Outcome of Pituitary Hormone Deficits After Surgical Treatment of Non-functioning Pituitary Macroadenomas (NFPMA)

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Research Article

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Abstract

Objectives: Non-functionning pituitary macroadenomas (NFPMA) are benin tumors that cause symptoms of mass effects including hypopituitarism. Their primary treatment is trans-sphenoidal surgery. We aimed to determine the outcome of pituitary hormone deficits after surgical treatment of NFPMA and to identify factors predicting hormonal recovery.

Design: We retrospectively included 246 patients with NFPMA diagnosed and operated in one of the two participating centers. All hormonal axes were evaluated except growth hormone (GH). Postoperative improvement of pituitary endocrine function was considered if at least one hormonal deficit had recovered and a lower total number of deficits was observed one year after surgery.

Results: 80% (n=197) of patients had one or more pituitary deficits and 28% had complete anterior hypopituitarism. Besides GH, the gonadotropic and thyrotropic axes were the most commonly affected (68% and 62%, respectively). The number of hypopituitary patients dropped significantly to 61% at one year ($p<0.001$) and a significant improvement was observed for all hormonal axes, except central diabetes insipidus. Among patients with preoperative hypopituitarism, 88/175 (50%) showed improved pituitary function at one year. Both hyperprolactinemia at diagnosis and a lower tumor diameter independently predicted favourable endocrine outcome.

Conclusions: Hypopituitarism is present in 80% of patients with NFPMA and nearly half of them will benefit from sustained improvement after surgery. Hyperprolactinae-mia at diagnosis and lower tumor dimensions are associated with favourable endocrine prognosis. This supports the option of early surgery in NFPMA patients with pituitary deficits independent of the presence of visual disturbances.

Introduction

Non-functioning pituitary adenomas (NFPAs) are benign pituitary tumors that are typically associated with no clinical or biochemical signs of hormone excess (1,2,3). Thus, most of them are diagnosed as macroadenomas (NFPMAs) when patients present symptoms of mass effects such as visual field defects, chronic headache and/or hypopituitarism (4). Occasionally they are discovered incidentally during a radiological examination performed for another indication (5,6). The prevalence of partial and complete hypopituitarism varies widely among studies, ranging from 37-85% and 6-29% of patients, respectively (7,8,9,10,11) and depending on patient selection criteria and criteria used for definition of pituitary deficiency.

Transsphenoidal surgery is the primary treatment of NFPMAs (12,13). Even though tumor cannot be fully resected, surgery improves visual field defects in over 80% of patients and relieves headaches in the majority of them (14,15,16). Surgical resection can also reverse hypopituitarism and improvement of pituitary function has been reported in 16-48% of patients with macroadenomas (16,17). However, the number of studies specifically addressing the outcome of pituitary function after surgery of NFPMAs only remains limited. They often used various diagnostic criteria for pituitary deficits, some included small numbers of patients and some provided conflicting results. Moreover, factors independently associated with

recovery of postoperative pituitary function have been infrequently evaluated in large series of patients (8,9,18,19).

The aims of the present study were: (i) to assess the prevalence of pituitary hormone deficits at diagnosis in a large series of patients undergoing surgery for a NFPMA, (ii) to evaluate post-operative evolution of pituitary functions, and (iii) to identify factors predicting hormonal recovery after primary surgical treatment.

Patients And Methods

Patients

This retrospective study included 246 patients with an initial diagnosis of NFPMA (diameter ≥ 10 mm on magnetic resonance imaging (MRI)) diagnosed and operated between 1988 and 2015 (median year of surgery: 2009) in one of the two participating centers (UCL Cliniques St Luc Brussels; n=144; Bicêtre Hospital Paris, n=102). A subset of these patients (n=106) was included in a previously published study on factors predicting postoperative relapse (20). We only included patients who had undergone primary pituitary surgery by the transsphenoidal route for NFPMA and with available endocrine evaluation both at baseline (n=246) and postoperatively, at 3 (n=244) and/or 12 months (n=219) after surgery. No patient had previously received tumor-directed medical treatment or radiotherapy and 27 patients presenting with acute symptomatic pituitary apoplexy were excluded from the study because of the known deleterious effects of this complication on pituitary functions. Follow-up was ended if the pituitary tumor required a further treatment within the first year after initial surgery.

