











Original Article

Clinical and biochemical response to the management of macroprolactinomas in Latin American men, Cali, Colombia and Habana, Cuba

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Abstract

Introduction: Prolactinomas are the most common producing pituitary tumors in clinical practice. Although they are more common in women, in men their behavior is different, more aggressive, and with an uncertain response to pharmacological treatment.


Objective: To describe the clinical and biochemical characteristics and the response to pharmacological and surgical treatment of a group of men with invasive macroprolactinomas.

Materials and methods: A retrospective cohort study was carried out with the clinical data of men diagnosed with invasive macroprolactinomas from the Pituitary Diseases Clinic of the National Institute of Endocrinology, Havana, Cuba and from the Imbanaco Clinic, Cali, Colombia (2022–2017), with an age range between 10–80 years. An analysis of the demographic and clinical characteristics, signs, symptoms, hormonal biochemical profile, magnetic resonance imaging of the anatomy of the hypothalamic–pituitary region, medical and surgical treatment was performed. Proportions and measures of central tendency were estimated through univariate analysis. The two types of treatment were compared using Student's t-test or Kruskal–Wallis test.

Results: 30 men were analyzed, mean age was 44 ± 13.8 years; 5.2 ± 4.1 years of disease evolution; 96% presented headache, 80% hypopituitarism. The mean baseline serum prolactin was $487 \mu\text{g/L}$. Treatment with surgery plus dopamine agonists was performed in 53%, with a decrease of 86% and 96% in serum prolactin at 6 and 12 months, respectively;

Highlights

- Prolactinomas in men are larger and more aggressive compared to women. The most common symptoms are headache, hypopituitarism, and visual disturbances.
- The most affected axis in men is the gonadal axis, followed by the somatotrope, corticotrope, and thyrotrope.
- Surgical treatment accompanied by medical management with dopamine agonists achieved the most significant decrease in tumor size at 12 months.
- Management with dopamine agonists, especially cabergoline, showed consistent results and an adequate response that allows it to be considered as the first-line management in this group of patients.

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patients receiving dopamine agonists had a 71% and 95% decrease in serum prolactin at 6 and 12 months, respectively. Initially, patients with surgical treatment obtained a greater reduction in tumor size, but there were no differences at one year of follow-up.

Conclusion: Combined treatment with surgery plus dopaminergic agonists did not have a greater reduction in prolactin levels during the first year of treatment, regardless of tumor size. In male patients with invasive macroprolactinomas, pharmacological treatment with dopamine agonists is the first-line treatment of choice.

Keywords: Prolactinoma, men, surgical procedures, dopamine agonists, hyperprolactinemia, prolactine.

Respuesta clínica y bioquímica al manejo de macroprolactinomas en hombres latinoamericanos, Cali, Colombia y la Habana, Cuba

Resumen

Introducción: los prolactinomas son los tumores hipofisarios productores más comunes en la práctica clínica. Aunque son más comunes en mujeres, en hombres su comportamiento es distinto, más agresivo y con una respuesta al tratamiento farmacológico incierta.

Objetivo: describir las características clínicas y bioquímicas, y la respuesta al tratamiento farmacológico y quirúrgico de un grupo de hombres con macroprolactinomas invasivos.

Materiales y métodos: se realizó un estudio de cohorte retrospectivo con los datos clínicos de hombres con diagnóstico de macroprolactinomas invasivos de la Clínica de Enfermedades Hipofisarias del Instituto Nacional de Endocrinología en Habana, Cuba y de la Clínica Imbanaco en Cali, Colombia (2022-2017), con un rango de edad entre 10-80 años. Se realizó un análisis de las características demográficas, clínicas, signos, síntomas, perfil bioquímico hormonal, imágenes por resonancia magnética de la anatomía de la región hipotálamo-hipofisaria y tratamiento médico y quirúrgico. Se estimaron proporciones y medidas de tendencia central por medio de análisis univariado. Se comparó los dos tipos de tratamiento con las pruebas T de student o Kruskal Wallis.

Resultados: se analizaron 30 hombres, la edad media fue $44 \pm 13,8$ años; $5,2 \pm 4,1$ años de evolución de la enfermedad; 96 % presentaron cefalea, 80 % hipopituitarismo. La prolactina sérica inicial media fue $487 \mu\text{g/L}$. Se realizó tratamiento con cirugía más agonistas de dopamina en el 53 %, con una disminución del 86 % y 96 % en la prolactina sérica a los 6 y 12 meses, respectivamente; mientras que los pacientes que recibieron agonistas de la dopamina tuvieron una disminución del 71 % y 95 % en la prolactina sérica a los 6 y 12 meses, respectivamente. Inicialmente los pacientes con tratamiento quirúrgico obtuvieron una mayor reducción del tamaño tumoral, pero no hubo diferencias al año de seguimiento.

