

Reappraising the Role of Trans-Sphenoidal Surgery in Prolactin-Secreting Pituitary Tumors.

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Abstract

Backgrounds: Prolactinomas represent a unique challenge for endocrinologists and neurosurgeons. Considering recent innovations in surgical practice, the authors aimed to investigate the best management for prolactinomas.

Methods: A retrospective, cross-sectional and monocentric study was designed. Consecutive patients affected for prolactinomas were enrolled if treated with first line treatment with dopamine-agonist (DA) or trans-sphenoidal surgery (TS). Patients carried giant prolactinomas and those with a follow-up < 12 months were excluded.

Results: 259 patients were enrolled. The first treatment was DA for 140 patients and TS for 119 cases. 146 of 249 patients (58.6%) needed a second therapy. Mean follow up was 102.2 months (12-438 months). Surgery highly impacted on the cure rate, in particular in females ($p=0.0021$) and in microprolactinomas ($p=0.0020$). Considering multivariate analysis, female gender and surgical treatment in the course of clinical history were the only independent positive predictors of cure at the end of 5 years follow-up ($p=0.0016$, $p=0.0005$). The evaluation of serum prolactin (24 hours after TS) revealed that 86.4% of patients with post-operative $PRL \leq 10$ ng/ml resulted cured at the end of follow-up ($p < 0.0001$).

Conclusion: According to our experience, surgery allows a high cure rate of prolactinomas, particularly in females with microadenoma, with a good safety profile. TS for prolactinomas should be considered as concrete option, during the multidisciplinary evaluation, in centers of reference for pituitary diseases.

Introduction

Pituitary adenomas, or pituitary neuroendocrine tumors (WHO 2017), account for 10% to 15% of primary intracranial neoplasms. Among secreting pituitary tumors, prolactinomas are the most common (40-50% of total) [1]. Prolactinomas, with their various biological and clinical features, might represent an oncological and neurosurgical challenge. Dopamine agonists (DA) are considered as first-line treatment due to their efficacy and safety profile, [2,3] while trans-sphenoidal surgery (TSS) has been confined to failure of medical therapy, pituitary apoplexy with neurological worsening, and prolactinomas with wide cystic component. [4]. However, data on definitive cure with DA are debated, [2,4] and many patients remain on life-long therapy to avoid disease relapse. On the other hand, several papers report good results with TSS as first-line therapy for prolactinomas [5-8]. Moreover, the recent technical innovations introduced in TSS, such as high-definition surgical endoscopes and extremely reliable neuronavigation systems, have made possible to further expand the surgical possibilities and to obtain better results as complete tumor resection with lower complication rates. [9] Thus, in the neuro-oncological/endocrinological community, a debate on the possibility to expand the traditional indications of TSS as first-line treatment for prolactinomas is alive. [10,11]

In the present study, we conducted a thorough analysis of our surgical and medical experience of over 25 years in the treatment of prolactinomas with the aim to verify the role of surgery.

Methods

Study Design

We conducted a retrospective and cross-sectional study, reviewing the clinical, radiological and surgical charts of consecutive patients enrolled according to the following inclusion criteria: 1) Diagnosis of prolactinoma; 2) Treatment with DA (cabergoline or bromocriptine) or/and with neurosurgical operation via TSS (either endonasal endoscopic or sublabial microsurgical); 3) Diagnosis and treatment of prolactinomas conducted at our Institution between January 1st, 1992 and December 31, 2016.

Were excluded from the study: 1) Patients carrying giant prolactinomas (diameter > 4 cm); 2) Patients with a follow-up shorter than 12 months.

All the patients provided the informed consent agreeing to research principles of Institutional Ethics Committee.

Clinical management of patients

For each patient, diagnosis of prolactinoma was made following the international guidelines [4]. All patients diagnosed having a prolactinoma were evaluated by a multidisciplinary team with a neuro-endocrinologist and a neurosurgeon. According to Klibanski [12], TSS was offered as first line treatment in case of pituitary apoplexy, and macroprolactinomas in patients with a psychiatric disorder (for which dopamine agonists are contraindicated); contrarily to Klibansky, we recommended surgery as first choice even in macroadenomas determining visual field defects and in case of microadenomas in fertile women with a pregnancy desire. Each time, therapeutic strategy was jointly discussed between endocrinologists, neurosurgeons and the patient, considering risks and benefits, with the final choice based upon the patient's preference.

