Role of Pituitary Stalk and Gland Radiological Status on Endocrine Function and Outcomes after Endoscopic Transsphenoidal Surgery for Non-functioning Pituitary Adenomas

Catalina Vivancos Sánchez (✉ catalina.vivancos@gmail.com)

Hospital Universitario La Paz <https://orcid.org/0000-0002-6230-9287>

Alexis Palpán Flores

Hospital Universitario La Paz

Víctor Rodríguez Domínguez

Hospital Universitario La Paz

Álvaro Zamarrón Pérez

Hospital Universitario La Paz

Cristina Álvarez-Escolá

Hospital Universitario La Paz

Carlos Pérez López

Hospital Universitario La Paz

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Abstract

Purpose

To investigate endocrine function changes after nonfunctioning pituitary adenomas (NFPA) transsphenoidal surgery and to search for predictors of hypopituitarism resolution and development.

Methods

We included 117 patients with NFPA who underwent endoscopic transsphenoidal surgery from 2005 to 2019 by two neurosurgeons. 21 patients were excluded because of previous pituitary surgery or radiotherapy. We assessed symptoms at diagnosis, tumour volume, tumour removal, hormonal status at diagnosis, hormonal outcomes at 2- and 12-months follow-up, and complications. Pituitary stalk and gland MRI status (visible or not) were included, and its association to hormonal function was studied for the first time, to our knowledge.

Results

Pituitary gland visualization was more frequent in those patients who showed a smaller number of axes affected at 12 months ($p=0.011$). Pituitary stalk status showed no association to hormonal function. Hormonal normalization rate at 12 months was 13%. Endocrine improvement rate at 12 months was 16.7%. Worsening of hormonal function occurred in 19.8% of patients. Younger age was associated to hormonal improvement ($p=0.004$). Higher preoperative tumour volume and absence of gross total resection (GTR) ($p=0.049$) were associated with worsening in at least one hormonal axis after surgery ($p=0.015$).

Conclusion

Pituitary gland visibility was higher in those patients who showed better hormonal outcomes. Assessment of initial hormonal function and outcome after surgery regarding pituitary stalk status showed no significant association. Higher preoperative tumor volumes and absence of GTR were associated to postoperative endocrine function worsening, while younger age was associated to its improvement.

Introduction

Pituitary adenomas are benign tumors that derive from the adenohypophysis and constitute 10-15% of all intracranial tumors [1][2]. They can be classified as functioning and non-functioning pituitary adenomas (NFPA) [3] based on whether or not they produce clinically and biochemically evident hormonal hypersecretion [4]. NFPA represent between 14 and 54% of pituitary adenomas [5][6] and they can cause moderate hyperprolactinemia, secondary to dopaminergic inhibition due to compression of the pituitary stalk. Their clinical spectrum is wide: they can be diagnosed as incidentalomas or because of pituitary dysfunction and / or mass effect alterations. The most frequent symptoms are headache and progressive visual impairment [5][7]. Lack of symptoms due to hormonal hypersecretion causes an

estimated diagnostic delay of 1.96 ± 2.9 years [8]; therefore, they usually present as macroadenomas [3][9].

Ophthalmological and hormonal assessment of all pituitary axes are recommended in all cases of suspected NFPA prior to surgical treatment, given the prevalence of partial hypopituitarism, between 37% and 85% of cases [5][7][10]. Hypopituitarism is attributed to the compression and destruction, in some cases, of healthy glandular tissue by the expansive lesion, as well as by the interruption of the drive of the hypothalamic stimulating releasing hormones resulting from compression of the pituitary stalk [4][7][11]. The most reported affected axes at diagnosis are the GH axis (61-100%), the gonadotropic axis (36-96%), the corticotropic axis (17-62%) and the thyrotropic axis (8-81%), depending on the analysed series [3][5][10]. In addition, panhypopituitarism (6%-29%) and hyperprolactinemia (25-65%) may appear [3][5][10]. Diabetes insipidus is rare at the time of diagnosis of NFPA [4][12].

Natural history of NFPA seems to be related to their size at diagnosis, with a higher incidence and growth rate of macroadenomas compared to microadenomas [13][14][15]. The initial therapeutic approach of NFPA is still controversial. Although the presence of visual impairment is a clear surgical indication with a high rate of resolution of symptoms after transsphenoidal endonasal resection (around 61-78% in multiple series [3][6][16]); asymptomatic hypopituitarism is not considered an absolute indication for surgical treatment [17], as the probabilities of hormonal recovery are lower and variable (between 13% and 57% [6][7]), and there is a risk of new deficits or worsening of the previous ones [4][6].

