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Original Article

Nonfunctioning giant pituitary adenomas: Invasiveness and recurrence

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Abstract

Background: We report our surgical series of 35 patients with giant nonfunctioning pituitary adenomas (GNFPA). We analyzed the rule of Ki-67 antigen expression in predicting recurrence.

Methods: Thirty-five patients were operated between 2000 and 2010. Suprassellar extension of the tumors were classified according to Hardy and Mohr based on magnetic resonance (MR) studies. Pituitary endocrine function and MR scans were assessed preoperatively and at 1, 6, and 12 months postoperatively. Immunohistochemical studies were based in regard to the expression of the proliferative Ki-67 index and the hormonal receptor for luteinizing hormone, follicle stimulating hormone, growth hormone, thyroid stimulating hormone, adrenocorticotropic hormone, and prolactin. Tumors specimens were obtained from 35 patients with GNFPA. Endoscopic transsphenoidal surgery was the approach of choice.

Results: Thirty-five patients were submitted to 49 surgeries, 44 (89.8%) were transsphenoidal and 5 (10.2%) were transcranial. The most frequent preoperative complaints were visual acuity impairment and visual field defect in 25 (71.2%) and 23 (65.7%) cases, respectively. Improvement of visual acuitiy and visual field deficit after surgery was seen in 20 (80%) and 17 (73.9%) patients, respectively. Endocrinological deficits were encountered in 20 patients (57.1%). After surgery, 18 patients (51.4%) required hormonal replacement. Three patients had visual symptoms related to pituitary apoplexy and recovered after surgery. The Ki-67 labeling index (LI) ranged from <1% to 4.8%. The rate of recurrence in tumors with Ki-67 <3% was 7.7% (2 patients), Ki-67 >3% was present in 5 patients and the recurrence committed 3 patients.

Conclusion: In our series, regardless the improvement of visual function and compressing symptoms, 5 patients with expression of Ki-67 LI more than 3% experienced a recurrence.

Key Words: Invasiveness, Ki-67, pituitary adenoma, recurrence

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INTRODUCTION

Pituitary adenomas represent 10–15% of all primary brain tumors.[2] Although benign, some tumors can be aggressive.[25] Nonfunctioning pituitary adenoma (NFPA) is the most prevalent pituitary macroadenoma.[2,7,34] Because these tumors do not manifest signs of endocrine hyperfunction, clinical presentation of giant NFPA (GNFPA) is usually secondary to symptoms of mass effect such as visual disturbances, headaches, and impaired pituitary function.[3] Therefore, almost all NFPAs are large extrasellar macroadenomas. Transsphenoidal microsurgical resection of adenomas has been the mainstay of treatment in patients with symptomatic tumors and failed medical treatment.[1,3,24,26,39] Radiation therapy was originally the adjuvant treatment of choice for recurrent or residual pituitary adenomas; however, its side effects included visual dysfunction from optic neuropathy, stroke, and damage to other cranial nerves.[4,17,34] These benign tumors may recur after surgery and it would be very useful to understand those pathologic factors such as the proliferation markers, to predict progression, or recurrence as this knowledge could affect the use of adjuvant treatments. In this study, we retrospectively evaluated our surgical series of 35 patients with GNFPA and correlated the Ki-67 and the hormonal status with recurrence.

MATERIALS AND METHODS

We retrospectively reviewed 35 consecutive patients diagnosed with GNFPA whom underwent endonasal endoscopic transsphenoidal resection assisted by neuronavigation from January 2000 to December 2010 at Galeão Air Force Hospital (HFAG) and Antônio Pedro University Hospital (HUAP).

Each patient was investigated preoperatively with laboratory studies (total blood count, glucose, creatinine, serum sodium level, serum potassium level, coagulogram) and ophthalmological assessment. Endocrinological study included serum level of thyroid stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), growth hormone (GH), follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), estradiol, testosterone, tetra-iodothyronine, cortisol, and insulin such as growth factor-1.

Imaging studies included head computed tomography (CT) and magnetic resonance (MR). All tumors were classified as giant (≥30 mm suprasellar extension above the planum sphenoidale). Cavernous sinus invasion was classified according to Knosp *et al.*[19]

Endonasal endoscopic transsphenoidal surgery (ETSS) was the approach of choice. The details of this technique have been previously described.[6,10,39] The transcranial route was reserved for subfrontal, retrosellar, and lateral extensions, as a second procedure, after transsphenoidal approach. All patients received a histopathological diagnosis of pituitary adenomas.

