

# Factors influencing improvement of visual field after trans-sphenoidal resection of pituitary macroadenomas: a retrospective cohort study

Fen-Fen Yu<sup>1</sup>, Li-Li Chen<sup>2</sup>, Yi-Hua Su<sup>1</sup>, Li-Hun Huo<sup>1</sup>, Xian-Xuan Lin<sup>1</sup>, Rui-Duan Liao<sup>1</sup>

<sup>1</sup>Department of Ophthalmology, the First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, Guangdong Province, China

<sup>2</sup>Department of Pathology, the First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, Guangdong Province, China

**Correspondence to:** Rui-Duan Liao. Department of Ophthalmology, the First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, Guangdong Province, China. drlrd@163.com

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## Abstract

• **AIM:** To investigate the influencing factors of visual field improvement after trans-sphenoidal resection of pituitary macroadenomas.

• **METHODS:** This retrospective cohort study included 201 patients (366 eyes) with visual field defect induced by pituitary macroadenomas. All of them were treated with trans-sphenoidal surgery. Ophthalmologic evaluation, best-corrected visual acuity (BCVA), and visual field examination were performed before and 3mo after surgery. BCVA, visual field defect index mean deviation (MD), duration of symptoms, age, sex, and volume of tumors were compared. Expression of vascular endothelial growth factor (VEGF) and Ki-67 of tumor tissue were detected by immunohistochemical technique.

• **RESULTS:** The mean age of patients was 44.23±1.29y. Ninety-three patients were female and 108 were male. The mean tumor volume was 14.36±6.23 cm<sup>3</sup>. The mean duration of preoperative symptoms was 11.50±0.88mo. Mean preoperative MD was -17.50±0.82 dB. Mean Preoperative visual acuity was 0.64±0.04. Postoperative visual field improved in 270 (73.77%) eyes, unchanged in 96 (26.23%) eyes. Multivariate logistic regression displayed that the factors independently influencing visual field improvement were young age (OR=1.71, 95% CI: 1.325–2.387, *P*=0.013), low preoperative MD absolute value (OR=1.277, 95% CI: 1.205–1.355, *P*<0.001), small volume of tumor (OR=1.458, 95% CI: 1.060–4.289, *P*<0.001), low expression of VEGF in tumor tissue (OR=1.554, 95% CI: 1.089–2.457, *P*=0.022), and low expression of Ki-67 in tumor tissue (OR=1.552, 95% CI: 1.161–2.847, *P*=0.026).

• **CONCLUSION:** After pituitary macroadenomas trans-sphenoidal resection, the independent influencing factors of the visual fields recovery were low preoperative MD absolute value, young age, small volume of tumor, and expression levels of VEGF/ Ki-67.

• **KEYWORDS:** pituitary adenoma; visual field; influencing factors; vascular endothelial growth factor; Ki-67

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## INTRODUCTION

Pituitary adenoma, which accounts for 10% to 15% of all brain tumors<sup>[1]</sup>, is the third most frequently diagnosed brain tumor. The growing of pituitary tumors may compress the surrounding structures especially optic nerve, cause visual field defects including bitemporal hemianopia, visual disturbance. The frequency of visual field defects in pituitary adenomas varies from 37% to 96% in different studies<sup>[2,3]</sup>.

Trans-sphenoidal surgery is the most common surgical treatment for pituitary adenomas because it's minimal invasive and high success rate. It allows a safe decompression of the anterior visual pathways in the majority of patients, with a low complications rate<sup>[4]</sup>. Lines of evidence demonstrate that improvement in the visual function after trans-sphenoidal surgery for pituitary adenomas, ranging from 56% to 90%<sup>[5,6]</sup>.

Therefore, several studies attempt to find the predictive factors of visual outcome after optic chiasmal decompression. Barzaghi *et al*<sup>[7]</sup> showed that prognostic factors for visual field improvement after trans-sphenoidal resection were good preoperative visual function, young age and low cranio-caudal tumor. A minority of studies confirmed recently that the prognostic value of retinal nerve fiber layer thickness on visual field outcome after treatment of pituitary adenomas compressing the anterior visual pathway<sup>[8,9]</sup>.