Clinical characteristics and results of ophthalmological examination were recorded at diagnosis, whereas tumor characteristics at magnetic resonance imaging (MRI) were assessed preoperatively and after 3 and 12 months. Histological examination confirmed the diagnosis of pituitary adenoma in all patients. The study was approved by the Ethics Committee of the Cliniques universitaires Saint Luc (UCL) and no informed consent was requested as it was a retrospective study.

Hormonal evaluation

Four hormonal axes were considered in the evaluation of pituitary function. Thyrotropin (TSH) deficiency was defined as a free thyroxine (fT4) level below the normal range associated with low or normal TSH or, in 9 patients, as a fT4 in the lowest quartile of the normal range together with a more than 20%-reduction in fT4 compared to a previously recorded level, as proposed by the recent ETA guidelines for the diagnosis of central hypothyroidism (21). Patients were considered as corticotropin (ACTH)-deficient either if if they had a morning serum cortisol value below 138 nmol/L, which has been reported as the best cutoff value predicting ACTH insufficiency (22) or a suboptimal cortisol response to an insulin tolerance test (peak below 500 nmol/L). The diagnosis of gonadotropin deficiency was based on (i) a low morning serum testosterone (< 10 nmol/L) on at least two occasions with low or normal gonadotropins in men, (ii) amenorrhea with low serum estradiol and low/normal gonadotropins in premenopausal women, or (iii) gonadotropin concentrations below the normal age-related range in postmenopausal women. Diabetes insipidus (DI) was

defined as hypotonic polyuria > 4000 ml/day not reacting to fluid restriction but improving after desmopressin administration.

Prolactin concentrations were also recorded at diagnosis and during follow-up, while screening for growth hormone (GH) deficiency by provocative testing was not routinely performed preoperatively. Therefore, as the main goal of our study was to evaluate whether pituitary functions improved or worsened after surgery, we decided to not include the somatotropic axis in the evaluation of hormonal changes. Of note, a few patients could not be evaluated for a specific hormonal axis because of an interfering condition or treatment (L-T4 treatment for primary hypothyroidism in 3 patients; oral contraceptivesin 4 women and glucocorticoid treatment in one man).

Postoperatively, the same criteria were applied to define hormone deficiencies while normal (or normalized) hormone concentrations without any hormonal replacement indicated a normal pituitary axis. Pituitary endocrine function was considered improved if at least one hormonal deficit had recovered in patients with preoperative hypopituitarism together with a total number of deficits lower than before surgery. In contrast, deterioration was defined as the occurrence of at least one new deficit with a total number of deficient axes greater than in the preoperative period.

Radiological evaluation

The size of the tumor was assessed by dedicated pituitary MRI. The largest tumoral surface was calculated on a selected coronal view, using the following equation: S = 3.1416 x (a x b)/4 where a and b represent tumor width and height. Tumors were considered invasive if they extended laterally into the cavernous sinus region (23,24) or inferiorly into the sphenoid sinus. Tumor progression was defined as an increase in size of a postoperative residue between 3 and 12 months, while recurrence was defined as reappearance of a tumor mass in a patient without residual tumor mass.

Statistical Analysis

Differences between subgroups were analyzed using unpaired Student's t-tests for normally distributed continuous variables and Chi-Square (x^2) tests for categorical variables. Multiple logistic regression analysis was performed to determine factors that independently predicted improvement of pituitary function at the 12 month time-point after surgery. The SPSS software (version 25; SPSS Inc., Chicago, IL) was used and $P< 0.05$ was considered statistically significant.

Results

Patient characteristics at diagnosis

Table 1 shows the main characteristics of the total study group (n=246) and of the two different center subgroups (n=144 and 102, respectively). The mean age (± SD) was 55 ± 15 yr and the sex ratio showed a slight male predominance (138 men and 108 women, 52 being menopausal). The most prevalent presenting symptoms were visual disturbances (65%) and headache (35%). A clinical hypogonadism was detected in

28% of men and in 54% of pre-menopausal women, while galactorrhea was reported only by a minority of patients. Preoperative ophthalmologic evaluation showed a visual field deficit in 154/241 patients (64%) and a significant decrease in visual acuity (less than 0.5 at at least one eye) in 62/214 (29%) Pituitary tumors were discovered incidentally in 59 patients (24%). However, despite this incidental diagnosis, 49% of these patients had visual impairment, 20% complained from headaches and 78% had some degree of pituitary dysfunction.

