Trans-Sphenoidal Surgery in Prolactin Secreting Pituitary Tumors: A Long-Term Referral Center Experience.

Pier Paolo Mattogno
Policlinico Universitario Agostino Gemelli
Quintino Giorgio D'alessandris
Policlinico Universitario Agostino Gemelli
Sabrina Chiloiro
Policlinico Universitario Agostino Gemelli
Antonio Bianchi
Policlinico Universitario Agostino Gemelli
Antonella Giampietro
Policlinico Universitario Agostino Gemelli
Laura De Marinis (laura.demarinis@unicatt.it)
Policlinico Universitario Agostino Gemelli
Alessandro Olivi
Policlinico Universitario Agostino Gemelli
Carmelo Anile
Policlinico Universitario Agostino Gemelli
Liverana Lauretti
Policlinico Universitario Agostino Gemelli

Research

Keywords: Prolactinoma, transsphenoidal surgery, dopamine agonists, DA withdrawal, cure rate

Posted Date: May 26th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-30456/v1

Abstract

Backgrounds: Prolactin secreting pituitary tumors (PRL-omas) represent a unique challenge for endocrinologists and neurosurgeons. Considering recent innovations in surgical, we aimed to investigate the best management for PRL-omas.

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

Results: 259 patients were enrolled. The first treatment was DA for 140 patients and TSS 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 micro- PRL-omas (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 TSS) revealed that 86.4% of patients with post-operative PRL≤10 ng/ml resulted cured at the end of follow-up (p< 0.0001).

Conclusion: According to our experience, surgery allows a higher cure rate of PRL-omas, in particular in females with micro-PRL-omas, with a good safety profile. TSS for PRL-oma should be considered as first line therapy, in the management of patients, during the multidisciplinary evaluation, in center of reference for pituitary diseases, in order guarantee a valid surgical outcome and a safety profile.

Introduction

Pituitary tumours account for 10–15% of primary intracranial neoplasms. Among secreting pituitary tumors, PRL-omas are the most common (40–50% of total).[1] PRL-omas, due to their biological and clinical features, represent a challenge for endocrinologists and neurosurgeons. Dopamine agonists (DA) are the gold standard as first-line management of PRL-omas due to their efficacy and safety profile.[2,3] Data on cure after withdrawn DA are less clear.[2,4] Trans-sphenoidal surgery (TSS) is confined to failure of medical therapy, pituitary apoplexy with neurological worsening, and cystic PRL-oma.[4] Nonetheless, various papers also report good results with TSS as first-line therapy for PRL-omas.[5–7] 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.[8] Thus, in the neuro-endocrinology community, a debate on the possibility to expand the traditional indications of TSS as first-line treatment for PRL-omas is still alive.[9,10]

The aim of the present study was to ascertain the role of surgery in the treatment of PRL-omas, though the analysis of our surgical and medical experience of over 25 years in the treatment of PRL-omas.

Methods

Study Design

We conducted a retrospective and cross-sectional study, reviewing the clinical, radiological and surgical charts of enrolled patients.

Patients were consecutively enrolled according the following inclusion criteria:

1) Diagnosis of PRL-omas;
2) treatment with with first line therapy with DA (cabergoline or bromocriptine) or with first line neurosurgical operation via TSS (either endonasal endoscopic or sublabial microsurgical);
3) Diagnosis and treatment of PRL-omas conducted at our Institution between January 1st, 1992 and December 31, 2016;

Were excluded from the study:

1) patients carried a giant PRL-omas (diameter > 4 cm);
2) patients with a follow-up shorter than 12 months .

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

Clinical management of patients

PRL-omas were diagnosed according to guidelines, that had been approved at the time of diagnosis for each patient. With regard of therapeutic management, over the years, at our institution, all patients affected by PRL-omas had underwent a multidisciplinary evaluation by the endocrinologist and the neurosurgeon. According to Klibanski ([11]), TSS was offered as first line treatment in:

- pituitary apoplexy
- cystic PRL-omas
- macro-PRL-omas in a patient with a psychiatric condition for which dopamine agonists are contraindicated
- after a joint discussion between endocrinologists, neurosurgeons and patient, concerning risks and benefits, with the final choice based upon the patient's preference.

