

Abstract

Background

There were few reports about the influence of tumor characteristics on the postoperative visual field outcomes after transsphenoidal surgery for pituitary adenoma. The purpose of this study was to explore the tumor characteristics that influenced perioperative visual field changes.

Method

Patients who underwent transsphenoidal surgery under a diagnosis of pituitary adenoma at Kyoto University Hospital between April 2012 and December 2018 were retrospectively enrolled.

Correlations among circumpapillary retinal nerve fiber layer thickness, preoperative and postoperative mean deviation (MD) of visual field, MD change after surgery, and maximum tumor diameter were evaluated by measuring Pearson's correlation coefficient. We evaluate the influences on postoperative MD by using a generalized estimating equation (GEE) for univariate and multivariate regression analyses. We also compared the characteristics of cystic and solid tumors.

Results

Thirty-two eyes of 18 patients were included in this study (nine males and nine females).

Postoperative MD was positively correlated with maximum tumor diameter only in multivariate

regression ($\beta = 0.22$ [95% CI, 0.004 to 0.43], $p = 0.046$), although maximum tumor diameter was negatively correlated with postoperative MD in univariate regression ($\beta = -0.16$ [95% CI, -0.58 to 0.26], $p = 0.46$). In the investigation of perioperative MD changes, eyes with cystic tumors showed significantly better improvement than those with solid tumors (8.93 ± 7.85 dB vs. 0.18 ± 6.56 dB, $P=0.007$).

Conclusion

Cystic and solid tumors show different characteristics of visual loss and visual field defects. The MD in eyes with cystic tumors improved significantly more than that in eyes with solid tumors.

1 Introduction

Pituitary tumors constitute 12%-15% of all intracranial lesions(1). Visual impairment is the most common complaint, with vision loss occurring in 32%-70% of patients(1). The visual field of patients with pituitary adenoma usually recovers after transsphenoidal surgery for removal of the tumor (2). The prognostic value of factors such as age, duration of symptoms, tumor size, and volume, preoperative visual acuity or visual field loss, optic atrophy, and pattern electroretinograms have been explored with respect to vision loss, but none of these factors was shown to consistently predict visual recovery following surgery (3,4).

Optical coherence tomography (OCT) can identify reduction of the retinal nerve fiber layer thickness (RNFLT) (3–7). Pituitary adenomas can compress the optic chiasm, causing RNFLT reduction (3–5,8,9). The functional impairment of the visual field caused by pituitary adenomas can also be evaluated quantitatively by measurement of mean deviation (MD) in static perimetry, which represents the average difference from the normal expected value in the patients' specific age group (10).

Previous studies have suggested that the preoperative circumpapillary RNFLT (cpRNFLT) was significantly correlated with the difference between preoperative and postoperative MD (3,7), but there were few reports about the influence of tumor characteristics and cpRNFLT on the postoperative visual field outcomes after transsphenoidal surgery for pituitary adenoma.

First, we explore the correlations between postoperative MD and maximum tumor diameter by using a generalized estimating equation (GEE) for univariate and multivariate regression analyses. We found

that tumor diameter was not less correlated than cpRNFLT with postoperative MD, Second, we focused on the tumor characteristics and compared the characteristics of cystic and solid tumors.

Methods

This retrospective study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board and Ethics Committee of the Kyoto University Graduate School of Medicine.

Inclusion Criteria

Patients who underwent treatment at Kyoto University Hospital between April 2012 and December 2018 were retrospectively enrolled. The inclusion criteria were as follows: (1) patients who were referred from the department of neurosurgery for assessments of visual acuity and visual field, (2) patients who underwent transsphenoidal surgery and were pathologically diagnosed as showing pituitary adenoma, (3) eyes that underwent Spectralis HRA +OCT (Heidelberg Engineering, Heidelberg, Germany) examinations before the surgery and Humphrey visual field analyzer (HFA; Carl Zeiss-Meditec, Dublin, CA, USA) assessments using the 30-2 SITA standard testing protocol both before and after the surgery.

Exclusion Criteria

We excluded patients who showed no bitemporal hemianopsia defined by Mills's criteria (see below) in Humphrey visual field analyzer assessments both before and after the surgery (10).

Optical Coherence Tomography

Quantitative RNFL measurements were obtained using the Spectralis OCT instrument with the built-in software. The average RNFL thickness for the entire circumference around the optic disc— at a diameter of 3.46 mm—was obtained for each eye with a mean of 16 scans.

Visual Field Testings

Automated perimetry was conducted using HFA SITA standard 30-2. Only VF tests with reliable results were used for analysis; reliability was defined in terms of fixation loss < 20% and false-positive error rate and false-negative rate < 33%. In automated perimetry, the reduction in visual field sensitivity at each test point was evaluated with reference to the total deviation from a normative database or the pattern deviation from comparison with the findings for other test points in the same examination. In this study, we defined temporal hemianopia in HFA results based on Mills criteria (10), i.e., a threshold sensitivity difference of 2 dB or more for four pairs along the vertical median or 3 dB or more for three pairs along the vertical median was diagnosed as a temporal hemianopia (10).

