

## Original Article

## Pre- and postoperative magnetic resonance imaging appearance of the normal residual pituitary gland following macroadenoma resection: Clinical implications

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### Abstract

**Background:** To assess the relationship between the preoperative magnetic resonance imaging (MRI) appearance of the normal residual pituitary gland (NRPG) and pituitary functional outcome following transsphenoidal resection of pituitary macroadenomas.

**Methods:** We retrospectively reviewed the medical records of 100 consecutive patients with a pituitary macroadenoma, who underwent transsphenoidal resection. The preoperative configuration of the displaced NRPG was stratified as superior, superolateral or lateral. The extent of postoperative restitution of the NRPG was divided into four groups: Group 1 — normal residual gland or almost normal; Group 2 — more than 50% restitution; Group 3 — less than 50% of the normal residual gland; and Group 4 — barely visible or absent residual gland. The pre- and postoperative NRPG appearance was correlated with pituitary functional status.

**Results:** Preoperatively, the NRPG was identifiable in 79 patients, with extrasellar displacement in 53%. The displacement pattern was superior in 8%, superolateral in 32%, and lateral in 58% of the patients. If the NRPG was displaced laterally, the ipsilateral cavernous sinus was not invaded by the pituitary macroadenoma. Partial or complete pituitary function was lost in 6 / 23 (26.1%) patients with superior or superolateral displacement of the NRPG, compared to only 1 / 36 (2.8%) patients without superior displacement of the NRPG ( $P = 0.025$ ). Progressive postoperative reconstitution of the NRPG was related to the preservation of the pituitary hormonal axis (Pearson Chi-Square  $P < 0.001$ ).

**Conclusions:** Progressive displacement of the NRPG preoperatively, and lack of restitution of the NRPG on postoperative MRI appeared to correlate with the postoperative pituitary functional loss.

**Key Words:** Endoscopic resection, macroadenoma, MRI, pituitary gland, transsphenoidal surgery

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## INTRODUCTION

Functional preservation of the normal residual pituitary gland (NRPG) during removal of pituitary macroadenomas remains a challenge in certain cases. Since the first description of microscope-assisted selective adenoma removal first introduced by Hardy,<sup>[11]</sup> intraoperative identification of the NRPG was possible in a majority of cases, thus facilitating preservation during surgery<sup>[16,18]</sup> and reducing the incidence of postoperative pituitary insufficiency. Furthermore, high-resolution magnetic resonance (MR) imaging with and without administration of gadolinium provided an accurate preoperative assessment and staging of pituitary tumors.<sup>[13,19,25,26]</sup>

Several authors have investigated the MR appearance of the normal pituitary gland, including size and shape, as a function of patient age,<sup>[8,9,28]</sup> the signal intensity of the adenohypophysis and the neurohypophysis on unenhanced T1-weighted images,<sup>[2,4,14,15]</sup> as well as the dynamic enhancement pattern of the pituitary gland after contrast administration.<sup>[17,21,27]</sup> The shape and location of the NRPG in patients with pituitary macroadenomas, however, has received limited attention in the literature. The normal pituitary gland can be identified reliably in small lesions, but in large tumors with severe displacement and compression, its recognition is more challenging. In addition, on postoperative MR images, differentiation between the pituitary gland remnant and residual tumor may be difficult.

The objectives of the present study were, (1) to assess the detectability, location, and configuration of the NRPG on MRI before and after resection of pituitary macroadenomas, and (2) to correlate the NRPG appearance with postoperative pituitary function, in patients with pituitary macroadenomas.

## MATERIALS AND METHODS

### Study design and patient population

The study design is a retrospective chart review of consecutive patients operated at the Sir Mortimer B. Davis-Jewish General Hospital from 1991 to present, for pituitary macroadenomas. The inclusion criteria included, (1) surgery via a transsphenoidal approach for pituitary macroadenoma with histological confirmation; (2) adequate MRI imaging was performed preoperatively; and the available clinical and endocrinological data were collected both (3) pre- and (4) postoperatively at follow-up. A macroadenoma was defined as having a maximal diameter of at least 10 mm. A postoperative MRI was performed at a minimum of four to six months from the time of surgery, to minimize artifacts related to residual hemostatic materials, fat graft, and scar tissue. Patients were excluded if they had previously received radiation

therapy or had undergone surgical resection elsewhere. All patients were operated via the transsphenoidal approach, using either microscopic or endoscopic visualization, and had sellar floor reconstruction with bone fragments, without fat packing. Postoperative lumbar drainage was done in cases with intraoperative cerebrospinal fluid (CSF) leak.