Baseline endocrinological evaluation revealed hypopituitarism in 197/246 patients (80%), with more than half of all patients showing at least two pituitary deficits and 28% having complete anterior hypopituitarism. The gonadotropic and thyrotropic axes were the most commonly affected with 68% and 62% of evaluable patients showing biochemical evidence of central hypogonadism and hypothyroidism, respectively. Corticotropic insufficiency was noted in 32% of patients while diabetes insipidus was present in only two patients (0.8%) with a silent hemorrhagic tumour at the time of clinical presentation. Hyperprolactinaemia was observed in about one half of the patients, with maximal prolactin concentrations being 5.9-fold above the upper normal limit for age and gender With the exception of headache, no significant difference was observed between the cohorts from the two participating centers (**Table 1**).

Pituitary tumor Imaging and post-surgical outcome

Overall, mean tumor height and width were close to 25 mm and 59% of patients had invasive tumors. NFPMAs had a slightly greater height in the Belgian subgroup but in contrast were larger and more invasive in the French cohort (possibly resulting from local differences in patient recruitment and surgical threshold). The tumoral surface was however similar between the two subgroups (**Table 2**). The presence of a post-surgical tumor remnant was observed in 64% of all patients, and was more frequent in the Bicêtre (72%) than in the Brussels cohort (59%), a difference attributable to a more frequent cavernous sinus invasion. Overall, 27 patients (13%) had tumor progression or recurrence after one year of follow-up.

When compared with the 49 patients without preoperative hypopituitarism, patients with at least one pituitary deficiency had larger and taller tumors, but there was no difference in invasiveness (**Table 3**). Interestingly enough, the difference was more significant for tumor width than height. Visual impairment and hyperprolactinemia were also more frequent in pituitary-deficient patients, while age and sex ratio were not significantly different. There was also no significant difference between these two subgroups regarding the prevalence of a postoperative tumor residue or in the rate of tumor progression or recurrence at one year (data not shown).

Postoperative hormonal evaluation

At the first hormonal evaluation performed three months after surgery, the proportion of patients with at least one pituitary deficit had dropped from 80% to 69% ($p < 0.001$) and this percentage further decreased to 61% at 12 months ($p < 0.001$) (**Figure 1A).** In particular, the number of patients with two deficits or more was reduced from 55 to 38% at one year ($p<0.001$) and the mean number of affected pituitary axes was also significantly reduced from 1.63 at baseline to 1.26 at 12 months ($p<0.001$). Sustained improvement was observed for all investigated anterior pituitary hormonal axes, but was more pronounced for the

gonadotropic and thyrotropic than for the corticotropic axis (**Figure 1B**). In contrast, and as expected, central DI was more frequent both at three (11.6%) and 12 months (7.4%) compared to less than 1% preoperatively ($p< 0.001$). The presence of DI one year after surgery was positively associated with tumor size at the time of surgery ($p< 0.01$).

When considering only patients with preoperative hormonal deficiency and available follow-up at one year (n=175), improvement of pituitary endocrine function was observed in 87 subjects (50%), while worsening was seen in 25 (14%). Among the 44 patients who had normal pituitary function at baseline, only 10 had a new postoperative deficit (with the caveat that GH secretion was not analyzed in the present study). Altogether a deterioration of endocrine pituitary function was thus observed in only 35/219 patients (16%).

When comparing patients with and without hyperprolactinaemia (**Table 4**), more hyperprolactinemic patients had hypopituitarism at diagnosis and a greater number of these patients showed improvement or recovery of normal pituitary function 12 months postoperatively. However, these differences involved all anterior pituitary hormonal axes, and not specifically the gonadotropic axis. In other terms, hypogonadism was not particularly more prevalent in patients with hyperprolactinemia and did not recover more frequently in those who normalized their prolactin levels postoperatively (data not shown).