Magnetic Resonance Imaging

We measured the length of the tumor in the axial, coronal, and sagittal planes. The maximum length was chosen as the maximum tumor diameter in these measurements. The type of tumor (cystic or solid tumor) was retrospectively determined by the reports from radiologists or conference records at the neurosurgery department.

Statistical Analyses

Comparisons of categorical data were performed by Fisher's exact test. Correlations among cpRNFLT, preoperative and postoperative MD, MD change after surgery, and maximum tumor diameter were evaluated by measuring Pearson's correlation coefficient.

To compare the means between two groups and evaluate the influences on postoperative MD, we used a generalized estimating equation (GEE) for univariate and multivariate regression analyses. In the GEE framework, each eye was considered dependent within an individual. In the multiple regression analysis, we included age, sex, cpRNFLT, MD in HFA, maximum diameter of the tumor, and visual acuity as the predictive preoperative factors.

All p values were presented as two-sided values. Statistical significance was defined as $p < 0.05$. All analyses were performed using R ver. 3.6.0. (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients

Among the 1844 patients referred from the department of neurosurgery to the department of ophthalmology, 159 were diagnosed with pituitary adenoma and underwent transsphenoidal surgery between January 2012 and December 2018. A total of 23 patients underwent Humphrey visual field tests both before and after the surgery and OCT before the surgery. Five eyes of 5 patients were

excluded because they were not diagnosed with bitemporal hemianopia based on Mills criteria. Thus, 32 eyes of 18 patients were eventually included for the subsequent analyses.

Baseline characteristics of the patients and the results of preoperative and postoperative examinations are summarized in Table 1.

Correlations between cpRNFLT and visual field outcome

The correlations between cpRNFLT and visual field outcomes are depicted in Supplementary Figure 1. The cpRNFLT was correlated significantly with both preoperative and postoperative MD, although it showed a stronger correlation with the postoperative MD ($P < 0.001$, Supplementary Figure 1A) than with the preoperative MD ($P = 0.004$, Supplementary Figure 1B). Preoperative cpRNFLT was not correlated significantly with the magnitude of mean deviation (MD) change from the preoperative to the postoperative assessment ($P = 0.36$, Supplementary Figure 1C).

The factors influencing postoperative MD

To evaluate the factors influencing postoperative MD, we performed univariate and multivariate regression analysis using a GEE (Table 2). Postoperative MD was significantly correlated with cpRNFLT ($\beta = 0.34$ [95% CI, 0.14 to 0.53], $p < 0.001$ in univariable regression; $\beta = 0.20$ [95% CI, 0.07 to 0.33], $p = 0.0025$ in multivariate regression). Postoperative MD was correlated with preoperative MD or preoperative visual acuity (logMAR) only in univariable regression ($\beta = 0.5$ [95% CI, 0.14 to

0.86], $p = 0.0065$ or $\beta = -10.5$ [95% CI, -19.5 to -1.51], $p = 0.022$). Postoperative MD was positively correlated with maximum tumor diameter only in multivariate regression ($\beta = 0.22$ [95% CI, 0.004 to 0.43], $p = 0.046$), although maximum tumor diameter was negatively correlated with postoperative MD in univariate regression ($\beta = -0.16$ [95% CI, -0.58 to 0.26], $p = 0.46$, Table 3 or Sup Table 1). The maximum tumor diameter also showed a negative correlation with cpRNFLT but not significantly ($r = -0.17$, $p = 0.44$).

Size and tumor characteristics

To explore why the correlations between postoperative MD and maximum tumor diameter differed between univariate and multivariate regressions, we sequentially evaluated the type of tumor. As shown in Figure 1, two eyes had maximum tumor diameters greater than 40 mm. We excluded these two eyes as outliers and performed univariate and multivariate analysis (Supplementary Table 1). When these eyes were excluded as outliers, the maximum tumor diameter was no longer correlated with postoperative MD in univariable regression ($\beta = -0.40$ [95% CI, -0.98 to 0.18], $r = -0.37$, $p = 0.18$) (Figure 1) and in multivariable regression ($\beta = 0.15$ [95% CI, -0.18 to 0.48], $p = 0.38$, Figure 1 and Supplementary Table 1). Also, the maximum tumor diameter was no longer correlated with change in the MD ($\beta = 0.47$ [95% CI, -0.09 to -1.1], $r = 0.40$, $p = 0.10$, in univariable regression). However, the maximum tumor diameter still showed a significant negative correlation with cpRNFLT ($\beta = -1.43$ [95% CI, -2.8 to 0.047], $r = -0.48$, $p = 0.04$, in univariable regression).