Follow-up

During the follow-up, all patients underwent: prolactin dosage, one and three months after pituitary surgery/start of DA therapy, and then every six months; pituitary MRI, three and six months after pituitary surgery/start of DA therapy, and then every year.

Outcome at the end of follow was classified as: 1) cured: in cases of regression of clinical symptoms, normalization of basal prolactin levels (below the gender-specific normal upper limit) and absence of neuroradiological evidence of residual/recurrent tumor, after at least 12 months from neurosurgical treatment or DA discontinuation; 2) controlled disease: in cases with normal serum PRL concentration and stable neuroimaging, during DA therapy; 3) uncontrolled disease: in cases with high serum PRL concentration (above the gender-specific normal upper limit) and/or tumor progression on neuroimaging, during DA therapy. Outcomes 2) and 3) were grouped into "not cured".

Statistical analysis

Continuous variables were expressed as mean (range), categorical variables as absolute and relative frequency. Comparison of continuous variables between groups was performed using the Mann-Whitney *U* test. Comparison of categorical variables was performed by chi-square statistic using the Fisher exact test when appropriate. A multivariate analysis model was built using logistic regression to calculate the Odds Ratio (OR) of cure, by adjusting for the following parameters: size of the adenoma, gender, surgical treatment in the course of clinical history, type of first treatment, cavernous sinus invasion. A $p < 0.05$ was considered significant. A ROC curve was built to assess the diagnostic accuracy for cure of post-operative serum prolactin; the value with the highest Youden index [sensitivity-(1-specificity)] was designed as best cut-off. StatView ver 5.0 software was used (SAS Institute, Cary, NC).

Results

Patient Population

Among all patients treated for prolactinoma at our Institution in the study period, 259 (164 women and 95 men) fulfilled the criteria for enrollment in the present study. Baseline characteristics of patients are detailed in Table 1. Sixtyfour % of female patients were affected by microadenomas, whereas the majority of male patients harbored a macroadenoma (78.9%; $p < 0.0001$, Fisher exact test). Mean age was 35.2 years; females were significantly younger than males ($p < 0.0001$, Mann-Whitney *U* test). Mean follow-up was 102.2 months (range, 12-438 months) and did not differ significantly between genders.

At last follow-up, 113 patients (43.6% of cases) were considered cured. The remaining 146 patients (56.4 %) were not cured, carrying either a controlled or an uncontrolled disease.

Impact of surgery as first-line treatment

Surgery as first-line treatment was offered to 45.9% of patients and detailed data are provided in Table 1. Overall, surgery as first-line treatment did not significantly impact on rate of cure (Table 2). Female patients harboring microadenoma built up the subgroup of patients taking the best advantage from surgery as first therapy.

Impact of surgery as second-line treatment

About half of the patients initially treated with DA received surgery as second-line treatment due to intolerance or resistance to medical therapy. Thus, overall, 194 out of 259 patients (74.9%) were surgically treated during the study period. Surgery determined a significant increase in rate of cure than DA alone in the whole cohort (50% vs 24.6%, $p = 0.0005$, Fisher Exact Test). As detailed in Table 2, female patients, particularly those harboring microadenoma, had still the best advantage from surgery. Contrarily, surgery was not beneficial in males in terms of cure rate.

Adjustment for other factors impacting the rate of cure

We then aimed at assessing the other parameters which had an impact on final rate of cure. Results are shown in Table 3. Females ($p<0.001$), patients carrying microadenomas ($p=0.0057$) and not-cavernous sinus invasive adenomas (Knosp 0-II vs III-IV, $p=0.02$) had a higher cure rate at the end of follow-up.

At multivariate analysis, surgery (either as first or second-line), female sex and microadenoma emerged as independent prognosticator of cure at the end of follow-up (Table 3). Noteworthy, among these factors, surgery was the most significant ($p<0.0001$) and had the highest odds ratio for cure (5.1).

Validation of results in long follow-up patients

In order to validate the results on the positive role of surgery for cure in prolactinomas, we explored the results on those patients with follow-up of at least 5 years.

One hundred sixty-four patients met this criterion, 128 of which had undergone TSS (as first-line or as second-line treatment). As shown in Table 4, TSS determined a significant increase in cure rate both at univariate ($p=0.0042$) and at multivariate analysis ($p=0.0005$), thus confirming our findings.

