

Comparative Study of FPA and NFPA: The relationship between the clinical characteristics and visual function impairment in patients with pituitary adenoma

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Abstract

Background

To investigate the relationship between the clinical characteristics and visual function impairment in patients with functioning pituitary adenoma (FPA) and non-functioning pituitary adenoma(NFPA).

Methods

Case series study. The medical records of pituitary adenomas patients were reviewed retrospectively. Cases with ophthalmic evaluation were enrolled. Tumor types were confirmed by histologic analysis in all cases. The diameter measured on MRI were recorded. The tumor volume was calculated. All the observation indexes of the two groups were compared. The correlation between visual field and tumor volume was studied and the scatter plot was drawn.

Results

30 in FPA and 43 in NFPA group were enrolled. There were 23% of FPA and 41.9% of NFPA had the first symptom in eyes, the former was higher than the latter. The best corrected visual acuity of FPA was better than that of NFPA group. There were 34 (56.7%) and 73 (84.9%) eyes had visual field defect respectively. The visual field defect of FPA was lighter than that of NFPA. Except for the anteroposterior diameter, there was no difference in the other dimensions of tumor diameter between the two groups. The tumor volume of FPA was smaller than that of NFPA group. The tumor size exhibited positive correlation with MD and negative correlation with MS in both groups.

Conclusions

The tumour growth of FPA was slower and less visual function deficiency than that of NFPA. Special attention on multi-types of visual field defects caused by FPA and NFPA is needed.

Background

The pituitary gland formed by the adenohypophysis (anterior pituitary) and the neurohypophysis (posterior pituitary), lying in the sella turcica with cavernous sinus on both sides and optic chiasmata above. [1] Adenohypophysis wrapped around the front and both sides of the neurohypophysis in the shape of "V", accounting for about 80% of the volume of the pituitary gland. It can secrete thyrotropin, adrenocorticotrophic hormone, gonadotropin and growth hormone. Neurohypophysis account for 20% of the volume of the pituitary gland, is responsible for storing and releasing the vasopressin and oxytocin secreted by the hypothalamus. Pituitary adenoma is a common tumour in the brain. According to a recent study, 15.5% of the central nervous system tumours are pituitary adenoma, next to meningioma (37.1%) and glioma (15.6%). [2] According to whether synthesizing and secreting bioactive hormones, they are divided into non-functioning pituitary adenoma(NFPA) and functioning pituitary adenoma(FPA), among which FPA is divided into prolactinoma, growth hormone tumour, adrenocorticotrophic hormone tumour,

thyroid hormone tumour, gonadotropic hormone tumour and multi hormone adenoma. FPA are usually treated for systemic symptoms, which are related to excessive hormone secretion. NFPA are adenomas with no clinical evidence of hormone hypersecretion. They usually present with the effects of local pressure such as visual disturbances, headache, as well as pituitary hormone decrease. [3] Many studies have confirmed that the damage of visual function caused by pituitary tumour is various, which is related to the type, size, location and growth speed of the tumour. [4] However, there is no report about the different damage of visual function caused by FPA and NFPA.

In this study, we assessed the medical records of patients who underwent surgery for pituitary adenomas. We identified the clinical features of patients with NFPA or FPA and investigated whether the visual function impairment were different between the two types.

Methods

Patients' Characteristics

We retrospectively reviewed the medical records of pituitary adenomas patients who underwent endoscopic endonasal or transcranial approach surgery in our hospital between september 2016 and december 2019 and asked for ophthalmic consultation. Tumor-types were confirmed by histologic analysis in all cases.

Inclusion criteria for this study were as follows: 1) patients with primary pituitary adenomas as confirmed by magnetic resonance imaging (MRI); 2) patients with available preoperative data records of three plane sizes of pituitary adenomas and 3) ophthalmic examination: vision, intraocular pressure, fundus, Octopus visual field examination. Exclusion criteria were as follows: 1) patients with any other ophthalmic or systemic comorbidities that could affect visual function, such as cataracts, glaucoma, retinopathy or acute cerebral infarction or 2) patients with nervous system symptoms caused by tumor, unable to cooperate with ophthalmic examination.

