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Original Article

Clinical, pathological and endocrinological evaluation of patients with microscopic transsphenoidal pituitary surgery

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Abstract

Aim: Detailed evaluation of patients in preoperative stage is an important factor that reduces morbidity and mortality as well as the operation itself. In our study, we aimed to examine clinically, pathologically and endocrinologically, the patients who were decided to undergo transsphenoidal surgery, in light of the literature.

Materials and Methods: In this retrospective observational study, preoperative and pathological data of consecutive pituitary adenoma patients who applied to our department from January 2019 to June 2020 and underwent transsphenoidal surgery with microscopic methods, were examined.

Results: The study included a total of 31 patients. Distribution of patients in relation to pathological diagnoses was as follows: Functional pituitary adenoma (n: 15), non-functional adenoma (n: 11), apoplexy (n: 2), carcinoma metastasis (n: 2) and craniopharyngioma (n: 1). No statistically significant difference was found between functional and non-functional adenomas, in terms of tumor size, cavernous sinus invasion, Ki-67 index and p53 staining pattern ($p > 0.05$) whereas presence of suprasellar extension and visual field defect were significantly more in non-functional adenomas ($p = 0.015$, $p = 0.045$, respectively).

Conclusion: Highly invasive character was detected in both functional and non-functional pituitary Ki-67 indexes were low in the study population, increased p53 expression was noticeable. We can state that the Ki-67 index may not be directly proportional to the invasive behavior of the disease.

Keywords: Microscopic; pituitary adenoma; transsphenoidal pituitary surgery

INTRODUCTION

Pituitary tumors are categorized according to their size (micro or macro) or whether they are hormonally functional. Based on the hormone secreted, they are grouped as: Prolactin (PRL), growth hormone (GH), adrenocortical hormone (ACTH), follicle-stimulating hormone (FSH) / luteinizing hormone (LH) and thyroid-stimulating hormone (TSH) secreting functional tumors (1). In a population study of 592 patients including ten years of data, Tjörnstrand et al., reported that the most common cause of pitiutary adenomas was non-functional adenomas (54.1%), followed by prolactinomas (31.6%), somatotropinomas (9%), corticotropinomas (4.2%) and TSH-secreting adenomas (0.7%) (2).

Pituitary tumors constitute approximately 15-20% of primary intracranial neoplasms. Most of these tumors are non-invasive, benign and intrasellar. Invasiveness is defined as the spread to the cavernous sinüs, base and / or diaphragm of the sella, which is evaluated in preoperative imaging. Any pituitary tumor, which is considered to be "invasive", is not considered to be malignant as it may show a benign course even in dura invasion. In addition to invasive behavior, the features of atypical tumors are, high mitotic index, Ki-67 index of above 3% and wide p53 nuclear staining (3). Malignant pituitary tumors (pituitary carcinomas) are very rare and diagnosed only when the brain, spinal cord and / or distant metastases are present (4).

The main purpose of surgical treatment of pituitary adenomas is to protect the important surrounding tissues, in particular the normal adenohypophysis and pituitary stalk. Another aim is to remove the pituitary

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adenoma and correct the local effects of the mass and metabolic disorders that may develop due to hormonal hypersecretion. The options for surgical treatment of pituitary adenomas are transcranial and transsphenoidal surgeries. Transfenoidal surgery has become the gold standard option in surgical treatment since it is a minimally invasive approach, has low morbidity and mortality rate and satisfactory comfort for the patient. The transcranial approach is the preferred method for pituitary adenomas that grow laterally and are difficult and hazardous to remove by transsphenoidal method (5). However, detailed evaluation of patients in preoperative stage is an important factor that reduces morbidity and mortality as well as the operation itself (6). In our study, we aimed to examine clinically, pathologically and endocrinologically, the patients, who were decided to undergo transsphenoidal surgery.