While some authors support conservative management when presenting only as asymptomatic hypopituitarism, considering that the visual symptoms caused by the growth of NFPA that contact the optic chiasm (in about 24% of cases) resolve with subsequent surgical treatment [13][18], others do not recommend the “watch and wait” strategy [5]. Even so, all authors agree on endocrine function testing since hypopituitarism is not only related to a worsening in quality of life and morbidity of patients, but also to an increase in mortality [11][14][19]. In the case of NFPA, aggressive tumor resection to the detriment of hypopituitarism is not acceptable unless the indication is clear.

In reference to the surgical technique, there has been a trend towards the endoscopic endonasal transsphenoidal approach in recent years. Since there are several studies that report greater preservation of the pituitary hormonal function with the purely endoscopic technique [20][21][22][23], others do not find significant differences in comparison to microscopic surgery [24][25][26].

Finally, previously reported predictors of hypopituitarism improvement after NFPA's surgery have shown variable results. While in some series a smaller tumour size, gross total resection, normal or slightly elevated prolactin levels, and non-invasive adenomas are related to this improvement [7], others do not find predictive factors of hormonal recovery [6].

Methods

Patients

We retrospectively analysed the data of 117 patients with NFPA who received transsphenoidal endoscopic endonasal resection between 2005 and 2019. All patients had been evaluated and treated by the same Endocrinology team and by two neurosurgeons (each in their first 100 cases of treatment of NFPA by endoscopic approach) following the same surgical technique. This study has been approved by the institutional Ethics Committee of our center and adheres to the STROBE protocol for cohort studies [27].

Patients 18 years of age or older with a confirmed histopathological diagnosis of NFPA, and with any of the following surgical criteria were included: 1) neurological symptoms, 2) visual impairment, secondary to compression of the optic chiasm or optic nerves, 3) hormonal deficit in symptomatic patients 4) adenomas with tumour growth. We excluded twenty-one patients who had received previous pituitary surgery or radiotherapy.

Preoperative and Postoperative Clinical Variables

Demographic data, preoperative symptoms, postoperative complications, mean admission days, and preoperative and postoperative hormonal status at 2 and 12 months were assessed.

Preoperative plasma levels of TSH, T4, FSH / LH, estradiol (women), testosterone (men) and prolactin were analysed. The presence of low levels of IGF-1 (standardized by gender and age) accompanied by a deficit in the other three pituitary hormonal axes was considered diagnostic for GH deficiency; if not, insulin tolerance test (peak serum GH levels ≤ 5 ng/ml at any time during the hypoglycemic phase of the test (Glycemia <40 mg/dl) or GHRH + arginine test (for BMI $< 25\text{kg/m}^2$: <11 ng/ml; for BMI $25\text{--}30\text{kg/m}^2$: < 8.0 ng/ml and for BMI $\geq 30\text{kg/m}^2$: < 4.0 ng/ml) were performed. Basal cortisol levels by blood sampling at 9 a.m. below $5\mu\text{g/dL}$ were diagnostic for adrenal insufficiency. If cortisol levels were not diagnostic but ACTH deficiency suspected (basal cortisol levels $5\text{--}15\mu\text{g/dL}$), Synacthen test (cortisol levels below $18\mu\text{g/}$ after $250\mu\text{g}$ ACTH stimulation) or insulin tolerance test (cortisol levels below $18\mu\text{g/}$ during the hypoglycemic phase of the test (Glycemia <40 mg/dl)) were performed.

For postoperative variables, resolution of the preoperative deficit was considered when: 1) normalization of free T4 and TSH; 2) FSH / estradiol normalization; 3) FSH / LH / testosterone normalization; 4) Baseline cortisol $>10\mu\text{g/dl}$ or cortisol after ACTH stimulation $> 20\mu\text{g / dl}$; and 5) GH / IGF-1 normalization.

Imaging

All patients had a preoperative magnetic resonance imaging (MRI) study performed at the authors' center including axial, coronal and sagittal slices of 2 mm, in 1.5 or 3 Teslas machines, in a specific pituitary protocol including T1, T2 and T1 + contrast sequences. Post-surgical control was obtained on the same machines with the same image characteristics, between 3 and 6 months after surgery.