Conclusión: el tratamiento combinado con cirugía más agonistas de dopaminérgicos no tuvo una mayor reducción los niveles de prolactina durante el primer año de tratamiento, independiente del tamaño tumoral. En pacientes hombres con macroprolactinomas invasivos el tratamiento farmacológico con agonistas de la dopamina es el tratamiento de elección de primera línea.

Palabras clave: prolactinoma; hombres; procedimiento quirúrgico; agonistas de dopamina; hiperprolactinemia, prolactina.

Destacados

- Los prolactinomas en hombres son más grandes y agresivos comparado con las mujeres. Los síntomas más comunes son cefalea, hipopituitarismo y alteraciones visuales.
- El eje más afectado en hombres es el gonadal, seguido por el somatotropo, corticotropo y tirotripo.
- El tratamiento quirúrgico acompañado de manejo médico con agonistas dopaminérgicos logró el mayor descenso de tamaño del tumor a los 12 meses.
- El manejo con agonistas dopaminérgicos, especialmente cabergolina, mostró resultados consistentes y con una respuesta adecuada que permiten que se considere, en este grupo de pacientes, como el manejo de primera línea.

Introduction

Prolactinomas are the most common secreting pituitary tumors, accounting for about 50% of all pituitary adenomas, they have an estimated prevalence of 50 per 100.000 individuals and incidence of 3 to 5 new cases/100.000 individuals/year; and a higher incidence in women of childbearing age (1, 2).

In men, approximately 80% of prolactinomas are larger than 10 mm (1, 2). The larger size and aggressiveness of the tumor in men compared to women impact the clinical presentation. Estrogens have been suggested to be a primary stimulus for prolactin secretion and pituitary adenoma formation (3), even though men have lower levels of estrogen, they have a higher expression of its receptors in tumors (4). However, it has been reported that the most aggressive prolactinomas in men are negative for estrogen receptors, so it could be considered that given the alteration of the regulatory mechanisms, estrogen receptors are not essential for the production of prolactin and other paracrine factors could be important, such as the local conversion of testosterone to estrogen in the pituitary gland mediated by the aromatase enzyme (4, 5). For men, half of the symptoms depend on the tumor mass, including headache and visual disturbances, while the other half are symptoms of hypogonadism, such as loss of libido, erectile dysfunction, gynecomastia, infertility, or osteopenia (1, 6).

Dopamine agonists are well-tolerated drugs in the management of prolactinomas they are effective in lowering prolactin levels, reducing tumor size and controlling clinical symptoms, therefore they are the first treatment option. Of these, cabergoline is the drug of choice because at a dose of 1 mg per week it achieves normalization of serum prolactin levels in 90% of cases of microadenomas and 80% in macroadenomas, in which a reduction in tumor size of 80% is obtained (7, 8). In micro and macroprolactinomas, dopamine agonists are the standard of care (7), including those considered invasive, which also respond with a rapid decrease in tumor volume and prolactin levels (9). In some cases, there may be resistance to dopamine agonists, in the case of bromocriptine it is defined as the failure to

normalize prolactin levels despite administering 15 mg/day of bromocriptine for three months, while resistance to cabergoline is the failure in normalizing prolactin levels and/or reducing tumor size by less than 50% despite administering it at 2.0 mg/week (10). A small proportion of patients are resistant to management with dopamine agonists, despite increasing the dose, especially those with a prolactinoma that invades the cavernous sinus (7, 11). Finally, in prolactinomas with mass effect surgery or radiosurgery may be indicated, however, there is a greater probability of hypopituitarism and recurrence (12). Other indications for surgical treatment include intolerance to the side effects of medications, the desire to become pregnant, or those related to the patient's preference (13).

Yoo *et al.* (13) described that men undergoing resection surgery were less likely to normalize serum prolactin levels, since the tumor is more aggressive and is able to spread to the suprasellar region or the cavernous sinus. In the review by Penn *et al.* (14) they showed that even though surgical treatment of prolactinoma is a safe procedure, with efficacy in hormonal and symptom control, it is less likely that it will not remit with surgery alone in men.

