	P=0,37[b]

*mean±satandard deviation ,[o] median±interqartile range [a]Student T test, [b]Mac Niemann, [c]Fisher Exact Test

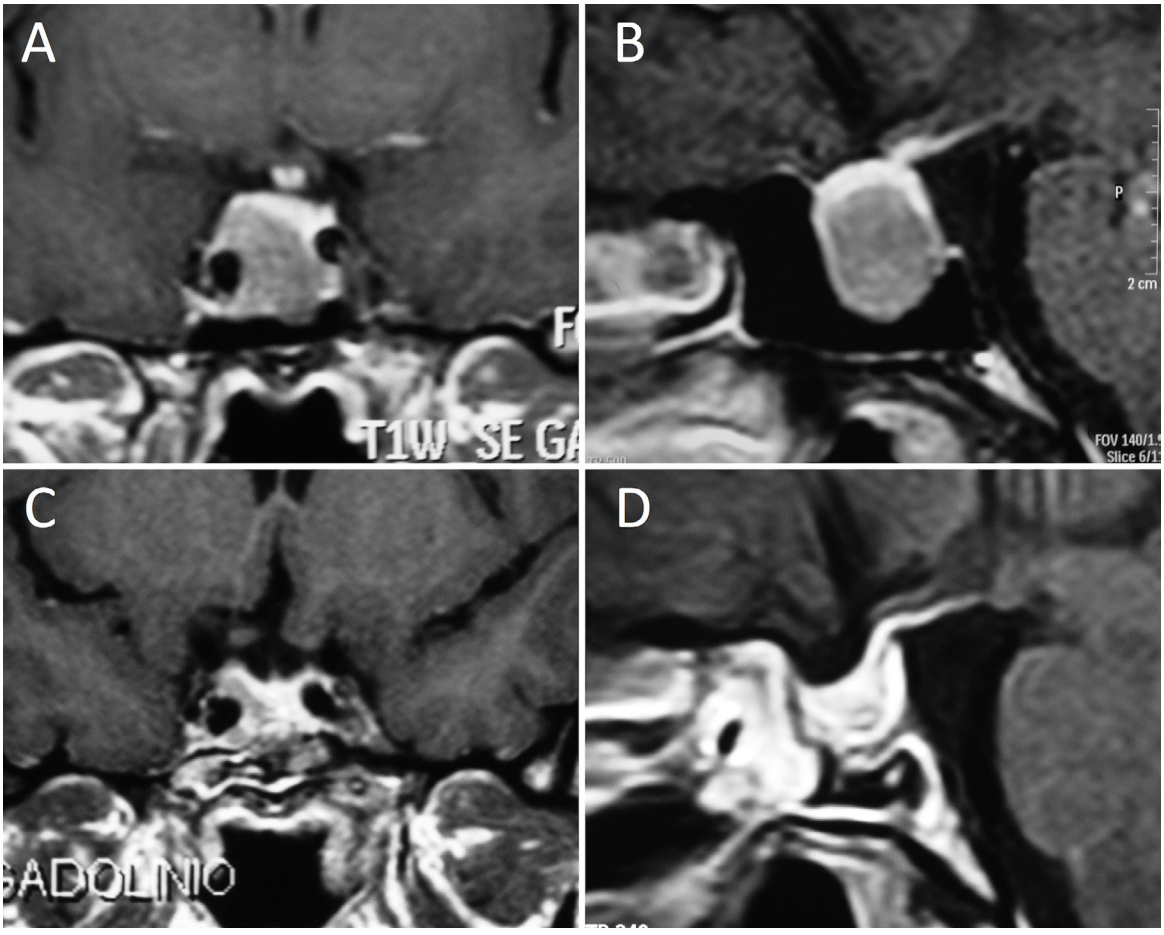

Figure 1: Patient 1 coronal (A) and sagittal (B) contrast-enhanced T1-weighted MRI brain scan showing macroadenoma with cavernous sinus invasion. Follow-up coronal (C) and sagittal (D) MRI obtained 3 months after microsurgical removal of the macroadenoma; a remanent was left in the cavernous sinus