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 MR three and six months after pituitary surgery/start of DA therapy and then every year.

Follow-up

Outcome of patients at the end of follow was classified as:

1) cured: in cases of regression of clinical symptoms, stable normalization (below the gender-specific normal upper limit) of basal prolactin levels and absence of neuroradiological evidence of residual/recurrent tumor, at least 12 months after neuro-surgery 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 healing by adjusting for the following parameters: size of the adenoma, age at diagnosis, gender, surgical treatment in the course of clinical history, type of first treatment (TSS/DA). A logistic regression model was also built to calculate the OR of healing depending on treatment. A $p < .05$ 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. StatViewver 5.0 software was used (SAS Institute, Cary, NC).

Results

Patient Population

Among all patients treated for PRL-oma 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. The 64% of female patients were affected by micro-PRL-omas, whereas the majority of male patients harbored a macro-PRL-omas (78.9%; $p < .0001$, Fisher exact test). Mean age was 35.2 years; females were significantly younger than males ($p < .0001$, Mann-Whitney *U* test). Mean follow-up was 102.2 months (range, 12–438 months) and did not differ significantly between genders.

Group	Whole cohort	First-line treatment	
		TS	DA
n (%)	259 (100)	119 (45.9)	140 (54.1)
Female, *n* (%)	164 (63.3)	56 (34.1)	108 (65.9)
Male, *n* (%)	95 (36.7)	63 (66.3)	32 (33.7)
Micro-PRL sec. PitNET, *n* (%)	125 (48.3)	41 (32.8)	84 (67.2)
Macro-PRL sec. PitNET, *n* (%)	134 (51.7)	78 (58.2)	56 (41.8)
Female: micro-PRL sec. PitNET, *n* (%)	105 (64.0)	29 (27.6)	76 (72.4)
Female: macro-PRL sec. PitNET, *n* (%)	59 (36.0)	27 (45.8)	32 (54.2)
Male: micro-PRL sec. PitNET, *n* (%)	20 (21.1)	12 (60)	8 (40)
Male: macro-PRL sec. PitNET, *n* (%)	75 (78.9)	51 (68)	24 (32)
Age, mean (range)(years)	35.2 (18-78)	35.6 (18-78)	34.8 (18-76)
Knosp: 0-II, *n* (%)	227 (87.3)	99 (83.2)	127 (90.7)
Knosp: III-IV, *n* (%)	33 (12.7)	20 (16.8)	13 (9.3)
Follow-up, mean (range)(months)	102.2 (12-438)	100.9 (12-438)	103.2 (12-420)
DA, dopamine-agonist; NA, not applicable; TS, trans-sphenoidal.			

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

Treatments

The choice of first-line treatment is detailed in Table 1. Medical therapy was more frequently used in women (65.9%), particularly in those with micro PRL-omas (72.4%). Contrarily, men received surgery as first-line treatment in 66.3% of cases ($p < .0001$, Fisher exact test), irrespective of adenoma size. Overall, micro PRL-omas were more frequently managed with DA as first-line treatment (67.2%), while macro PRL-omas with surgery (58.2%; $p < .0001$, Fisher exact test).

A second-line treatment (DA in patients initially treated with TSS or vice versa) was necessary in 59.7% of patients initially treated with TSS (for partial removal/recurrence or persistence of hyperprolactinemia) and in 53.6% of patients initially treated with DA (p = *NS*), for intolerance/resistance to DA. Males harboring macro-PRL-omas and initially treated with TSS were likely to undergo a second-line treatment with DA. Conversely, female patients harboring macro-PRL-omas and initially treated with DA were likely to undergo a second-line TSS. As expected, cases with Knosp III/IV managed initially with TSS were at risk to undergo a second-line DA. Duration of treatment with DA was significantly shorter in patients

underwent first line treatment with TSS (mean: 61.2 months range: 0-432) as compared to those underwent first line treatment with DA (mean: 74.9 range: 0-360, p = 0.0002).

Rate of cure

Among the whole study population, 113 patients (43.6% of cases) were considered cured were considered cured at last follow-up. The remaining 146 patients carried a controlled/uncontrolled disease.