Tumour volume was measured in cm^3 with the semi-automatic Brainlab Smartbrush® software and we considered total resection if there was no evidence of tumour on postoperative MRI. We believe that this

is a reliable method in this type of tumours because most of them are irregular, have expansive nodules, and can encompass the carotid arteries. In addition, we measured the degree of invasion of the cavernous sinus according to the Knosp [28] classification and the pituitary stalk and pituitary gland status (visible or not visible).

Surgical technique

We performed a bi-nostril endoscopic endonasal transseptal approach with 3 or 4 hands technique, in collaboration with ENT for the nasal phase. We used intraoperative Doppler in most cases. Maximal safe tumour resection was performed. Closure was performed using a pedunculated flap or with free mucosa from the middle turbinate and autologous fat in the selar defect together with a dural sealant (Duraseal; Confluent Surgical, Waltham, Massachusetts). All procedures were performed with the same instruments, including a 4mm endoscope with 0° and 30° lenses (Karl Storz Endoscope, Germany).

Statistical methods

Univariate statistical analysis included proportions for categorical variables; means, medians and standard deviations with 95% confidence intervals for continuous variables. The bivariate analysis was carried out according to the type of variable; Fisher's test and chi square for dichotomous and categorical variables; t-test and Mann-Whitney U test to compare continuous with dichotomous variables. Finally, the multivariate analysis was performed using a Logistic regression test to assess the independence of possible associated factors to the number of affected axes, and to the worsening hormonal status at twelve months of follow-up. Significance was considered with p values <0.05. Statistical package Stata version 14 (StataCorp LLC, Texas, USA) and Microsoft Excel 2019 implemented under the MacOS operating system were used.

Results

We analysed the data obtained from 96 patients (55.2% men and 44.8% women) with a mean age of 55.7 ± 14.1 years. The mean follow-up time was 69 ± 43.4 months (from 12 to 164 months). Clinical manifestations at diagnosis are summarized in **Table 1**. Prevalence of incidentalomas was 9.4% (9 patients).

Table 1 Clinical manifestations at diagnosis. N (%)

Asymptomatic	9 (9.4)
Campimetric impairment	59 (61.5)
Headache	43 (44.8)
Suffocation	2 (2.1)
Impaired consciousness	1 (1.04)
Amenorrhea / Galactorrhoea	11 (11.46)
Cranial nerves impairment	10 (10.4)
Pituitary apoplexy	7 (7.29)
Other	13 (13.5)
Libido disorder	7 (7.3)
Asthenia	4 (4.2)
Disorientation	1 (1)
Hyponatremia	1 (1)

During follow-up, six patients received radiosurgery at 3 months and 11 patients were reoperated, all of them after 12 months from the first surgery.

Preoperative hormonal status

56.3% (54/96) of the patients presented preoperative hypopituitarism with at least one hormonal axis affected. The distribution of deficits at diagnosis can be seen in **Table 2**. The presence of initial hypopituitarism was more frequent in males ($p < 0.05$). In our series, age was not related to preoperative hypopituitarism.

Table 2 Endocrine deficits at diagnosis, 2 months follow-up and 12 months follow-up

Deficit	Preoperative n (%)	2 months follow-up n (%)	12 months follow-up n (%)
Hypogonadism	43 (44.8)	38 (39.6)	36 (37.5)
Hypothyroidism	34 (35.4)	38 (39.6)	35 (36.5)
Adrenal insufficiency	17 (17.7)	45 (46.9)	28 (29.2)
GH deficiency	24 (25)	22 (22.9)	23 (24)
Hyperprolactinemia	31 (32.3)	2 (2.1)	2 (2.1)
Diabetes insipidus	0 (0)	11 (11.5)	3 (3.1)
Panhypopituitarism	4 (4.2)	6 (6.3)	4 (4.2)

Postoperative hormonal evolution

We observed postsurgical hypopituitarism with at least one hormonal axis affected at 2 months in 69.8% of patients, and in 57.3% of patients at 12 months.