As an important angiogenesis stimulator, vascular endothelial growth factor (VEGF) can promote the procedure of

angiogenesis and enhance the development and progression of tumors. Expression of Ki-67 antigen can reflect the proliferation and invasiveness of cells. Studies<sup>[10,11]</sup> showed recently that markers of Ki-67 and VEGF have a major role in tumor behavior of invasive pituitary adenoma, but further researches are needed when displaying the relation between these markers and visual outcome after trans-sphenoidal surgery. This study aims to demonstrate the factors influencing improvement of visual field after trans-sphenoidal resection of pituitary macroadenomas. In addition, we investigate the relation between Ki-67, VEGF and visual outcome after trans-sphenoidal surgery.

## SUBJECTS AND METHODS

A retrospective cohort study, 264 consecutive patients with pituitary adenoma, who were underwent trans-sphenoidal surgery between January 1, 2013 and June 30, 2014 at Ophthalmology and Neurosurgery Departments, the First Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong Province, China. The research adhered to the tenets of the Declaration of Helsinki. The Institutional Review Board had approved the protocol prospectively.

We retrieved data of sampled subjects for this study from the health information system (HIS) in our institution. A total of 201 participants (366 eyes) met the criteria and were included in the analysis. Inclusion criteria were: 1) chiasmal compressive lesion confirmed by magnetic resonance imaging (MRI); 2) the maximum diameter of tumor  $\geq 1.0$  cm; 3) preoperative visual field impairment was determined by a visual field analyzer; 4) patients that underwent trans-sphenoidal approach for the first time; 5) histological diagnosis of pituitary adenomas. Exclusion criteria were: 1) any previous treatment, including radiotherapy or medical treatment; 2) any ocular diseases other than compressive optic neuropathy; 3) a history of diabetes or any other systemic illness that might affect the retina and optic nerve; 4) a spherical refractive error outside the range of  $\pm 5$  D; 5) postoperative complications such as hemorrhage and tumor recurrence; 6) postoperative treatment, including surgical, radiotherapeutic or medical treatment. All patients underwent the ophthalmologic evaluation and brain MRI before surgery and 3mo after surgery.

**Brain Imaging** Brain MRI was performed before and 3mo after surgery. Compression of the optic chiasm was confirmed before surgery. Tumor size was evaluated by measuring the longest width (a), length (b), and height (c). According to Cavalieri's principle, pituitary tumor volume was calculated using the following formula:  $\text{volume} = 4/3\pi (a/2 \times b/2 \times c/2)$ <sup>[12]</sup>. Compression relief was confirmed on follow-up MRI after surgery.

**Ophthalmologic Evaluation** All patients underwent the ophthalmologic evaluation before surgery and 3mo after surgery. Slit-lamp examination, intraocular pressure

measurement and fundus examination were performed to excluding other causes of visual loss such as cataract, glaucoma, and retinal detachment. Past medical history and duration of symptoms were recorded. Visual field and visual acuity were evaluated.

The visual field was assessed using a Humphery field analyzer 750 (Humphrey, Dublin, CA, USA) using a 4-mm<sup>2</sup> Goldmann size III stimulus. The 30-2 SITA standard strategy was used. The depth of deficit was measured by the mean deviation (MD) (normal  $\leq 1$  dB). To minimize the measurement bias, the reliability criteria was defined as fixation losses  $< 20\%$ , false positive and false negative errors  $< 15\%$ . The postoperative visual field was evaluated as improved, worse and unchanged. The improvement was defined as: if there was a decrease  $\geq 1$  dB of MD absolute value.

Best-corrected visual acuity (BCVA) was assessed using standardized optotypes and measured with the Snellen decimal conversion. Light perception, hand motion or finger count at 50 cm before the eye were assimilated to 0.01.

**Immunohistochemical Examination** The tissues were fixed with 10% formalin, then dehydrated with alcohol, embedded with paraffin wax and sectioned into slices 5  $\mu\text{m}$  thick. One slice was used for pathological examination and the other two slices were used to detect VEGF and Ki-67 expression, respectively. The antibody immunohistochemical streptavidin-biotin complex (SABC) kit and rabbit anti-human VEGF (or Ki-67) antibodies were purchased from Boster Company (Wuhan, Hubei Province, China). The sections were rehydrated and incubated overnight at 4°C with the primary antibody. Anti-rabbit IgG, streptavidin-biotin complex, and 3, 3'-diaminobenzidine (DAB) were added in sequence.