MATERIALS and METHODS

Study design

This retrospective observational study was carried out between January 2019 and June 2020. Data of patients who applied to the University of Health Sciences Kartal Dr. Lutfi Kırdar Education and Research Hospital, deparments of Endocrinology & Metabolism and Neurosurgery, were examined. Thirty-nine patients were diagnosed with pituitary adenoma after clinical, biochemical and radiological evaluation, and underwent transsphenoidal surgery using microscopic approach. Preoperative data and postoperative pathology reports of these patients were examined. Eight patients were excluded due to lack of medical data. A total of 31 patients who met the inclusion criteria were included in the study consecutively. The clinical trial protocol was approved by the ethics committee of University of Health Sciences Kartal Dr. Lütfi Kırdar Education and Research Hospital (Date:22/07/2020 Number:2020/514/182/12), and complied with the Declaration of Helsinki.

Inclusion criteria: (a) Male and female patients aged 18 years and over (b) Clinically, biochemically and radiologically diagnosed pituitary tumor (c) Pituitary surgery with microscopic transsphenoidal approach (d) completed cytological, histopathological and immunohistochemical studies

Exclusion criteria: (a) Lack of medical data (b) Having received medical treatment before transsphenoidal surgery (such as caberogolin, bromocriptine or somatostatin analogues) (c) Having received radiotherapy before transsphenoidal surgery (such as conventional, gamma knife, cyberknife or linear accelerator [LINAC])

Biochemical analyses

Blood samples of all patients were drawn through the antecubital vein after overnight fasting and were collected into a dry tube (at least 8 hours). The levels of prolactin, TSH, free triiodothyronine (FT3), free thyroxine (FT4), LH, FSH, ACTH, GH, serum insulin like growth factor-1 (IGF-1), estradiol, testosterone and cortisol were measured. Assessment of serum hormone levels was performed by electrochemiluminescence immunoassay (ECLIA) method (Elecsys and Cobas Modular analytics E 710, Cobas e 601, Mannheim, Germany).

The diagnosis of acromegaly was made on the basis of suspicious clinical findings, high insulin-like growth factor-1 (IGF-1) levels, and growth hormone (GH) responses to the oral glucose tolerance test (OGTT). The diagnosis of Cushing's disease was made by evaluating clinical findings, high-normal serum ACTH value, basal cortisol value, 24-hour urine cortisol excretion and results of dexamethasone suppression test. Diagnosis of prolactinoma was made based on clinical findings and basal prolactin level. However, in order to exclude the hook effect, the samples were diluted with 1: 100 dilution and retested in suspicious prolactinoma patients with a significantly low PRL level and in patients with PRL levels above 200 µg / l, which is the cut-off value of our center. Again, to exclude suspected cases of macroprolactin, 'recovery' values found after precipitation with polyethylene glycol (PEG) were examined.

Tumor evaluation and microscopic transnasal transsfenoidal technique

All patients were radiologically evaluated preoperatively with cranium X-ray, paranasal sinus and sellar computed tomography (CT) (Toshiba Activation 16 multislice CT; Tokyo, Japan) and contrast-enhanced pituitary magnetic resonance imaging (MRI) (1.5 Tesla GE device Optima MR360, Milwaukee, Wisconsin, USA). In T1-weighted MRI imaging, the maximum diameter of the tumor was measured in all planes (craniocaudal, transverse and antero-posterior). The tumor was categorized as microadenoma (<10 mm) or macroadenoma (≥ 10 mm) according to the longest diameter (7). Views (PACS; INFINITT Healthcare Co., Ltd., Seoul, South Korea) were evaluated by a single and experienced radiologist. All patients were operated with a microscopic (M525 F40 surgical microscope, Leica AG, Heerbrugg, Sweden) transnasal transsphenoidal approach.

Immunohistochemistry, p53 expression and Ki-67 index

The classification was based on the immunohistochemical hormone expressions of neuroendocrine pituitary tumors published by the World Health Organization (WHO) in 2017. 3-4 micrometer sections were taken from paraffin blocks of the operation material and hematoxylin & eosin and reticulin dyes (to distinguish adenoma tissue from normal adjacent adenohypophysis tissue) were applied histochemically. In adenoma tissues, besides the hormones of ACTH (Thermo, AH26), GH (Thermo, GH01), PROLACTIN (Thermo, PRL02), FSH (Thermo, FSH03), LH (Thermo, LH01) and TSH (Biocare, TSH01 / 02), Ki-67 and P53 were studied. Cytoplasmic staining (diffuse, focal or diffuse focal) in adenoma tissue was considered positive for identification of ACTH, GH, PROLACTIN, FSH, LH and TSH. Nuclear staining was considered positive while estimating Ki-67. The ratio of stained to all cells was calculated in at least 1000 cells in the most densely stained area (hot spot) in the adenoma tissue. Strong nuclear staining was

considered positive for P53 and calculated as percentage. Principally extensive positive staining was taken into account. Ki-67 labeling index is a subjective method. In order to overcome heterogeneity among physicions, all pathology specimens were examined by a single and an experienced pathologist.