For Colombia and the rest of Latin America, the evidence in the literature on the results of treatment with dopaminergic agonists and the indications for surgical management is less solid, however, in some cases the difference in the schemes used with the use of bromocriptine or cabergoline and a different cumulative dose of the drug, have made the results contrast with those of other series of patients with prolactinomas (10, 15). Therefore, with this work we intend to show our experience on the effectiveness of the treatment of macroprolactinoma in 30 patients from Habana, Cuba (Hypophysis Clinic – Diseases of the National Institute of Endocrinology) and in Cali, Colombia (Imbanaco Clinic).

Patients and methods

In this retrospective cohort study, data were taken from the medical records of male patients diagnosed with invasive macroprolactinoma between 2002 and 2017. Twenty-one patients

were obtained from the National Institute of Endocrinology, in Habana, Cuba, and nine from the Imbanaco Clinic in Cali, Colombia.

The demographic and clinical characteristics of every patient were extracted. Magnetic resonance imaging (MRI) or computerized axial tomography (CAT) were performed to evaluate anatomical images of the hypothalamic-pituitary region. Two researchers separately performed the measurements of the diameters of macroadenomas, to compare before and after the therapy used in each patient.

The degree of alteration in pituitary function prior to and 6–12 months after the therapeutic intervention used in the patients was determined. The endocrinology departments of the Imbanaco Clinic in Cali, Colombia and the National Institute of Endocrinology in Habana, Cuba authorized this research.

Data management and statistical analysis

The characteristics of the patients are reported, presented with means and standard

deviation, and those that are not normal will be presented with median and interquartile ranges. A univariate analysis was performed to determine the behavior of the numerical variables, the normality of the variables will be determined through a Shapiro Wilk test, those with a $p > 0.05$ are considered to have a normal distribution. If the distribution was normal, they were evaluated with the Student's t-test; otherwise Kruskal Wallis was used. Response to treatment was evaluated and compared using the Kolmogorov-Smirnov test. A threshold of significance was adopted for all tests $p < 0.05$. Data storage was performed in Excel 2013 and analysis with the statistical package Stata 16[®].

Results

A total of 30 male patients with invasive macroprolactinoma diagnoses were evaluated. The mean age was $44.2 \text{ SD} \pm 13.8$ years, and the disease duration was $5.2 \text{ SD} \pm 4.1$ years (Table 1). Among the symptoms analyzed, patients presented: headaches (96%), hypopituitarism (80%), visual disturbances (76%), asthenia

Table 1. Description of demographic characteristics of patients with macroprolactinoma diagnosis (2004–2014)

Characteristic	Total (n=30) Mean \pm SD*	Min* – Max*
Age	44.2 \pm 13.8	(10 – 72)
Weight (Kg)*	82.7 \pm 14.7	(56 – 117)
Height (cmts)*	171.2 \pm 7.2	(157 – 195)
BMI (Kg/m ²)*	28.1 \pm 3.7	(22 – 38.5)
Evolution time (years)	5.2 \pm 4.1	(1 – 14)
Systolic blood pressure (mm/Hg)*	119.2 \pm 16	(90 – 148)
Diastolic blood pressure (mm/Hg)*	76.5 \pm 9.2	(60 – 90)

Note: Kg: kilograms; cmts: centimeters; m: meters; mmHg: millimetres of mercury; SD: standard deviation; Min: minim; Max: maxim

Source: The authors

(73%), gynecomastia, infertility and unilateral amaurosis (30%), erectile dysfunction and a decreased libido (26%), and galactorrhea (20%). (Table 2).

On its first visit, the more affected axis was the gonadal one (testosterone), followed by the somatotrophic, corticotropic, and thyrotropic (70, 25, 15, and 10% respectively) (Table 3). In the laboratory results the median

serum prolactin level at admission was 487 µg/L, and FSH/LH was 1.89/2.51 mUI/ml, respectively. The mean serum cortisol level was 9.5 SD±6.7 µg/dl, TSH was 2.1 SD±1.6 mU/L, and testosterone was 3.6 SD±3.1 nmol/L. The mean macroprolactinoma diameters size before treatment were 26.1 SD±10.3 (anteroposterior), 37.7 SD±11.5 (vertical), and 22.0 SD±6.3 (lateral) (Table 4).