### Clinical and Endocrinological Evaluation

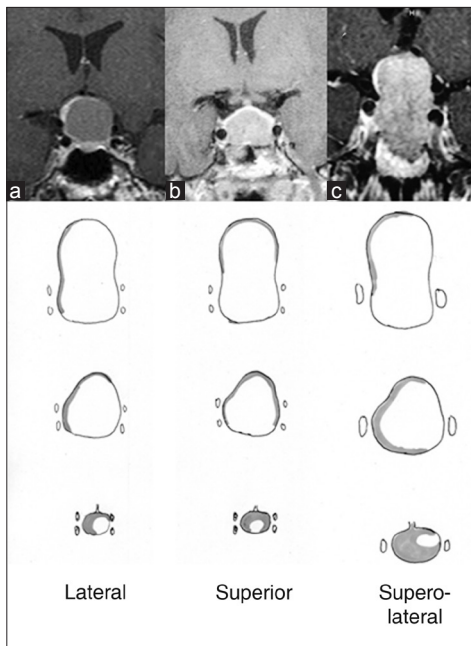
All patients underwent neuro-ophthalmological examination and evaluation of the endocrinological function before and after surgery and at the last follow-up. Based on the hypophyseal-adrenocortical axis integrity and need for corticosteroid replacement therapy, the postoperative anterior pituitary functions were classified as 'eupituitary' (normal function), 'hypopituitary' (partial function), and 'panhypopituitary' (no function). The posterior pituitary function was assessed based on a clinical diagnosis of diabetes insipidus. All patients received hydrocortisone parenterally prior to surgery, which was rapidly tapered over four-to-five days postoperatively. Evaluation of endocrinological function was performed using conventional stimulation tests by injection of the adrenocorticotropic hormone (ACTH), with continued oral administration over a time period of six weeks after surgery. Basal and stimulated (30 minutes) cortisol and basal thyroid-stimulating hormone (TSH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were measured in the serum, as well as the basal levels of prolactin, insulin-like growth factor 1, total or free T3 and T4, and also estradiol or testosterone. The basal values for the hormones tested were assigned according to the manufacturers' instructions for the hormone assays used.

### Imaging

The MRI studies were performed using a 1.5 Tesla magnet (Gyrosan Philips Netherlands and Signa General Electric USA). T1-weighted images (372 – 548 / 16 – 20 TR / TE) were obtained before and after the Gd-DTPA injection. Section thickness was 2.0 mm with a matrix size of 256 × 256 and a field of view of 16 – 18 cm. The pre- and postoperative MR images were independently evaluated by two observers (GM, JLV), including a neuroradiologist (JLV), and the data were ultimately classified by consensus. In all the patients, the axial, sagittal, and coronal series were evaluated, to specifically identify the NRPG including the neurohypophyseal bright spot (BS) and the residual adenohypophysis (RAH) on the pre- and post-gadolinium images, respectively. The maximal diameters in each plane were used to calculate the NRPG volume, which was compared with a database of 102 normal controls,<sup>[20]</sup> in order to obtain a percentage of the preoperative compression of the NRPG as well as the percent of the postoperative reconstitution. All pre- and postoperative MR images were also evaluated according to the detectability, location, and configuration of the

pituitary gland. The NRPG was accepted as visible only in the presence of a clear delineation by enhancement after contrast injection. The BS was used as an ancillary locator of the RAH as part of the normal gland (NRPG), based on an earlier study by senior authors.<sup>[20]</sup> The respective topography and displacement of the BS and the NRPG were evaluated according to their intrasellar and extrasellar locations. The tuberculum sellae was used as the arbitrary landmark between the intrasellar and the extrasellar space.