Decompression of pituitary gland, optic pathway, and surrounding brain structures were the main goals of the surgery. Asymptomatic cavernous sinus invasion was managed conservatively, leaving residual tumor during surgery. Postoperatively, further assessments were performed at 1, 6, and 12 months after surgery and annually after the 1st year.

Immunohistochemical analysis

We obtained paraffin blocks for each case at the archives of HUAP and HFAG and subject them to immunocytochemistry for specific antibodies: ACTH, FSH, GH, LH, PRLs, and TSH. Ki-67, a nuclear antigen expressed in G1, G2, and synthesis phases of the cell cycle but not in the quiescent G0 phase, was measured to assess proliferation using the MIB-1 technique in paraffin – embedded tissue.[12]

Stored paraffin blocks related to the selected cases were obtained for optical microscopy, cut and subjected to immunohistochemical technique (mouse monoclonal anti-ACTH, DAKO, clone O2A3, IgG1 isotype, kappa, code M3501, dilution 1:400; mouse monoclonal anti-FSH, DAKO, clone 10, isotype IgG1, Kappa code M3504, 1:50 dilution; mouse monoclonal anti-LH, DAKO, clone C93 1:300 dilution; rabbit polyclonal anti-GH/somatotrophin-GH, DAKO, GH immunogenic purified isolated from human pituitary gland, code A0570, 1:400 dilution; rabbit monoclonal anti-human-PRL, DAKO, code 0569, dilution 1:200–1:300; rabbit monoclonal anti-TSH, DAKO, clone 0042, code M3503, 1:50 dilution; mouse monoclonal anti-human-Ki-67 DAKO, clone MIB-1, code M7240, 1:200 dilution). Filed and or cut slides stained with hematoxylin eosin were analyzed together with an immunocytochemical study for correct identification of adenomas. Strong and diffuse markings were considered positive; otherwise, the cases were negative or focally positive. We counted 1000 cells tumors/case and the results were expressed in percentage of tumor cells with positive nuclei.

RESULTS

Clinical data

Thirty-five consecutive patients were assessed, 19 males (54.2%) and 16 females (45.8%); mean age was 48.2 ± 2.3 years, ranging between 34 and 76 years. The review period ranged from 1 to 10 years. Table 1 resumes clinical characteristics of the study population. The most common symptoms were visual acuity impairment and visual field disturbance, encountered in 25 (71.2%) and 23 (65.7%) patients, respectively. A headache was encountered in 20 (57.1%). Twenty patients (57.1%) had endocrinological disturbance before surgery: Panhypopituitarism was seen in

13 (37.1%) patients, hypothyroidism was encountered in 5 (14.2%), and 2 patients had sexual dysfunction. CT and MR of the sellar region were available in all patients. Five patients had a subfrontal extension and 7 patients showed cavernous sinus invasion without symptoms and signs.

Surgical data

The transsphenoidal approach was the first choice, and all the surgeries were done under image-guide navigation. A single ETSS was performed in 21 patients [Figure 1]. Nine patients required two surgeries [Figure 2] and five underwent a single ETSS plus subfrontal craniotomy as a part of deliberate second stage operation.

Table 1: Clinical and demographical data of the study population

Characteristic	Number of patients (%)
Mean age in years (range)	48.2 (34-76)
Sex	
Male	19 (54.3)
Female	16 (45.7)
Symptom	
Visual field disturbance	23 (65.7)
Visual acuity impairment	25 (71.2)
Headache	20 (57.1)
Endocrinological disturbance	20 (57.1)
Panhypopituitarism	13 (37.1)
Hypothyroidism	5 (14.2)
Sexual dysfunction	2 (5.7)
Cranial nerve deficit	3 (1)
Number of procedures	
One	21 (60)
Two (ETSS)	9 (25.7)
Two (ETSS + transcranial)	5 (14.2)
Cavernous sinus invasion	7 (20)