Table 2. Clinical and paraclinical characteristics of men with macroprolactinoma diagnosis (2004–2014)

Patient's presentation	n=30	(%)
Headache	29	(96%)
Hypopituitarism	24	(80%)
Partial	15	(50%)
Complete	9	(30%)
Visual disturbances	23	(76%)
Asthenia	22	(73%)
Gynecomastia	9	(30%)
Infertility	9	(30%)
Amaurosis	9	(30%)
Unilateral	9	(30%)
Bilateral	0	(0%)
Erectile dysfunction	8	(26%)
Decreased libido	8	(26%)
Diabetes insipidus	6	(20%)
Transitory	3	(10%)
Permanent	3	(10%)
Galactorrhea	6	(20%)
Arachnoidocele	6	(20%)
CSF Rhinorrhea	1	(3%)

Source: The authors

Table 3. Affected pituitary axis of men with macroprolactinoma diagnosis (2004–2014)

Affected pituitary axis at first visit (%)	# patients (%)
Gonadal	21 (70%)
Somatotroph	8 (25%)
Corticotroph	5 (15%)
Thyrotroph	3 (10%)

Note: The definition of the commitment of each axis was adjusted by age

Source: The authors

Table 4. Laboratory results and imaging characteristics before treatment of men with macroprolactinoma diagnosis (2004–2014)

Laboratory and imaging tests	Total (n=30) Mean \pm SD*	Min* – Max*
Cortisol ($\mu\text{g/dl}$)	9.5 \pm 6.7	(1.5 – 35)
TSH (mU/L)	2.1 \pm 1.6	(0.1 – 7.6)
T4 (nmol/L)	77 \pm 32.8	(13.6 – 140)
T3 (nmol/L)	1.6 \pm 0.6	(0.8 – 2.6)
Testosterone (nmol/L)	3.6 \pm 3.1	(0.2 – 15.8)
	Median	Min – Max
Prolactin ($\mu\text{g/L}$)	487	(146 – 5009)
FSH (mUI/ml)	1.89	(0.2 – 21)
LH (mUI/ml)	2.51	(0.45 – 12)
Macroprolactinoma diameter size before treatment (mm)	Mean \pm SD	Min – Max
Anteroposterior	26.7 \pm 10.3	(12 – 61)
Vertical	34.7 \pm 11.5	(8 – 62)
Lateral	22.0 \pm 6.3	(13 – 40)

Note: SD: standard deviation; Min: minim; Max: maxim; * at first visit

Source: The authors

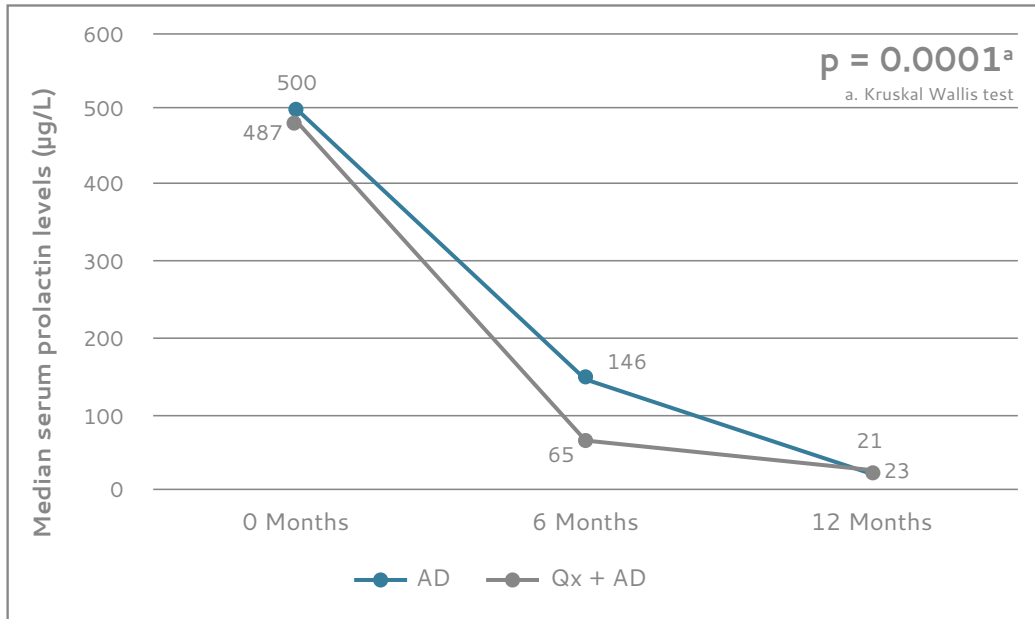


Figure 1. Median serum prolactin levels ($\mu\text{g/L}$) according to the therapeutic intervention of men with macroprolactinoma diagnosis

Note: A statistically significant difference is observed at 6 months of treatment.

