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Intraoperative unfolding and postoperative pruning of the pituitary gland after transsphenoidal surgery for pituitary adenoma: A volumetric and endocrinological evaluation

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Abstract

Purpose To describe the volumetric changes that the pituitary gland (PG) undergoes during and after transsphenoidal surgery (TSS), and to evaluate if unfolding and/or pruning are related to endocrinological outcome measures.

Methods Retrospective evaluation of data prospectively collected of a cohort of patients undergoing TSS for a pituitary adenoma with the adjunctive use of high field 3 Tesla intraoperative MRI. All patients underwent a full endocrinological workup preoperatively, as well as at 6 weeks and 1 year postoperatively. A decrease in PG volume ≥15% between the intraoperative and 3-month, or between the 3-month and 12-month measurements, was considered early and late pruning, respectively.

Results The PG unfolds significantly during TSS, and subsequently undergoes pruning up until 1 year postoperatively, in most cases returning to the preoperatively measured PG volume. A smaller baseline PG volume predicts intraoperative unfolding. Early pruning of the PG after surgery was associated with new functional deficits. Baseline pituitary compression also correlated to newly occurring deficits after surgery. A larger 1-year pituitary volume was associated with biochemical remission in secreting adenomas.

Conclusions The PG shows dynamic change during and after TSS for pituitary adenoma. Small baseline and 3-month PG volumes, as well as early pruning were independently associated with new deficits. Our findings warrant prospective validation in a larger cohort with higher statistical power.

Keywords Pituitary surgery · Hormonal function · Outcome prediction · Pituitary adenoma · Transsphenoidal surgery

Introduction

Transsphenoidal surgery (TSS) is a well-established treatment for pituitary adenoma, and constant technical improvements have led to safer and more extensive resections with a low rate of recurrence and minimal perioperative morbidity and mortality [1–6]. Among other improvements, intraoperative high field strength magnetic

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resonance imaging (3T-ioMR) is increasingly being used to enhance resection rates and volumetric extent of resection [2]. In addition, 3T-ioMR provides an opportunity for studying the intraoperative dynamic changes that the sella undergoes. In our institutional experience, 3T-ioMR allowed to visualize a significant intraoperative variation of the intercarotid distance [7]. We realized however that also the pituitary gland (PG) often undergoes significant volumetric changes visible at the 3T-ioMR.

To the authors' best knowledge, there is no published data on the volumetric course of the pituitary gland during and after TSS. It is known that intrasellar increase in pressure and direct compression of the gland are the cause of hormonal dysregulation [8, 9]. We hypothesize that the PG expands during TSS, and that this unfolding may relate to functional improvement. Consequently, the aim of this study was to describe the volumetric changes that the PG undergoes during and after surgery, and to evaluate if unfolding and/or pruning are related to endocrinological outcome measures.

Materials and methods

Patients

We retrospectively evaluated a consecutive patient series that underwent endoscopic transnasal transsphenoidal surgery for PA performed by two senior neurosurgeons (L.R. and C.S.) at the Department of Neurosurgery of our institution. To be included, patients had to have a minimum of complete preoperative, intraoperative, and 3-month postoperative neuroimaging data, as well as complete baseline, directly postoperative, and 1-year postoperative endocrinological data. Exclusion criteria were transcranial or combined procedures, and decompressive procedures for visual field deficits alone. From October 2012 onwards, all patients were treated according to the same PA protocol as previously described [2]. Clinical and radiological data were collected in a prospective database. In August 2013, high field 3T-ioMR was introduced into our clinical practice and is routinely performed unless contraindicated. Patient included in the study declared informed consent. Data were treated according to the ethical standards of the Declaration of Helsinki. This study was approved by the local review board (KEK St-V-Nr 2015-0142).