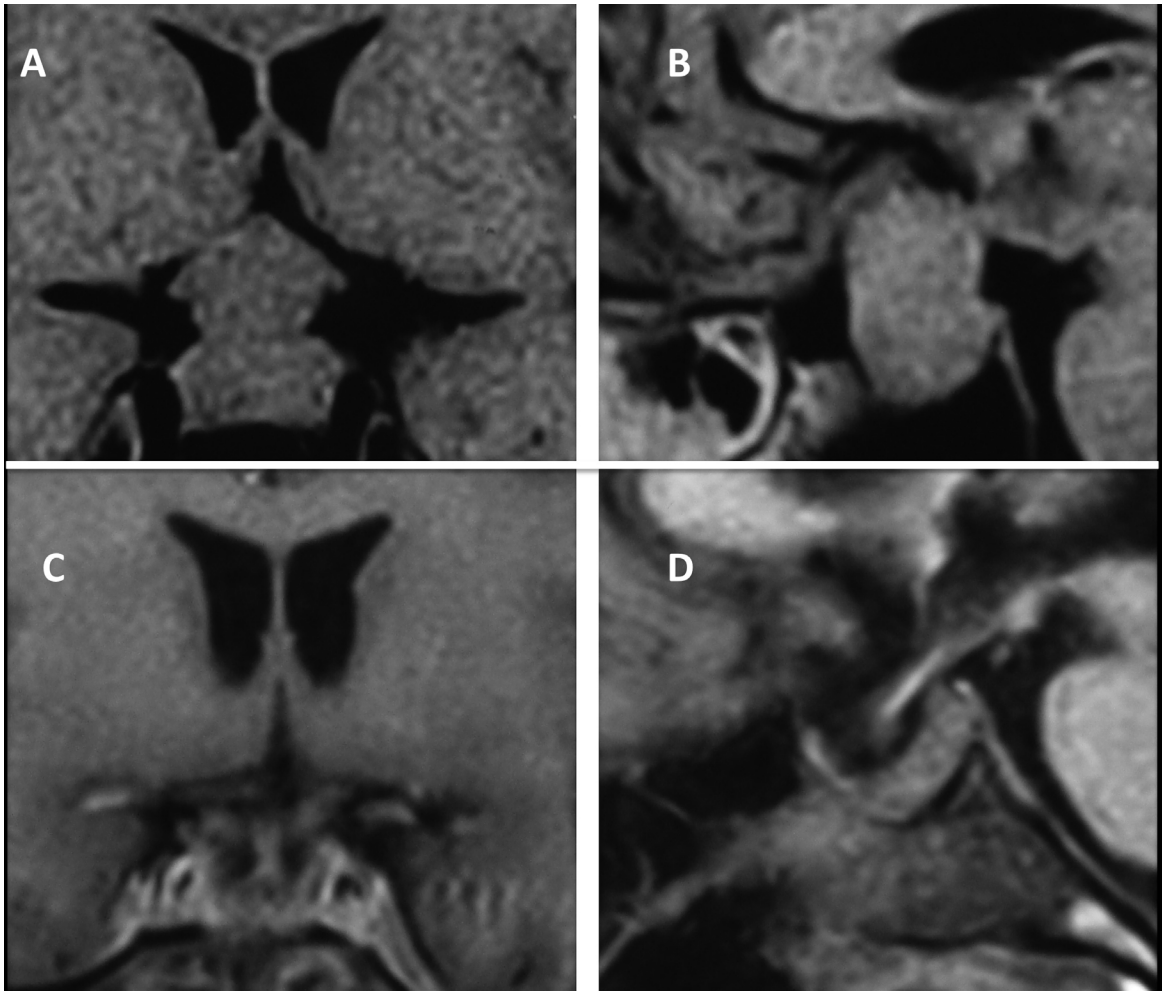

Figure 2: Patient 2 coronal (A) and sagittal (B) contrast-enhanced T1-weighted MRI brain scan showing macroadenoma with no cavernous sinus invasion. Follow-up coronal (C) and sagittal (D) MRI with total removal of the lesion