In the whole cohort, at univariate analysis (Table 2), we found an higher rate of cure at the end of follow-up in females (53% p < 0.001), in patients carried a micro-PRL-omas (52.8% p = 0.0057), in patients carried a not-cavernous sinus invasive PRL-omas (Knosp 0-I and II grades: 46.5%, p = 0.02) and in patients underwent pituitary surgery during the clinical history (50% p = 0.0005).

	Whole Court			**> 5ys FU population**		
	Cured, n°	**Cured, %**	***p****	**Cured, n°**	**Cured, %**	***p****
Total	113/259	43.6	NA	71/164	43.3	NA
Micro-PRL secreting PitNet	66/125	52.8	**.0057**	40/79	50.6	.0831
Macro-PRL secreting	47/134	35.1		31/85	36.5	
Male	26/95	27.4	**< .0001**	14/58	24.1	**.0003**
Female	87/164	53.0		57/106	53.8	
Surgery	97/194	50	**.0005**	63/128	49.2	**.0042**
No Surgery	16/65	24.6		8/36	22.2	
Knosp 0-II	105/226	46.5	**.0230**	64/140	45.7	0.1808
Knosp III-IV	08/33	24.2		7/24	29.1	
Ys, years; FU, follow up; DA, dopamine-agonist; TSS, trans-sphenoidal. *, Fisher exact test						

Table 2
Univariate analysis of predictive factors for rate of cure in whole court and subgroup of patients with follow-up >=5 years.

We conducted a subgroup analysis according to the chosen first-line treatment. Among the group of patients underwent surgery as first-line treatment, we found that the cure rate was higher in female patients (cure rate 67.9% vs 45.4% for first line treatment with DA, $p = .0080$), also independently from the dimension of the PRL-omas. In fact, the rate of cure was significantly higher in female patients treated with first-line surgery as compared to those treated with first-line DA, both in cases of micro- PRL-omas (cure rate 69% *vs* 48.7% for DA, $p = .0080$) both in cases of macro-PRL-omas (cure rate 66.7% *vs* 37.5% for DA, $p = .0037$) (Table 3).

	Rate of cure					
Group	First-line treatment		*p**	Surgery		*p**
	TS, n (%)	DA, n (%)		yes	no	
Whole Cohort	56/119 (47.1)	57/140 (40.7)	.3172	97/194 (50.0)	16/65 (24.6)	.0005
Female	38/56 (67.9)	49/108 (45.4)	.0081	72/113 (63.7)	15/51 (29.4)	< .0001
Male	18/63 (28.6)	8/32 (25)	.8102	25/81 (30.9)	1/14 (7.1)	.1026
Micro-PRL sec. PitNET	25/41 (61.0)	41/84 (48.8)	.2530	52/78 (78.8)	14/47 (21.2)	< .0001
Macro-PRL sec. PitNET	31/78 (39.7)	16/56 (28.6)	.2028	45/116 (38.8)	2/18 (11.1)	.00313
Female: micro-PRL sec. PitNET	20/29 (69.0)	37/76 (48.7)	.0080	44/62 (71.0)	13/43 (30.2)	< .0001
Female: macro-PRL sec. PitNET	18/27 (66.7)	12/32 (37.5)	.0370	28/51 (54.9)	2/8 (25)	.1455
Male: micro-PRL sec. PitNET	5/12 (41.7)	4/8 (50)	> .9999	8/16 (50)	1/4 (25)	.5913
Male: macro-PRL sec. PitNET	13/51 (25.5)	4/24 (16.7)	.5566	17/65 (26.2)	0/10 (0)	.1043
DA, dopamine-agonist; TS, trans-sphenoidal. *, Fisher exact test						

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

In addition, we tried to investigate if the surgery conducted at any time during the patients' clinical history may play a role in the outcome. We found that patients underwent pituitary surgery had a higher rate of cure, both in cases of micro- PRL-omas (surgical treated patients: 78.8% vs not-surgical treated patients: 21.2% $p < 0.0001$) and both in cases of macro- PRL-omas (surgical treated patients: 38.8% vs not-surgical treated patients: 11.1% $p = 0.03$ Table 3).