Surgical complications

No deaths occurred. The overall surgical complications rate was 3,6%. In detail: 2 patients (1.0%) had nasal aesthetic changes; 4 (2.1%) had CSF leak needing reoperation; 3 (1.5%) needed chronic steroid replacement therapy, 2 of them also desmopressin.

Selection biases

Due to the non-randomized design of the study, surgery was not homogeneously distributed among subgroups. As shown in Table 1, TSS was more frequent in males than in females (both as first-line treatment, $p>0.0001$, and during the disease course, $p=0.0045$) and in macroadenomas than in microadenomas ($p<0.0001$ both as first- and second-line), whereas cavernous sinus invasion was homogeneously distributed among groups.

1st Day post-operative serum PRL as biomarker for cure

The dosage of PRL conducted in fasting condition, in the morning of the first day after surgery was significantly lower in cured vs not cured patients ($p<0.0001$, Mann-Whitney U test; Figure 1). The best cut-off was set at 37.5 ng/ml. Moreover, by applying a clinically relevant cut-off value of 10 ng/ml, 86.4% of patients with lower values vs 27.3% of patients with higher values resulted to be cured at the end of follow-up ($p<0.0001$, Fisher exact test).

Discussion

In this study, we investigated the role of TSS in the treatment of prolactinomas, reviewing our cohort of patients that had been managed with surgical and/or medical therapies, over a period of 25 years.

Our findings demonstrate that patients in which the adenoma was surgically removed had the highest probability of reaching the cure. In fact, in this cohort of patients, TSS acts as an independent positive prognostic factor for cure of prolactinomas, together with female gender and microadenoma. Notably, in patients with follow-up longer than 5 years, the only independent positive prognosticators for cure remained surgery and female sex, thus confirming our assumption. Moreover, the prognostic value of surgery was independent from timing, thus highlighting its role also when performed as a second-line treatment, after DA failure.

Notably, our results allow to identify a group of patients that may strongly benefit by surgical removal of prolactinomas. In fact, we showed that female patients treated with first-line surgery had the higher rate of cure, regardless of tumor dimension; among them, women harboring microadenoma were the subgroup mostly benefiting from surgery (Table 2).

According to current guidelines [4], the first-line therapeutic choice for prolactinoma is the medical therapy with DA, whereas surgery is usually confined to a complementary therapy for patients resistant to DA. However, recent studies have proved that a recurrence of prolactinoma may be observed in 20-77% of cases after the withdrawal of DA [13], matching with tumoral dimension, invasion of cavernous sinus, nadir prolactin value reached during DA treatment [14], persistence of tumoral residual disease and duration of treatment with DA [15].

Our evidences are in line with what published by high-volume centers [10,16-27]: TSS is linked to low surgical complications, and a remission rate of about 80% and 40% respectively for micro and macroprolactinomas. Consistently, Andereggen et al. [28] showed that at 10 years follow-up, the control of hyperprolactinaemia required DA-agonist therapy in 32% of patients who underwent primary surgical therapy and in 64% of patients who had primary medical therapy and that the primary surgical therapy is a protective factor for long-term treatment with DA.

Then, it has been suggested that surgical removal of the adenoma should be part of the patients counselling for the decision of the initial treatment, due to the low morbidity of this procedure, if performed by an experienced neurosurgeon [29]. In addition, the available of tumoral tissue may allow a detailed pathological analysis, for investigating both biomarkers of aggressiveness, as Ki67, p53, mitotic count, minichromosome maintenance 7 (MCM7) and estrogen receptors, and biomarkers of treatment response, as dopamine and somatostatin receptors [30-33]. In fact, a very detailed pathological analysis may facilitate the identification of cases with high risk of recurrence and may orient towards a personalized therapy, in particular in cases of difficult and aggressive prolactinomas [34].

The main limitation of our study are its retrospective design and the lack of randomization. The main selection biases were the prevalence of males and macroadenomas in surgical patients, probably due to visual disturbances as a reason for surgery. However, this study describes a real life scenario of a large and monocentric series of patients, managed at a historical pituitary unit with a long-standing commitment on research about prolactin in physiological and pathological conditions [35-43]. Moreover, multivariate analysis is expected to reduce biases. Another limitation is that, in this study, the complex

endocrine syndrome induced by prolactinomas has not been analyzed: focusing on a few selected serological and neuro-radiological aspects of the illness was essential in order to reliably analyze a considerable number of patients with a long follow-up.

