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3D volumetric measurements of GH secreting adenomas correlate with baseline pituitary function, initial surgery success rate and disease control

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Abstract

Objective—There is scarce data on the clinical utility of volume measurement for growth hormone (GH) secreting pituitary adenomas. The current study objective was to assess the association between pituitary adenoma volumes and baseline endocrine evaluation, initial surgical success rate and disease control among patients with acromegaly.

Methods—A retrospective cohort study conducted at a clinical research center including patients with acromegaly due to GH secreting pituitary adenomas. Baseline hormonal evaluation and adenoma characteristics according to MRI were collected. Volumetric measurements of pituitary adenomas were performed using a semi-automated lesion segmentation and tumor-volume assessment tools. Rates of post-operative medical treatment, radiation therapy and re-operation were gathered from the patients' medical records.

Results—Twenty seven patients (11 females) were included, median age 21.0 years (Inter quartile range 29 years, range 3–61 years). Patients harboring adenomas with a volume <2000 mm^3 had higher chance to achieve disease remission [94.1% (n=16) vs. 50.0% (n=4), p<0.05]. Adenoma volumes positively correlated with baseline plasma GH levels before and after oral glucose administration, and with plasma IGF-I and PRL levels. Adenoma volume had negative correlation with morning plasma cortisol levels. Finally, patients harboring larger adenomas

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required 2nd surgery and/or medical treatment more often compared with subjects with smaller adenomas.

Conclusions—Accurate 3D volume measurement of GH secreting pituitary adenomas may be used for the prediction of initial surgery success and for disease control rates among patients with a GH secreting pituitary adenomas.

Keywords

Volumetric measurement; acromegaly; hypopituitarism

Introduction

Growth hormone (GH) secreting pituitary adenomas account for acromegaly in >99% of patients, whereas the remaining causes of acromegaly are non-pituitary tumors secreting GH or growth hormone releasing hormone [1]. Excessive production of GH and insulin-like growth factor-I (IGF-I) leads to disproportionate growth [2], and other systemic problems [3,4]. In children, GH excess causes gigantism [5]. The majority of the patients with GH-secreting tumors present with large (diameter >1 cm) and invasive tumors (2, 5), that may cause compression of the normal pituitary gland and hypopituitarism [7], and damage to other surrounding structures, including the optic chiasm, the cavernous sinuses and their contents, the sphenoid sinus and the brain tissue.

Surgical resection of pituitary tumors has been found superior to medical treatment in terms of remission rates [8]; accordingly, the current guidelines for management of patients with acromegaly recommend surgical resection as first line of therapy for these patients [9]. However, due to the typical invasive character of somatotroph adenomas, a subset of the patients require further treatment, such as re-operation, medical treatment with dopamine agonists, somatostatin analogs or GH receptor antagonist, and/or irradiation therapy [6].

Adenoma diameter in patients with acromegaly has been correlated with GH levels and long term outcomes [10]. However, newly developed techniques for three dimensional (3D) volumetric measurements might enable an improved estimate of tumor burden. This technique has been used in the past to evaluate adenoma dynamics among patients treated medically [11]. Until today, only one study has assessed the use of 3D measurements of GH-secreting pituitary tumors [12], and did not find a correlation between 3D-measured volumes and peripheral plasma GH levels; the study found, interestingly, a correlation with plasma IGF-I levels.

In the present study, we used a new method to assess 3D volume of GH-secreting tumors and examined any correlation of the data with the pre-operative GH levels during oral glucose tolerance test (OGTT), initial surgery success rate, and prognosis.

Patients and methods

We conducted a retrospective analysis, including patients that were admitted to the National Institutes of Health between 1996 and 2015. All patients were recruited through clinical protocols 97-CH-0076 and 95-CH-0059 conducted by the *Eunice Kennedy Shriver* National

Institute of Child Health and Human Development (NICHD) and gave written informed consent. Study patients were diagnosed with acromegaly according to their clinical manifestations that were confirmed by a GH plasma level >1 ng/mL two hours following an oral glucose tolerance test (OGTT, 75 gr glucose for adults or 1.75 gr/kg body weight for children).