The configuration of the pituitary gland was assessed in coronal projection. It was considered normal when the infundibulum was medially located in a gland of symmetric shape. Displacement and the shifts of the BS and the NRPG were classified as superior, superolateral or lateral in position [Figure 1]. Superior displacement of the NRPG was defined as a symmetrical upward displacement of the NRPG, relative to the macroadenoma, typically outside of the sella turcica. Superolateral displacement was defined as a residual pituitary gland visible along the superior border and the lateral border of the macroadenoma, also typically outside the sella



**Figure 1:** Schematic of observed preoperative distortion patterns of the normal residual pituitary gland, with corresponding examples on coronal post-contrast T1-weighted magnetic resonance imaging. Lateral (a), superior (b) and superolateral (c) displacement of the normal residual pituitary gland (NRPG) was observed in 58, 8, and 32%, respectively. Superior displacement of the NRPG was defined as a symmetrical upward displacement of the NRPG, relative to the macroadenoma, typically outside of the sella turcica. Superolateral displacement was defined as a residual pituitary gland visible along the superior border and the lateral border of the macroadenoma, also typically outside of the sella turcica. Lateral displacement of the gland was defined as a pituitary tissue along a single lateral border of the macroadenoma, often with both a sellar and suprasellar component. Inferior displacement of the NRPG was not observed in our series of macroadenomas

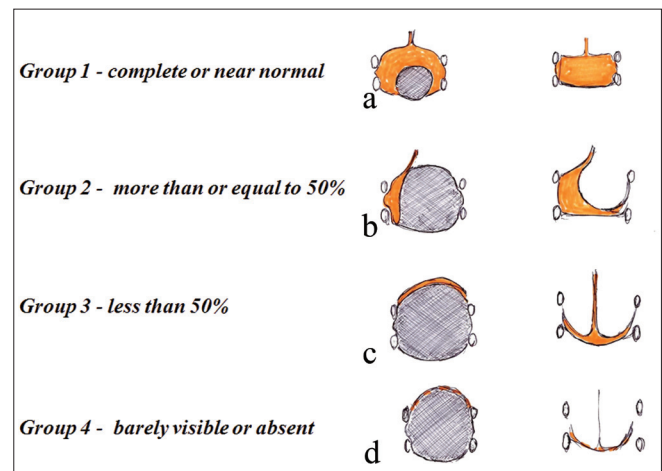
turcica. Lateral displacement of the gland was defined as pituitary tissue along a single lateral border of the macroadenoma, often with both a sellar and suprasellar component. Inferior displacement of the gland was not observed in any case within our series. The preoperative MRI studies were correlated with intraoperative findings such as the location, extension, and invasiveness of the adenoma. The modified Vezina–Hardy classification was used to stage both the size and the suprasellar extension of the macroadenomas.<sup>[18]</sup>

In the postoperative MRI, the appearance of the NRPG was subdivided into four groups, based on the extent of morphological restitution: Group 1 — complete or near normal, Group 2 — more than 50% restitution, Group 3 — less than 50% of the expected normal residual volume, Group 4 — barely visible or absent residual gland [Figure 2].

### Outcome analysis and statistics

The patients were reviewed for the improvement in their vision and endocrine function restoration in the functionally active tumor, and remission was noted in the nonfunctioning tumors. The preoperative location of the pituitary gland was correlated with the postoperative topographic restitution of the NRPG and the functional endocrine outcome.

The pituitary functional status based on residual gland appearance was analyzed using the Chi-square test. A P value of < 0.05 was considered to be statistically significant. The statistics software used for data analysis was the IBM SPSS version 19 (SPSS: An IBM Company, 2008).