Source: The authors

Regarding therapeutic intervention 53.3% required surgery plus dopamine agonists. Most of the patients (10/16 – 62%) had transcranial surgery and received cabergoline, followed by (3/16 – 19%) who had trans-sphenoidal surgery plus treatment with bromocriptine. Serum prolactin at six months decreased by 86% in the group that required surgery plus dopamine agonists and by 96% at twelve months. In the dopamine agonist group, (11/14 – 79%) of patients received cabergoline and (3/14 – 21%) of patients received bromocriptine; serum prolactin decreased significantly by 71% at six months and 95% at twelve months ($p = 0.0001$) (Figure 1). However, in patients who received surgery

plus dopamine agonists, we observed a greater reduction in prolactin levels at six months (Table 5 and 1).

In both treatments, the linear trend of the mean decrease of the anteroposterior, vertical and lateral diameters was observed at twelve months. When categorized, according to therapeutic intervention, the surgical plus dopamine agonists group got the most significant tumor size reduction at 12 months: <11.4mm vs. <8.3mm (anteroposterior diameter), <23mm vs <17.9mm (vertical diameter) and <8.7mm vs <3.2mm (lateral diameter), showing statistically significant differences ($p = <0.000$) (Table 6).

Table 5. Therapeutic intervention in male patients with invasive macroprolactinoma (2004–2014)

Therapy	n=30	(%)
Surgery + DA*	16	
Trans-sphenoidal surgery + BRC*	3	(19%)
Trans-sphenoidal surgery + CAB*	2	(13%)
Transcranial surgery + BRC*	1	(6%)
Transcranial surgery + CAB*	10	(62%)
DA*	14	
BRC*	3	(21%)
CAB*	11	(79%)

Note: DA: Dopamine agonists; BRC: Bromocriptine; CAB: Cabergoline

Source: The authors

Table 6. Mean tumor diameter according to the therapeutic intervention of men with macroprolactinoma diagnosis (2004–2014)

Diameter (mm)	Surgery + DA*			DA*		
	Baseline	12 m	p value	Baseline	12 m	p value
Antero-posterior	26.7	15.3	<0.000 a	26	17.7	0.0003 a
Vertical	35	12	<0.000 a	34.6	16.7	0.0001 a
Lateral	23.7	15	<0.000 a	19.9	16.7	0.22 a

Note: *DA: Dopamine Agonist. a. T de Student test

Source: The authors

Discussion

Prolactinomas have a prevalence of 50 per 100.000 and an incidence of 3 to 5 new cases/100.000/year, mean age of 44 +/- 13.8 years at diagnosis, and greater frequency in women (16).

In our study with 30 patients we found that the most frequent symptom in men was headache, in 29 patients (96%), which is consistent with the evidence in the literature, in which the presenting symptoms in males were due to symptoms of sellar mass effect in 93.18% (n=41; headache in 33, visual field defect in 17) (17). Prolactinoma occurs more frequently in women, but men may present some symptoms secondary to prolactinoma as a result of the effect of excess prolactin or the occupation of space by the tumor mass. Male patients may present decreased libido, erectile dysfunction, infertility and gynecomastia in rare cases. These symptoms occurred in our series in 26%, 26% and 30%, respectively (5, 18). In the pediatric population, delayed puberty, gynecomastia, and galactorrhea are part of the clinical manifestations, however, they more frequently present with neuro-ophthalmological signs (visual disturbances, headaches, etc.) due to mass effect, as in adults, given the higher incidence of macroadenomas (4). A 10-year-old boy was included in our cohort, because his diagnosis was late due to the fact that he only presented a headache, without alteration in pubertal development, similar to the clinical course in adults.

In this group, we noticed that a wide range in the prolactin levels and a decrease of the other hormones studied expressed complete or partial hypopituitarism in most patients (30 and 50%, respectively), in accordance to Iglesias P *et al.*, who described that macroprolactinomas were related with hypopituitarism in 78% to the diagnosis (16).

Testosterone levels were low in male patients with macroprolactinoma and hyperprolactinemia, with an inverse relation to prolactin levels (19). Although hyperprolactinemia may be a fundamental cause of hypogonadism due to suppression of pulsatile GnRH (20), we cannot rule out any gonadotropic hypofunction from

the mass or compressive effect of these invasive adenomas.

Similarly, the most commonly associated pituitary axis affected was the gonadal, which is consistent with the registry of 35 men with macroprolactinoma from 1980 to 2001 who received medical treatment, where the gonadal axis was the most affected. (21).