All patients were evaluated for other pituitary hormonal deficiencies at presentation. Central hypocortisolism was defined as a low plasma cortisol levels (<18 mcg/dL) 30 minutes following an intra venous administration of 250 mcg adrenocorticotropic hormone (ACTH, Synacthen) or as a morning plasma cortisol <5 mcg/dL [13], in conjunction with an inappropriately low plasma ACTH level (<52 pg/mL). Hypogonadotropic hypogonadism was assessed only among patients older than 17 years, and was defined as low plasma levels of total testosterone in males (<262 ng/dL) or estradiol in females (<10 pg/mL), with an inappropriately low levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH). Central hypothyroidism was defined as low plasma free thyroxine levels (FT4, <0.8 ng/dL) with an inappropriately low thyroid stimulating hormone (TSH, <4 micIU/mL) levels. Plasma prolactin (PRL) levels were drawn one hour after catheter insertion in a quiet environment (normal <25 ng/ml). Data on post-operative treatment (re-operation, radiation therapy or medical therapy) were retrieved from the patients' medical records. Finally, basal GH plasma levels achieved during follow-up were collected for each patient (median follow-up 90 days [IQR 721]), with GH plasma levels <2.5 ng/mL reflecting a controlled disease.

All patients underwent MRI scans of the pituitary gland using T1-weighted sequences before and after intra venous administration of gadolinium. Volumetric measurements of pituitary adenomas were performed using semi-automated lesion segmentation and tumor-volume assessment tools provided by a picture archiving and communication system (PACS) upgrade (Vue PACS version 12.1.5, Carestream Health, currently installed in NIH/Clinical Center, Department of Radiology and Imaging Sciences), which allows storage and tabulation of measurements directly within the PACS (Figure 1).

Statistical analysis

Statistical calculations were performed with SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). Results are expressed as median (Interquartile range, IQR) unless otherwise indicated. For group comparisons, Mann-Whitney test was used to analyze differences in numerical variables, and the chi-square test was employed to analyze differences in categorical variables. For correlation analysis adenoma volumes and biochemical values were logarithmically transformed to induce approximate normality. The Pearson product was used for analysis of correlations between variables. The p value for significance was set at less than 0.05.

Results

Age, gender, presentation and diagnoses

The current analysis included 27 patients with a median age at diagnosis of 21.0 years (IQR 29, range 3–61 years), eleven (40.7%) women. Eight of the patients had acromegaly in the context of a genetic disorder: 5 had Carney's complex, 2 - familial isolated pituitary adenoma, and one subject had neurofibromatosis type 1. Patients' adenoma volumes and full biochemical evaluations results are detailed in table 1. Patients were followed for 5.2 months (IQR 14.9). Ten patients (37.0%) harbored adenomas invading either the cavernous or sphenoid sinuses, 5 patients (18.5%) required re-operation, 10 (56.5%) – medical therapy, and 4 (16.7%) received irradiation therapy following the first operation.

Adenoma volumes and baseline parameters

Pituitary adenoma volumes correlated positively with GH levels during the OGTT, both at baseline and following glucose administration (figure 2), and maintained a positive correlation with plasma IGF-I levels (figure 3A). In addition, tumor volumes correlated positively with the degree of hyperprolactinemia (figure 3B), but negatively with morning plasma cortisol levels (figure 3C).

Adenoma measurements and baseline parameters

Adenoma measurements (median 9 mm, IQR 14 mm) correlated positively with adenoma volumes by 3D ($r=0.8$, $p<0.001$) and with plasma GH levels ($r=0.4$, $p=0.04$) but not with IGF-I levels ($r=0.2$, $p=0.4$). Adenoma measurement also correlated positively with PRL levels ($r=0.5$, $p=0.03$), but did not correlate with basal cortisol levels ($r=-0.5$, $p=0.1$).

Adenoma volumes and prognosis

Patients harboring adenomas with a volume <2000 mm^3 had a higher probability to achieve disease remission [94.1% (n=16) vs. 50.0% (n=4), $p<0.05$]. Comparison of baseline tumor characteristics and second-line therapies according to adenoma volumes are detailed in table 2. We also calculated the odds ratio for disease control according to tumor volume. Adenoma volume <2000 mm^3 had an odds ratio of 15.9 (95% confidence interval 1.4–200, $p=0.03$) for disease control, defined as plasma GH levels <2.5 ng/mL.