The study protocol was reviewed and approved by the Ethical Committee of the Peking University International Hospital. This study was performed in accordance with the Declaration of Helsinki for biomedical research involving human patients. Written informed consent was obtained from each subject after an explanation of the risks, benefits, and alternatives of the study.

Ophthalmologic and neurologic Evaluation

The basic information of all the patients was counted, including name, gender, age, first symptom and duration of them. All patients were required to undergo a preoperative assessment, which comprised evaluation of best corrected visual acuity (BCVA), intraocular pressure, fundus examination, visual field using visual standard automated perimetry (HAAG-STREIT, Octopus900). We will classify them according to the characteristics of visual field deficiency. The diameter measured by three dimensions of the tumor were recorded, and the tumor volume (Cavalieri's principle) was calculated by the formula: tumor volume

$= \frac{4}{3} \pi (a / 2b / 2c / 2)$ (a, b, c respectively represent the diameter measured by three dimensions of the tumor). [5]

According to the postoperative pathological and immunohistochemical examination, all the patients were divided into two groups: FPA and NFPA. The sex ratio, age, duration of symptoms, BCVA, tumor size (the diameter of three dimensions and the volume of the tumor) and visual field parameters (including mean deviation, MD and mean sensitivity, MS) and visual field deficiency of the two groups were compared. The correlation between visual field parameters and tumor volume of the two groups was studied, and the scatter plot was drawn.

Statistical Analysis

Patients' demographic and clinical data were summarized using standard descriptive statistics and frequency tabulation. The Chi-square test was conducted to compare nonparametric values. The t-test of two independent samples is used for other indexes. Differences were considered statistically significant when P values were < 0.05. All analyses were performed using IBM SPSS statistic 24 software.

Results

Patients' Characteristics

Although 136 patients were initially identified, 63 of them were excluded because of insufficient data. A total of 146 eyes of 73 patients were included in the analysis. Among them, 35 patients (47.9%) were male, 38 patients (52.1%) were female, the age was range from 15 to 74 years (48.41 ± 13.36), the shortest time of onset was one week, the longest time was six years, the average time was 374.61 days. The first symptoms included visual acuity decline, visual field defect and other ocular manifestations (48 eyes of 24 people, 32.9%); headache, dizziness and other nervous system manifestations (44 eyes of 22 people, 30.1%); acromegaly, amenorrhea, lactation and other endocrine system manifestations (30 eyes of 15 people, 20.5%); there were also occasional physical examination findings (24 eyes of 12 people, 16.4%). See Table 1 for patient characteristics.

Table 1
Patients' characteristics and clinical findings

Variable	Value	
Number of patient	73	
Male: Female	35(47.9%):38(52.1%)	
Age at diagnosis(years)	15(75)(48.41 ± 13.36)	
Duration of symptom(days)	7(2160)(374.61 ± 473.76)	
Initial symptom(case)	Ophthalmologic	25(34.2%)
	Neurologic	21(28.8%)
	Endocrinium	16(21.9%)
	Physical examination	11(15.1%)
BCVA	0.70 ± 0.37	
Visual field parameter (dB)	MD	11.57 ± 8.39
	MS	16.49 ± 8.48
Tumor size	transverse diameter(cm)	2.40 ± 0.99
	Anteroposterior diameter(cm)	2.05 ± 0.96
	craniocaudal diameter(cm)	2.22 ± 1.02
	volume(cm ³)	8.17 ± 9.37
BCVA: best correct visual acuity; MD: mean deviation; MS: mean sensitivity		

Comparison of characteristics and clinical findings between FPA and NFPA

11 males and 19 females in the FPA group and 23 males and 20 females in the NFPA group were enrolled. The mean age of FPA (40.76 ± 12.57) was lower than that of NFPA (52.67 ± 11.56) (P = 0.000). There were 23% of FPA and 41.9% of NFPA had the first symptom in eyes, the former was significantly higher than the latter ($X^2 = 10.671$ P = 0.014). There was no difference in the three dimensions of tumor diameter between the two groups except that the anteroposterior diameter of which the FPA group was smaller than NFPA group. Meanwhile, the tumor volume of the FPA (6.16 ± 6.52 cm³) was smaller than NFPA (9.62 ± 10.64 cm³). (t = -2.088, P = 0.039). See Table 2 for details.