Statistical analysis

Normality of distribution was examined by using the Shapiro-Wilk W test. Descriptive statistical methods including percent, mean ± standard deviation (SD) or median (interquartile range [IQR] or minumum-maximum), were used to provide the basic features of the data, according to the evaluation of distribution for normality. Comparison of the data of functional and non-functional pituitary adenomas was done by use of the Independent t-test and Fisher's Exact Test. All statistical analyzes were carried out using SPSS 23.0 version (IBM Corporation, Armonk, NY, US). A p <0.05 was considered to indicate statistical significance.

RESULTS

A total of 31 patients were included in the study. Nineteen patients (61.2%) were male and 12 (38.8%) patients were female. The mean age was 50.3 ± 12.6 years. Four (15.3%) patients had microadenoma and 22 (84.7%) had macroadenoma. The tumor size of 3 patients with non-adenomatous lesions of sella and 2 patients who developed apoplexy was larger than 1 cm. Hormonal analysis revealed that 11 patients (42.3%) had non-functional tumors whereas 15 (57.7%) patients had functional tumors. The most common complaints at presentation were; headache in 21 patients (67.7%), fatigue in 19 (61.2%) patients, visual impairment/loss in 14 (45.1%) patients, sexual reluctance and erectile dysfunction in 12 (38.7%) patients, facial hair loss in 11 (35.4%) patients, enlargement of the hands and feet in 8 patients, galactorrhea in 8 patients (25.8%), and amenorrhea in 6 (19.3) patients (Tables 1 and 2).

Table 1. Pathololological and clinical evaluation

Case No	Age	Sex	Type of Pathology	Immunohisto-chemistry	Function	Ki-67 (%)	p53
1	59	M	Corticotroph	ACTH	+	1	-
2	38	F	Plurihormonal	PRL, ACTH, GH	-	2	-
3	64	M	Gonadotroph	FSH	+	2	-
4	68	F	Mammosomatotroph	PRL, GH	-	2	+
5	32	F	Lactotroph	PRL	+	1	-
6	58	M	Apoplexy	Null	N/A	N/A	N/A
7	34	F	Hyperplasia	All positive	-	2	-
8	56	F	Null Cell	Null	-	4	+
9	38	M	Craniophrangioma	N/A	N/A	N/A	N/A
10	48	M	Somatotroph	GH, PRL	+	4	+
11	74	M	Somatotroph	GH, PRL	+	2	+
12	50	M	Mammosomatotroph	GH, PRL	+	2	+
13	54	F	Somatotroph	GH, PRL	+	2	+
14	69	M	Gonadotroph	FSH, LH	-	1	+
15	58	M	Gonadotroph	FSH, LH	-	2	-
16	47	M	Plurihormonal	PRL, ACTH, GH	-	1	+
17	56	M	Metastasis	N/A	N/A	N/A	N/A
18	65	M	Gonadotroph	LH, FSH	-	2	-
19	38	F	Mammosomatotroph	GH, PRL	+	4	-
20	38	F	Somatotroph	GH, PRL	+	1	+
21	39	M	Somatotroph	GH	+	3	+
22	57	F	Lactotroph	PRL	+	1	-
23	67	F	Lactotroph	PRL	+	4	-
24	55	M	Metastasis	N/A	-	-	-
25	72	M	Gonadotroph	FSH, LH	-	2	-
26	58	M	Apoplexy	N/A	N/A	N/A	N/A
27	38	M	Null Cell	Null	-	4	+
28	41	F	Corticotroph	ACTH	+	2	-
29	22	M	Lactotroph	PRL	+	3	-
30	46	F	Null Cell	Null	-	1	+
31	38	M	Lactotroph	PRL	+	7	+

ACTH: Adrenocorticotropic hormone; PRL: Prolactin; GH: Growth hormone; LH: Luteinizing hormone; FSH: Follicle-stimulating hormone N/A: Not applicable

According to the immunohistochemistry analyses, rate of hormonal expression was as follows: GH-only in 5 patients, PRL-only in 5 patients, GH + PRL in 3 patients, ACTH-only in 2 patients, FSH+ LH in 5 patients, and plurohormonal (more than 2) expression in 3 patients. Apart from these, 3 patients had null cell adenoma, 2 patients had carcinoma metastasis (lung and gastrointestinal system), 2 patients had apoplexy, 1 patient had craniopharyngioma, and 1 patient had pituitary hyperplasia (Tables 1 and 2).