When we compared the rates of male/female hypogonadism and central hypocortisolism between patients with small vs. large adenomas, by using several cutoffs, we found higher rates of hypogonadism (table 3), but no significant differences in terms of central hypocortisolism. None of the patients in our cohort had central hypothyroidism. No difference was found between the genders in terms of initial surgery success rate or recurrence rates.

Adenoma measurements and prognosis

Fourteen patients (51.9%) had macroadenomas (adenoma diameter >10 mm) and 13 harbored pituitary microadenomas (≤10 mm). The presence of a macroadenoma vs. a microadenoma as per standard measurements did not predict disease remission (basal GH<2.5 ng/mL, 33.3% vs. 7.7%, respectively, $p=0.1$), or need for further medical therapy (45.5% vs. 41.7%, $p=0.9$) or irradiation (25.0% vs. 8.3%, $p=0.3$). However, only patients with macroadenomas required re-operation (41.7% vs. 0, respectively, $p=0.01$).

Subgroup analysis among subjects with sporadic acromegaly

Correlation between adenoma volumes with baseline plasma GH levels (r=0.5, p=0.02), plasma GH one hour following oral glucose loading (r=0.4, p=0.06), mean PRL levels (r=0.6, p=0.02), and baseline morning plasma cortisol levels (r=−0.7, p=0.05) maintained their significance and/or had the same trend as found for the full cohort.

Discussion

In this study we evaluated the utility of 3D volume measurement of GH-secreting adenomas, in terms of GH and IGF-I secretion, baseline pituitary function, initial surgery success rate and disease control. We found a positive correlation between the measured adenoma volumes and plasma GH levels before and after oral glucose administration, positive correlation with plasma IGF-I and PRL levels, and negative correlation with morning plasma cortisol levels. We have also shown that patients harboring larger adenomas required a 2^{nd} surgery and/or medical treatment more often compared with subjects with smaller adenomas, and that patients with smaller adenoma volumes achieved disease remission more frequently. Comparing to volumetric measurements, standard adenoma measurements showed correlation with plasma GH and PRL levels, but not with plasma IGF-I and cortisol levels. In addition, longer adenoma diameter (>10 mm) predicted need for re-operation, but did not predict requirement for medical or irradiation therapy, unlike 3D volumetric measurements.

Thus, in our analysis 3D volume measurements correlated with initial surgery success rates and with disease control better than standard measurements. In addition, 3D volume measurements were found to be better predictors for post-surgical outcomes [14] for anterior pituitary tumors in general. In line with this finding, using an adenoma volume cutoff of <2000 mm^3 in our analysis yielded a stronger odds ratios for disease remission compared with standard adenoma measurements in other studies of GH-secreting adenomas [15,16].

Another parameter that may correlate with the tumor volumes is the expression of IGF-I in GH-responsive organs. Pituitary IGF-I expression has not been consistently studied and it would be ideal if we had the opportunity to study it in our patients; although there is extensive information for brain IGF-I expression [17,18]. A future study may attempt to correlate volume with IGF-I expression.

The use of 3D volume measurement of pituitary adenomas causing acromegaly is new, and the literature on this topic is scarce. Nevertheless, one study showed that decrease in adenoma volume correlated better with the change in IGF-I plasma levels [12] than standard measurements, in support of the findings in the present study. We extend these previous findings by showing better 3D volumetrics correlation with initial surgery success and remission rates than the standard adenoma measurements. These data need to be confirmed in a larger study; it remains to be seen whether this can easily been done in any center. The patients included in our study were followed in a tertiary care referral clinical research center, with all the study tests and procedures performed according to a standardized research protocol that allowed relatively straightforward 3D calculations. Moreover, the current study population includes 8 patients with genetic syndromes, which explains the young age of a subset of the patients, and the relatively high number of microadenomas. Nevertheless, even after excluding those patients correlation analysis revealed similar findings as found for the full cohort.