Table 2
Comparison of characteristics and clinical findings between FPA and NFPA

Variable		FPA(n = 30)	NFPA(n = 43)	P-value
Sex	male	12(16.4%)	23 (31.5%)	0.315
	female	18(24.7%)	20 (27.4%)	-
Age(years)		40.76 ± 12.57	52.67 ± 11.56	0.000
Duration (days)		541.84 ± 472.36	304.40 ± 465.95	0.005
Initial symptom	Ophthalmologic	7 (23.3%)	18(41.9%)	0.014
	Neurologic	3(10%)	18(41.9%)	-
	Endocrinium	16(53.3%)	0	-
	Physical examination	4(13.3%)	7(16.2%)	-
Tumor size	transverse diameter (cm)	2.27 ± 0.92	2.52 ± 1.04	0.155
	anteroposterior diameter (cm)	1.80 ± 0.73	2.22 ± 1.05	0.013
	craniocaudal diameter (cm)	2.05 ± 0.97	2.35 ± 1.04	0.100
	volume (cm ³)	6.16 ± 6.52	9.62 ± 10.64	0.039

Comparison of visual function impairment between FPA and NFPA

The BCVA of FPA (0.81 ± 0.30) was better than that of NFPA (0.61 ± 0.39), and the difference was statistically significant ($t = 2.930$, $P = 0.004$). By comparing MD and MS, the degree of visual field defect of FPA group was lighter than that of NFPA (MD: $t = -3.082$, $P = 0.002$; MS: $t = 3.448$, $P = 0.001$). 34 eyes (56.7%) and 73 eyes (84.9%) had visual field defect in the two groups respectively ($\chi^2 = 54.822$, $P = 0.000$). Types of VF defects in the patients are summarized in Table 3. Among the abnormal VF, most type of VF defects were temporal hemianopsia among which majority not break through vertical midline and others break through vertical midline. Hemianopia with horizontal midline as boundary is followed by. Interestingly there were 2 in FPA and 3 in NFPA with nasal defect. Several typical and atypical visual field defects are shown in Fig. 1.

Table 3
Comparison of visual function impairment between FPA and NFPA

Variable		FPA(n = 30)	NFPA(n = 43)	P-value
BCVA		0.81 ± 0.30	0.61 ± 0.39	0.004
VF parameter(dB)	MD (dB)	8.87 ± 6.98	13.33 ± 8.82	0.002
	MS (dB)	19.55 ± 7.06	14.54 ± 8.83	0.001
Types of VF deficiency(eyes)	Normal	26(43.3%)	17(19.8%)	0.000
	Temporal hemianopsia not break through vertical midline	19(31.7%)	35(40.7%)	-
	Temporal hemianopsia break through vertical midline	5(8.3%)	3(3.5%)	-
	Hemianopia with horizontal midline as boundary	3(5.0%)	7(8.1%)	-
	Nasal defect	2(3.3%)	5(5.8%)	-
	Others	5(8.3%)	19(22.1%)	-
BCVA: best correct visual acuity; VF: visual field; MD: mean deviation; MS: mean sensitivity.				

Correlation between the tumor size and the visual field parameters

We analyzed the correlation between the tumor size and the visual field parameters of the two groups. It was found that the tumor size exhibited significantly positive correlation with MD ($p < 0.05$) and negative correlation with MS ($p < 0.005$) in both of the two groups. The correlation between visual field parameter (MD and MS respectively) and tumor volume are shown in Fig. 2.