Cavernous sinus invasion and suprasellar extension were observed in 12 (38.7%) and 17 (54.8%) patients, respectively. Fourteen patients (45.1%) suffered from visual field defects.

The mean duration of surgery was 80 minutes. While 5 gonadotroph, 2 plurohormonal, 3 null cell adenoma, and 1 pituitary hyperplasia were accepted as non-functional; 5 somatotroph, 5 lactotroph, 3 mammosomatroph and 2 corticotroph adenomas were accepted as functional, after hormonal evaluation.

The median Ki-67 indexes of the non-functional and functional adenoma groups are 2% [IQR= 6] and 2% [IQR= 3], respectively. P53 expression was positive in 7 (46.7%) patients in the non-functional adenoma group and in 6 (54.5%) patients in the functional adenoma group. No statistically significant difference was found between functional and non-functional adenomas, in terms of tumor size, cavernous sinus invasion, Ki-67 index and p53 staining pattern (p> 0.05) whereas presence of suprasellar extension and visual field defect were significantly more in non-functional adenomas compared to functional ones (p = 0.015, p = 0.045, respectively), (Tables 1 and 3).

Table 2. Radiological and ophthalmic findings

Case No	Age	Sex	Type of Pathology	Tumor Size (CC*T*AP)	Invasion of Cavernous Sinüs	Suprasellar Extension	Visual Field Defect
1	59	M	Corticotroph	20*21*18	-	-	-
2	38	F	Plurihormonal	25**16*18	+	+	+
3	64	M	Gonadotroph	41*29*25	+	+	+
4	68	F	Mammosomatotroph	48*28*24	+	+	+
5	32	F	Lactotroph	6.5*4*11	+	-	-
6	58	M	Apoplexy	17*16*14	-	+	-
7	34	F	Hyperplasia	28*14*18	+	-	-
8	56	F	Null Cell	45*33*33	-	+	+
9	38	M	Craniophrangioma	25*20*18	-	+	+
10	48	M	Somatotroph	13*9*8	-	-	-
11	74	M	Somatotroph	3.5*5*4	-	-	-
12	50	M	Mammosomatotroph	9*8*9	+	-	-
13	54	F	Somatotroph	28*24*22	+	-	-
14	69	M	Gonadotroph	20*22*24	-	+	+
15	58	M	Gonadotroph	15*10*12	-	+	-
16	47	M	Plurihormonal	16*15*10	+	-	-
17	56	M	Metastasis	17*15*14	-	+	+
18	65	M	Gonadotroph	27*29*18	-	+	+
19	38	F	Mammosomatotroph	9*8*8	-	-	-
20	38	F	Somatotroph	15*12*10	-	+	+
21	39	M	Somatotroph	12*10*9	-	-	-
22	57	F	Lactotroph	23*15*20	+	-	-
23	67	F	Lactotroph	32*26*22	-	+	+
24	55	M	Metastasis	22*21*16	+	+	+
25	72	M	Gonadotroph	19*16*21	+	+	+
26	58	M	Apoplexy	17*14*15	-	-	-
27	38	M	Null Cell	25*20*18	-	+	+
28	41	F	Corticotroph	6*7*7	-	-	-
29	22	M	Lactotroph	23*14*29	-	-	-
30	46	F	Null Cell	21*17*14	-	+	+
31	38	M	Lactotroph	24*18*21	+	+	+