VEGF-positive cells were distinguished by brown immunoreactivity in cytoplasm under a light microscope (HPF,  $\times 400$ ). A score corresponding to the sum of both (a) staining intensity (0=negative; 1=weak; 2=intermediate; 3=strong) and (b) percentage of positive cells (0=0% positive cells; 1  $\leq 25\%$  positive cells; 2=26% -50% positive cells; 3>50% positive cells) was calculated. The sum of (a)+(b) reached a maximum score of 6. A score greater than 2 means the value of a positive immunohistochemical assay<sup>[13]</sup>. Ki-67 positive cells were distinguished by brown granules in nucleus. The Ki-67 antigen labeling index (Ki-67 LI) was determined by counting a total of at least 1000 neoplastic nuclei subdivided in 10 fields chosen randomly at  $\times 400$  magnification<sup>[11]</sup>. A value of greater than 3% as the threshold LI for distinguishing positive from negative<sup>[14]</sup>.

**Statistical Analysis** Data were processed using the SPSS ver. 13.0 (SPSS Inc., Chicago, IL, USA). The baseline characteristics of individuals were compared using  $t$ -test for continuous variables and  $\chi^2$  test for categorical variables.

**Table 1 Influencing factors and VF defect outcome**

Factors	VF improved	VF unchanged	<i>n</i> (%)
Preoperative VF (MD, dB)	-13.50±0.82	-25.15±1.26	0.001
Preoperative visual acuity	0.74±0.04	0.35±0.07	<0.001
Age (a)	40.01±1.20	56.10±2.31	0.029
Volume of tumor (cm <sup>3</sup> )	12.59±2.23	22.16±5.27	0.020
Duration of symptoms (mo)	10.79±1.38	12.03±0.80	0.045
Sex			>0.05
M	136/270 (50.37)	46/96 (47.92)	
F	134/270 (49.63)	50/96 (52.08)	
VEGF expression			0.030
Positive	104/270 (38.52)	58/96 (60.42)	
Negative	166/270 (61.48)	38/96 (39.58)	
Ki-67 expression			0.039
Positive	122/270 (45.19)	65/96 (67.71)	
Negative	148/270 (54.81)	31/96 (32.29)	

VF: Visual field.

Pearson's correlation coefficient was used to analyze relation between preoperative visual field and preoperative visual acuity. For the univariate analysis, the relation between postoperative visual field improvement and the individual study variables were evaluated using Pearson's correlation coefficient (for continuous variables, such as MD value, age, and tumor volume) and Spearman's correlation coefficient (for categorical variables, such as expression of VEGF/Ki-67). Multivariate logistic regression was used to compare which variable independently was a positive or negative factor of postoperative visual field improvement. Two-sided  $P < 0.05$  was considered statistically significant.

**RESULTS**

We reviewed the data of 201 patients. Ninety-three patients were female (46.27%) and 108 were male (53.73%). The mean age of patients was 44.23±1.29y (range 15-73y). The mean tumor volume was 14.36±6.23 cm<sup>3</sup> (range 2.15-31.70 cm<sup>3</sup>). The mean duration of preoperative symptoms was 11.50±0.88mo (range 2-22mo).

Among 201 patients (366 eyes), all with preoperative visual field impairment, the preoperative mean MD was -17.50±0.82 dB (range -30.80 to -1.40). Preoperative visual acuity impairment was present in 218 eyes (59.56%), with the mean of 0.64±0.04 (range 0-1). The MD absolute value preoperative was inversely correlated with the visual acuity (Pearson's correlation coefficient,  $P < 0.001$ ).

Postoperative visual field improved in 270 (73.77%) eyes, unchanged in 96 (26.23%) eyes. Postoperative visual acuity improved in 196 (53.55%) eyes, unchanged in 170 (46.45%). There were no differences between visual field improved group and visual field unchanged group in terms of sex ( $P > 0.05$ ). Preoperative MD absolute value ( $P = 0.001$ ), age ( $P = 0.029$ ), volume of tumor ( $P = 0.020$ ), duration of symptoms ( $P = 0.045$ ), expression of VEGF in tumor tissue ( $P = 0.030$ ), expression of Ki-67 ( $P = 0.039$ ) in tumor tissue