Hypogonadotropic hypogonadism occurred in 37.5% of cases at 12 months, assuming a decrease of 7.3%. In contrast, adrenal insufficiency was 11.5% higher at 12 months. Hyperprolactinemia resolved in 93.5% of cases. The rate of diabetes insipidus at 2 months was 11.5%, resolving in 8 patients (persistent DI of 3.1%). **Table 2.**

Postoperative hormonal evolution is described according to the classification of *Ku et al.*[29] in **Figure 1** and **Figure 2**. Postoperative hormonal normalization rate was 13% (7/54). The rate of improvement in at least one hormonal axis at 12 months was 16.7%. On the other hand, 19.8% of patients presented with at least one new hormonal axis affected 12 months after surgery. Of the thirty-two patients with initial normal hormonal function, including prolactin levels, three presented alterations after surgical treatment (9.4%).

Pituitary gland and stalk

Eighty-nine patients had valid and complete imaging studies with preoperative and postoperative MRI. The pituitary stalk was visible in 50 of them (56.2%) preoperatively, and in 85 patients (95.5%) postoperatively. The pituitary gland was visible in 52 patients (58.4%) preoperatively and in 86 of them (96.6%) postoperatively.

There was a statistically significant difference in the distribution of the number of altered hormonal axes at 12 months in relation to the initial gland status (visible or not visible), $p = 0.011$. **Table 3** and **Figure 3** show a trend where, in those cases where the pituitary gland was visible at diagnostic MRI, the number of affected hormonal axes at 12 months follow-up was lower.

Patients in whom gland was visible had a lower preoperative tumour volume (Visible (n = 52) Mean Vpreop 6.09 ml SE 0.75 [95 CI 4.59-7.60]; vs Not Visible (n = 37) Mean Vpreop 11.41 ml SE 1.68 [95 CI 8.01-14.82] p = 0.002). The distribution of affected hormonal axes at 12 months follow-up by preoperative tumour volume did not reach statistical significance (p=0.104), although it did show a similar trend by volume ≥ 10 ml.

We performed a multivariate analysis including both preoperative volume ≥ 10 ml and gland visibility, showing that independence of the variable gland non visualization remained significant. (Unadjusted: Vol ≥ 10 ml OR 2.66 [95 CI 0.97-7.29] p=0.058 / Non visualization OR 5.84 [95 CI 2.00-17.04] p=0.001 vs Adjusted: Vol ≥ 10 ml OR 1.84 [95 CI 0.62-5.47] p= 0.272 / Non visualization OR 5.14 [95 CI 1.72-15.36] p= 0.003).

Table 3 Distribution of the number of altered hormonal axes at 12 months in relation to the initial gland status (visible or not visible); p = 0.011.

Pituitary gland	N° of altered axes at 12 months follow-up					Total
	0	1	2	3	4	
Visible	28	10	8	5	1	52
	53.85%	19.23%	15.38%	9.62%	1.92%	100%
Not visible	11	4	6	13	3	37
	29.73%	10.81%	16.22%	35.14%	8.11%	100%
Total	39	14	14	18	4	89

The switch to gland visualization after surgery was not associated with hormonal evolution (p> 0.05).

Regarding to the pituitary stalk, there was no association between its initial visualization and the presence of hyperprolactinemia (p>0.05), nor with the improvement or worsening of hormonal function at 12 months, including hyperprolactinemia and diabetes insipidus (p> 0.05). Neither was hormonal evolution associated with the fact that the stem was visualized postoperatively in those patients in whom it was not initially visible (p> 0.05). **Figure 4.**

Other predictive factors of postoperative hormonal improvement or worsening

The mean preoperative tumour volume was 8.31 ± 8.15 ml. The mean degree of resection was $94.7 \pm 9.4\%$, achieving a gross total resection in 50 patients (GTR 56.2%). The mean postoperative tumour volume was 0.52 ± 1.13 ml.

Age was associated with hormonal improvement in our series, including resolution of hyperprolactinemia (Improvement (n = 32) 49.47 years SE 2.82 [CI95 43.72-55.22] vs No improvement (n = 64) 58.84 years SE 1.50 [CI95 55.84 -61.85], p = 0.004).

A higher preoperative tumour volume was associated with worsening in at least one hormonal axis after surgery (Worsening (n = 16) Mean Vpreop 11.9 ml SE 2.14 [95 CI 7.36-16.47]; vs No worsening (n = 73) Mean Vpreop 7.52 ml SE 0.93 [IC95 5.67-9.36] p = 0.015). **Figure 5.**

Patients in whom GTR was achieved had a lower preoperative tumour volume (GTR (n = 50) Mean Vpreop 6.16 ml SE 0.78 [95 CI 4.59-7.73]; vs No GTR (n = 39) Mean Vpreop 11.06 ml SE 1.61 [95 CI 7.80-14.31] p = 0.002). 10% of the patients in whom a total resection was achieved presented postoperative hormonal deterioration in at least one axis, compared to 28.2% of those in which GTR was not achieved (p=0.049).