Among the strong points of the study, though collected in a 25-year timeframe, our monocentric series is highly homogeneous as concerns indications, treatment, and follow-up. To further reduce the confounding factors of our analysis, giant prolactinomas have been excluded, because in such invasive cases a multimodality treatment, including radiotherapy and life-long DA, is often required.

In conclusion, TSS may represent a valid alternative to DA therapy, particularly in females with microadenomas, as provides the highest chance to cure at long-term follow-up.

Concurring with aforementioned reports, our experience prompts surgery among the first-line possible treatments for the management of prolactinomas in reference centers.

Declarations

Funding: No funding was received for this research.

Conflict of Interest: All authors certify that they have no affiliations

with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical Approval: The study was approved by local ethics committee. The study was conducted according to the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Authors' Contribution: Conceptualization (Mattogno P.P., Lauretti L.), methodology (Mattogno P.P., Lauretti L., D'Alessandris Q.G., Chiloire S.), formal analysis (D'Alessandris Q.G.), data collection (Mattogno P.P., Chiloire S., Bianchi A., Giampietro A.), Draft preparation and editing (Mattogno P.P., D'Alessandris Q.G., Lauretti L., Chiloire S.), supervision (Pontecorvi A., Olivi A., De Marinis L., Anile C.).

Data availability statement: Source data are available from the corresponding author upon reasonable request.

References

1. Ezzat S, Asa SL, Couldwell WT, Barr CE, Dodge WE, Vance ML, McCutcheon IE. (2004) The prevalence of pituitary adenomas: a systematic review. *Cancer*. 101(3):613-9.
2. Colao A, Di Sarno A, Guerra E, Pivonello R, Cappabianca P, Caranci F, Elefante A, Cavallo LM, Briganti F, Cirillo S, Lombardi G. (2007) Predictors of remission of hyperprolactinaemia after long-term withdrawal of cabergoline therapy. *Clin Endocrinol (Oxf)*. 67(3):426-33.
3. Watanabe S, Takano S, Akutsu H, Sato H, Matsumura A. (2011) [Prolactinoma treatment status in the cabergoline era](#). *No Shinkei Geka*. 39(11):1045-54.
4. Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, Wass JA; Endocrine Society. (2011) Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 96(2):273-88. doi: 10.1210/jc.2010-1692.
5. [Akin S](#), [Isikay I](#), [Soylemezoglu F](#), [Yucel T](#), [Gurlek A](#), [Berker M](#). (2016) Reasons and results of endoscopic surgery for prolactinomas: 142 surgical cases. *Acta Neurochir (Wien)*. 158(5):933-4.
6. [Song YJ](#), [Chen MT](#), [Lian W](#), et al. (2017) Surgical treatment for male prolactinoma: A retrospective study of 184 cases. *Medicine (Baltimore)*. 96(2):e5833.
7. Menucci M, Quiñones-Hinojosa A, Burger P, Salvatori R. Effect of dopaminergic drug treatment on surgical findings in prolactinomas. *Pituitary*. 2011 Mar;14(1):68-74. doi: 10.1007/s11102-010-0261-4.
8. Zamanipoor Najafabadi AH, Zandbergen IM, et al. Surgery as a Viable Alternative First-Line Treatment for Prolactinoma Patients. A Systematic Review and Meta-Analysis. *J Clin Endocrinol Metab*. 2020 Mar 1;105(3):e32–41.
9. Lauretti L, D'Alessandris QG, Rigante M, Ricciardi L, Mattogno PP, Olivi A. (2018) O-arm in Endonasal Endoscopic Cranial Base Surgery: Technical Note on Initial Feasibility. *World Neurosurg*. 117:103-108.
10. Behan LA, Moyles P, Cuesta M, Rogers B, Crowley RK, Ryan J, Brennan P, Smith D, Tormey W, Sherlock M, Thompson CJ. (2017) The incidence of anterior pituitary hormone deficiencies in patients with microprolactinoma and idiopathic hyperprolactinaemia. *Clin Endocrinol (Oxf)*. 87(3):257-263.
11. Micko A, Vila G, Höftberger R, Knosp E, Wolfsberger S. (2019) Endoscopic Transsphenoidal Surgery of Microprolactinomas: A Reappraisal of Cure Rate Based on Radiological Criteria. *Neurosurgery*. 1;85(4):508-515.
12. Klibanski A. (2010) Clinical practice. Prolactinomas. *N Engl J Med*. 362(13):1219-26.
13. Sala E, Bellaviti Buttoni P, Malchiodi E, Verrua E, Carosi G, Profka E, Rodari G, Filopanti M, Ferrante E, Spada A, Mantovani G. (2016) Recurrence of hyperprolactinemia following dopamine agonist withdrawal and possible predictive factors of recurrence in prolactinomas. *J Endocrinol Invest*. 29(12) 1377-1381.
14. Chanson P, Maiter D. (2017) “ Prolactinoma” in Melmed S. Eds. *The Pituitary 4th Edition*, Elsevier; 467-514.
15. Ji MJ, Kim JH, Lee JH, Lee JH, Kim YH, Paek SH, Shin CS, Kim Sy. (2017) Best candidates for dopamine agonist withdrawal in patients with prolactinomas. *Pituitary*. 20, 578-584.