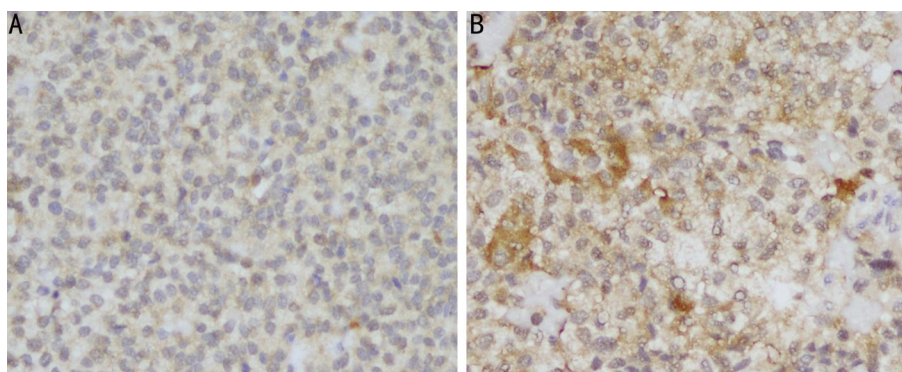
were all significantly lower in the visual field improved group than in the visual field unchanged group. Preoperative visual acuity ( $P < 0.001$ ) was higher in the visual field improved group than in the visual field unchanged group (Table 1).

In univariate analysis, the postoperative visual field improvement was positively associated with the young age ( $P = 0.030$ ), low preoperative MD absolute value ( $P = 0.002$ ), small volume of tumor ( $P = 0.005$ ), low expression of VEGF in tumor tissue ( $P = 0.022$ ), and low expression of Ki-67 ( $P = 0.029$ ). Multivariate logistic regression displayed that the factors independently influencing visual field improvement were young age (OR=1.71, 95%CI: 1.325-2.387,  $P = 0.013$ ), low preoperative MD absolute value (OR=1.277, 95%CI: 1.205-1.355,  $P < 0.001$ ), small volume of tumor (OR=1.458, 95%CI: 1.060-4.289,  $P < 0.001$ ), low expression of VEGF in tumor tissue (OR=1.554, 95%CI: 1.089-2.457,  $P = 0.022$ ), and low expression of Ki-67 (OR=1.552, 95%CI: 1.161-2.847,  $P = 0.026$ ; Figures 1, 2).

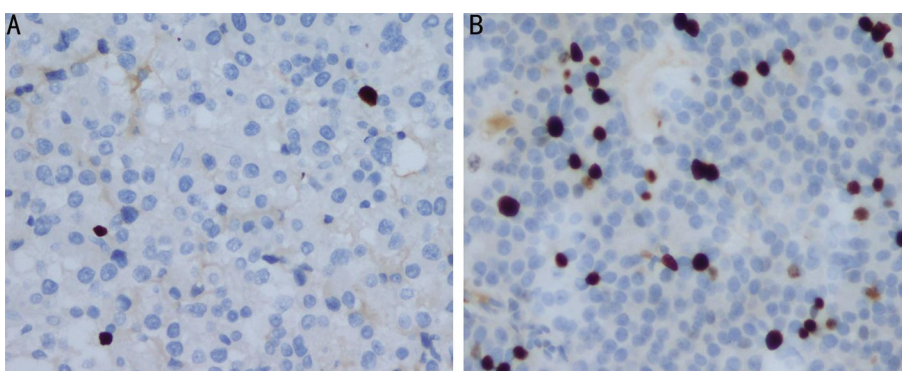
**DISCUSSION**

Pituitary adenomas suprasellar extension can compress the optic chiasm, resulting in damage of vision. Visual field impairment is the most common symptom of visual damage (even the primary symptom of pituitary adenomas sometimes). Generally, it is necessary for a decompression of the anterior visual pathways by surgery, especially in patients with macroadenomas (tumor with diameter >10 mm). Visual assessment, especially documentation of visual field, is vital to decisions about management and evaluations of the therapeutic effect [15]. In our study, we displayed the influencing factors including age, duration of symptom, volume of tumor, and expression of VEGF/Ki-67 for the improvement of visual field after trans-sphenoidal resection of pituitary macroadenomas.