The multivariate analysis conducted on the whole study cohort confirmed that female sex, the surgery as first/second-line treatment and micro-PRL-omas were found to be independent predictive factors for a cure at the end of follow-up (odds ratio for no cure 0.323, 0.196 and 0.469, respectively; $p = .0009$, $p < .0001$ and $p = .0182$, respectively) (Table 4).

	Whole Court				> 5ys FU population			
	P-Value	Odds Ratio	95% Lower	95% Upper	P-Value	Odds Ratio	95% Lower	95% Upper
Not cured: constant	.5143	0.751	0.318	1,776	.5060	0.695	0.237	2.033
Surgery: Yes	**< .0001**	0.196	0.087	0.439	**.0005**	0.158	0.056	0.445
Age	.921	1,001	0.981	1,022	.5640	1.007	0.982	1.033
Sex: Female	**.0009**	0.323	0.166	0.627	**.0016**	0.257	0.11	0.598
Size: Micro-PRL secreting PitNET	**.0182**	0.469	0.250	0.879	.0997	0.516	0.235	1.134
I treatment: TSS	.6573	0.863	0.451	1,650	.7586	1.131	0.516	2.475
Knosp III-IV	.618	1,280	0.485	3,381	.6406	0.758	0.237	2.427
Ys, years; FU, follow up; TSS, trans-sphenoidal surgery.								

Table 4
Multivariate analysis of predictive factors for a cure in the whole cohort and subgroup of patients with follow-up >=5 years.

Cure in long follow-up

In order to validate the results on predictive factors for a cure, we focused on those patients with long follow-up, of at least 5 years from the diagnosis of PRL-omas.

One hundred sixty-four patients met this criterion, 128 of which had undergone at least one surgical treatment in the course of their clinical history. At univariate analysis for cure rate, female sex and surgical adenoma removal as first or second choice confirmed their positive predictive value for cure (p = .0003 and p = .0042, respectively; Fisher exact test), whereas tumor size showed only a nonsignificant trend to an improved cure rate (Table 2).

Patients treated only with surgery had the best chance of cure. Importantly, neurosurgical adenoma removal, whenever during the clinical course, persistently determined a higher cure rate in the whole cohort, in female patients, in micro-PRL-omas, and in the subgroup of female patients harboring micro-PRL-omas (p = .0042, p = .0021, p = .0020 and p = .0041, respectively; Fisher exact test; Table 5).

Group	Rate of cure					
	First-line treatment		*p**	Surgery		*p**
	TS, *n*(%)	DA, *n*(%)		yes, *n*(%)	no, *n*(%)	
Whole Cohort	31/72 (43.1)	40/92 (43.5)	>0.9999	63/128 (49.2)	8/36 (22.2)	0.0042
Female	22/35 (62.9)	35/71 (49.3)	0.2179	49/78 (62.8)	8/28 (28.6)	0.0021
Male	9/37 (24.3)	5/21 (23.8)	>0.9999	14/50 (28)	0/8 (0)	0.1788
Micro-PRL secreting PitNET	13/24 (54.2)	27/55 (49.1)	0.8076	33/52 (63.5)	7/27 (25.9)	0.0020
Macro-PRL secreting PitNET	18/48 (37.5)	13/37 (35.1)	>0.9999	30/76 (39.5)	1/9 (11.1)	0.1458
Female: micro-PRL secreting PitNET	10/16 (62.5)	25/49 (51.0)	0.5656	28/41 (68.3)	7/24 (29.2)	0.0041
Female: macro-PRL secreting PitNET	12/19 (63.2)	10/22 (45.5)	0.3501	21/37 (56.8)	1/4 (25)	0.3210
Male: micro	3/8 (37.5)	2/6 (33.3)	>0.9999	5/11 (45.5)	0/3 (0)	0.2582
Male: macro	6/29 (20,7)	3/15 (20)	>0.9999	9/39 (23.1)	0/5 (0)	0.5661
DA, dopamine-agonist; TS, trans-sphenoidal. *, Fisher exact test						

Table 5
Rate of cure depending on first treatment and surgery in patients with follow-up >= 5 years.

Finally, female sex and surgical treatment were the only independent positive predictors of cure at the end of follow-up in patients with follow-up > 5 years (odds ratio for no cure 0.257 and 0.158, respectively; $p = .0016$ and $p = .0005$, respectively; Table 4).