In conclusion, accurate 3D volume measurements of GH secreting pituitary adenomas may be used for the prediction of initial surgery success and for disease control rates among patients with a GH secreting pituitary adenomas. 3D volumetric measurement had stronger correlations with IGF-I plasma levels and post-operative hypocortisolism, and better prediction of any required second line treatment measures compared with the standard preoperative adenoma measurements.

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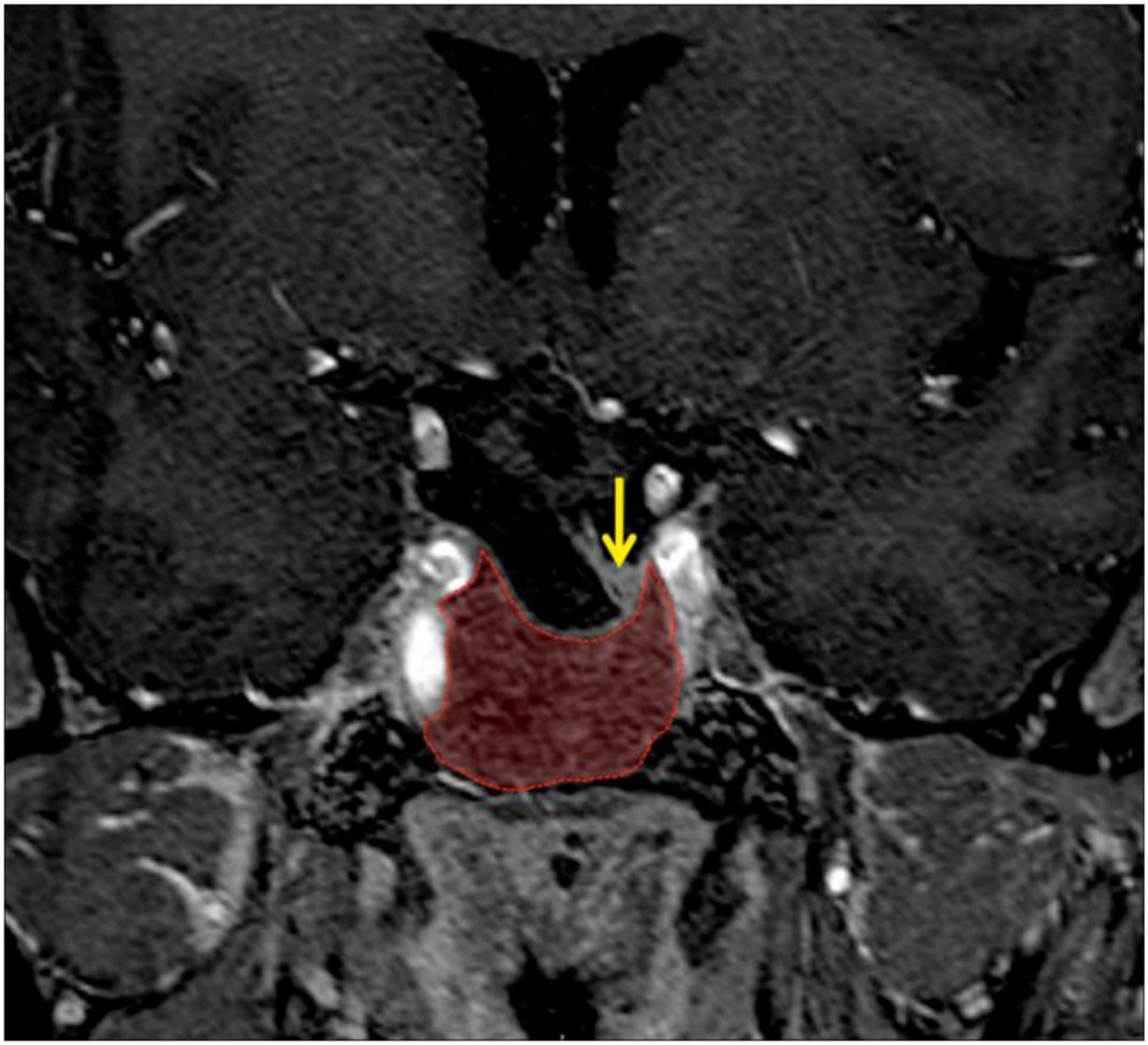

Figure 1 -

Coronal post-contrast T1-weighted 3D-Gradient echo magnetic resonance image of the pituitary gland showing large pituitary adenoma (red dash line) extending inferiorly and completely occupying the sphenoid sinus. The normal pituitary gland is atrophic (yellow arrow).