CC: Craniocaudal; T: Transverse; AP: Antero-posterior

Table 3. Comparison of functional and non-functional adenomas

		Functional Adenomas (n:15)	Non-functional Adenomas (n:11)	p
Age*		48.1± 14.4	53.7± 13.8	0.324[a]
Sex	Male (n,%)	8 (53.3%)	6 (54.5%)	0.951[b]
	Female (n,%)	7 (46.7%)	5 (45.5%)	
Tumor size	Microadenoma (<1 cm) (n,%)	4 (26.7%)	0 (0.0%)	0.113[b]
	Macroadenoma (≥ 1 cm) (n,%)	11 (73.3%)	11 (100%)	
Invasion of cavernous sinüs (n,%)		6 (40.0%)	5 (45.5%)	0.781[b]
Suprasellar extension (n,%)		4 (26.7%)	9 (81.8%)	**0.015[b]**
Visual field defect (n,%)		4 (26.7%)	8 (72.7%)	**0.045[b]**
Ki-67 index (%)†		2 [6]	2 [3]	0.376[b]
p53 expression (n,%)		7 (46.7%)	6 (54.5%)	0.691[b]

*Data are presented as mean ± SD
†Data are presented as median (interquartile range [IQR])
[a] Independent t-test, [b] Fisher's Exact Test

DISCUSSION

We, in the present study, examined the clinical, pathological and endocrinological feautures of patients who underwent transsphenoidal pituitary surgery by microscopic method, over an 18-month period. The ultimate diagnosis was functional adenoma in the majority of the operated pituitary lesions. Compared to functional counterparts, suprasellar extension and visual field defects were found to be significantly more in non-functional adenomas.

Approximately 30-35% of pituitary adenomas do not secrete hormones (8). Improvements in immunocytochemistry, electron microscopy, cell culture, and molecular techniques have shown that clinically non-functioning pituitary adenomas are divided into two categories: gonadotropinomas which are staining positive for FSH/LH and null-cell adenomas which lack gonadotropin α-subunit in immunohistochemical staining.

Approximately 30-35% of pituitary adenomas do not secrete hormones. Majority (80-90%) of these are gonadotroph adenomas (gonadotropinoma) which constitute 40% to 50% of all pituitary macroadenomas (8,9). Recently, several patients with gonadotropinomas have been reported to have hormonal hypersecretion syndromes such as ovarian hyperstimulation, testicular enlargement and early puberty (10,11).

The present study provided that many cases which were reported as pituitary adenoma in old reports are currently referred to as gonadotroph adenoma, after a single experienced pathologist's assessment. In other words, the term gonadotropinoma, appears more frequently compared to historic controls. In addition to patients with gonadotropinoma, no findings were obtained in detailed functional screening of the patients with hyperplasia and plurihormonal adenomas and these 3 groups of patients together, were accepted to have non-functional pituitary adenomas.

Invasive adenomas are considered agressive tumors with tendency to extend into surrounding tissues such as cavernous sinuses, bone and sphenoid sinus. However, suprasellar enlargement, alone, is not accepted as a criteria for invasiveness (12). There is no consensus in regard to the relationship between Ki-67 index and invasiveness and recurrence of pituitary adenoma(13). P53 expression which plays role in cell proliferation, apoptosis and genomic instability is also associated with agressive tumor behaviour in pituitary adenomas (14,15). In a study conducted by Botelho et al., p53 immunopositivity was reported as 26.9% in mixed adenomas secreting GH and PRL, whereas this rate was reported as 33.3% in GH- or PRL- only secreting adenomas (16). In our study, somatotroph, lactotroph and mammosomatotroph adenomas constitute 86.6% of the functional adenoma group, and the p53 immunostaining (40%) is higher than that reported in the literature (16-18). The median values of Ki -67 labeling index, an another invasiveness criteria, are below the cut off value (> 3%) used by WHO for atypical adenoma assignment. However, p53 expression of our patients in both functional and non-functional groups was found to be high (46.7% and 54.5%, respectively). Based on this data, we can explain the high percentage of cavernous sinus invasion in our study. On the other hand, the higher rate of suprasellar extension and the visual field defects in non-functional compared to functional group, is supporting why suprasellar extension is not accepted as an invasiveness criterion, given that functional and non-functional groups have similar invasiveness index rates.

Selection bias which is the main limitation of the study is due to the mono-institutional and retrospective design of the work. The second limitation is the small sample size.