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 pituitary surgery was significantly lower in cured *vs* not cured patients ($p < 0.0001$, Mann-Whitney *U* test; Fig. 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 ($p < .0001$, Fisher exact test).

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.

Discussion

In this study, we investigated the role of the trans-sphenoidal pituitary surgery in the treatment of PRL-omas, reviewing our cohort of patients that had been managed with surgical and/or medical therapies, over a period of 25 years.

Our finding demonstrated that patients underwent pituitary surgery had the high probability of reaching the cure for PRL-omas. In fact, in this cohort, for the first time, we proved that the TSS acts as a positive prognostic factor for the cure of PRL-omas, together with the female gender and the small (lower than 10 mm) dimension of the pituitary tumor.

In addition, in the group of patients with a follow-up longer than 5 years, surgery alone was linked to 91% of chance of cure and carried a 57% rate of cure also when performed after DA failure. Similarly, in patients with follow-up longer than 5 years, the only independent positive prognosticators for cure remained female sex and surgery, independently from the dimension of the pituitary tumors.

Our results allow us to describe a group of patients that may strongly benefit by surgical removal of PRL-omas. In this study in fact we demonstrated that female patients treated with first-line surgery had a high rate of cure, as compared to patients treated with DA (as first line therapy), also independently from the pituitary tumor dimension.

Our results are similar to previous reports, as remission rate after surgery is reported in around 80% of micro- PRL-omas and in around 40% of macro-PRL-omas ([12–24]).

According to current guidelines ([4]), however, the first-line therapeutic choice for prolactinoma is the medical therapy with DA, instead surgery is usually confined to a complementary therapy for patients resistant to DA.

However, recent studies had proved that a recurrence of prolactinoma may be observed in 20–77% of cases after the withdrawal of DA ([25]), according to tumoral dimension, invasion of cavernous sinus, nadir prolactin value reached during DA treatment ([12]), persistence of tumoral residual disease and duration of treatment with DA ([26]).

Our evidences deserve special consideration because, in high-volume centers with low surgical complications, the positive influence of surgery in long-term remission/cure could decrease the concerns that obviously accompany any surgical procedure. In fact, in the most recent years, it was suggested that the trans-sphenoidal pituitary surgery should be considered an important part of the patients counselling for the decision of the initial treatment, according to the low morbidity of this procedure, if performed by

an experienced neurosurgeon ([27]). 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 both biomarkers of treatment response, as dopamine and somatostatin receptors ([28–31]). 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 PRL-omas.

In addition, our results suggested an additional benefit of the surgical management of PRL-omas: the duration of adjuvant treatment with DA (after first line pituitary surgery) is significantly shorter as compared to those reported in patients treatment with DA as first line therapy. Our finding is in-line with a previous paper of Andereggen et al. ([32]) that 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.

The main limitation of our study are its retrospective design and the lack of randomization. However, this study described a real life scenario of a large and monocentric series of patients, managed at a historical pituitary unit, that had make a strong effort in the research on prolactin in physiological and pathological conditions ([33–41]).

Our study has the privilege to analyze a homogeneous case series: though collected in a 25-year timeframe, indications, treatment, and follow-up evaluation were conducted by the same medical staff. To further reduce the confounding factors of our analysis, giant PRL-omas have been excluded, because in such invasive cases a multimodality treatment, including radiotherapy and life-long DA, is often required. In addition, in this study lacks a detailed analysis of the various aspects that characterize the clinical and endocrine syndrome of PRL-omas and that can be differently controlled/cured by the chosen treatment. On the other hand, focusing on a few selected serological and neuro-radiological aspects of the illness was essential in order to analyze a considerable number of patients with a long follow-up.

In conclusion, surgery allows a higher cure rate of PRL-omas: tran-sphenoidal surgery may represents a valid alternative to DA therapy, particularly in females with micro-PRL-omas, as provides the highest chance to cure in the long-term follow-up. According to our experience and data, surgical removal of PRL-omas should be considered also as first line treatment in the management of affected patients, during the multidisciplinary evaluation, in center of reference for pituitary diseases, that may guarantee a valid surgical outcome and a safety profile.

Declarations

Conflict of Interest:

None.