Discussion

In our study, the general situation of FPA group and NFPA group were statistically analyzed, including age, sex ratio, clinical manifestations and tumor size. The parameters of NFPA group were similar to those of previous studies. [6] However, there was no comparison between FPA and NFPA previously. Our study found that there was no significant difference in gender distribution between the two groups. But the mean age of FPA group was lower than that of NFPA group. There was no difference in the dimensions of tumor diameter between the two groups except the anteroposterior diameter. Meanwhile, the tumor volume of the FPA group was smaller than that of the NFPA group. This is consistent with some other study that come to conclusion giant pituitary adenomas are frequent among NFPA. [7]

It was reported that the main complaint of patients with pituitary adenoma was a decrease in visual function many years ago. [8] Nowadays, with accurate tests for hormone detection and advances in neuroimaging, the diagnosis of pituitary adenomas is made earlier. Only 30% of patients presenting with pituitary tumors complain of visual problems. [9] This is similar to our results. But the researchers suggest that neurologic manifestations are the initial symptoms in less than 10% of cases. In our study, FPA group is consistent with this figure, but NFPA group has a higher proportion of neurological symptoms.

When it comes to neuro-ophthalmological manifestations caused by pituitary tumour, we should start with the anatomical structure of the pituitary gland. Pituitary gland is located in the dural sac of sellar region, with cavernous sinuses on both sides. The optic chiasma is located above the pituitary gland. When the tumor increases upward and exceeds the sellar, the optic chiasma center will be compressed, the chronic compression of optic chiasm by the tumor may result in axoplasmic stasis and chiasmal blood supply hampered, which may cause bilateral temporal hemianopsia and decrease of vision. Besides, various patterns of visual field deficiency (VFD) have been described in patients with pituitary adenomas, with the precise type of defect depending on the anatomy of the optic chiasm and its relationship to the tumor. The compression in the anterior angle of the optic chiasm produces temporal and superior visual field defects. In cases of non-central tumor, it presents as a combination of severe central visual loss in one eye and subtle defects in the superior temporal visual field respecting the vertical midline in the contralateral eye. Posterior lesions may involve the optic tracts producing a homonymous hemianopsia.[10][11] In our study, the diversity of VFD is also existing. The proportion of patients with normal visual field in FPA group was higher than that in NFPA group. In the NFPA group, the hemianopsia in the vertical middle line of temporal side was the most common, while in the FPA group, the quadrant defect in the upper or lower temporal side was the most common. However, atypical visual field defects were seen in both groups, including the upper or lower visual field defects bounded by the horizontal middle line and nasal quadrant defect.

It can be seen that no matter FPA or NFPA, when the growth of tumor increases to a certain extent, it will cause damage to visual function. [12] [13] But earlier than that, FPA may show some systemic symptoms related to excessive hormone secretion. [9][14] It is also reported in the literature that the diagnosis of NFPA is more delayed than that of FPA. But this is different from our research. We found that the symptoms in the FPA group lasted longer than NFPA group before treatment, which shows that the public's awareness of the systemic symptoms caused by excessive secretion of such hormones is weak. Most of our patients did not pay attention on it when it did not cause the severe symptoms that can obviously affect normal life such as visual dysfunction or headache. It is reported in the literature that NFPA account for 36% – 54% of the pituitary adenoma patients. [14][15][16]. In our study, the proportion is as high as 58.9%, which also indicates that some patients with FPA may not come to see a doctor. Therefore, we should strengthen the publicity and education to the public, which can help the earlier detection and treatment of this kind of tumor. Meanwhile training ophthalmologists and to entertain early diagnosis of these insidious is also important. And then we can greatly improve the prognosis and reduce the social burden.

According to our results, it can be inferred that the effect on visual function of FPA is relatively smaller than that of NFPA. Other scholars have studied the effect of pituitary tumor size on visual field. Rivoal confirmed that the pituitary tumor patients with visual field defect were all the patients with large tumor volume, only the tumor size and the degree of visual field defect had a significant correlation. [17] Thomal also confirmed that the decrease of visual acuity and the degree of visual field defect were significantly related to the tumor volume. [18] Beltrame et al further confirmed that in patients with large tumor volume, the thickness of retinal nerve fiber layer can be clearly detected by OCT, which is the cause of more serious damage to vision and visual field. [19] However, there is no comparative study on the effect of tumour volume to visual field between FPA and NFPA previously. According to the relevant equation and scatter diagram, it can be found that the same volume of FPA has less damage to visual field than that of NFPA. This may be related to the growth pattern of NFPA, because some invasive pituitary tumours are also included in NFPA group. [20] In addition, there is a mechanism of vascular dysfunction to visual function damage caused by pituitary tumor, which is more likely to exist in NFPA. [21] [22]