CONCLUSION

As a result, in our study, highly invasive character was detected in both functional and non-functional pituitary adenomas. However, Ki-67 indexes were low in the study population, on the other hand, increased p53 expression was noticeable. Based on these findings, we can state that the Ki-67 index may not be directly proportional to the invasive behavior of the disease. Multicenter and prospective clinical studies are needed to represent a further advance in this field.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: The clinical trial protocol was approved by the ethics committee of University of Health Sciences Kartal Dr. Lutfi Kirdar Education and Research Hospital (Date:22/07/2020 Number:2020/514/182/12), and complied with the Declaration of Helsinki.

REFERENCES

1. Raappana A, Koivukangas J, Ebeling T, et al. Incidence of pituitary adenomas in Northern Finland in 1992-2007. J Clin Endocrinol Metab 2010;95:4268-75.
2. Tjörnstrand A, Gunnarsson K, Evert M, et al. The incidence rate of pituitary adenomas in western Sweden for the period 2001-2011. Eur J Endocrinol 2014;171:519-26.
3. Ertan Y, Sarsik B, Akalin T. Tipik ve atipik hipofız adenomlarında hormon immunreaktivite dağılımı Turkish Journal of Pathology. 2009;25:106-11.
4. Chatzellis E, Alexandraki KI, Androulakis II, et al. Aggressive pituitary tumors. Neuroendocrinology 2015;101:87-104.
5. Youssef AS, Agazzi S, van Loveren HR. Transcranial surgery for pituitary adenomas. Neurosurgery 2005;57:168-75.
6. D'Haens J, Rompaey KV, Stadnik T, et al. Fully endoscopic transsphenoidal surgery for functioning pituitary adenomas. A retrospective comparison with traditional transsphenoidal microsurgery in the same institution. Surg Neurol 2009;72:336-40.
7. Klibanski A. Clinical practice. Prolactinomas. New England Journal of Medicine 2010;362:1219-26.
8. Türkiye Endokrinoloji ve Metabolizma Derneği, Hipofiz Hastalıkları Tanı, Tedavi ve İzlem Kılavuzu 2019. Ankara: Miki Yayıncılık; 2019:45-51.
9. Chaidarun SS, Klibanski A. Gonadotropinomas. Semin Reprod Med 2002;20:339-48.
10. Thakkar A, Kannan S, Hamrahian A, et al. Testicular "hyperstimulation" syndrome: a case of functional gonadotropinoma. Case Rep Endocrinol 2014;2014:194716.
11. Gorbacheva AM, Przhiyalkovskaya EG, Azizyan VN, et al. An ovarian hyperstimulation syndrome caused by gonadotropinoma in a young woman. Probl Endokrinol (Mosk) 2019;65:278-88.
12. Sav A, Rotondo F, Syro LV, et al. Invasive, atypical and aggressive pituitary adenomas and carcinomas. Endocrinol Metab Clin North Am 2015;44:99-104
13. Salehi F, Agur A, Scheithauer BW, et al. Ki-67 in Pituitary Neoplasms: A Review--Part I. Neurosurgery 2009;65:429-37.
14. Thapar K, Scheithauer BW, Kovacs K, et al. P53 expression in pituitary adenomas and carcinomas: correlation with invasiveness and tumor growth fractions. Neurosurgery 1996;38:765-71.
15. Basaran R, Onoz M, Bolukbasi FH, et al . Low o6-methylguanıne-dna methytransferase (mgmt) and pan-cytokeratın (pan-ck) expressıon vıa ımmunohıstochemıstry ın pıtuıtary adenomas Acta Endocrinol (Buchar) 2017;13:282-93.
16. Botelho CH, Magalhães AV, Mello PA, et al. Expression of p53, Ki-67 and c-erb B2 in growth hormoneand/or prolactin-secreting pituitary adenomas. Arq Neuropsiquiatr 2006;64:60-6.
17. Grimm F , Maurus R , Beschorner R, et al. Ki-67 Labeling index and expression of p53 are non-predictive for invasiveness and tumor size in functional and nonfunctional pituitary adenomas. Acta Neurochir (Wien) 2019; 161:1149-56.
18. Badiu C, Dumbrava M, Stancu C, et al. Immunoreactivity for glycoproteic hormones and tumor size in pituitary adenomas. Acta Endocrinol (Buchar) 2006;2:1-9.