Disclosure of Funding:

None.

References

1. Ezzat S, Asa SL, Couldwell WT, Barr CE, Dodge WE, Vance ML, McCutcheon IE. The prevalence of pituitary adenomas: a systematic review. Cancer. 2004;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. Predictors of remission of hyperprolactinaemia after long-term withdrawal of cabergoline therapy. Clin Endocrinol (Oxf). 2007;67(3):426-33.
3. Watanabe S, Takano S, Akutsu H, Sato H, Matsumura A. Prolactinoma treatment status in the cabergoline era. No Shinkei Geka. 2011;39(11):1045-54.
4. Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, Wass JA; Endocrine Society. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011 Feb;96(2):273-88. doi: 10.1210/jc.2010-1692.
5. Akin S, Isikay I, Soylemezoglu F, Yucel T, Gurlek A, Berker M. Reasons and results of endoscopic surgery for prolactinomas: 142 surgical cases. Acta Neurochir (Wien). 2016; 158(5):933-42.
6. Andereggen L, Frey J, Andres RH, et al. 10-year follow-up study comparing primary medical vs. surgical therapy in women with prolactinomas. 2017; 55(1):223-230.
7. Song YJ, Chen MT, Lian W, et al. Surgical treatment for male prolactinoma: A retrospective study of 184 cases. Medicine (Baltimore). 2017; 96(2):e5833.
8. Lauretti L, D'Alessandris QG, Rigante M, Ricciardi L, Mattogno PP, Olivi A. O-arm in Endonasal Endoscopic Cranial Base Surgery: Technical Note on Initial Feasibility. World Neurosurg. 2018; 117:103-108.
9. Micko A, Vila G, Höftberger R, Knosp E, Wolfsberger S. Endoscopic Transsphenoidal Surgery of Microprolactinomas: A Reappraisal of Cure Rate Based on Radiological Criteria. Neurosurgery. 2018; doi: 10.1093/neuros/nyy385.
10. Behan LA, Moyles P, Cuesta M, Rogers B, Crowley RK, Ryan J, Brennan P, Smith D, Tormey W, Sherlock M, Thompson CJ. The incidence of anterior pituitary hormone deficiencies in patients with microprolactinoma and idiopathic hyperprolactinaemia. Clin Endocrinol (Oxf). 2017; 87(3):257-263.
11. Klibanski A. Clinical practice. Prolactinomas. N Engl J Med. 2010 Apr 1;362(13):1219-26.
12. Chanson P., Maiter D. " Prolactinoma" in Melmed S. Eds. The Pituitary 4th Edition, Elsevier, 2017; 467-514,
13. Hamilton DK, Vance ML, Boulos PT, Laws ER. Surgical Outcomes in Hyporesponsive Prolactinomas: Analysis of Patients With Resistance or Intolerance to Dopamine Agonists. Pituitary, 2005; 8 (1), 53-60 DOI: 10.1007/s11102-005-5086-1