Our study shows more serious defects on preoperative visual



**Figure 1** Representative images of immunohistochemical staining for VEGF in pituitary adenomas tissues (HP,  $\times 400$ ). Microscopy showed that the brown granules in the tumor cell cytoplasm A: A negative immunohistochemical assay, the score was 1; B: A positive immunohistochemical assay, the score was 6.



**Figure 2** Representative images of immunohistochemical staining for Ki-67 in pituitary adenomas tissues (HP,  $\times 400$ ). Microscopy showed that the brown granules in cell nucleus A: A negative immunohistochemical assay, the Ki-67 LI was  $< 1\%$ ; B: A positive immunohistochemical assay, the Ki-67 LI was 5%.

field lesser chance to restore the postoperative visual field. Barzaghi *et al*<sup>[7]</sup> presented that the factors independently predictive for a complete recovery were low preoperative MD absolute value, young age and low diameter of tumor, while not sex and duration of the preoperative symptoms. Our study further supports this existing conclusion. Although MD values were correlated intensively between the visual acuity in this study, the incidence of visual acuity decrease (68.85%) was significantly lower than the visual field defect (100%). We consider that the tumor usually compress firstly the chiasmatic crossing fibres, lead to a bitemporal hemianopsia, then compress macular fibres and cause visual acuity damage at a later stage<sup>[16]</sup>.

Furthermore, we demonstrated that expression of VEGF was correlated inversely with restore of postoperative visual field. Generally, visual field defect occurs mostly when the chiasma compression exceeds a certain level. While, in some cases, visual field defects were observed, even though no suprasellar extension was detected. These suggest that direct compression of the chiasm by pituitary adenoma may not be the only mechanism involved in visual field impairment. Vascular or inflammatory phenomena should be considered as influencing factors<sup>[17,18]</sup>. In our study, pituitary adenomas tissue VEGF levels were lower in postoperative visual field improved patients than visual field unchanged patients. One

reasonable explanation is vascular steal syndrome. It was reported that decreased blood flow and local compression were observed in cerebral regions next to arteriovenous malformation<sup>[19]</sup>. Partial infarction of nerve fiber bundles following vascular steal syndrome was described as a possible reason for unusual visual field defects<sup>[20]</sup>.

VEGF is the main positive regulator in the process of tumor angiogenesis<sup>[21]</sup>. Expression level of VEGF was correlated closely with neovascularization and microvessel density (MVD)<sup>[22]</sup>. Accompanied by increased vascular permeability and occlusion of vessel, VEGF is involved in the occurrence and development of tumors by promoting angiogenesis. The ensuing siphon effects result in partial ischemia in regions next to pituitary adenomas including optic chiasma, and weaken the repair capacity of optic nerve.

Another influencing factor of visual fields improvement after trans-sphenoidal resection is expression level of Ki-67. Ki-67 is a nuclear antigen expressed in the G<sub>1</sub>, S, G<sub>2</sub>, and M phases of cellular cycle. It is widely considered as a marker of cellular proliferation. A high Ki-67 antigen labeling index suggest a high proliferation rate and, thus, tight clinical-radiological follow-up, in relation to possible postoperative relapse of pituitary adenoma<sup>[23]</sup>. Mastronardi *et al*<sup>[24]</sup> showed that Ki-67 can be considered a useful marker in the determination of the invasive behavior of pituitary

adenomas, even if this index seem to having no significant correlations with tumor size. We considered that invasive behavior of tumors affect the restoration of optic nerve.

As far as we known, our study is the first time to demonstrate the relation between Ki-67/VEGF and visual outcome after trans-sphenoidal surgery. In order to minimize the measurement bias, we use the Humphery computerized to assess the visual field perimeters. This machine not only provides a fully quantitative assessment of visual field (MD value) but also incorporates tests for reliability [25]. Nevertheless, some limitations in our study should be addressed. First, multi-centric clinical study should be performed to promote the generalizability of our study results. Second, further studies such as molecular biology field and vascular imaging field are needed to explore the specific mechanism.

In conclusion, after pituitary macroadenomas trans-sphenoidal resection, the independent influencing factors of the visual fields recovery were low preoperative MD absolute value, young age, small volume of tumor, and expression levels of VEGF/Ki-67. Anti-VEGF therapy could be proposed to become an adjuvant treatment of visual rehabilitation in pituitary adenomas patients.

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