Predictive factors of hormonal outcome

To determine possible predictors of postoperative improvement of endocrine function, the following parameters were evaluated in the subgroup of patients with preoperative pituitary deficits: gender, age at diagnosis, visual impairment, hyperprolactinemia, tumor dimensions and tumor invasiveness. In univariate analysis, female gender ($p<0.05$), hyperprolactinemia at diagnosis ($p<0.001$) and lower tumor height and width ($p<0.001$) were associated with a global improvement of pituitary function (**Table 5**). However, in multivariate analysis the only parameters independently predicting favorable endocrine outcome were hyperprolactinaemia and either tumor height or width. Indeed, as these two parameters were closely associated ($r=0.683$; $p<0.001$), they had to be included in separate multivariate analyses. However, here also we observed that tumor width was a more powerful factor than tumor height to predict postoperative evolution of pituitary functions (**Table 5**).

Discussion

As they are not associated with clinically relevant hormonal hypersecretion, NFPMA remain most often undiagnosed until they present symptoms of tumor mass effect. (1). We confirm in our study that most of these tumors present with headaches and/or visual alterations. NFPMA may also be diagnosed incidentally in about one quarter of cases (1,4). However, autopsy series show that macroadenomas represent less than 1% of pituitary tumors discovered postmortem, thus suggesting that there may be some connection between the presence of an “incidental” macroadenoma and the symptoms leading to brain imaging. In our surgical series, NFPMA were diagnosed “incidentally” in 24% of patients, and even though pituitary incidentalomas by definition are not diagnosed on the basis of tumor-related symptoms, a significant proportion of these patients had headaches, visual deficit at examination and/or pituitary dysfunction that had remained so far undiagnosed .

Hypopituitarism is a common complication of NFPMA at diagnosis. About 60-80% of patients have at least one pituitary hormone deficiency prior to surgery and, depending on the studies, the somatotropic and gonadotropic deficits are the most frequently affected (3,4,11). The prevalence of central hypothyroidism may however be underestimated as the diagnosis of TSH insufficiency remains often difficult given the wide range of normal free thyroxine values in the general population, and the paucity of specific symptoms and signs (21,22). In fact, we found a quite similar prevalence of gonadotropin and TSH deficits in our patients with NFPMA (68% and 62%, respectively), while ACTH deficiency was much less frequent (32%) and diabetes insipidus was very uncommon. Like in many other centers, GH deficiency was not systematically assessed preoperatively. As changes in pituitary function are expected after surgery, preoperative GH testing seems useless as it would need to be repeated after surgery (6). Moreover, our regular practice is to perform GH stimulation testing only in patients who could further benefit from GH therapy. However, when it is done in a systematic way, the majority of patients will be found to be GH-deficient (25).

Preoperative hypopituitarism was associated with tumor size and invasiveness, hyperprolactinemia and the presence of visual disturbances as previously reported by different studies (17,18,26,27,28). Interestingly, we found that tumor width was more closely associated with endocrine dysfunction than tumor height. It is tempting to hypothesize that larger tumors will be more prone to compress the normal gland or the pituitary stalk while taller ones will more frequently induce visual complications, although both dimensions are usually correlated.

Preoperative hyperprolactinemia was observed in nearly half of our patients, as usually observed (28,29,30). It mainly results from pituitary stalk compression (28) and was still present postoperatively in only 16% of patients, indicating that surgery had a significant effect on relieving stalk effect. Previous studies as well as our own data have suggested that in patients with mildly elevated prolactin levels prior to surgery, pituitary function was more likely to recover (17,26,29). These observations suggest the presence of intact pituitary tissue and imply that the mechanism of hypopituitarism may be compression of the portal circulation rather than destruction of the normal pituitary gland (29). A functional inhibitory effect of hyperprolactinaemia on the gonadal function might also be evoked but our data indicate that this is not the main mechanism explaining hypopituitarism in patients with NFPMA.

According to recent guidelines on diagnosis and treatment of NFPMA, surgery is indicated in patients with enlarging tumors or symptomatic tumors with mass effects (1,5,12,13). Surgical management of NFPAs indeed provides successful symptom relief with acceptable morbidity and mortality (16,31). Overall, transsphenoidal surgery – whether microscopic or endoscopic – leads to complete adenoma resection in 20-40% of cases and allows significant debulking in most of them, with an overall complication rate of 5-9% (32,33,34). In contrast, few large studies have extensively evaluated the impact of surgery on pituitary hormonal functions in patients with NFPMA.