3.4 Postoperative hormone deficit

Postoperative new hormone deficit was seen in 14% of the patients, all except two having deficit of the anterior pituitary axis. Postoperative hormonal deficit correlated with the size of the tumor (macroadenomas having a higher risk, OR 1.35 $p<0.05$), with biochemical control of acromegaly (OR 6.81 $p<0.05$) and with cavernous sinus invasion (OR 5.05 $p<0.05$) in a statistically significant manner.

3.5 Surgery morbidity and mortality

Two out of 81 patients developed complications postoperatively (2.4% morbidity) and had a cerebrospinal fluid fistula graded as IIb according to the new classification by Landriel et al, requiring a surgical closure [19]. Both patients recovered well after the second surgery and were discharged without neurological deficits. They had macroadenomas and persistent disease postoperatively. No patient died after surgery; only one of the 380 patients treated with transsphenoidal approach died as a result of surgical complications in the past five years; the recorded mortality rate was 0.26%.

4 Discussion

Acromegaly caused by GH-secreting adenomas is an infrequent disorder but represents a large proportion of the pituitary tumors requiring surgery. It is still a challenge for experienced neurosurgeons because, despite newer diagnostic and therapeutic tools, many patients continue to have symptoms and biochemical abnormalities postoperatively [3]. The transnasal approach allows tumor resection in most microadenomas; however, larger adenomas represent a major challenge. Complete surgical resection is possible with this technique only where the lesion is located within the internal walls of the cavernous sinus. Tumors with vertical growths exceeding the sella are technically more difficult to manage, but complete resection can be accomplished. Because of these anatomical constraints, it can be hypothesized that cavernous sinus invasion leaves part of the tumor out of surgical sight and thus hinders disease management in this group of patients [20].

In our series, 72.8% of patients achieved biochemical cure according to hormone levels obtained 3 months after surgery. This outcome is within the highest remission results published. Gittoes et al reported a cure rate of 64% when surgery was performed by a single experienced neurosurgeon [21.] Shimon et al achieved biochemical remission in 74% of 91 patients, including 7 who had previously undergone surgery [18]. Recent published papers refer similar remission rates using an endoscopic technique (70% Jane et al., 74,6% Gondim et al.) [10,11,22]. Relapse is a possibility even after biochemical cure and normal MRI. In fact, Beauregard et al reported 82% and 52% rates of biochemical remission in short- and long-term follow-up, respectively [23]. Biermasz et al revealed a 19% relapse rate in a 10-year follow-up cohort study, whereas Freda et al reported that 5.4% of patients had recurrent disease after being followed up by a mean of 5.4 years [20,24]. We have no data from longer follow-up studies, hence long-term results from these patients are unavailable but might be eventually lower than the data presented in this paper.

All microadenomas—which presented no cavernous sinus invasion—could be cured in the follow up period. They represented 33.3 % of all cases which is a larger proportion compared with other series (25% of 1658 patients according to Sesmilo et al.) [25]. Conversely, macroadenomas represented a major challenge. In fact, all patients with persistent disease (22%) had macroadenomas. Tumors larger than 1 cm can exceed the sella and grow, thereby compromising the optic chiasm, invading the sphenoid sinus or extending to the sides and compromise one or both cavernous sinuses. Surgery proved to be an excellent approach to achieve complete resection in larger adenomas except for cases with lateral growth.

In order to validate our hypothesis, that lateral invasion is the main factor precluding complete resection; we performed a multivariate analysis regarding all the variables that are considered to change surgical outcomes (preoperative GH and IGF-1 values, the size of the tumor and cavernous sinus invasion). The logistic regression showed that a statistically significant association was still present between cavernous sinus invasion and disease persistence; tumor size and preoperative GH levels did not show such correlation, therefore they may have acted as confounders in our study group.