We performed a multivariate analysis strategy to identify the independent predictors of postoperative hormonal worsening among demographic and radiologic variables that were significant in the bivariate analysis or could act as confusion factors. The following variables were involved (**Table 4**): age ≥ 70 , preoperative volume ≥ 10 ml, not GTR and not visible gland previous to surgery. Age threshold was considered according to previous literature [30] and volume threshold according to previous findings regarding its association to GTR and gland visibility. We found that independence of the variable preoperative volume ≥ 10 ml remained significant.

Table 4 Multivariate logistic regression analysis for postoperative hormonal worsening. OR: Odds ratio. CI: Confidence Interval. Vpreop: preoperative volume. GTR: Gross Total Resection.

Variable	Unadjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Age ≥ 70 years	1.61	0.49 - 5.19	0.428	2.42	0.53 - 11.04	0.253
Vpreop ≥ 10 ml	5.94	1.87 - 18.83	0.002	3.80	1.06 - 13.70	0.041
No GTR	4.30	1.34 - 13.87	0.015	2.71	0.74 - 9.92	0.131
Not Visible Gland	3.98	1.25 - 12.69	0.020	2.47	0.67 - 9.05	0.173

Finally, neither the preoperative tumour volume nor the degree of resection predicted postoperative hormonal improvement (p>0.05). Knosp degree (preoperative, postoperative and the change between both) was not associated to hormonal function (p>0.05).

Discussion

Although NFPA are histologically benign tumours, they can lead to an increase in morbidity and mortality. Especially in those cases that present with hypopituitarism as the only alteration, there is still some controversy regarding the surgical indication, given the reported variability in the rates of improvement and worsening of pituitary function after surgery (improvement 13-57% [4][6][7], worsening 2-33% [4][6][7][31]; in the present study 16.7% and 19.8% , respectively). Therefore, it is important to establish a good pre and perioperative management.

With the present study we aim to provide data about the hormonal function and outcomes of a homogeneously treated series of NFPA, as well as to introduce a new subject of study that could be helpful in the management of these patients: the association of the pituitary stalk status (visible or not visible on MRI) with preoperative hormonal function and postoperative evolution, including hyperprolactinemia and diabetes insipidus. We would expect that compression of the pituitary stalk by the tumour could translate into its non-visualization on MRI and into hyperprolactinemia (even hypopituitarism due to altered blood flow and interruption of the drive of the hypothalamic stimulating releasing hormones); while the switch to its visualization on MRI after tumour resection could be associated with changes in hormonal function.

We found no association between pituitary stalk initial visualization (visible in 50 of the patients (56.2%)) and the presence of hyperprolactinemia ($p>0.05$), nor with the improvement or worsening of hormonal function at 12 months, including hyperprolactinemia and diabetes insipidus ($p>0.05$). While in the majority of patients it persisted (56.2%) or became visible (39.3%) after endoscopic transsphenoidal surgery, no significant association with hormonal evolution was found.

On the other hand, pituitary gland visualisation on MRI showed a trend where, in those cases where it was visible at diagnosis, the number of affected hormonal axes at 12 months follow-up was lower. Gland visualisation was related to lower preoperative tumour volume, as it would be expected. Nevertheless, tumour volume failed to reproduce the same association with the distribution of number of axes affected. In the multivariate analysis, independence of the variable gland non visualization remained significant. Only 4 patients presented with all four axes deficiency, possibly affecting statistical significance, since the mean tumoral volume of this group was higher than those in the other groups of patients (with 1, 2 or 3 axes deficiency). In the same line, another group reported that an increased preoperative gland volume could predict the chances of a patient with any preoperative deficit experiencing normalization of at least one hormonal axis [[7]. We believe the pituitary stalk and gland status (visible or not visible on MRI) could be an interesting object of further study.

In reference to the role of tumour size as a predictor of recovery, literature provides controversial findings [6][7][32]. In the present study a greater preoperative tumour volume was associated with worsening in at least one hormonal axis after surgery. This association could be related to the greater surgical manipulation of the gland, the vascular reperfusion effect, and sudden decompression in cases with previous selar hypertension due to a greater mass effect. Another factor to take into account, although it is outside the objective of this study, would be tumour hardness [33]. On the other hand, we observed that

GTR protects against postoperative hormonal worsening, and it is known that there are higher GTR rates when the tumour volume is lower [22][34], as demonstrated in our study. We would say that patients in whom pituitary gland is visualized on preoperative MRI, with smaller tumour size and in which GTR is achieved, are the ones more likely of having at least hormonal stability after surgery with a smaller number of axes affected.