**Figure 2:** Schematic of the postoperative position of the normal residual pituitary gland (NRPG). Patterns of postoperative reconstitution of the normal pituitary gland are shown in the right hand column, with common corresponding preoperative morphologies of the gland on the left. Group 1 (a): Complete or near-normal reconstitution of the NRPG; group 2 (b): Reconstitution greater than or equal to 50%; group 3 (c): Less than 50%; and group 4 (d): NRPG barely visible or absent on postoperative magnetic resonance imaging

## RESULTS

### Clinical Symptoms and Endocrinological function:

From 1997 to present, 100 patients (55 males and 45 females) underwent transsphenoidal removal of a pituitary macroadenoma. The baseline characteristics are presented in Table 1. The average patient age was 48.2 years (range 20 – 80 years), with a mean follow-up of 39.5 months. The average tumor volume was  $2.4 \pm 1.2 \text{ cm}^3$  (range 0.25 – 4.8  $\text{cm}^3$ ). There were 55 non-functioning pituitary adenomas and 45 secretory adenomas (17 GH, 12 PRL, 8 ACTH, 8 mixed). Visual symptoms and signs were present in 47 patients (8 with bitemporal visual field defects combined with visual loss, 31 with bitemporal visual field defects without visual loss, 6 with diplopia, and 2 with visual loss). Thirty-three patients complained of headache preoperatively. The macroadenoma was incidentally discovered in nine patients. Following surgery, visual improvement was noted in 43 / 47 patients (91.5%) with complete normalization of visual fields in 11 patients. All patients reported improvement in the headaches experienced before surgery. Endocrinological cure was achieved in 33 / 45 (73.3%) of the secretory tumors, and pituitary function was preserved in 78.8% of the patients.

### Magnetic resonance imaging characterization of the normal residual pituitary gland

Preoperative visualization of the NRPG on MRI was possible in 76 cases, and the BS was visible in 67 of these patients. In all cases where the NRPG was identified, it enhanced more than the macroadenoma; 56.9% of the 76 cases with a visible NRPG also had a positive 'sign of the stalk,' and in 84.8% the BS was also visible. In 53.2% of these patients the NRPG was completely displaced to an extrasellar location. Preoperatively, distortion of the NRPG was noted in 75 of the 79 cases (94.9%). The most frequent pattern of displacement of the NRPG was lateral in 47 cases (58.3%; Figure 1a), followed by superolateral [Figure 1c] and superior [Figure 1b] in 21 and seven cases, respectively [Table 2]. In four patients, the pituitary gland showed a nearly normal configuration. No case of inferior displacement of the pituitary gland was noted in our series of macroadenomas. In cases of severe displacement and deformation of the pituitary gland its detectability was markedly improved by contrast administration. On Gd-DTPA-enhanced T1-weighted MR images, a crescent-shaped pituitary gland appeared as a narrow rim of enhancing tissue on the periphery of the adenoma. In the laterally displaced, the pituitary gland was interposed between the medial wall of the cavernous sinus and the adenoma. In these cases the cavernous sinus was not invaded ipsilateral to the side of the pituitary gland displacement. Intraoperatively, the normal residual gland was visible in 68% of the patients. No significant

correlation was found between the immunohistological classification of the adenoma and the preoperative displacement pattern.

### Postoperative magnetic resonance imaging

Postoperatively, the location of the pituitary gland could be identified in 85 cases. In 34 / 40 (85.0%) patients with preoperative extrasellar displacement of the NRPG, the pituitary gland descended from the extrasellar to the intrasellar space following surgery. Postoperative re-expansion of the gland was seen, documented from an increase in its shortest diameter on the coronal images, in 85% of the cases. The pattern of postoperative restitution of the NRPG is shown in Table 3. In 32 cases the NRPG was located postoperatively in a median position and had a near-normal configuration (Group 1) [Figure 3a] and in 53 cases the gland had re-expanded to less than

**Table 1: Baselines characteristics of patient cohort (n = 100)**

Characteristics	No.
Males : females	55 : 45
Mean age	48.2 years (20 – 80 years)
Mean follow-up	39.5 months
Immunohistological sub-type	
Non-functioning adenoma	37
Growth hormone secreting	16
Prolactin secreting	10
Mixed Growth hormone-Prolactin secreting	8
Adrenocorticotrophic hormone	8
Mean tumor volume	2.4 $\text{cm}^3$ (0.25 – 4.7 $\text{cm}^3$ )
Modified Hardy–Vezina Grading	
Giant (Grades C and D)	9
Large (Grade B)	40
Moderate (Grade A)	37
No suprasellar extension (Grade 0)	13