Neuroimaging

Patients underwent preoperative, intraoperative, and postoperative volumetric contrast-enhanced T1-weighted MRI at a field strength of 3 Tesla (3T-MRI, Siemens 3-T Skyra VD13). Source DICOM images of the volumetric sequences of each 3-T MR image (preoperative, intraoperative, and postoperative) were uploaded onto iPlan® software for volumetric measurements (iPlan Cranial, BrainLab) for each patient. PGs and adenomas (PA) were manually contoured on source images to allow subsequent 3D rendering and volumetric measurement [2]. The PG volume included the pituitary stalk. Measurements were made by a board-certified neurosurgeon with extensive experience in pituitary surgery and imaging, and were continually entered into the prospective registry. We estimated the measurement error by repeated measures using the mean deviation in percent from the mean of measurements. Using this method, a mean measurement error for pituitary volumes of 11% was found. Consequently, we defined pituitary unfolding as a ≥15% increase in volume between the preoperative and intraoperative measurements. A ≥15% decrease in PG volume between the intraoperative and 3-month, or between the 3-month and 12-month measurements, was considered early and late pruning, respectively.

Outcome measures

All patients underwent a full endocrinological workup preoperatively, as well as at 6 weeks and 1 year postoperatively by board certified endocrinologists. Hormone levels were determined, including TSH, fT4, estradiol, testosterone, prolactin, IGF-1, GH, fasting glucose, and early morning cortisol. Values below and above normal range and clinical symptoms were assessed. In male patients, basal testosterone as well as LH and FSH were recorded. In female patients without anamnestic regular cycle or under hormonal contraceptives, we recorded estradiol, LH, and FSH. Hormonal substitution therapies included Desmopressin (Minirin®) as a nasal spray or applied intravenously, levothyroxine (Eltroxin® or Euthyrox®), glucocorticoids (intravenous dexamethasone and oral or intravenous hydrocortisone), and intramuscular testosterone (Nebido®). We defined a hypothalamic-pituitary axis (HPA) deficit as the necessity for hormonal substitution therapy, based on hormone levels and clinical presentation according to internationally accepted guidelines [10]. We recorded the number of compromised HPA, as well as any functional gains and losses throughout the follow-up period. Functional improvement was defined as a decrease in the number of compromised HPA from the baseline to the 1 year follow-up. Biochemical remission (BR) was defined as normalization of hypersecretion into the normal reference range as defined by accepted international guidelines [11, 12].

Statistical analysis

Continuous data are presented as mean ± standard deviation for normally distributed and median (interquartile range, IQR) for non-normally distributed continuous data, while categorical data are reported as numbers and percentages. Longitudinal data were examined using paired *t*- tests. Intergroup differences in baseline pituitary volume were assessed using Welch's two-sample *t* test. Intergroup differences in intraoperative, 3 month, and 1 year pituitary volumes were assessed using analysis of covariance (ANCOVA) to adjust for baseline pituitary volumes. Independent predictors of pituitary volumetric changes and endocrinological outcomes were analyzed by means of logistic regression. For predictors of endocrinological outcomes, we included intraoperative PG unfolding as a predictor and performed adjustment for sex, age, and baseline pituitary and tumor volumes. For regression analyses, numerical variables were dichotomized as follows: number of HPA deficits (<2 / ≥2), age (<60 / ≥60 years), tumor volume (<10 / ≥10 cm^3). Odds ratios (OR) and their 95% confidence intervals (CI) were obtained. All statistical analyses were carried out in R version 3.4.4 (The R Foundation for Statistical Computing, Vienna, Austria). A $p \leq 0.05$ on two-tailed tests was considered significant.

Results

A total of 92 patients were included. Baseline patient and PA characteristics are provided in Table 1. Thirty-three patients (36%) presented with secreting adenomas, while 59 (64%) underwent surgery for nonfunctioning adenomas. Eleven patients (12%) had undergone prior transsphenoidal surgery. Overall, gross total resection (GTR) was achieved in 62 patients (67%), with a median EOR of 100 (IQR: 98.6–100) %. Median residual tumor volume was 0 (IQR: 0–0.098) cm^3. On the 3 months postoperative MRI, residual tumor was present in 30 cases (33%). Of the 33 patients with secreting adenomas, 26 (79%) experienced BR at 1 year. Complete 1-year neuroimaging data was available from 74 patients (80%). Endocrinological outcomes were complete for all patients (Table 2). At the 1-year endocrinological workup, 20 (22%) patients saw 30 functional HPA improvements (11 thyrotroph, 10 gonadotroph, 8 corticotroph, and 1 diabetes insipidus). In 10 (11%) patients 12 new HPA deficits were seen (5 thyrotroph, 4 gonadotroph, 2 corticotroph, and 1 diabetes insipidus). We observed no cases of panhypopituitarism.