This study has some limitations. It has an inherent selection bias of a retrospective study. Because our hospital is located in capital of the country where the vast majority of patients who come to see a doctor are transferred from other places, the disease degree is more serious and complex. In addition, the long-term treatment effect of these medical records should be observed and followed up for a long time.

Conclusion

In our study, FPA patients was younger than NFPA. The tumour growth of FPA was slower and less visual function deficiency than that of NFPA. The tumor size exhibited positive correlation with MD and negative correlation with MS in both groups. Special attention on multi-types of visual field defects caused by FPA and NFPA is needed.

Abbreviations

FPA
functioning pituitary adenoma
NFPA
non-functioning pituitary adenoma
MRI
magnetic resonance imaging
BCVA
best correct visual acuity
VF
visual field
MD
mean deviation
MS

mean sensitivity

Declarations

Ethics approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki and was approved by the Ethical Committee of Peking University International Hospital. Written informed consent was obtained from each subject after an explanation of the risks, benefits, and alternatives of the study.

Consent for publicationWritten informed consent was obtained from all patients for the publication of personal or clinical details along with any identifying images to be published in this study. Availability of data and material

The data used to support the findings of this study are available from the corresponding author upon request.

Competing interestsThe authors declare that they have no competing interests.Funding

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Authors' contributions

Yongzhen Bao: The corresponding author, formulated criteria for enrollment or exclusion, guided the application of statistical methods.

Jiayin Qin: Collect the clinical data of patients, carried out ophthalmic examination and wrote the major part of the manuscript.

Kai Li: Provided neurosurgical information, assisted in diagnosis and grouping.

Xijuan Wang: Carried out ophthalmic examination and shared writing the manuscript.

All authors read and approved the final manuscript.