14. Kreutzer J, Buslei R, Wallaschofski H, Hofmann B, Nimsky C, Fahlbusch R, Buchfelder M. Operative Treatment of Prolactinomas: Indications and Results in a Current Consecutive Series of 212 Patients. Eur J Endocrinol. 2008; 158 (1); 11-8
15. 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. 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. 2010; 95 (4), 1708-16
16. Sinha S, Sharma BS, Mahapatra AK. Microsurgical Management of Prolactinomas - Clinical and Hormonal Outcome in a Series of 172 Cases. Neurol India. 2011; 59 (4), 532-6
17. Babey M, Sahli R, Vajtai I, Andres RH, Seiler RW. Pituitary Surgery for Small Prolactinomas as an Alternative to Treatment With Dopamine Agonists. Pituitary. 2011; 14 (3), 222-30
18. Qu X, Wang M, Wang G, Han T, Mou C, Han L, Jiang M, Qu Y, Zhang M, Pang Q, Xu G. Surgical Outcomes and Prognostic Factors of Transsphenoidal Surgery for Prolactinoma in Men: A Single-Center Experience With 87 Consecutive Cases. Eur J Endocrinol. 2011; 164 (4), 499-504
19. Primeau V, Raftopoulos C, Maiter D. Outcomes of Transsphenoidal Surgery in Prolactinomas: Improvement of Hormonal Control in Dopamine Agonist-Resistant Patients. Eur J Endocrinol. 2012; 166 (5), 779-86
20. Sinkūnas K, Rastenyte D, Deltuva VP, Knispelis R, Tamasauskas A. Transsphenoidal Surgery for Prolactinomas: Results and Prognosis. Medicina (Kaunas). 2007; 43 (9), 691-7
21. Tamasauskas A, Sinkunas K, Bunevicius A, Radziunas A, Skiriute D, Deltuva VP. Transsphenoidal Surgery for Microprolactinomas in Women: Results and Prognosis. Acta Neurochir (Wien). 2012; 154 (10), 1889-93
22. Ikeda H, Watanabe K, Tominaga T, Yoshimoto T. Transsphenoidal Microsurgical Results of Female Patients With Prolactinomas. Clin Neurol Neurosurg. 2013; 115 (9), 1621-5
23. Loyo-Varela M, Herrada-Pineda T, Revilla-Pacheco F, Manrique-Guzman S. Pituitary Tumor Surgery: Review of 3004 Cases. World Neurosurg. 2013; 79 (2), 331-6
24. Paluzzi A, Fernandez-Miranda JC, Stefko ST, Challinor S, Snyderman CH, Gardner PA. Endoscopic Endonasal Approach for Pituitary Adenomas: A Series of 555 Patients. Pituitary. 2014; 17 (4), 307-19
25. Sala E, Bellaviti Buttoni P, Malchiodi E, Verrua E, Carosi G, Profka E, Rodari G, Filopanti M, Ferrante E, Spada A, Mantovani G. Recurrence of hyperprolactinemia following dopamine agonist withdrawal and possible predictive factors of recurrence in prolactinomas. J Endocrinol Invest. 2016; 29 (12) 1377-1381
26. Ji MJ, Kim JH, Lee JH, Lee JH, Kim YH, Paek SH, Shin CS, Kim Sy. Best candidates for dopamine agonist withdrawal in patients with prolactinomas. Pituitary. 2017: 20, 578-584
27. Rutkowski MJ, Aghi MK. Medical versus surgical treatment of prolactinoma: an analysis of treatment outcomes. Expert Rev Endocrinol Metab. 2018; 13 (1), 25-33
28. Chiloiro 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: Radically

resected pituitary adenomas: prognostic role of Ki 67 labeling index in a monocentric retrospective series and literature review. Pituitary 2014;17(3):267-76