While early studies concluded that transsphenoidal surgery carried a significant risk of sacrificing remaining anterior pituitary function, especially in patients with large and compressing tumors (30,35), it is clear from more recent reports that postoperative pituitary function can now be better preserved and even be improved or normalized. We performed a review of several studies published on this issue over the last two decades

(**Table 6).** Large variations are observed between these studies, likely because of differences in patient recruitment and surgical indication, in the definition of pituitary deficits, as well as in surgeon's experience and procedure. Overall, resolution of one or more hormonal deficits by surgery can be expected in 15-50 of patients, but obviously some studies reported a clear improvement in pituitary function (8,9,17,28,36,37) whereas others could not demonstrate such beneficial effect (15,19,38,39). In the present study, we observed that 50% of all patients with a preoperative hormone deficiency showed improvement of pituitary function after surgery, while a deterioration was seen in less than 20% of all operated patients (whether hormone-deficient or not). Therefore, although Endocrine Society guidelines indicate that hypopituitarism is only a relative surgical indication in patients with NFPA (12), our data suggest that transsphenoidal surgery should not only aim at resolution of visual deficits but also at preservation or improvement of pituitary functions in case of tumor progression (9,33). Furthermore, we also found that permanent DI, which is a common complication of pituitary surgery (5-10%), is more likely to occur when operating a large tumor, which also argues for early surgery.

We also tried to identify factors influencing the outcome of pituitary function after surgery. Few large studies have previously addressed this question (17,18,37). We found that hyperprolactinaemia and a lower tumor diameter were significantly and independently associated with a higher chance of pituitary function recovery. Either tumor width or height predicted endocrine outcome, thus extending results from previous studies (8,18). More precisely in the study of Jahangiri et al, residual size of the normal pituitary gland rather than tumor volume predicted the ability of pituitary axes to improve after transsphenoidal surgery. We did not evaluate this parameter in our study but it is likely that residual normal gland and tumor size (in particular tumor width) are inversely correlated and that endocrine normalization should reflect the amount of functional pituitary tissue which is relieved by decompression. We did not find, however, an association between age and post-operative endocrine outcome, in contrast with a previous report showing that younger age predicted better hormonal recovery (18). .

The main limitations of our study are inherent to its retrospective nature. There were some missing data and each hormone outcome was analyzed in a different (though large) sample size. We also did not perform preoperative testing of GH secretion, which could have led to an underestimation of the degree of pituitary dysfunction. However, isolated GH deficiency is rather rare. On the other hand, our cohort of patients with a confirmed and operated NFPMA was quite large, patients were managed with similar protocols in both centers, surgeries were performed by a limited number of experienced neurosurgeons, and follow-up data at one year were available for 88% of the patients.

In conclusion, in this large cohort of patients operated for a NFPMA, we show that hypopituitarism is present in 80% of the patients before surgery and that, besides GH, the gonadotropin and TSH axes are the more frequently affected. Among patients with preoperative hypopituitarism, nearly half of them will benefit from sustained improvement of pituitary function. Hyperprolactinemia at diagnosis and a lower tumor diameter are independently associated with a favorable endocrine prognosis. As resolution of one or more hormonal deficits can be achieved in a significant number of patients, we suggest that early surgery by experienced pituitary neurosurgeons should be discussed in patients with a growing tumor and hypopituitarism, regardless of visual disturbances.

Declarations

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This work has not received any funding

Conflicts of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Ethics approval

The study was approved by the Ethics Committee of the Cliniques Universitaires Saint Luc (UCL) and no informed consent was requested as it was a retrospective study.

Consent for publication

All authors approve the submission

Availability of data and material

Data and code for statistical analyses are available upon request.