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Figures

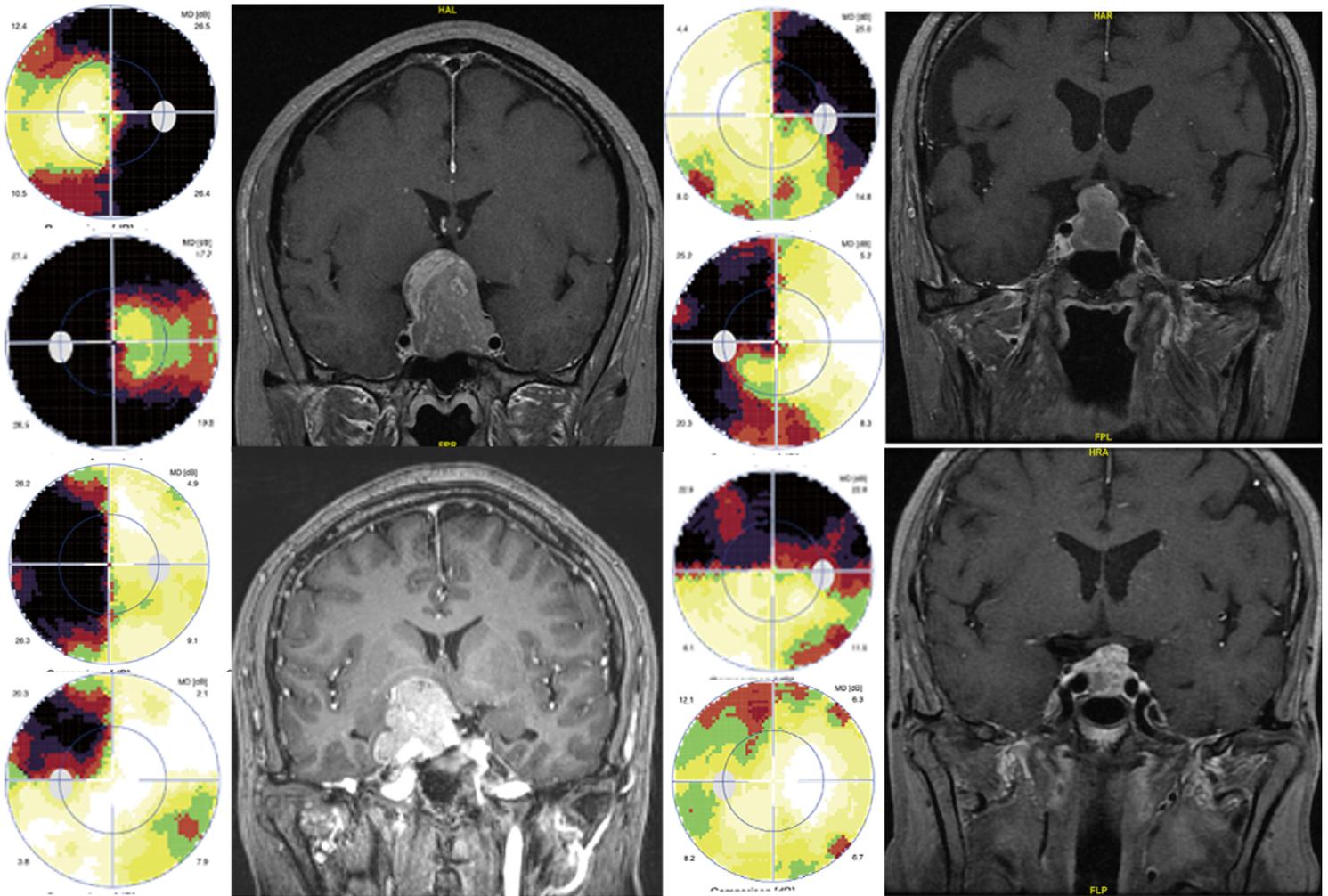


Figure 1

Visual field and MRI of four patients with pituitary adenoma. Top-left: Case 1. A 53-years-old female with NFPA at diagnosis. Visual field: bilateral temporal hemianopsia breaking through the vertical midline. Contrast-enhanced MRI shows that the pituitary dumbbell shaped mass with clear boundary is significantly enhanced, with the size of $2.7 \times 2.6 \times 4.0$ cm. The mass protrudes to the sella and compresses the optic chiasm. Top-right: Case 2. A 70-years-old male with NFPA at diagnoses. Visual field: bilateral superior temporal quadrant visual field defect and breakthrough to inferior temporal. Contrast-enhanced MRI shows that the tumor is significantly enhanced with a size of $1.9 \times 1.8 \times 2.5$ cm and a clear boundary. The pituitary stalk shifts to the left, and the optic chiasm moves up. Bottom-left: Case 3. A 47-years-old male with FPA(Parasellar prolactinoma) at diagnoses. Visual field: nasal hemianopsia in right eye and quadrant visual field defect in left eye. Contrast-enhanced MRI shows that the tumor is significantly enhanced, with the size of $2.0 \times 2.7 \times 3.0$ cm and irregular boundary. The pituitary stalk shifts to the left and the anterior part of optic chiasm is elevated obviously on the right side. Bottom-right: Case 4. A 67-years-old male with NFPA at diagnoses. Visual field: superior hemianopsia in right eye and superior local defect in left eye. Contrast-enhanced MRI shows that the tumor size is $1.8 \times 1.7 \times 1.9$ cm and the left optic chiasm is compressed to move up.