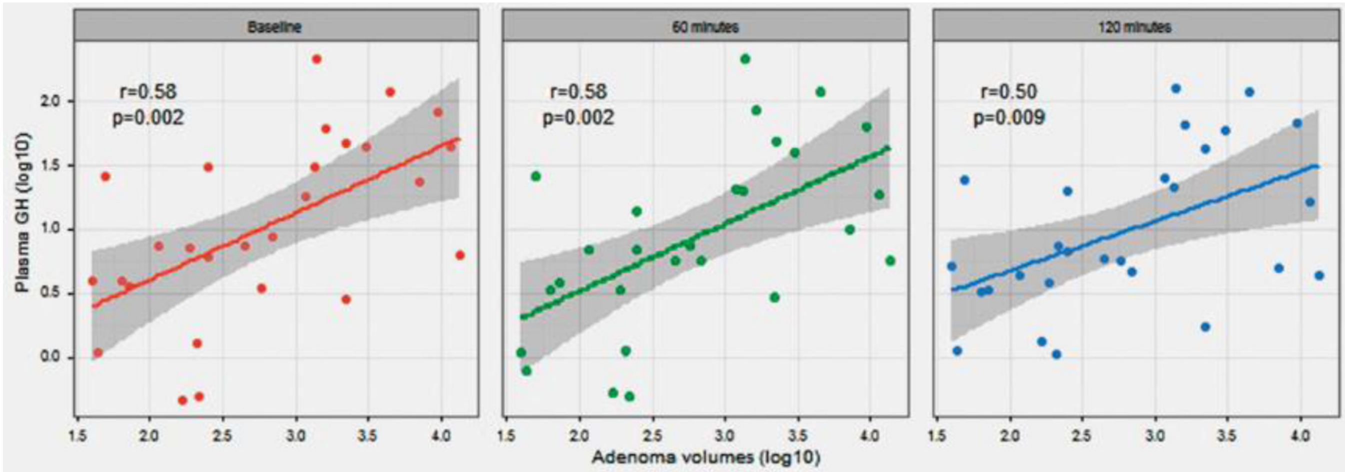

Figure 2 -
Correlation analysis between adenoma volumes and growth hormone levels: at baseline, 60 minutes and 120 minutes after 75gr oral glucose administration.

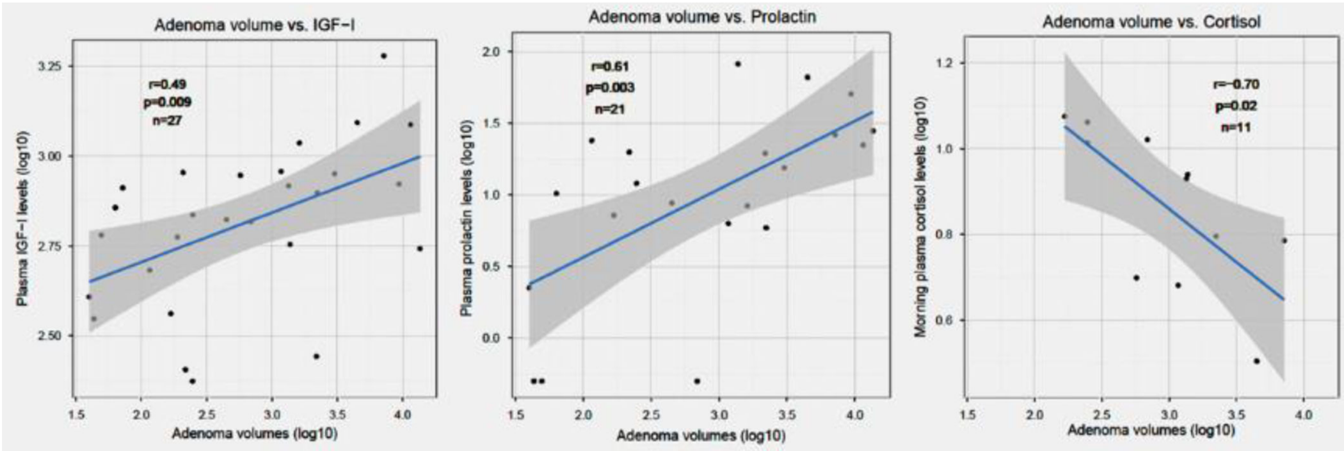

Figure 3 -

Correlation analysis between adenoma volumes and plasma insulin-like growth factor-I (IGF-I, A), prolactin (B), and morning cortisol levels (C).