Krentowska-Korec et al observed that disease management was associated with baseline and post-OGTT GH and IGF-1 values, as well as with tumor size and invasiveness [26]. However, the authors did not perform a multivariate analysis in this case, so tumor diameter and hormone values may have been actually associated with cavernous sinus invasion and thus constituted no independent predictors of cure. In fact, the authors found that preoperative lab values were associated with tumor size, which made them less reliable as surgical outcome predictors. Recent published series using a microsurgical approach report, when performing a multivariate analysis, show size and cavernous sinus invasion as bad outcome predictors (table 2) [27-31]. Tumor size larger than 15 mm was found as a non-remission variable only in one study.[28] In the present series size alone did correlate with a poor outcome when performing a univariate analysis but because of its association with cavernous sinus invasion (none of the microadenomas were invasive) it did not act as an independent predictor of bad outcome.

Different outcome from other series may be based on the fact that most series depends on follow up, proportion of macroadenomas and adenomas invading the cavernous sinus, i.e. van Bunderen et al. report a 30 % of remission but 27 out of 30 patients presented parasellar extension [26-28,30,31]. The fact that 33.3 % of our cases were microadenomas and neither of them invasive and that we followed the patients for 6 months may explain for a different remission rate.

Table 2: Predictors of persistent disease in published series from 2000 onwards. Only series with a multivariate analysis which used a microsurgical technique are included into the table.

References	Number of patients	Remission percentage (%)	Predictors of persistent disease based on multivariable analysis
Minniti et al.	92	55	Cavernous sinus invasion Size
Attanasio et al.	96	63,5	None
Kreutzer et al.	57	70,2	Dural invasion
Bourdelot et al.	83	59	Size*
van Bunderen et al.	30	30	Cavernous sinus invasion
Present series	81	72,8	Cavernous sinus invasion

*>15 mm

Hypopituitarism is a well-known consequence of sellar adenomectomy. Fatemy et al stated that postoperative hormone deficits correlate with tumor diameter in a series of 449 patients, where new anterior axis hormone deficits were found in 5% of the cases and permanent diabetes insipidus in 2.2 % [32]. Fourteen out of 81 of our patients needed long-term hormone replacement. Patients with macroadenomas and cavernous sinus invasion who were cured after surgery had a comparatively higher rate of hypopituitarism, as is well described in the relevant literature [32].

Surgical morbidity and mortality values were within the range of specific data published in specialized sites. Barker et al reported that death and complications associated with the surgical procedure differed between sites according to surgical volume. In a series of 5497 transsphenoidal surgeries, mortality was 0.6% and morbidity, 3% [33] .Of 668 surgeries for GH-producing adenomas, Nomikos et al found an overall mortality rate of 0.1 % and a complications rate of < 2% [34].

5 Conclusion

In summary, we achieved a high postoperative cure rate for this group of patients. Morbidity was low and there was no mortality. Cavernous sinus invasion was the main obstacle for complete tumor resection and, consequently, for biochemical control. The possibility that lateral growth could be controlled with endoscopy remains to be studied.

Conflicts of Interest Disclosure: All authors state there are no actual or potential conflicts of interest with regard to the manuscript submitted for review.