Pituitary unfolding

Figure 1 demonstrates a typical clinical case of pituitary unfolding and pruning. On average, the PG expanded by 0.126 cm^3 (95% CI 0.093–0.160) during surgery ($p < 0.001$, Table 3). Out of the 92 patients, 64 (70%) exhibited intraoperative unfolding. From the intraoperative to the 3-month measurement, there was no change in volume ($p = 0.102$). Only a smaller baseline PG volume predicted unfolding ($p < 0.001$), while adenoma type, volume and parasellar extension as defined by the Micko-Knosp classification [13], as well as sex and age did not (all $p > 0.05$). When controlling for confounders in a multivariate analysis, intraoperative unfolding was not predictive of functional improvement, new deficits, number of HPA deficits, or biochemical remission at the 1-year endocrinological workup (all $p > 0.05$, Supplementary Table 1). Figures 2–4 illustrate PG volumes over time.

Table 1 Baseline patient characteristics and surgical results at 3 months of the 92 patients that were included

Characteristic	Value
Male sex, *n* (%)	50 (54)
Age, mean ± SD (years)	52.4 ± 15.4
Tumor type, n (%)	
Non-functioning	59 (64)
GH-secreting	23 (25)
Prolactin-secreting	6 (7)
ACTH-secreting	3 (3)
Plurihormonal	1 (1)
Preoperative adenoma volume, mean ± SD (cm^3)	0.293 ± 0.184
Modified Knosp classification, n (%)[a]	
Grade 0	19 (21)
Grade 1	15 (16)
Grade 2	29 (32)
Grade 3 A	16 (17)
Grade 3B	6 (7)
Grade 4	7 (8)
Gross total resection, *n* (%)	62 (67)
Extent of resection, median (IQR) (%)	100 (98.6–100)
Residual adenoma volume at 3 months, median (IQR) (cm^3)	0 (0–0.098)

SD standard deviation, *IQR* interquartile range

[a]Classification described by Micko et al. [13]

Pituitary pruning

Significant pruning of the PG by −0.132 cm^3 (95% CI −0.079 to −0.184) was observed between the 3-month and 1-year measurements ($p < 0.001$). In 47 (64%) of 74 patients with 1-year neuroimaging data, late pruning of the PG occurred. No predictors of PG pruning were identified among baseline PG volume, adenoma type and volume, extent of resection, intraoperative unfolding, sex, age, and hormonal deficits, (all $p > 0.05$). Late pruning was not associated with any endocrinological outcome measure at 1 year in the multivariate analysis (all $p > 0.05$). Early pruning, on the other hand, was observed in 13 (14%) patients

Table 2 Detailed axis-specific pituitary deficits throughout the follow-up period