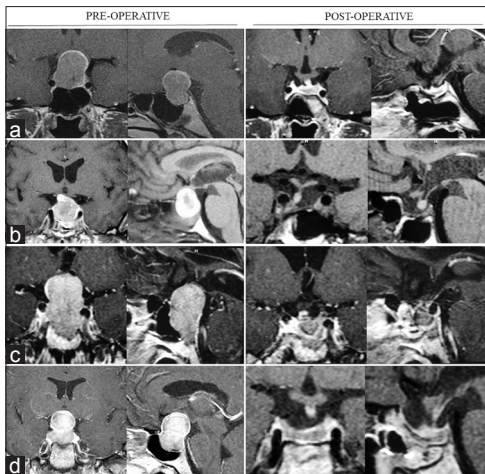
**Table 2: Displacement Patterns of the Normal Residual Pituitary Gland**

Location of normal residual pituitary gland	No. (%)
Superior	7 (8.9)
Superolateral	21 (32.8)
Lateral	47 (58.3)

**Table 3: Postoperative Anatomical Gland Restitution of the Normal Residual Pituitary Gland (n = 100)**

Postoperative Gland restitution	No.
Group 1 (Near Normal Gland)	32
Group 2 (> 50% Gland Restitution)	29
Group 3 (< 50% Gland Restitution)	24
Group 4 (Absent or barely visible Gland)	15



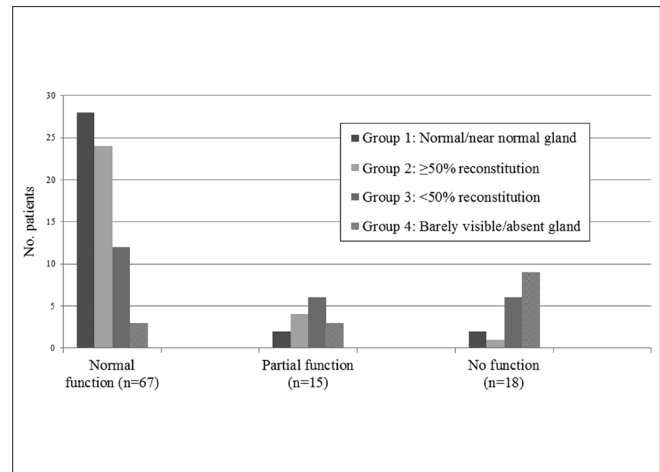


**Figure 3: Case illustrations of pituitary macroadenomas (left) with varying degrees of reconstitution of the normal residual pituitary gland (NRPG) on postoperative magnetic resonance imaging (right). Group 1 example (a) in a patient with an acidophilic stem cell macroadenoma. The NRPG is displaced superiorly in a rim-like fashion (left); group 1 (near-normal) reconstitution of the gland (right) with intact pituitary function postoperatively. Group 2 example (b) in a non-functioning macroadenoma, with superior focal displacement of the NRPG (left); Group 2 (> 50%) reconstitution (right), with normal pituitary function postoperatively. Group 3 illustration (c) in a 31-year-old female with lateral gland displacement (left); Group 3 (< 50%) NRPG reconstitution (right), with normal endocrine function. Group 4 example (d) in a non-functioning macroadenoma with thin rim-like superior displacement of the NRPG preoperatively (left); Group 4 (barely visible) reconstitution of the gland postoperatively (right), with associated hypopituitarism**

or more than 50% of normal (Groups 2 and 3; Figure 3b and c), but not completely normal. In 15 patients, the NRPG could be barely visualized (Group 4; Figure 3d). Among patients with none-to-moderate suprasellar extension (Hardy-Vezina Grade 0 and A), 67.0% had 50–100% restitution of the NRPG, whereas 77.8% with giant pituitary adenomas (Hardy–Vezina Grades C and D) had barely visible NRPG on postoperative MRI.