References

[1] Lopes MB: Growth hormone-secreting adenomas: pathology and cell biology. *Neurosurg Focus* 29: E2, 1990
[2] Melmed S: Acromegaly. *N Engl J Med* 322: 966-977, 1990
[3] Melmed S, Colao A, Barkan A, Molitch M, Grossman AB, Kleinberg D, Clemmons D, Chanson P, Laws E, Schlechte J, Vance ML, Ho K, Giustina: Acromegaly Consensus Group. Guidelines for acromegaly management: an update. *J Clin Endocrinol Metab* 94: 1509-1517, 2009
[4] Renehan AG, O'Connell J, O'Halloran D, Shanahan F, Potten CS, O'Dwyer ST, Shalet SM: Acromegaly and colorectal cancer: a comprehensive review of epidemiology, biological mechanisms, and clinical implications. *Horm Metab Res* 35:712-725, 2003
[5] Holdaway I. M. , Rajasoorya C: Epidemiology of acromegaly. *Pituitary* 2: 29-41, 1999
[6] Melmed S: Medical progress: Acromegaly. *N Engl J Med* 355: 2558-2573, 2006
[7] Colao A, Attanasio R, Pivonello R, Cappabianca P, Cavallo LM, Lasio G, Lodrini A, Lombardi G, Cozzi R: Partial surgical removal of growth hormone-secreting pituitary tumors enhances the response to somatostatin analogs in acromegaly. *J Clin Endocrinol Metab* 91: 85-92, 2006