Nr.	Baseline				6 weeks				1 year					
	Hypothyroidism	Hypoadrenalism	Hypogonadism	DI	Hypothyroidism	Hypoadrenalism	Hypogonadism	DI	Hypothyroidism	Hypoadrenalism	Hypogonadism	DI	New deficit	Improvement
1	No	No	No	No	No	Yes	No	No	No	Yes	No	Yes	No	No
3	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	No	No	No	No	Yes
5	Yes	No	No	No	Yes	Yes	No	No	Yes	Yes	No	No	Yes	No
6	Yes	Yes	No	No	Yes	Yes	No	No	Yes	Yes	No	No	No	No
7	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	No
8	No	Yes	Yes	No	No	Yes	Yes	No	No	No	No	No	No	Yes
9	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No
10	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No
12	No	Yes	Yes	No	No	Yes	Yes	Yes	No	No	No	No	No	Yes
13	No	No	Yes	No	No	No	Yes	No	No	No	No	No	No	Yes
16	Yes	No	Yes	No	Yes	Yes	Yes	No	No	No	No	No	No	Yes
17	Yes	Yes	No	No	Yes	Yes	No	No	Yes	Yes	No	No	No	No
19	Yes	Yes	Yes	No	Yes	No	No	No	No	No	No	No	No	Yes
20	No	No	Yes	No	No	No	No	No	No	No	No	No	No	Yes
22	Yes	No	Yes	No	Yes	No	Yes	No	No	No	Yes	No	No	Yes
26	No	No	Yes	No	No	No	Yes	No	No	No	Yes	No	No	No
28	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No	Yes	No	No	Yes
30	Yes	No	No	No	Yes	No	No	No	Yes	Yes	No	No	Yes	No
31	No	No	No	No	No	No	No	No	Yes	No	Yes	No	Yes	No
32	Yes	Yes	No	No	Yes	Yes	No	No	Yes	No	No	No	No	Yes
35	Yes	No	No	No	Yes	No	No	No	No	No	No	No	No	Yes
37	No	No	Yes	No	No	Yes	Yes	No	No	Yes	No	No	No	No
40	No	Yes	No	No	No	Yes	No	No	No	Yes	No	No	No	No
41	No	No	Yes	No	No	No	Yes	No	No	No	Yes	No	No	No
42	No	Yes	No	No	No	Yes	No	No	Yes	Yes	No	No	Yes	No
44	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	No
45	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	No
46	Yes	No	No	No	Yes	No	No	No	Yes	No	No	No	No	No
49	Yes	No	Yes	No	Yes	No	No	No	No	No	No	No	No	Yes
50	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	Yes
51	No	Yes	No	No	No	Yes	No	No	No	No	No	No	No	Yes
52	No	No	No	No	No	No	No	No	Yes	No	Yes	No	Yes	No
54	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes
55	No	Yes	No	No	No	Yes	No	No	No	Yes	No	No	No	No
56	Yes	Yes	No	No	Yes	Yes	No	No	Yes	No	Yes	No	Yes	No
58	No	No	Yes	No	No	No	Yes	No	No	No	Yes	No	No	No
59	No	No	Yes	No	Yes	No	Yes	No	No	No	Yes	No	No	No
61	No	No	Yes	No	No	No	Yes	No	No	No	Yes	No	No	No
63	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	Yes
65	No	No	Yes	No	Yes	No	No	No	Yes	No	No	No	Yes	No
67	No	No	No	No	No	No	No	No	No	No	No	Yes	Yes	No
70	No	No	Yes	No	No	No	Yes	No	No	No	Yes	No	No	No
71	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	No
73	Yes	Yes	No	No	Yes	Yes	No	No	Yes	Yes	No	No	No	No
74	No	No	Yes	No	No	No	Yes	No	No	No	No	No	No	Yes
76	No	Yes	No	No	Yes	No	No	No	Yes	Yes	No	No	Yes	No
77	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No
78	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No
80	No	Yes	No	No	No	Yes	Yes	No	No	Yes	Yes	No	Yes	No
82	No	Yes	No	No	No	Yes	No	No	No	Yes	No	No	No	No
83	Yes	No	No	No	Yes	No	No	No	No	No	No	No	No	Yes
84	Yes	No	No	No	Yes	No	No	No	Yes	No	No	No	No	No
86	Yes	No	No	No	Yes	No	No	No	No	No	No	No	No	Yes
89	Yes	No	No	No	Yes	No	No	No	No	No	No	No	No	Yes
90	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	No
92	Yes	No	No	No	Yes	No	No	No	Yes	No	No	No	No	No

Individual values are given for all 56 patients (61%) who experienced any form of hormonal deficits at any point. Summary statistics are provided in the results section