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Tables

TABLE 1. Baseline characteristics at diagnosis in all patients with a non-functioning pituitary macroadenoma(n=255)

	All patients (N=246)	St Luc (N=144)	Bicêtre (N=102)	P
Sex ratio (men/women)	138/108	81/63	57/45	NS
Age (years ; mean ± SD)	56 ± 15	57 ± 15	54 ± 15	NS
Visual disturbances*	159/245 (65%)	92/143 (64%)	67/102 (66%)	NS
Headache	86/246 (35%)	60/144 (42%)	26/102 (26%)	P=0.01
Clinical hypogonadism:				
Erectile dysfunction *(men)*	39/138 (28%)	24/81 (30%)	13/51 (26%)	NS
Menstrual cycle disorders	29/54 (54%)	12/28 (43%)	16/24 (67%)	NS
Galactorrhea	17/245 (7%)	8/143 (6%)	9/102 (10%)	NS
Incidental finding	60/245 (24%)	35/143 (25%)	24/102 (24%)	NS
Number of deficient hormonal axes				NS
None	49 (20%)	34 (24%)	15 (15%)	
1	62 (25%)	32 (22%)	30 (29%)	
2	66 (27%)	36 (25%)	30 (29%)	
3	68 (28%)	41 (29%)	27 (27%)	
4	1 (0.4%)	1 (0.7%)	0 (0%)	
Type of hormonal deficiency				NS
gonadotrope	165/242 (68%)	95/140 (68%)	70/102 (69%)	
thyreotrope	150/243 (62%)	84/141 (60%)	66/102 (65%)	
corticotrope	79/245 (32%)	45/144 (31%)	34/101 (34%)	
diabetes insipidus	2/246 (0.8%)	1/144 (0.7%)	1/102 (1%)	
Hyperprolactinaemia (%)	119/246 (48%)	76/144 (53%)	43/102 (42%)	NS
PRL concentration (xULN)§	2.2 (1.03-5.9)	2.3 (1.07-5.3)	2.0 (1.03-5.9)	NS

*Visual disturbances include both visual field defects and reduced visual acuity; ULN : upper limit of normal; § : Prolactin (PRL) concentrations are shown only for the subset of patients with hyperprolactinemia

TABLE 2. Pituitary tumor characteristics at diagnosis and outcome after surgery

	All patients (N=246)	**St Luc Brussels N=144**	**Bicêtre Paris N=102**	**P value**
Tumor height (*mm*)	24.7 ± 9.2	25.7 ± 9.6	23.1 ± 8.3	0.042
Tumor width (*mm*)	24.5 ± 8.1	23.2 ± 8.0	26.2 ± 7.8	0.01
Tumor surface (mm^2)	517 ± 390	516 ± 423	519 ± 342	NS
Invasive adenoma	144/243 (59%)	76/144 (53%)	67/99 (68%)	0.024
Post-surgical tumor residue	153/239 (64%)	83/142 (59%)	70/97 (72%)	0.03
Progression or relapse at 1 year	27/202 (13%)	8/112 (7%)	19/90 (21%)	0.01

TABLE 3. Comparison between patients with and without pituitary deficiency at baseline

	Patients without pituitary deficit (n=49)	**Patients with pituitary deficit(s) (n=197)**	**P value**
Sex ratio (men/women)	23/26	115/82	NS
Age (years ; mean ± SD)	52 ± 16	56 ± 14	NS
Visual disturbances*	23/49 (47%)	136/196 (69%)	0.004
Hyperprolactinaemia	17/49 (35%)	102/197 (52%)	0.032
Tumor height *(mm)*	22.1 ± 8.1	25.3 ± 9.4	0.032
Tumor width (*mm*)	20.9 ± 7.3	25.4 ± 8.0	0.001
Invasive adenoma	28/49 (57%)	115/194 (59%)	NS

*Visual disturbances include both visual field defects and reduced visual acuity

TABLE 4. Comparison of pre- and post-surgical pituitary function in patients with and without hyperprolactinaemia at diagnosis