ETSS: Endoscopic transsphenoidal surgery

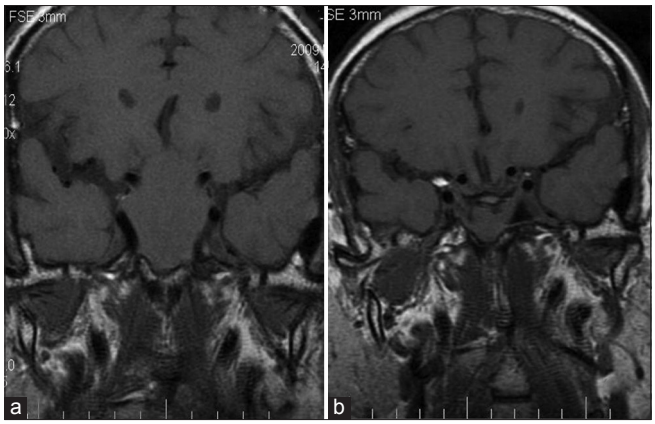

Figure 1: (a) Coronal T1-weighted magnetic resonance imaging scan demonstrating giant sellar lesion with suprasellar and parasellar extensions (Knosp Grade 1), optic chiasm compression. (b) Postoperative (endoscopic transsphenoidal surgery) coronal T1-weighted magnetic resonance imaging, showing an excellent decompression of optic chiasm

After surgery, 17 patients (73.9%) improved visual field deficit and 20 (80%) improved visual acuity. Two patients experienced visual worsening after the surgery. A headache improved in 15 (75%) patients and hormonal replacement was required in 18 (51.4%) patients [Table 2]. Thirteen patients required levothyroxine and corticosteroid replacement, 4 patients needed the chronic use of levothyroxine only and 1 patient. Three patients with cranial nerve palsies (oculomotor and abducent) had complete resolution of their deficits.

Table 3 resumes the complications that occurred. Cerebrospinal fluid (CSF) leak was detected intraoperatively in 7 patients. These cases were managed with autologous fat, fibrin glue, and pedicle nasoseptal flap. One patient developed persistent CSF leak 1-week after surgery and required reoperation. Reconstruction of skull base defect was carried with autologous fascia, fibrin glue, and nasal packing. A lumbar drain was inserted too. Complete resolution of CSF leak was achieved.

Transitory diabetes insipidus occurred in 9 (25.7%) patients. Mean duration was 2.1 ± 0.4 weeks. No patient developed permanent diabetes insipidus.

The most dangerous complication was an injury to a cavernous segment of carotid artery during an ETSS. The patient developed pseudoaneurysm that was treated with a stent, but developed severe motor deficit.

Reoperation due to recurrence was necessary in 5 patients, and 3 of them (60%) had Ki-67 Li more than 3%. There was no mortality.

Immunohistochemical data

On the basis of immunohistochemical studies, the following data were obtained: There were 9 null-cell

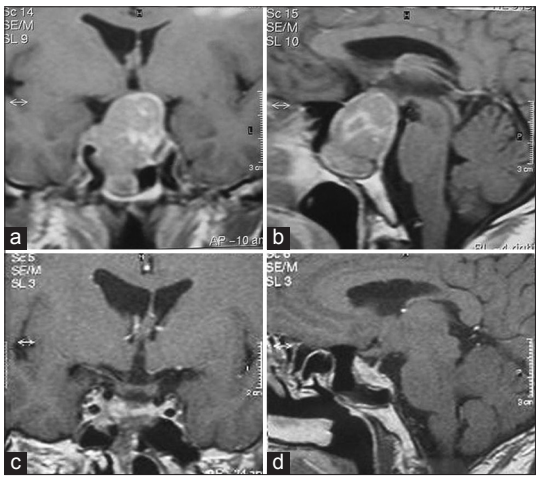

Figure 2: (a and b) Postgadolinium coronal (a) and sagittal (b) preoperative T1-weighted magnetic resonance imaging, showing intense enhancement of sellar tumor, with suprasellar and parasellar extensions. (c and d) Postoperative (after two surgeries) coronal (c) and sagittal (d) postoperative T1-weighted magnetic resonance imaging after radical removal

adenomas, 16 gonadotrophic adenomas, five silent ACTH-cell adenomas, two silent TSH (STSH) adenomas, two plurihormonal adenomas (GH, PRL, and glycoprotein) one silent somatotroph adenoma [Table 4]. Of the 7 tumors with the invasion of the cavernous sinus, 4 were immunoreactive for silent ACTH adenomas, one for STSH (silent thyrotrophic adenoma), and 2 for gonadotrophic adenomas.

MIB-1 was applied in all patients. The samples were positive in all cases. The Ki-67 Li ranged from 1% to 4.8%. In 30 cases, the Ki-67 Li was <3%. In 5 (14.2%) patients Ki-67 Li was above 3% [Figure 3]. Recurrence rate in tumors with Ki-67 <3% was 7.7% (2 patients), whereas 60% of tumors with Ki-67 >3% recurred [Table 5].