29. Coli A, Asa SA, Fadda G, Scannone D, Chiloiro S, De Marinis L, Lauretti L, Ranelletti L, Lauriola L. Minichromosome Maintenance Protein 7 as Prognostic Marker of Tumor Aggressiveness in Pituitary Adenoma Patients. Eur J Endocrinol. 174 (3); 307-14
30. Li CZ, Gui SB, Zong XY, Zhang YZ. The Expression of Estrogen Receptor Subtypes in Prolactinomas and Their Relationship to Tumor Biological Behavior. Biomed Environ Sci. 2015; 28(11):820-2. doi: 10.3967/bes2015.113.
31. Shimazu S, Shimatsu A, Yamada S, Inoshita N, Nagamura Y, Usui T, Tsukada T. Resistance to Dopamine Agonists in Prolactinoma Is Correlated With Reduction of Dopamine D2 Receptor Long Isoform mRNA Levels. Eur J Endocrinol. 2012; 166(3):383-90. doi: 10.1530/EJE-11-0656
32. Andereggen L, Frey J, Andres RH, El-Koussy M, Beck J, Seiler RW, Christ E. 10-year Follow-Up Study Comparing Primary Medical vs. Surgical Therapy in Women With Prolactinomas. 2016; 55(1), 223-230
33. Barbarino A, De Marinis L, Maira G, Menini E, Anile C. Serum Prolactin Response to Thyrotropin-Releasing Hormone and Metoclopramide in Patients With Prolactin-Secreting Tumors Before and After Transsphenoidal Surgery. J Clin Endocrinol Metab. 1978; 47(5), 1148-51
34. Barbarino A, De Marinis L, Menini E, Anile C, Maira G. Prolactin-secreting Pituitary Adenomas: Prolactin Dynamics Before and After Transsphenoidal Surgery. Acta Endocrinol (Copenh), 1979; 91 (3), 397-409
35. Barbarino A, De Marinis L, Anile C, Menini E, Merlini G, Maira G. Dopaminergic Mechanisms Regulating Prolactin Secretion in Patients With Prolactin-Secreting Pituitary Adenoma. Long-term Studies After Selective Transsphenoidal Surgery. 1982; 31 (11), 1100-4
36. Barbarino A, De Marinis L, Mancini A, Menini E, D'Amico C, Passeri M, Sambo P, Anile C, Maira G. Prolactin Dynamics in Patients With Non-Secretin Tumours of the Hypothalamic-Pituitary Region. Acta Endocrinol (Copenh). 1985; 110 (1), 10-6
37. De Marinis L, Mancini A, Minnielli S, Masala R, Anile C, Maira G, Barbarino A. Evaluation of Dopaminergic Tone in Hyperprolactinemia. Thyroid-stimulating Hormone Response to Metoclopramide in Differential Diagnosis and Postoperative Follow-Up of Prolactinoma Patients. Metabolism. 1985; 34 (10), 917-22
38. Maira G, Anile C, De Marinis L, Barbarino A. Prolactin-secreting Adenomas: Surgical Results and Long-Term Follow-Up. Neurosurgery, 24 (5); 736-43
39. Maira G, Anile C, De Marinis L, Barbarino A. Prolactin-secreting Adenomas--Surgical Results. Can J Neurol Sci. 1990; 17 (1), 67-70
40. 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. Efficacy of the Combined Cabergoline and Octreotide Treatment in a Case of a Dopamine-Agonist Resistant Macroprolactinoma. Pituitary. 2011; 14 (4), 351-7

41. Del Gatto V, Bima C, Chiloiro S, Giampietro A, Bianchi A. Use of 111In-pentetreotide Scintigraphy for Diagnosis and Management of Resistant Macroprolactinoma. Endocrine. 2018; 60 (3), 532-534

Figures

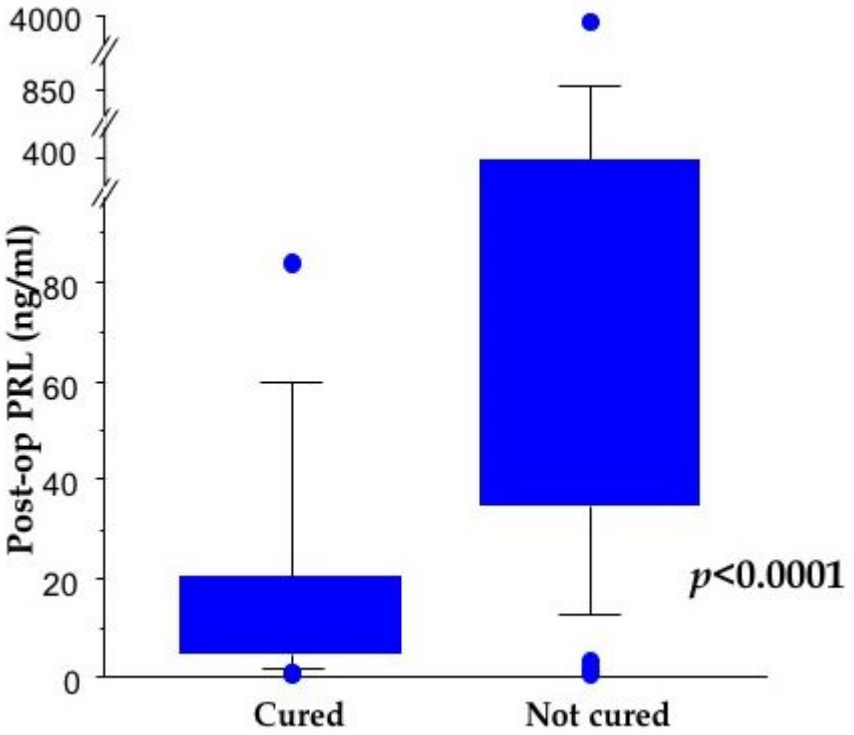

Figure 1

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