### Postoperative Function

Postoperative pituitary function was analyzed according to the preoperative displacement pattern of the NRPG. Partial or complete pituitary function was lost in 6 / 23 (26.1%) patients with superior or superolateral displacement of the NRPG, compared to only 1 / 36 (2.8%) patients without superior displacement of the NRPG (Pearson Chi-Square  $P = 0.025$ ). The type of postoperative appearance of the residual pituitary gland grouped by endocrine status is shown in Figure 4. Patients with an intact pituitary axis were more likely to have a higher grade of anatomical restitution of the pituitary gland postoperatively, than patients with incomplete or absent endocrine function (Pearson Chi-Square  $P < 0.001$ ).



**Figure 4: Proportion of patients with normal, partial or no postoperative pituitary function according to the type of postoperative magnetic resonance imaging restitution of the normal residual pituitary gland.**

## DISCUSSION

MRI is universally used in the postoperative surveillance of pituitary adenomas, for the detection of residual or recurrent tumors. There are, however, no established reproducible criteria for the assessment of postoperative studies, particularly for differentiating implanted material from the residual or recurrent tumor, or for correlating the MRI findings with the clinical and endocrine status.<sup>[6,27]</sup>

This study investigated the detectability, location, and configuration of the pituitary gland on pre- and postoperative unenhanced and Gd-DTPA-enhanced T1-weighted MRI, and also assessed the relationship between the MRI appearance of the NRPG and pituitary functional status.

The NRPG was identified in 79% of the patients on preoperative MRI, and in all cases showed a stronger enhancement pattern than the pituitary adenoma. The gadolinium uptake significantly improved the detectability of the pituitary gland, particularly in cases of severe deformation of the pituitary gland. The improved detectability of the pituitary gland, after contrast administration, was due to the rapid and marked contrast enhancement of the pituitary gland, which exceeded that of an adenoma in most cases.<sup>[17,26]</sup> In 84.8% of the cases, the bright spot (BS) was visible preoperatively. As the BS was identified more frequently than the RAH,<sup>[20]</sup> it served as an important surrogate for the location of the normal residual pituitary gland, in patients who did not have a clear delineation of the NRPG. The presence of the BS did not play a significant role in cases where the delineation between the NRPG and the lesion was clearly evident. In addition, the ‘Sign of the Stalk’ was also used

to help locate the normal pituitary gland, as the stalk was also strongly enhancing with contrast imaging, and was also useful in localizing the pituitary gland when followed distally, both in coronal and sagittal reconstructions.<sup>[7]</sup>

Detectability of the NRPG was better on postoperative MRI, due to postoperative re-expansion of the pituitary gland and the high contrast between the pituitary gland and the surrounding cerebrospinal fluid, after tumor resection. Furthermore, the functional preservation of the pituitary gland appeared to be related to the extent of postoperative re-expansion of the NRPG on MRI.

The expansive growth of pituitary macroadenomas leads to compression, displacement, and deformation of the pituitary gland, and is dependent of the size, location, and extension of the adenoma. Most macroadenomas showing suprasellar extension tend to gradually displace the pituitary gland up to the extrasellar space possibly due to a pulsion phenomenon, resulting in an eccentric rim of normal gland, which forms a capsule in 53.2% of the cases. In a study by Bonneville *et al.*, extrasellar displacement of the NRPG was observed in nearly all macroadenomas greater than 20 mm in diameter.<sup>[1]</sup> Furthermore, 49% of the non-functioning pituitary macroadenomas had extrasellar displacement of the NRPG in our series. This could be explained by the large size of the adenomas, due to delayed presentation with compressive symptoms, whereas, 76% of the secretory adenomas had lateral and intrasellar location of the NRPG, due to earlier detection, related to the more eloquent endocrine manifestation. Lateral displacement of the NRPG could therefore be more frequent initially and ultimately be displaced superiorly, with increasing adenoma size. This was corroborated in an earlier study from our institution.<sup>[20]</sup>