16. Babey M, Sahli R, Vajtai I, Andres RH, Seiler RW. (2011) Pituitary Surgery for Small Prolactinomas as an Alternative to Treatment With Dopamine Agonists. *Pituitary*. 14 (3), 222-30.
17. Hamilton DK, Vance ML, Boulos PT, Laws ER. (2005) Surgical Outcomes in Hyporesponsive Prolactinomas: Analysis of Patients With Resistance or Intolerance to Dopamine Agonists. *Pituitary*, 8 (1), 53-60.
18. Ikeda H, Watanabe K, Tominaga T, Yoshimoto T. (2013) Transsphenoidal Microsurgical Results of Female Patients with Prolactinomas. *Clin Neurol Neurosurg*. 115 (9), 1621-5.
19. Kreutzer J, Buslei R, Wallaschofski H, Hofmann B, Nimsky C, Fahlbusch R, Buchfelder M. (2008) Operative Treatment of Prolactinomas: Indications and Results in a Current Consecutive Series of 212 Patients. *Eur J Endocrinol*. 158 (1); 11-8.
20. Loyo-Varela M, Herrada-Pineda T, Revilla-Pacheco F, Manrique-Guzman S. (2013) Pituitary Tumor Surgery: Review of 3004 Cases. *World Neurosurg*. 79 (2), 331-6.
21. Paluzzi A, Fernandez-Miranda JC, Stefko ST, Challinor S, Snyderman CH, Gardner PA. (2014) Endoscopic Endonasal Approach for Pituitary Adenomas: A Series of 555 Patients. *Pituitary*. 17 (4), 307-19.
22. Primeau V, Raftopoulos C, Maiter D. (2012) Outcomes of Transsphenoidal Surgery in Prolactinomas: Improvement of Hormonal Control in Dopamine Agonist-Resistant Patients. *Eur J Endocrinol*. 166 (5), 779-86.
23. Qu X, Wang M, Wang G, Han T, Mou C, Han L, Jiang M, Qu Y, Zhang M, Pang Q, Xu G. (2011) Surgical Outcomes and Prognostic Factors of Transsphenoidal Surgery for Prolactinoma in Men: A Single-Center Experience With 87 Consecutive Cases. *Eur J Endocrinol*. 164 (4), 499-504.
24. Raverot G, Wierinckx A, Dantony E, Auger C, Chapas G, Villeneuve L, Brue T, Figarella-Branger D, Roy P, Jouanneau E, Jan M, Lachuer J, Trouillas J. (2010) Prognostic Factors in Prolactin Pituitary Tumors: Clinical, Histological, and Molecular Data From a Series of 94 Patients With a Long Postoperative Follow-Up. *J Clin Endocrinol Metab*. 95 (4), 1708-16.
25. Sinha S, Sharma BS, Mahapatra AK. (2011) Microsurgical Management of Prolactinomas - Clinical and Hormonal Outcome in a Series of 172 Cases. *Neurol India*. 59 (4), 532-6.
26. Sinkūnas K, Rastenyte D, Deltuva VP, Knispelis R, Tamasauskas A. (2007) Transsphenoidal Surgery for Prolactinomas: Results and Prognosis. *Medicina (Kaunas)*. 43 (9), 691-7.
27. Tamasauskas A, Sinkunas K, Bunevicius A, Radziunas A, Skiriute D, Deltuva VP. (2012) Transsphenoidal Surgery for Microprolactinomas in Women: Results and Prognosis. *Acta Neurochir (Wien)*. 154 (10), 1889-93.
28. Anderegg L, Frey J, Andres RH, et al. (2017) 10-year follow-up study comparing primary medical vs. surgical therapy in women with prolactinomas. 55(1):223-230.
29. Rutkowski MJ, Aghi MK. (2018) Medical versus surgical treatment of prolactinoma: an analysis of treatment outcomes. *Expert Rev Endocrinol Metab*. 13 (1), 25-33.
30. Chiloire S, Bianchi A, Doglietto F, de Waure C, Giampietro A, Fusco A, Iacovazzo D, Tartaglione L, Di Nardo F, Signorelli F, Lauriola L, Anile C, Rindi G, Maira G, Pontecorvi A, De Marinis L. (2014) Radically