	Patients without hyperprolactinaemia (n=127)	Patients with hyperprolactinaemia (n=119)	P
At Diagnosis			
Gonadotropic deficiency	81/127 (64%)	84/115 (73%)	NS
Thyrotropic deficiency	73/127 (58%)	77/116 (66%)	NS
Corticotropic deficiency	39/126 (31%)	40/119 (34%)	NS
Diabetes insipidus	2/127 (1.6%)	0/119 (0%)	NS
Number with a pituitary deficit	95/127 (75%)	102/119 (86%)	0.032
Number of deficient axes (mean± SD)	1.56 ± 1.17	1.71 ± 1.03	NS
12 months post-surgery			
Gonadotropic deficiency	54/108 (50%)	49/107 (46%)	NS
Thyrotropic deficiency	44/109 (40%)	50/108 (46%)	NS
Corticotropic deficiency	40/109 (37%)	25/110 (23%)	0.024
Diabetes insipidus	6/108 (6%)	10/109 (9%)	NS
Persistent hyperprolactinaemia	5/93 (5%)	25/97 (26%)	0.001
Number with a pituitary deficit	67/109 (62%)	66/10 (60%)	NS
Number of deficient axes (mean±SD)	1.33±1.29	1.21±1.26	NS
Improvement of pituitary axes	31/109 (28%)	57/110 (52%)	0.001

TABLE 5. Cox univariate and multivariate analyses of factors predicting post-surgical improvement of pituitary deficiencies

	Univariate analysis			Multivariate analysis		
Dependent variable	**Odds ratio**	**95% CI**	**P value**	**Odds ratio**	**95% CI**	**P value**
Older age at diagnosis (years)	0.978	0.967-1.008	NS			
Gender (female)	2.128	1.162-3.896	0.014	1.229	0.539-2.804	NS
Visual disturbances at diagnosis	0.814	0.431-1.537	NS			
Hyperprolactinaemia	2.231	1.225-4.066	<0.001	2.127	1.071-4.224	**0.031**
Tumor height (*mm*)*	0.957	0.922-0.994	0.023	0.963	0.926-1.000	**0.050**
Tumor width (*mm*)*	0.938	0.896-0.982	<0.001	0.942	0.899-0.987	**0.012**
Invasive tumor	0.692	0.379-1.265	NS			

*Tumor height and width being correlated, these variables were introduced separately in two different multivariate analyses.

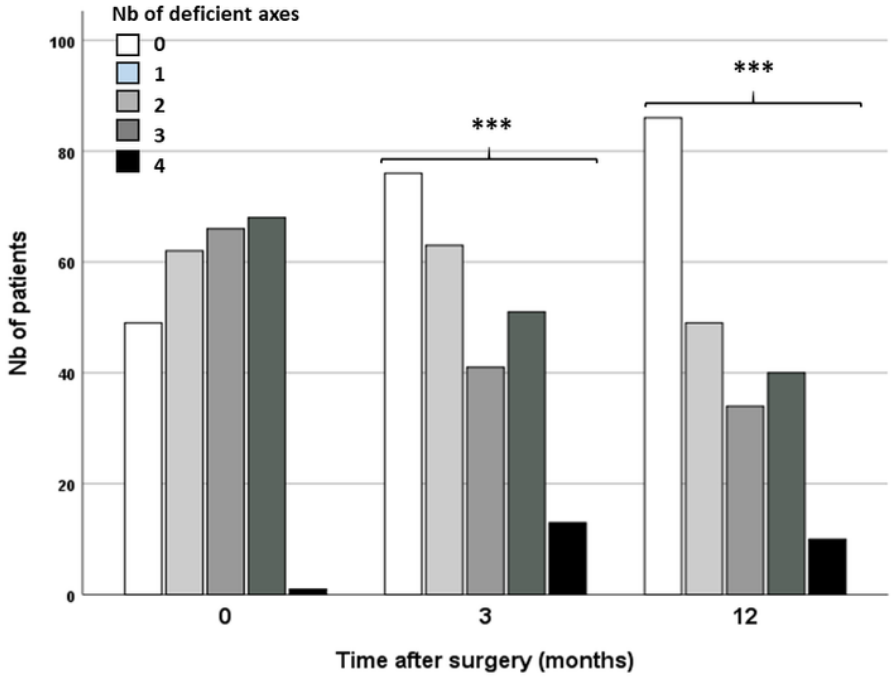
Table 6. Review of main studies published since 1999 on the outcome of pituitary hormonal deficits after surgery for a NFPMA