Preoperative identification of a laterally displaced normal pituitary gland played an important role in the evaluation for cavernous sinus invasion. Cavernous sinus infiltration is not uncommon, and is reported in 35 – 85% of the cases,<sup>[22,24]</sup> and substantially influences both the surgical procedure and the patient's outcome. Unfortunately, demonstration of the medial wall of the cavernous sinus is not always possible on T1-weighted images.<sup>[12]</sup> Therefore, indirect signs such as the obliteration of the compartments of the cavernous sinus by the tumor or encasement of the internal carotid artery have to be used as surrogate indicators for cavernous sinus infiltration.<sup>[5,23]</sup> However, when the pituitary gland is interposed between the medial wall of the cavernous sinus and the adenoma, infiltration of the cavernous sinus is highly unlikely, as in our series. Scotti *et al.*, have also characterized the interposition of the compressed pituitary gland between the cavernous sinus and adenoma tissue on unenhanced T1-weighted MR images and termed this as the 'rim sign'.<sup>[23]</sup> We have furthermore found the contrast-enhanced

MRI to be of use in evaluating for the 'rim sign' preoperatively.

Following resection of the pituitary macroadenomas, repositioning and re-expansion of the pituitary gland is generally seen and appears to occur physiologically. Postoperative repositioning of the pituitary gland, evidenced by lowering from extrasellar to intrasellar and / or shifting from lateral to medial, depends partly on the degree of preoperative displacement. In cases of suprasellar displacement of the pituitary gland, postoperative lowering into the intrasellar location occurs if the tumor has been adequately decompressed. Re-expansion, evidenced by a change of configuration from crescentic and cap-like to nearly normal, was found in 32% of the patients. Repositioning and re-expansion of the pituitary gland, after tumor resection, was found to be a slowly progressive process in most cases, as demonstrated on serial postoperative MR images, however, in some cases the pituitary gland could move back into the intrasellar resection cavity as soon as the tumor was removed. Furthermore, hemostatic materials left in the endosellar space, such as gelatin foam and oxidized cellulose, could acutely conceal the residual pituitary gland.<sup>[27]</sup> As such, from our experience, we found that the ideal time for the optimal assessment of the residual tumor and pituitary gland on postoperative MRI was between four and six months, so as to allow the foreign material or blood to resolve.

In spite of the extreme preoperative displacement of the NRPG in macroadenomas, some patients in our series retained normal pituitary function. The superior hypophyseal arteries, which arise from the supraclinoid portion of the internal carotid and posterior communicating arteries, supply the median eminence and the infundibulum via the primary portal system. The blood is then collected into vessels of various lengths within the infundibulum, which open into vascular sinusoids within the anterior lobe of the pituitary gland.<sup>[10]</sup> These sinusoids constitute the secondary plexus of the pituitary portal system or the secondary capillary bed. The hypothalamo-hypophyseal portal system might remain functional despite the mass effect from the macroadenoma, with persistence of the peptide hormone factor signaling from the hypothalamus to the anterior pituitary. The extent of re-expansion of the NRPG expectedly correlated with the pituitary function, postoperatively; however, a normal pituitary function was also seen in 3 / 67 patients with a barely visible gland. This could be explained either by the sufficient pituitary hormone production by the pars tuberalis remnant or median eminence, with direct CSF transport of the peptide hormones into the circulation. Conversely, among patients who had panhypopituitary function preoperatively, three had a near-normal appearance of the pituitary gland. The stretching of the stalk by the

growing adenoma, with subsequent ischemia of the gland from elongation and compression of the hypothalamo-hypophyseal portal system and necrosis of the cells, with the ghost appearance of the gland, could be suggested as an etiology.<sup>[3]</sup>

## CONCLUSION

The visibility of either the pituitary bright spot or the distorted residual pituitary gland on a preoperative MRI is a favorable sign for intraoperative identification and functional preservation of the normal residual gland. Postoperative pituitary hypofunction was more frequent in cases where the NRPG was displaced superiorly or superolaterally, preoperatively. Progressive postoperative restitution of the NRPG correlated with the functional preservation of the pituitary gland. Perioperatively, these MRI features could thus contribute toward predicting the endocrine functional outcome following pituitary macroadenoma surgery.

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