- resected pituitary adenomas: prognostic role of Ki 67 labeling index in a monocentric retrospective series and literature review. *Pituitary* 17(3):267-76.
31. Coli A, Asa SA, Fadda G, Scannone D, Chiloiro S, De Marinis L, Lauretti L, Ranelletti L, Lauriola L. (2016) Minichromosome Maintenance Protein 7 as Prognostic Marker of Tumor Aggressiveness in Pituitary Adenoma Patients. *Eur J Endocrinol.* 174 (3); 307-14.
 32. Li CZ, Gui SB, Zong XY, Zhang YZ. (2015) The Expression of Estrogen Receptor Subtypes in Prolactinomas and Their Relationship to Tumor Biological Behavior. *Biomed Environ Sci.* 28(11):820-2.
 33. Shimazu S, Shimatsu A, Yamada S, Inoshita N, Nagamura Y, Usui T, Tsukada T. (2012) Resistance to Dopamine Agonists in Prolactinoma Is Correlated With Reduction of Dopamine D2 Receptor Long Isoform mRNA Levels. *Eur J Endocrinol.* 166(3):383-90. doi: 10.1530/EJE-11-0656.
 34. Trouillas J, Delgrange E, Wierinckx A, Vasiljevic A, Jouanneau E, Burman P, Raverot G. Clinical, Pathological, and Molecular Factors of Aggressiveness in Lactotroph Tumours. *Neuroendocrinology.* 2019;109(1):70-76. doi: 10.1159/000499382.
 35. Barbarino A, De Marinis L, Anile C, Menini E, Merlini G, Maira G. (1982) Dopaminergic Mechanisms Regulating Prolactin Secretion in Patients With Prolactin-Secreting Pituitary Adenoma. Long-term Studies After Selective Transsphenoidal Surgery. *31* (11), 1100-4.
 36. Barbarino A, De Marinis L, Maira G, Menini E, Anile C. (1978) Serum Prolactin Response to Thyrotropin-Releasing Hormone and Metoclopramide in Patients With Prolactin-Secreting Tumors Before and After Transsphenoidal Surgery. *J Clin Endocrinol Metab.* 47(5), 1148-51 .
 37. Barbarino A, De Marinis L, Mancini A, Menini E, D'Amico C, Passeri M, Sambo P, Anile C, Maira G. (1985) Prolactin Dynamics in Patients With Non-Secretin Tumours of the Hypothalamic-Pituitary Region. *Acta Endocrinol (Copenh).* 110 (1), 10-6.
 38. Barbarino A, De Marinis L, Menini E, Anile C, Maira G. (1979) Prolactin-secreting Pituitary Adenomas: Prolactin Dynamics Before and After Transsphenoidal Surgery. *Acta Endocrinol (Copenh),* 91 (3), 397-409.
 39. De Marinis L, Mancini A, Minnielli S, Masala R, Anile C, Maira G, Barbarino A. (1985) Evaluation of Dopaminergic Tone in Hyperprolactinemia. III. Thyroid-stimulating Hormone Response to Metoclopramide in Differential Diagnosis and Postoperative Follow-Up of Prolactinoma Patients. *Metabolism.* 34 (10), 917-22.
 40. Del Gatto V, Bima C, Chiloiro S, Giampietro A, Bianchi A. (2018) Use of ¹¹¹In-pentetreotide Scintigraphy for Diagnosis and Management of Resistant Macroprolactinoma. *Endocrine.* 60 (3), 532-534.
 41. Fusco A, Lugli F, Sacco E, Tilaro L, Bianchi A, Angelini F, Tofani A, Barini A, Lauriola L, Maira G, Pontecorvi A, De Marinis L. (2011) Efficacy of the Combined Cabergoline and Octreotide Treatment in a Case of a Dopamine-Agonist Resistant Macroprolactinoma. *14* (4), 351-7.
 42. Maira G, Anile C, De Marinis L, Barbarino A. (1989) Prolactin-secreting Adenomas: Surgical Results and Long-Term Follow-Up. *Neurosurgery,* 24 (5); 736-43.