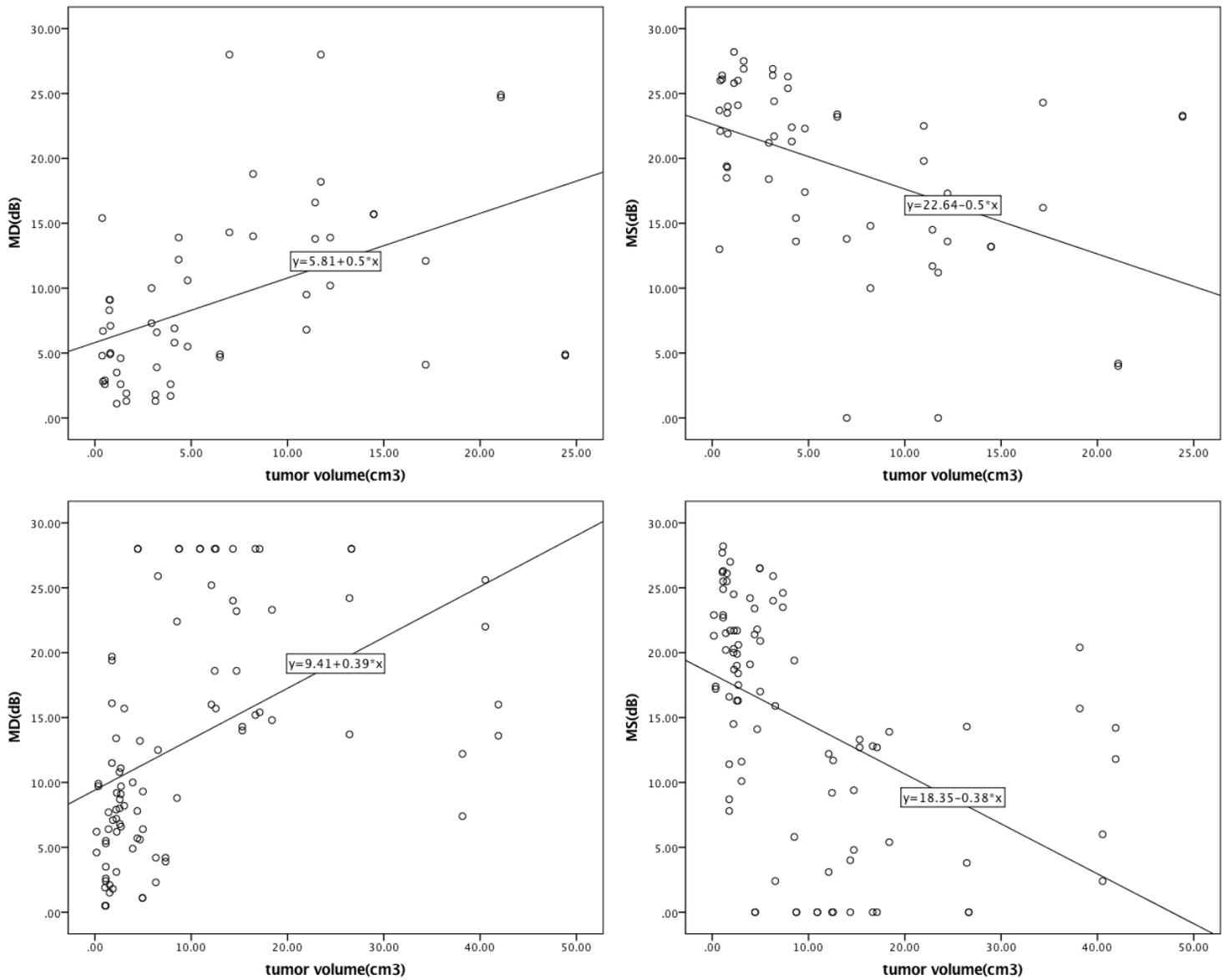


Figure 2

Correlation between the tumor size and visual field parameters. Top-left: Correlation between mean deviation(MD) and tumor volume in patients of FPA group. Pearson correlation coefficient=0.515, P=0.000. Top-right: Correlation between mean sensitivity(MS) and tumor volume in patients of FPA group. Pearson correlation coefficient=-0.512, P=0.000. Bottom-left: Correlation between mean deviation(MD) and tumor volume in patients of NFPA group. Pearson correlation coefficient=0.446, P=0.000. Bottom-right: Correlation between mean sensitivity(MS) and tumor volume in patients of NFPA group. Pearson correlation coefficient=-0.437, P=0.000.