Therefore, the fact that the symptoms are more subtle in men generates a delay in the diagnosis of macroprolactinomas (1). However, the literature suggests that prolactinoma is larger and generates more compressive symptoms, invasiveness and resistance to medical treatment in men (22). In our case, the degree of invasiveness of macroadenoma was broad, with a higher frequency in suprasellar growth and sphenoidal sinus, and less frequently in the lateral invasion to cavernous sinuses.

In our case series, the most frequent approach was transcranial surgery, associated with dopaminergic agonists (more frequently cabergoline). In patients who decided to use medical treatment, the drug of choice of dopaminergic agonists was cabergoline, which contrasts with a previous study of prolactinomas in men, where the most frequent approach was the transsphenoidal surgery with cabergoline (16). The first-line dopaminergic agonist in these patients is cabergoline. It is more effective than other dopamine agonists because of its long-lasting effect, greater inhibitory potency on tumor size and prolactin levels, and fewer collateral effects (9, 20). Cabergoline has a longer half-life that reaches almost 65 hours with a higher affinity for D2 receptors sites. Thus, the duration of action is maintained up to seven days after oral administration, compared to bromocriptine, which has a duration of action of one day (21).

Lower response to dopamine agonists has been reported in those patients with macrotumor invasion in cavernous sinuses (23, 24), which coincides with our results. When evaluating the decrease in the diameters at twelve months, the average lateral diameter of the macroadenoma was the one with the lowest decrease, and not significant statistically ($p = 0.22$) when compared to the anteroposterior and vertical diameters (and

significant statistically). Additionally, prolactin levels decreased significantly after one year of treatment with dopamine agonists, maintaining a gradual and sustained reduction.

There are no randomized controlled trials that have compared medical treatment with surgical resection of prolactinoma, and publications with an evolutionary evaluation of invasive macroprolactinoma in male patients are not so frequent (8, 23, 24). Therefore, we consider that the descriptive results of this study can provide essential elements contributing to a better medical intervention for these patients.

In what has been reported, pharmacological treatment and those patients who received a twelve-month surgical intervention, significantly reduced the level of serum prolactin. There was a statistically significant tumor size reduction in anteroposterior, vertical, and lateral diameters; however, there was a more significant reduction in those that received surgery. Nevertheless, we must consider that for prolactinomas (microadenomas, macroadenomas and those considered invasive), dopaminergic agonists are the therapy of choice (9, 25), and in patients with resistance to pharmacological treatment, even with the increase in the dose of dopaminergic agonists, neurosurgery is an important treatment alternative (7).

Initial tumor volume was directly related to prolactin levels, the higher the volume, the higher the hormone levels. Additionally, the lowest hormone levels matched the lower mean tumor volume after treatment. The treatment of choice in male patients with invasive macroprolactinoma is dopaminergic agonists, which was observed in a previous study where treatment with dopaminergic agonists alone reduced tumor volume by 78.7% and at the end of follow-up, normality was not reached in serum prolactin level in 83.3% (16).

In some studies, at diagnosis serum prolactin and tumor diameter were higher, and the rate of recurrence of prolactinoma was higher in men at follow-up at 24 and 96 months after stopping cabergoline (63% vs. 32%, respectively; $p < 0.001$) (26). In addition to selection bias, our study has

another limitation, to estimate recurrence rates in patients an extension in follow-up time is required.

Although the sample size was small, it was possible to demonstrate a statistically significant improvement in the parameters of decreased serum prolactin level and tumor size reduction, regardless of the intervention. A greater improvement was obtained in the first 6 months in patients with surgical treatment ($p = 0.0001$), however there was no significant difference at one year of follow-up.

The similar results in the control of hyperprolactinemia with surgery lead us to consider the direct surgical approach as an alternative to dopaminergic agonist therapy, especially in those patients in whom the tumors do not invade the cavernous sinus, with intolerance or insufficient response to pharmacological treatment.

Conclusion

Our study demonstrated the efficacy of both, medical management with dopaminergic agonists and surgical procedures, in terms of reducing serum prolactin levels and tumor size; however, this reduction was significantly greater in patients who required surgery. At the moment, dopaminergic agonists are considered the first-line treatment in men with invasive macroprolactinomas, which is consistent with the results of our study. Surgical management is reserved for a second line of treatment in patients with intolerance or insufficient response to dopamine agonist therapy.

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Conflicts of interest

The authors of this research declare that there are no conflicts of interest that may affect the content, results or conclusions of the article.

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