43. Maira G, Anile C, De Marinis L, Barbarino A. (1990) Prolactin-secreting Adenomas–Surgical Results. Can J Neurol Sci. 17 (1), 67-70.

Tables

Table 1
Baseline characteristics of study patients and first-line treatments.

Group	Whole cohort	First-line treatment		Surgery	
		TSS	DA	Yes	No
n (%)	259 (100)	119 (45.9)	140 (54.1)	194 (74.9)	65 (25.1)
Female, n (%)	164 (63.3)	56 (34.1)	108 (65.9)	113 (68.9)	51 (31.1)
Male, n (%)	95 (36.7)	63 (66.3)	32 (33.7)	81 (85.3)	14 (14.7)
Microadenomas, n (%)	125 (48.3)	41 (32.8)	84 (67.2)	78 (62.4)	47 (37.6)
Macroadenomas, n (%)	134 (51.7)	78 (58.2)	56 (41.8)	116 (86.6)	18 (13.4)
Female: microadenomas, n (%)	105 (64.0)	29 (27.6)	76 (72.4)	62 (59.0)	43 (41.0)
Female: macroadenomas, n (%)	59 (36.0)	27 (45.8)	32 (54.2)	51 (86.4)	8 (13.6)
Male: microadenomas, n (%)	20 (21.1)	12 (60)	8 (40)	16 (80)	4 (20)
Male: macroadenomas, n (%)	75 (78.9)	51 (68)	24 (32)	65 (86.7)	10 (13.3)
Age, mean (range)(years)	35.2 (18–78)	35.6 (18–78)	34.8 (18–76)	33.9 (18–78)	38.9 (18–76)
Knosp: 0-II, n (%)	227 (87.3)	99 (83.2)	127 (90.7)	168 (74.3)	58 (25.7)
Knosp: III-IV, n (%)	33 (12.7)	20 (16.8)	13 (9.3)	26 (78.8)	7 (21.2)
Follow-up, mean (range) (months)	102.2 (12–438)	100.9 (12–438)	103.2 (12–420)	108.8 (12–438)	82.7 (12–300)

DA, dopamine-agonist; NA, not applicable; TSS, trans-sphenoidal surgery.

Table 2
Rate of cure depending on first treatment and surgery in the whole cohort

Rate of cure						
Group	First-line treatment		p*	Surgery		p*
	TSS, n (%)	DA, n (%)		yes	no	
Whole Cohort	56/119 (47.1)	57/140 (40.7)	0.3172	97/194 (50.0)	16/65 (24.6)	0.0005
Female	38/56 (67.9)	49/108 (45.4)	0.0081	72/113 (63.7)	15/51 (29.4)	< 0.0001
Male	18/63 (28.6)	8/32 (25)	0.8102	25/81 (30.9)	1/14 (7.1)	0.1026
Microadenomas	25/41 (61.0)	41/84 (48.8)	0.2530	52/78 (78.8)	14/47 (21.2)	< 0.0001
Macroadenomas	31/78 (39.7)	16/56 (28.6)	0.2028	45/116 (38.8)	2/18 (11.1)	0.0031
Female: microadenomas	20/29 (69.0)	37/76 (48.7)	0.0080	44/62 (71.0)	13/43 (30.2)	< 0.0001
Female: macroadenomas	18/27 (66.7)	12/32 (37.5)	0.0370	28/51 (54.9)	2/8 (25)	0.1455
Male: microadenomas	5/12 (41.7)	4/8 (50)	> 0.9999	8/16 (50)	1/4 (25)	0.5913
Male: macroadenomas	13/51 (25.5)	4/24 (16.7)	0.5566	17/65 (26.2)	0/10 (0)	0.1043