DI diabetes insipidus

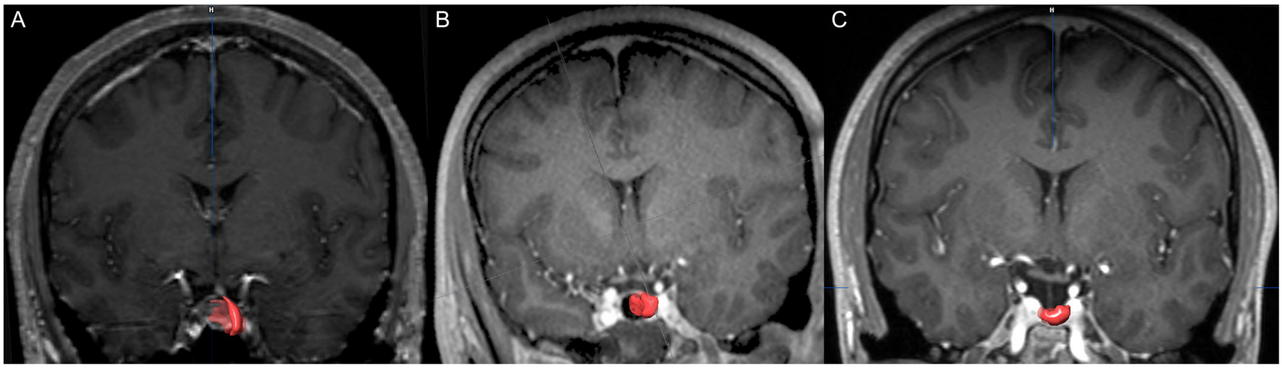

Fig. 1 This 33 year old female patient presented with a growth-hormone secreting pituitary adenoma of Micko-Knosp Grade 2. The three-dimensional volumetric segmentation on the preoperative coronal contrast-enhanced magnetic resonance imaging **a**, measuring 0.12 cm^3 in volume, is shown. On the intraoperative MRI **b**, the pituitary gland can be seen expanding to a volume of 0.58 cm^3. At the 1-year follow-up **c**, the pituitary gland had already pruned almost to its preoperative size with a volume of 0.22 cm^3

Table 3 Pituitary volumes throughout the follow-up period

Timepoint	Pituitary gland volume	Mean of the differences (95% CI)	*p*
Baseline	0.293 ± 0.184	–	–
Intraoperative	0.419 ± 0.183	0.126 (0.093 to 0.160)	<0.001*
3 months	0.436 ± 0.195	0.016 (−0.014 to 0.046)	0.28
1 year	0.319 ± 0.151	−0.132 (−0.079 to −0.184)	<0.001*

*p*values represent the significance of the change from the previously measured volume. Values represent mean ± standard deviation and are given in cm^3

CI confidence interval

*$p \leq 0.05$

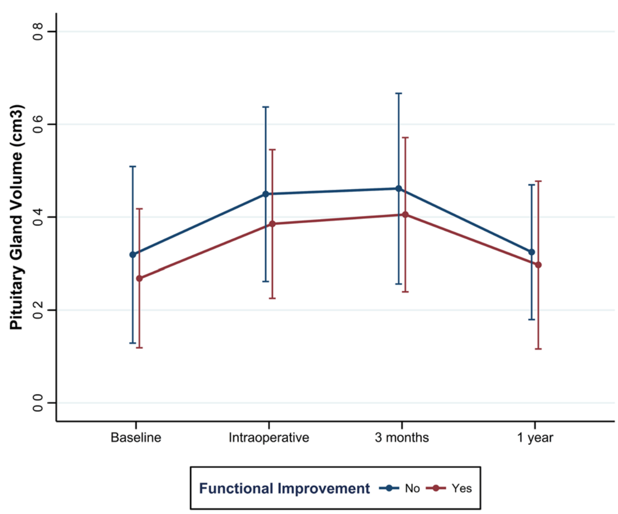

Fig. 2 Pituitary gland volumes throughout the follow-up period stratified by the presence of functional improvement at 1 year postoperatively. Of the 92 included patients, 20 (22%) experienced a functional improvement. Volumes included the pituitary gland itself, as well as its stalk. Error bars represent standard deviations