Follow-up data

Median follow-up period was 49 ± 3.8 months. Postoperative MR after 1 and 6 months showed no residual tumor in 11 patients (31.4%), and 21 patients (60%), respectively. After 1-year, 14 (40%) patients had a residual mass but without signs or symptoms of compression of surrounding brain structures. Some possible explanations for these findings are fat graft and small clot reabsorption, necrosis of residual tumor, and late diaphragma sellae descent.

Table 2: Comparative analysis of pre- and post-operative symptoms

Symptom	Number of patients (%)			
	Before surgery	Improved after surgery	No changes after surgery	Worsened after surgery
Headache	20 (57.1)	15 (75)	5 (25)	0 (0)
Visual field deficit	23 (65.7)	17 (73.9)	6 (26.1)	0 (0)
Visual acuity impairment	25 (71.2)	20 (80)	3 (12)	2 (8)
Hormonal disturbance	20 (57.1)	2 (10)	18 (90)	0 (0)

Table 3: Postoperative complications

Complication	Number of patients (%)
Visual worsening	2 (5.7)
Postoperative CSF leak	1 (2.8)
New hormonal deficit	0 (0)
Transitory diabetes insipidus	9 (25.7)
Pseudoaneurysm	1 (2.8)

CSF: Cerebrospinal fluid

Table 4: Immunohistochemical diagnosis for 35 patients with GNFPA

Characteristic	Number of patients (%)
Null-cell adenoma	9 (25.7)
Gonadotropin adenoma	16 (45.7)
Silent ACTH adenoma	5 (14.3)
Silent TSH adenoma	2 (5.7)
Silent somatotroph adenoma	1 (2.8)
Plurihormonal adenoma	2 (5.7)

TSH: Thyroid stimulating hormone, ACTH: Adrenocorticotropic hormone, GNFPA: Giant nonfunctioning pituitary adenomas

DISCUSSION

Nonfunctioning pituitary tumors are relatively common. However, due to the lack of clinical syndromes, these tumors are diagnosed late when patients present compression syndromes as a headache, hypopituitarism, and visual field defects. Although there are many reports of tumors shrinkage during therapies with dopamine agonists,[3,11] surgery is the first line treatment of patients with NFPAs.[1,5,24,26,39] These tumors can reach enormous proportion and invade local structures as cavernous sinus, sphenoid bone, dura and adjacent brain,[4,10,23,35] sometimes assuming aggressive behavior. Even though some authors report total removal of the giant pituitary tumor, in general, total removal of these tumors is very rare, and they progress frequently.[4,5,9,20,22]

In our series, 35 patients with GNFPAs were operated. All patients presented with suprasellar extension 30 mm or more above the planum sphenoidale; 5 patients had a subfrontal extension, and seven had cavernous sinus invasion confirmed by MR. The endoscopic transsphenoidal approach under image-guide navigation system was the first procedure even in patients with subfrontal extension. Our policy in relation to cavernous sinus invasion in asymptomatic patients with GNFPAs is expectant. The optimal management of GNFPAs sometimes requires two or more approaches to obtain a maximal removal.[26] We operated in deliberated two-stage approaches 5 patients who presented with subfrontal extension. Nine patients required 2 transsphenoidal surgeries, 5 of them due to recurrence and 4 as part of

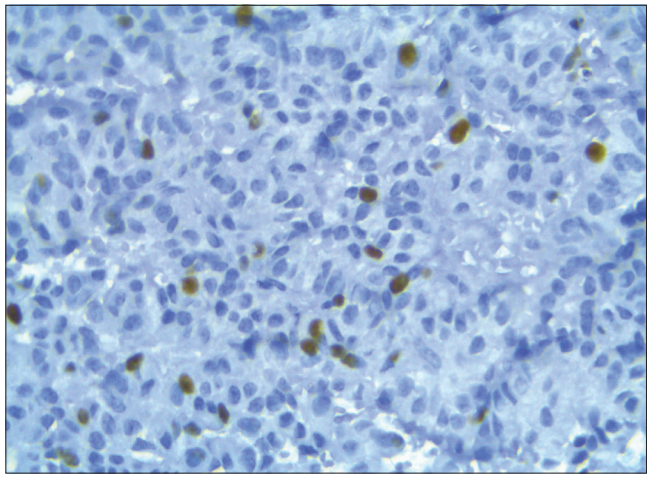

Figure 3: Immunohistochemistry with anti-Ki-67 monoclonal antibody in a giant pituitary adenoma. Index is >3%