Table 1

Study population characteristics.

	n	Median (IQR)	Minimum	Maximum
Adenoma volume (mm^3)	27	573.0 (2060.3)	40.0	13600.0
IGF-I (ng/ml)	27	686.0 (341)	236.0	1899.0
Growth hormone (ng/ml)	27	7.5 (39.9)	0.5	217.0
75g OGTT 1h	27	7.0 (23.1)	0.5	213.0
75g OGTT 2h	27	5.9 (21.2)	1.1	128.0
TSH (μIU/ml)	23	0.9 (0.5)	0.1	3.3
Free thyroxine (ng/dl)	25	1.1 (0.4)	0.8	2.0
LH (U/I)	27	2.4 (4.0)	0.1	26.2
FSH (U/I)	27	4.2 (7.0)	0.7	54.1
Estradiol (pg/ml) +	9	20.0 (48.1)	5.0	238.0
Total testosterone (ng/dl) +	14	153.0(258.0)	7.0	466.0
Cortisol after ACTH stimulation (μg/dl) *	10	19.3 (6.4)	12.0	24.8
Prolactin (ng/dl)	27	12.0 (17.7)	0.5	82.2

IQR: Interquartile range; OGTT: 75 g oral glucose tolerance test; IGF-I: Insulin-like growth factor-I; TSH: Thyroid stimulating hormone; LH: Luteinizing hormone; FSH: Follicle stimulating hormone

*Cortisol was measured 30 min after IV administration of 250 μg consyntropin

+Testosterone and estradiol are presented for men and women only, respectively

Table 2

Utility of various adenoma volume cutoffs. Comparison of invasiveness estimation, first surgery success, and disease control rates among patients below vs. above cutoffs.

Adenoma volume (mm^3)	Invasive n (%)	2nd line therapy required			GH<2.5 ng/ml on follow-up
		Re-operation n (%)	Medical treatment n (%)	Radiation n (%)	
< vs. ≥ 1 000	3 (20.0) vs. 7 (58.3)**	1 (8.3) vs. 4 (33.0)	5 (41.7) vs. 5 (45.5)	1 (8.3) vs. 3(25.0)	12 (92.3) vs. 8 (66.7)
< vs. ≥ 2 000	3 (15.8) vs. 7 (87.5)***	2 (12.5) vs. 3 (37.5)	5 (31.2) vs. 5 (71.4)*	1 (6.2) vs. 3 (37.5)*	16 (94.1) vs. 4 (50.0)**
< vs. ≥ 3 000	5 (23.8) vs. 5 (83.3)***	2 (11.1) vs. 3 (50.5)**	5 (29.4) vs. 5 (83.3)**	2 (11.1) vs. 2 (33.3)	17 (89.5) vs. 3 (50.0)***

*p<0.1

**p<0.05

***p<0.01.

Invasive, describes tumors invading the either the cavernous sinuses or the sphenoidal sinus

Table 3

Hypopituitarism rates according to different adenoma volumes cutoffs, comparison among patients below vs. above cutoffs.

Adenoma volume (mm^3)	Hypogonadotropic hypogonadism n (%)$^+$		Central hypocortisolism n (%)
	Male	Female	
< vs. ≥ 1 000	2 (28.6) vs. 7 (100)***	0/6 vs. 2 (66.7)**	0/9 vs. 2 (33.3)
< vs. ≥ 2 000	3 (37.5) vs. 6 (100)***	1 (14.3) vs. 1 (50.0)	1 (12.5) vs. 1 (33.3)
< vs. ≥ 3 000	4 (44.4) vs. 5 (100)***	1 (12.5) vs. 1 (100)**	1 (11.1) vs. 1 (50.0)