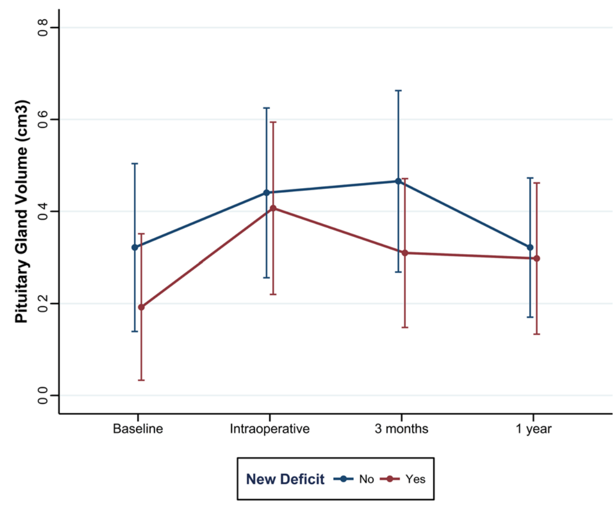

Fig. 3 Pituitary gland volumes throughout the follow-up period stratified by the presence of new postoperative hormonal deficits at the 1 year follow-up. Of the 92 included patients, 10 (11%) experienced new deficits. Volumes included the pituitary gland itself, as well as its stalk. Error bars represent standard deviations

and was an independent predictor of new deficits (OR: 6.25, 95% CI 1.23–32.3, $p = 0.024$) and ≥2 HPA deficits (OR: 5.24, 95% CI 1.03–30.38, $p = 0.049$) at 1 year, after adjustment for possible confounders.

Pituitary volumes

In addition to dynamic unfolding and pruning, we also looked at static PG volumes and their association with endocrinological outcome (Supplementary Table 2). Patients who had ≥2 HPA deficits at 1 year started off with significantly more compressed PG ($p < 0.001$) preoperatively, which Fig. 5 demonstrates, and also exhibited a lower 3-month volume ($p = 0.012$). Similarly, patients experiencing new hormonal deficits postoperatively had smaller baseline ($p = 0.040$) and 3-month ($p = 0.031$) PG

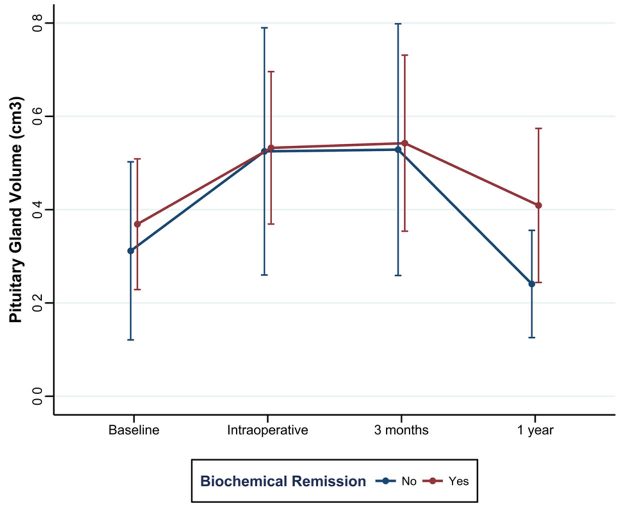

Fig. 4 Pituitary gland volumes throughout the follow-up period stratified by the presence of biochemical remission at 1 year postoperatively. Of the 33 patients with secreting adenomas, 26 (79%) experienced biochemical remission. Volumes included the pituitary gland itself, as well as its stalk. Error bars represent standard deviations

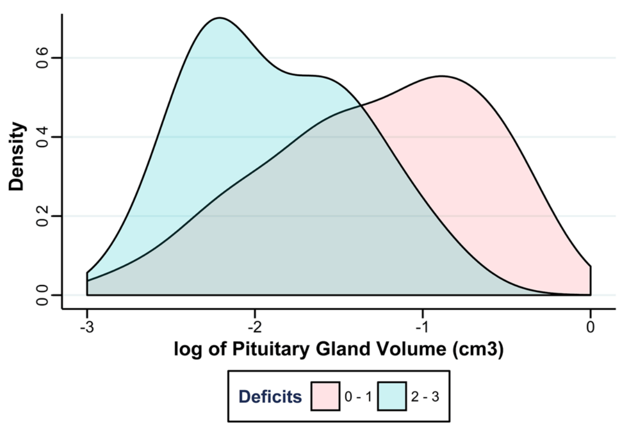

Fig. 5 Density plots of log values for baseline pituitary gland volumes stratified by the number of hypothalamo-pituitary axis deficits at 1 year. Volumes included the pituitary gland itself, as well as its stalk. There was a strongly significant difference in baseline volumes among the two groups ($p < 0.001$

volumes. A higher 1-year PG volume was significantly associated with BR ($p = 0.047$).