Table 5: Ki-67 index of 35 patients with GNFPA

Characteristic (%)	Number of patients (%)	Recurrence (%)
Ki-67 <3	30 (85.7)	2 (6.7)
Ki-67 >3	5 (14.3)	3 (60)

GNFPA: Giant nonfunctioning pituitary adenomas

the two-stage surgery. All patients reoperated due to recurrence underwent the second surgery 3 years after the first procedure. After 1 and 6 months after surgery, 11 and 21 patients were tumor free, respectively. Surgical treatment promoted several benefits. Visual symptoms improved in 17 (62.9%) of the 27 patients who had presented with visual complaints. The number of patients that required hormonal replacement was practically the same.

Ki-67 and p53 are referred as indicators of aggressive behavior in the World Health Organization classification of endocrine tumors.[8,12,20,21,28,30,31,32,36,37] In 1991, Kitz *et al*.[18] studied 120 pituitary adenomas using the monoclonal antibody MIB-1 in two-step avidin-biotin-peroxidase complex. The Ki-67 labeling index (LI) ranged from 0.2% to 4.6%. In 90 cases of transsphenoidally operated adenomas, the dura of the sellar floor was studied histologically and adenomas with histologically proven dural infiltration showed a statistically significant higher Ki-67 when compared with noninvasive adenomas. According to Thapar *et al*.,[35] invasion is defined as a gross, operatively or radiologically apparent infiltration of the dura or bone, but these criteria are not universally accepted.[32,33] They studied Ki-67 Li, in 37 noninvasive adenomas, 33 invasive adenomas, and 7 primary pituitary carcinomas. All tumors were classified by histology, immunohistochemistry, and electron microscopy. Sophisticated statistical analysis confirmed significant differences between each of three tumor groups. Pituitary carcinomas had a higher Ki-67 (11.91 ± 3.41), and invasive pituitary adenomas exhibited significantly higher growth fractions than did noninvasive tumors. Mastronardi *et al*.[23] studied the expression of Ki-67 in 103 pituitary adenomas. Sixty-five noninvasive and 38 invasive tumors were identified from surgically verified infiltration of the sellar floor and dura. The wall of the cavernous sinus was infiltrated in 16 cases. Ki-67 index was higher in functioning tumor as compared to nonfunctioning tumors, particularly in ACTH adenomas. Cavernous sinus infiltrating tumors showed a higher Ki-67 index when compared with noninfiltrating adenomas. Honegger *et al*.[14] studied 23 patients with NFPAs, and the growth rate was calculated for each patient with Ki-67 antigen. They concluded that expression of Ki-67 antigen is significantly correlated with the growth velocity of pituitary adenomas while invasive behavior is an independent feature. Although invasive tumors had significantly higher values of the Ki-67 index,[30,37] invasiveness of cavernous sinus did not alter the Ki-67 index significantly.[21,29]

Our study investigated the proliferative index of GNFPA. In our series, 35 patients with GNFPA were operated, and tumors were classified according to immunohistochemical studies. Pathological studies were performed on paraffin blocks. After immunohistochemical studies, blocks were submitted for Ki-67 evaluation. Most of the tumors were gonadotropic and null-cells adenomas. Of these, seven showed cavernous sinus invasion, four were immunoreactive for silent ACTH adenomas, two for gonadotropic adenomas, and one for STSH adenoma.

MIB-1 antibody was positive in all samples, and Ki-67 index ranged from <1% to 4.8%. Thirty patients had their samples with Ki-67 index <3% and in those patients, recurrence was noticed in 2 (6.67%) patients. Three of 5 reoperated patients had Ki-67 index >3%. Complete removal of GNPAs is very infrequent and in our series, after 1-year, 40% of the patients had residual tumors, but without symptoms. Our policy in relation to residual tumors is close observation of the patients, with surgery being indicated only if the tumor causes symptoms or shows progressive growth. Although modern methods of radiotherapy[15-17,22,34] including Gamma Knife have been used with successful control of tumors remnants, the procedure is not risk-free.[4] Losa *et al*.[21] obtained tumors specimens from 101 patients with NFPAs and Ki-67 index were assessed by immunohistochemical analysis. Twenty-three patients had a recurrence after a mean period of 28.6 ± 4.8 months. Invasiveness on the preoperative MR was the strongest predictor of recurrence, followed by previous pituitary surgery, younger age, and lack of postoperative radiotherapy. Ki-67 LI had no independent prognostic value. Again, Losa *et al*.[22] evaluated early results of surgery and long-term risk of tumor recurrence in 491 patients with NFPAs operated between 1990 and 2005 and the diagnosis of recurrence or residual tumor regrowth were based on neuroradiological criteria. After surgery, 173 patients had a residual tumor, and recurrence was seen in 83 patients. Cavernous sinus invasion, increasing tumor diameter, and the absence of tumor apoplexy had an unfavorable surgical outcome. Total resection in young patients was associated with a risk of tumor recurrence, and the authors suggested adjunctive radiotherapy in patients with incomplete tumor removal. Jagannathan *et al*.[15] recommended radiosurgery as useful in the treatment of both secretory and nonsecretory pituitary adenomas and cited new hypopituitarism as the most common complication although cranial neuropathies, visual injuries, and radiation-induced neoplasms have been cited. Because many tumors are not totally resected after the first surgery, the remnant tumors are a potential source of regrowth, and then