DA, dopamine-agonist; TSS, trans-sphenoidal surgery. *, Fisher exact test

Table 3
Rate of cure depending on first treatment and surgery in the whole cohort

	Rate of cure					
Group	First-line treatment		p*	Surgery		p*
	TSS, n (%)	DA, n (%)		yes	no	
Whole Cohort	56/119 (47.1)	57/140 (40.7)	0.3172	97/194 (50.0)	16/65 (24.6)	0.0005
Female	38/56 (67.9)	49/108 (45.4)	0.0081	72/113 (63.7)	15/51 (29.4)	< 0.0001
Male	18/63 (28.6)	8/32 (25)	0.8102	25/81 (30.9)	1/14 (7.1)	0.1026
Microadenomas	25/41 (61.0)	41/84 (48.8)	0.2530	52/78 (78.8)	14/47 (21.2)	< 0.0001
Macroadenomas	31/78 (39.7)	16/56 (28.6)	0.2028	45/116 (38.8)	2/18 (11.1)	0.00313
Female: microadenomas	20/29 (69.0)	37/76 (48.7)	0.0080	44/62 (71.0)	13/43 (30.2)	< 0.0001
Female: macroadenomas	18/27 (66.7)	12/32 (37.5)	0.0370	28/51 (54.9)	2/8 (25)	0.1455
Male: microadenomas	5/12 (41.7)	4/8 (50)	> 0.9999	8/16 (50)	1/4 (25)	0.5913
Male: macroadenomas	13/51 (25.5)	4/24 (16.7)	0.5566	17/65 (26.2)	0/10 (0)	0.1043

DA, dopamine-agonist; TSS, trans-sphenoidal surgery. *, Fisher exact test

Due to technical limitations, table 4 is only available as a download in the Supplemental Files section.

Figures

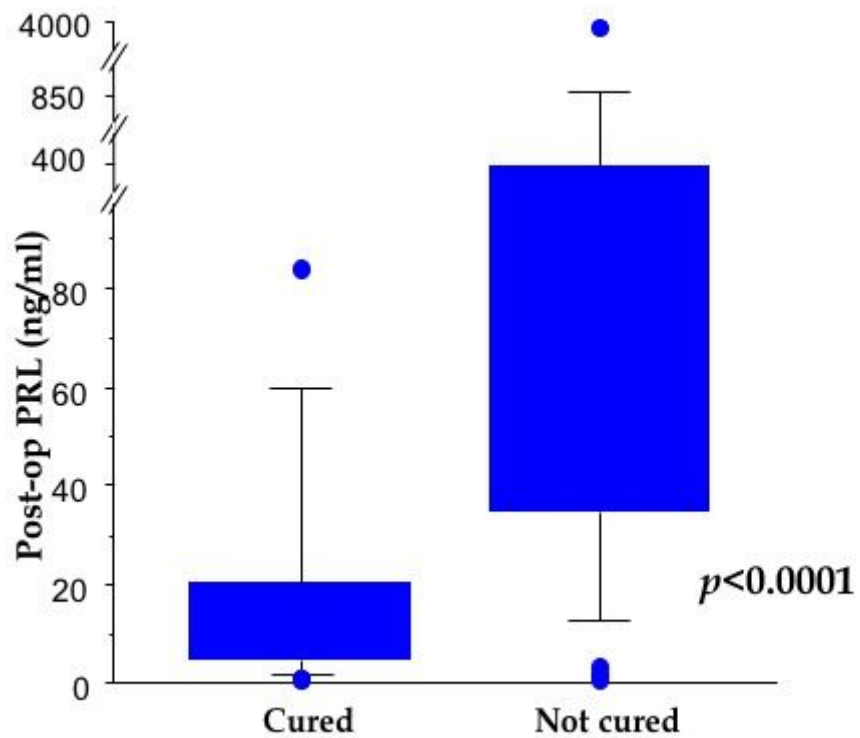


Figure 1

Box plot showing post-operative serum PRL in the subgroup of patients cured vs not cured at the end of 5-year minimum follow up

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table4.jpg](#)