Discussion

In an analysis of 92 patients with intra-operative imaging as well as long-term radiological and endocrinological follow-up, we found that the PG unfolds significantly during transsphenoidal surgery, and subsequently undergoes pruning postoperatively up until 1 year, in most cases returning to the preoperatively measured gland volume. A smaller baseline PG volume predicted intraoperative unfolding. While the occurrence of intraoperative unfolding was not linked to endocrinological outcomes, early pruning of the pituitary gland at 3-months follow-up (compared to intraoperative MRI) was associated with new functional deficits and thus a greater amount of compromised hormonal axis. Preoperative pituitary compression (smaller PG volume) also correlated to newly occurring deficits after surgery. Lastly, a larger 1-year pituitary volume was associated with biochemical remission in secreting adenomas.

While our study is the first to report intraoperative and long-term serial measurements of PG volume, postsurgical unfolding has been described previously. Steiner et al. found that 54% of patients showed reexpansion and repositioning of the PG, as well as lowering of the optic chiasm [14]. Dina et al. show that the PG increased in height compared to baseline, but then decreased between 4 and 9 months postoperatively, and attribute these changes to resorption of sellar packing material that lead to shrinking and deformation of the PG [15]. Rodriguez et al. also describe transient unfolding and subsequent pruning between 1 and 4 months [16]. Interestingly, Cho et al. found that PG volumes continually increased up to 3 months [17]. Thus, expansion from preoperative to early postoperative imaging is well-described in the literature.

However, through the lack of 3T-ioMR and as shown in our study, these previous studies have failed to identify the fact that the bulk of the unfolding takes place intraoperatively, with the gland remaining at a relatively stable size in the first few months postoperatively. In addition, we describe that PG volumes return to their preoperative values at 12 months, and that a smaller baseline PG volume, as a surrogate measure of gland compression, is an independent predictor of unfolding. Based on our data and the literature, it is likely that the unfolding that is observed during surgery represents rather a compensatory response that may be of inflammatory nature. This would explain why, after post-surgical inflammation has subsided and postoperative anatomical remodeling of the sella has taken place, PG volumes seem to prune back to smaller values.

We hypothesized that PG unfolding and pruning, may correlate to endocrinological outcomes. Intraoperative unfolding seems to occur in 70% of patients but does not appear to be related with pituitary function. Cho et al. found that PG unfolding from baseline to 3 months predicted recovery of preoperative hypopituitarism, which we were unable to corroborate. Similarly, late pruning occurred in 64% and was not associated with endocrinological outcomes. However, earlier pruning at 3 months, which was much rarer only in 14% of patients, seems to be independently associated with newly occurring hormonal losses. It currently remains unclear as to why this relationship exists. Early pruning may indicate glandular necrosis. It must also be considered that these deficits could indicate the occurrence of a damage to the pituitary gland after 3T-ioMR has taken place, which could explain the loss of PG volume. However, the latter is unlikely since, in most cases, we had obtained adequate view and location of the healthy PG on the 3T-ioMR. This is the first study examining the predictive value of dynamic volumetric changes of the pituitary during and after surgery, and data in larger cohorts may allow analyses with higher statistical power.