radiation therapy is considered. Kim *et al.*[16] followed 67 patients with pituitary macroadenomas with cavernous sinus invasion, most of them secretory adenomas. Eight patients harbored nonfunctioning adenomas. Thirty-five patients had their masses excised. They achieved 95.5% of tumor control and endocrinological improvement in 68%. There were no cranial nerve deficits. Sheehan *et al.*[34] conducted a review in 42 patients who were submitted to adjuvant radiosurgery and the follow-up varied from 6 to 102 months. Tumor control was achieved in 100% of patients with microadenomas and 97% in patients with macroadenomas. No patient developed new endocrinological deficit. In our series, no patient was submitted to radiotherapy. Some authors reported the high risk of recurrence of gonadotropic adenomas,[8] but this was not observed in our series. In order to avoid indiscriminate use of radiation therapy and its deleterious effects, Noh *et al.*[27] studied proliferative index of 35 pathological specimens from 72 patients of the subtotal resected group. Gamma Knife was reserved for residual tumor regrowth. Ki-67 index was higher in recurrent tumors when compared with nonrecurring tumors. Recurrent tumors were seen in 26 patients, and 9 patients showed no recurrent tumor at the end of follow-up. Overall, in our series, 3 of 5 (60%) patients that required reoperation had Ki-67 index >3%. Symptomatic recurrence was the only indication for reoperation in our series, and no adjuvant radiotherapy was indicated. We maintain close observation of the patients, and new surgical procedures are indicated whenever tumor regrowth begins to cause symptoms.

Cavernous sinus invasion is very challenging for a pituitary neurosurgeon. Some authors[12,16,21,22] consider that cavernous sinus invasion increases mortality, morbidity, and risk of recurrence. They recommend adjuvant radiotherapy. Chang *et al.*[4] identified cavernous sinus invasion as a stronger predictor of recurrence but recommended extreme care in adjunctive postoperative radiotherapy. New advances in pituitary surgery with endoscopy allow a magnificent view of the cavernous sinus. Frank and Pasquini[10] operated 65 pituitary adenomas with cavernous sinus invasion under the endoscopic vision and obtained radical tumor removal in 60% with extremely low morbidity. In our series, 7 patients presented with cavernous sinus invasion, no patient developed symptoms, and neither had a recurrence in the follow-up period. Even under endoscopic view, in cavernous sinus surgery through endonasal approach, repair of the vascular injury is extremely difficult. Our policy for cavernous sinus invasion in asymptomatic patients with GNFPAs is expectant, whereas symptomatic cases are managed with surgery (transcranial route) and adjuvant radiation therapy.

Several markers can be used as a predictive value with regard to the clinical course of the pituitary adenomas and Ki-67 LI was the most widely used,[31,32] although the results are conflicting[8,13,38] For Salehi *et al.*,[31,32] the discrepancy data regarding tumor behavior in part is due to heterogeneity of study criteria. They concluded that uniform definitions and new markers could improve treatment of pituitary tumors.

Although medical management play role in the treatment of some functioning pituitary adenomas, this is not true for NFPAs. The development of new agents for medical therapies including dopamine agonists as dopastin[20] can inhibit pituitary adenoma growth in cells culture.

Despite the advances in pituitary surgery with new refinements such as endoscopy and neuronavigation, radical removal of GNFPA remains challenging. Maximal removal and decompression of optic pathway and surrounding brain structures offer the best chance to control the disease. Close follow-up with surveillance scans should be performed, and extreme caution on radiation therapy indications are the best measures to those patients.

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Conflicts of interest
There are no conflicts of interest.

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