Finally, the distribution of hormonal deficits was in agreement with pre-existing literature [3][4][5][10][12]. The prevalence of initial hypopituitarism was 56.3% of patients. It is striking that only 25% of patients presented with preoperative GH deficit while it has been reported as the most frequent alteration in the literature. This may be due to the greater heterogeneity of its diagnosis, with values that depend on age and different laboratory standards.

Regarding postoperative evolution, hypogonadotropic hypogonadism was the deficit that improved the most at 12 months, with a reduction of 7.3% cases, and adrenal insufficiency was the deficit that appeared the most after surgery. In two other series of 305 [7] and 331 [6] NFPA, the same trend was observed by axis, in addition to obtaining greater normalization in the thyroid axis. Another series of 55 NFPA [31] showed that 5.7% of patients with previous normal hormonal function presented new hypopituitarism (9.4% in our study); and in their case only 7.4% of the patients totally regained hormonal function, compared to 13% in the present study. In agreement with previous studies, younger age was associated with post-surgical hormonal recovery[7][32]; as other authors have suggested, cardiovascular risk factors and their impact on pituitary vascularization could play an important role [32].

The results of this study arise from a cohort of patients that avoids the heterogeneity of procedures, by being treated by the same team in a single center. Furthermore, the experience curve of the two neurosurgeons makes the findings transferable to other tertiary centres. Hormonal evolution is presented visually and clearly, taking into account: the four adenohypophysis axes, the total hormonal evolution including hyperprolactinemia and diabetes insipidus, and the evolution for each axis. There are certain limitations to take into account, in addition to the previously argued, the retrospective nature of the study and the obtention of clinical information from medical reports, without being able to standardize all the endocrinological values to be obtained preoperatively.

Conclusion

To our knowledge, the status of the pituitary stalk, visible or not, is studied for the first time finding no association with hormonal function. The visualization of the gland is associated with a lower number of affected hormonal axes after surgery. In addition, a greater tumour volume and the absence of GTR are associated with hormonal worsening, while younger age is associated with its improvement. These findings provide new evidence and may be useful for the perioperative evaluation of patients with NFPA.

Abbreviations

NFPA: Non-functioning Pituitary Adenomas; DI: Diabetes Insipidus; SIADH: Syndrome of inappropriate antidiuretic hormone secretion; MRI: Magnetic Resonance Imaging; GTR: Gross Total Resection; GH: Growth Hormone; IGF-1: Insulin-like Growth Factor 1; TSH: Thyroid-stimulating Hormone; T4: Thyroxine; ACTH: Adrenocorticotrophic Hormone; FSH: Follicle-stimulating Hormone; LH: Luteinizing Hormone; CI: Confidence Interval.

Declarations

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Conflicts of interest. The authors declare no conflicts of interest.

Ethics approval. This study has been approved by the institutional Ethics Committee.

Consent to participate and for publication. All patients signed the informed consent for participating in the study and publishing images and data under anonymization.

Availability of data and material. All data are available under request.

Code availability. Not applicable.

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Figures

Figure 1

Postoperative hormonal outcome at 12 months follow-up according to Ku et al.[29] classification. Top bar shows results taking in account the four axes only and bottom bar shows results taking in account the affected axes plus prolactin and diabetes insipidus. Values represent absolute number of cases.

Figure 2

Postoperative hormonal outcome at 12 months follow-up according to Ku et al.[29] classification by axis. Values represent absolute number of cases.

Figure 3

Distribution of the number of altered hormonal axes at 12 months in relation to the initial gland status (visible or not visible); $p = 0.011$.

Figure 4

Preoperative coronal (a) and sagittal (b) MRI: pituitary stalk was not visible in a patient with NFPA. Postoperative coronal (c) and sagittal (d) MRI of the same patient: pituitary stalk is now visible after resection of the adenoma.

Figure 5

Boxplot representing association between preoperative tumoral volume in cm³ and hormonal outcome at 12 months (horizontal axis: 0= no worsening and 1= worsening) $p = 0.015$