[8] Consensus statement: benefits versus risks of medical therapy for acromegaly. Acromegaly Therapy Consensus Development Panel. Am J Med 97: 468-73, 1994
[9] Cappabianca P, Alfieri A, Colao A, Ferone D, Lombardi G, Divitis E: Endoscopic endonasal transsphenoidal approach: an additional reason in support of surgery in the management of pituitary lesions. *Skull Base Surg* 9: 109-117, 1999
[10] Gondim JA, Almeida JP, Albuquerque LA, Gomes E, Schops M, Ferraz T: Pure endoscopic transsphenoidal surgery for treat ment of acromegaly: results of 67 cases treated in a pituitary center. *Neurosurg Focus* (4): E7, 2010
[11] Gondim JA, Almeida JP, Albuquerque LA, Schops M, Gomes E, Ferraz T, Sobreira W, Kretzmann M T: Endoscopic endonasal approach for pituitary adenoma: surgical complications in 301 patients. *Pituitary* 14: 174-183, 2011
[12] Lasio G, Ferroli P, Felisati G, Broggi G: Image-guided endoscopic transnasal removal of recurrent pituitary adenomas. *Neurosurgery* 51:132-137, 2002
[13] Leach P, Abou-Zeid AH, Kearney T, Davis J, Trainer PJ, Gnanalingham KK: Endoscopic transsphenoidal pituitary surgery: evidence of an operative learning curve. *Neurosurgery* 67:1205-1212, 2010
[14] Spaziante R, de Divitiis E, Cappabianca P: Reconstruction of the pituitary fossa in transsphenoidal surgery: an experience of 140 cases. *Neurosurgery* 17:453-458, 1985
[15] Ciric I, Mikhael M, Stafford T, Lawson L, Garces R: Transsphenoidal microsurgery of pituitary macroadenomas with long-term follow-up results. *J Neurosurg* 59: 395-401, 1983
[16] Ciric I, Rosenblatt S, Zhao JC: Transsphenoidal microsurgery. *Neurosurgery* 51: 161-169, 2002
[17] Hardy J: Transsphenoidal microsurgery of the normal and pathological pituitary. *Clin Neurosurg* 16: 185-217, 1969
[18] Shimon I, Cohen ZR, Ram Z, Hadani M: Transsphenoidal surgery for acromegaly: endocrinological follow-up of 98 patients. *Neurosurgery* 48:1239-43, 2001
[19] Landriel Ibañez FA, Hem S, Ajler P, Vecchi E, Ciraolo C, Baccanelli M, Tramontano R, Knezevich F, Carrizo A: A new classi-fication of complications in neurosurgery. *World Neurosurg* 75: 709-15, 2011
[20] Freda PU, Wardlaw SL, Post KD: Long-term endocrinological follow-up evaluation in 115 patients who underwent transsph enoidal surgery for acromegaly. *J Neurosurg* 89: 353-358, 1998
[21] Gittoes NJ, Sheppard MC, Johnson AP, Stewart PM: Outcome of surgery for acromegaly-the experience of a dedicated pituitary surgeon. *QJM* 92: 741-745, 1999
[22] Jane JAJ, Starke RM, Elzoghby MA, Reames DL, Payne SC, Thorner MO, Marshall JC, Laws ERJ, Vance ML: Endoscopic transsphenoidal surgery for acromegaly: remission using modern criteria, complications, and predictors of outcome. *J Clin Endocrinol Metab* 96: 2732–2740, 2011
[23] Beauregard C, Truong U, Hardy J, Serri O: Long-term outcome and mortality after transsphenoidal adenomectomy for acromegaly. *Clin Endocrinol (Oxf)* 58: 86-91, 2003
[24] Biermasz NR, van Dulken H, Roelfsema F: Ten-year follow-up results of transsphenoidal microsurgery in acromegaly. *J Clin Endocrinol Metab* 85: 4596-4602, 2000
[25] Sesmilo G, Gaztambide S, Venegas E, Picó A, Del Pozo C, Blanco C, Torres E, Alvarez-Escolà C, Fajardo C, García R, Cámara R, Bernabeu I, Soto A, Villabona C, Serraclara A, Halperin I, Alcázar V, Palomera E, Webb SM; l REA investigators: Changes in acromegaly treatment over four decades in Spain: analysis of the Spanish Acromegaly Registry (REA). *Pituitary*16(1):115-21, 2013
[26] Krzentowska-Korek A, Gołkowski F, Bałdys-Waligórska A, Hubalewska-Dydejczyk A: Efficacy and complications of neurosurgical treatment of acromegaly. *Pituitary* 14: 157-162, 2011
[27] Attanasio R, Montini M, Valota M, Cortesi L, Barbo R, Biroli F, Tonnarelli G, Albizzi M, Testa RM, Pagani G: An audit of treatment outcome in acromegalic patients attending our center at Bergamo, Italy. *Pituitary* 11: 1–11, 2008
[28] Bourdelot A, Coste J, Hazebroucq V, Gaillard S, Cazabat L, Bertagna X, Bertherat J: Clinical, hormonal and magnetic resonance imaging (MRI) predictors of transsphenoidal surgery outcome in acromegaly. *Eur J Endocrinol* 150: 763–771, 2004
[29] Kreutzer J, Vance ML, Lopes MB, Laws ER Jr: Surgical management of GH-secreting pituitary adenomas: an outcome study using modern remission criteria. *J Clin Endocrinol Metab* 86: 4072–4077, 2001
[30] Minniti G, Jaffrain-Rea ML, Esposito V, Santoro A, Tamburrano G, Cantore G: Evolving criteria for post-operative biochemical remission of acromegaly: can we achieve a definitive cure? An audit of surgical results on a large series and a review of the literature. *Endocr Relat Cancer* 10:611–619, 2003
[31] van Bunderen CC, van Varsseveld NC, Baayen JC, van Furth WR, Aliaga ES, Hazewinkel MJ, Majoie CB, Freling NJ, Lips P, Fliers E, Bisschop PH, Drent ML: Predictors of endoscopic transsphenoidal surgery outcome in acromegaly: patient and tumor characteristics evaluated by magnetic resonance imaging. Pituitary. Apr 26. [Epub ahead of print] 2012
[32] Fatemi N, Dusick JR, Mattozo C, McArthur DL, Cohan P, Boscardin J, Wang C, Swerdloff RS, Kelly DF: Pituitary hormonal loss and recovery after transsphenoidal adenoma removal. *Neurosurgery* 63: 709-718, 2008
[33] Barker FG, Klibanski A, Swearingen B: Transsphenoidal surgery for pituitary tumors in the United States, 1996-2000: mortality, morbidity, and the effects of hospital and surgeon volume. *J Clin Endocrinol Metab* 88: 4709-4719, 2003
[34] Nomikos P, Buchfelder M, Fahlbusch R: The outcome of surgery in 668 patients with acromegaly using current criteria of biochemical 'cure'. *Eur J Endocrinol* 152:379-387, 2005