1st author	Year	Ref #	Nb of patients	Type of surgery	Type of adenoma	% with pituitary deficits at diagnosis	% with pituitary deficits after surgery	Factors predicting outcome
Webb	1999	9	234	211 TSS/23 TC	All types (56 NFPMA)	50%	33%	Invasion
Nomikos	2004	17	822	750 TSS/72 TC	All types (721 NFPMA)	85%	72%§	PRL,tumor size
Dekkers	2006	15	109	TSS	NFPMA	80%	95%	None
Fatemi	2008	8	444	NA	All types (223 NFPMA)	87%	45%	Age
O'Sullivan	2009	38	159	NA	NFPMA	GH : 90% - LH : 71% TSH : 25% - ACTH : 50%	GH : 91% - LH : 78% TSH : 50% - ACTH : 75%	NA
Berkmann	2012	40	114	TSS	NFPMA	73%	63%	NA
Lampropoulos	2013	36	184	TSS	All types (97 NFPMA)	77%	52 %	Tumor size
Jahangiri	2016	18	305	TSS	NFPMA	50%	34%	Age, tumor size
Laws	2016	39	80	TSS	All types (55 NFPMA)	40%	44%	NA
Magro	2016	41	300	TSS	NFPMA	60%	56%	NA
Watts	2017	42	127	125 TSS/2 TC	NFPMA	35% ≥2 deficits	38% ≥2 deficits	NA
Jceng Hee Kim	2018	19	331	TSS	NFPMA	69%	81%	None
Zhang	2019	28	164	TSS	NFPMA	80%	16%	NA
Hwang	2020	37	209	TSS	NFPMA	60%	17%	Age, tumor size
Our series	2020		246	TSS	NFPMA	80%	60%	PRL, tumor size

Overall results*	3089	NFPMA only	2294 (74%)	1798 (58%)

§: 69% in patients with TSS and 100% in patients with TC surgery; NFPMA; non-functioning pituitary macroadenoma; TSS: transsphenoidal surgery; TC: transcranial surgery: NA: information not available; *: the study of Watts et al was not taken into account in these calculations

Figures



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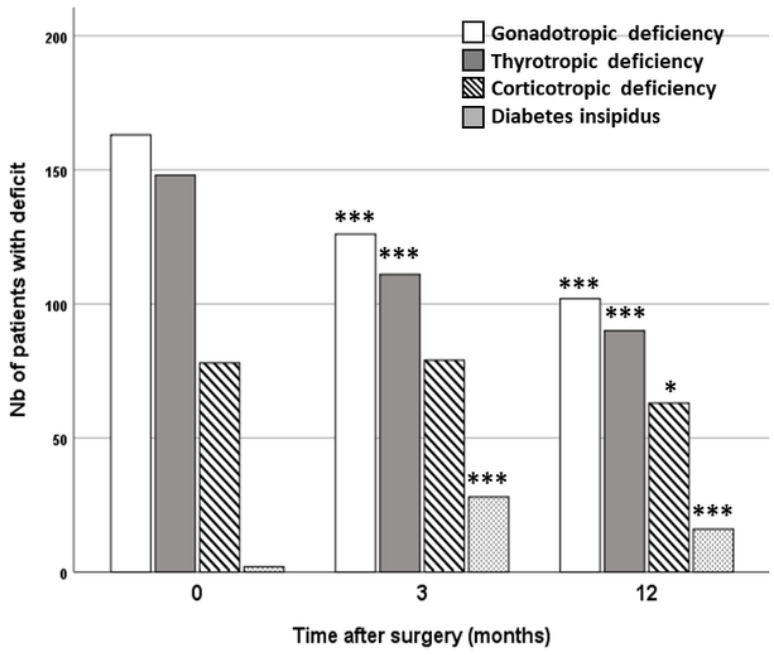

B

Figure 1

A. Numbers of patients with a non-functioning pituitary macroadenoma presenting 0, 1, 2, 3 and 4 pituitary deficits at diagnosis and 3 and 12 months after surgery. ***: P< 0.001 vs preoperative values when comparing the numbers of patients with no deficit, patients with 0 or 1 deficit, and patients with 0, 1 or 2 deficits (all lower at 3 and 12 months than at baseline), or when comparing the numbers of patients with 4 deficits (higher at 3 and 12 months vs baseline). B. Number of patients with a non-functioning pituitary macroadenoma having a deficit in each hormonal axis at diagnosis and 3 and 12 months after surgery. *, ***: P< 0.05 and 0.001, respectively, for the corresponding hormonal axis.