Although 22 % had improvement in endocrinological function, we still observed in 11% of patients new deficits, which is in line with the rates in the peer-reviewed literature which range between 5 and 22% [5, 6, 8, 18, 19]. Smaller baseline and 3-month PG volumes were associated with both newly occurring hormonal deficits as well as with 2 or more HPA deficits at 1 year. A small PG volume is a marker for increased intrasellar pressure and direct compression by tumorous tissue, both of which have been related to worse PG function [9]. Jahangiri et al. conclude that low preoperative PG volume precludes hormonal recovery, while larger PG volume predicts improvement, as does younger age [20]. Fatemi et al. found that larger adenoma volume correlates with new deficits. They also identified the absence of intraoperative cerebrospinal fluid leaks and younger age as predictors of functional improvement, which occurred in 50% in their cohort [8]. Similarly, Nelson et al. find that higher preoperative adenoma volume and very low hormonal function are associated with new deficits [21]. Webb et al. found that only histological noninvasiveness and absence of residual tumor, but not tumor volume, predicted functional improvement [19]. We found that neither dynamic unfolding nor larger static PG volumes were associated with functional improvement, as do multiple other reports [16, 18, 19]. Hypopituitarism only becomes clinically apparent after most of the anterior lobe has been compromised. Therefore, the surgical improvement rate of baseline hypopituitarism is generally low and variable.

The pathophysiological explanation behind the association of low preoperative PG volume and newly occurring deficits is unclear. It is conceivable that extreme intrasellar pressure and compression of the PG may lead to ischemia through constriction of the portal vessels, resulting in atrophy which is persistent up to 3 months [9, 18]. Injury to the parenchymal tissue caused by rapid expansion and subsequent inflammation can also be considered. Lastly, it is possible that there is simply a higher chance of inadvertent partial hypophysectomy if the PG is very small and thus more difficult to identify.

Interestingly, we identified a larger 1-year PG volume as predictor for BR. A possible explanation is that a larger PG volume may correspond to enhanced decompression through removal of all tumorous tissue. Another possible explanation would be that after normalization of adenomatous hormonal hypersecretion, the hypothalamic releasing hormones would return to normal levels thus stimulating a hypertrophy of the normal pituitary tissue. It must however be noted that the effect size of this association was small. Other than extent of resection, little is known about predictors of biochemical remission in the literature.

A better understanding of the predictive effect of intraoperative unfolding and of static volumes may have distinct clinical applications. Knowledge of whether preoperative hypopituitarism can be resolved by surgical decompression or not may prevent unsuccessful TSS that carries the risk of new deficits. This would be of particular value in surgical decision making when medical treatment alone may be an option or in case such as large incidentaloma without clinical symptoms. There have been hundreds of analyses on prediction and on technical improvements for achieving GTR [1, 13]. This is still crucial in secreting adenomas to achieve biochemical remission, as residual tumor produces excess mortality and even precludes improvement of hypopituitarism [19, 22]. In nonfunctioning adenomas, research and clinical practice should primarily focus on refining surgical indications. As an example, in those cases where the indication for surgery is hypopituitarism, it is important to identify reliable predictive factors for hormonal recovery as well as newly occurring deficits.

Limitations

Our study is primarily limited by its retrospective nature. While we included a consecutive series of all patients with complete data operated from 2012 onwards, this means that selection bias cannot be ruled out. We included 92 patients, possibly limiting our statistical power. Furthermore, all data stem from a single center, possibly creating center-bias and limiting the generalizability of our findings. This also applies to the criteria for endocrinological evaluation and laboratory reference ranges. The fact that our data were prospectively collected, and that the sample size was relatively small, may explain the somewhat increased incidence of hormonal deficits compared to retrospective reports in the literature. Variability in volumetric measurements may pose another limitation. Highly vascularized tumors, as well as the presence of edema postoperatively are likely to introduce measurement error. Volumetric measurements were carried out by experienced raters, and we quantified measurement error by repeated measurements.

Conclusions

Our data suggest that, generally, the pituitary gland expands during transsphenoidal surgery for pituitary adenoma, and subsequently prunes back to its pre-operative size at the 1-year follow-up. Pituitary unfolding and late pruning both do not predict endocrinological outcomes after surgery. However, early pruning was independently predictive of new hormonal deficits and multiple compromised hypothalamo-pituitary axis at 1 year. Furthermore, small baseline and 3-month pituitary gland volumes were also associated with new deficits. Biochemical remission in patients with secreting adenoma correlated to higher 1-year pituitary gland volumes. Our findings warrant prospective validation in a larger cohort with higher statistical power.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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

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