Since the tumors with maximum diameter greater than 40 mm had a cystic component, we compared the characteristics between eyes with cystic and solid tumors (Table 3). Preoperative visual acuity (logMAR) and preoperative MD in the eyes with solid tumors were significantly better than those in eyes with cystic tumors ($p = 0.02$ and $p < 0.001$ respectively). The MD in eyes with cystic tumors improved significantly more than that in eyes with solid tumors ($p = 0.002$), but there was no significant difference in postoperative MD between eyes with cystic and solid tumors. Maximum tumor diameter in eyes with cystic tumors was significantly larger than that in eyes with solid tumors. The representative cases with cystic tumor or solid tumor are depicted in Figure 2.

Discussion

The MD of HFA in patients with cystic tumors significantly improved more than that in patients with solid tumors. The maximum diameter of cystic tumors was significantly larger than that of solid tumors (Table 3). The preoperative MD of cystic tumors was significantly lower than that of solid tumor, and the change in MD of cystic tumors was larger than that of solid tumors (Table 3). These findings suggest that the visual field defect caused by cystic tumors has reversible elements. The rapid growth of cystic tumors is thought to cause a rapid reduction in visual acuity. As a result, treatment is started relatively early and tumor compression is released before irreversible degeneration of the optic nerve.

130 Only a few reports on the surgical outcomes of cystic pituitary adenoma have described the visual
131 prognosis. However, many reports have described the results of preservation of facial nerve function
132 in cystic and solid vestibular schwannomas (VSs) (11,12). In patients with VSs, a relatively rapid
133 increase in volume followed by the appearance of acute symptoms as a result of compression of
134 facial nerve are frequently observed in cases involving cystic tumors. Moreover, in relation to
135 symptoms, cystic VSs differ from solid tumors in terms of the patterns of onset. This difference may
136 result from differences in the progression rate because cystic tumors increase more rapidly than solid
137 tumors (11,13,14). The enlargement of cystic tumors is augmented by fluid accumulation due to a
138 direct osmotic effect and/or extravasation of serum proteins from an impaired blood-tumor barrier
139 (13). Most studies on cystic VSs reported that facial nerve outcomes after cystic VS resection were
140 worse than the results for solid VSs of comparable sizes (14). This difference may be due to the tight
141 adhesion of the nerve to the tumor surface, causing difficulties in preserving the arachnoidal plane,
142 unusual positioning of displacement dependent on the pattern of development and growth of the cyst,
143 and the low resistance to traction after cyst evacuation. In some studies, facial nerve outcomes
144 showed no significant difference between cystic and solid VSs(11,15). However, all studies showed a
145 consensus that cystic tumors enlarge more rapidly than solid tumors. Thus, the visual field
146 improvement in patients with cystic tumors is expected to be better than that in patients with solid
147 tumors if treatment is started early in the stage of RGC dysfunction (Table 3).

148 The correlation between tumor size and the postoperative MD has been a topic of debate (8,9). In this
149 study, the max diameter of the tumor was significantly correlated with postoperative MD in
150 multivariable regression but not in univariable regression. However, after excluding two eyes with
151 maximum tumor diameter greater than 40 mm as outliers, the maximum tumor diameter was not
152 correlated with postoperative MD in both multivariable and univariable regression (Sup. Table 1). The
153 results were different in multivariable and in univariable regression. As mentioned earlier, the size and
154 change in the MD of cystic tumors tended to be larger than that of solid tumors in the current study.
155 Since half of the cases involved cystic tumors in this study, the larger size of these tumors may have
156 resulted in better results in multiple regression analysis for postoperative MD.

157 The cpRNFLT showed a stronger correlation with postoperative MD ($P < 0.001$, Supplementary
158 Figure 1A) than with preoperative MD ($P = 0.004$, Supplementary Figure 1B). However, the
159 cpRNFLT was not significantly correlated with the operative change in MD in this study. The
160 preoperative visual field deficiency reflects both degenerated retinal ganglion cells (RGCs) and
161 surviving but dysfunctional RGCs. Even when retinal nerve fibers are injured by laser-induced
162 axotomy, the structural changes caused by retrograde degeneration occurred over 4 weeks (16).
163 Another good example is traumatic optic neuropathy (17,18), in which the optic atrophy appears
164 sometime after the injury and progresses over approximately one month after the injury. Unlike laser-
165 induced axotomy or traumatic optic neuropathy, the irreversible axonal degeneration caused by
166 compression of pituitary tumors will take more time, indicating that surviving but dysfunctional RGCs

may exist in patients with progressive pituitary tumors compressing the optic chiasm. However, in contrast to the preoperative MD, a reduction in the cpRNFLT reflects only degenerated RGCs that occur as a result of irreversible loss of nerve fibers (3). Although the function of the surviving but dysfunctional RGCs may be restored by releasing the compression, the function of the degenerated RGCs is not restored after surgery. Thus, both the reduction of cpRNFLT and postoperative visual field defect reflect only degenerated RGCs, which is why cpRNFLT was more significantly correlated with postoperative MD than with preoperative MD and the change in MD.

The current study had several limitations. First, since we could only collect the data for 32 eyes of 18 patients, the sample size was too small to detect statistically significant differences. This study was also retrospective in nature. In particular, the interval between the operation and the postoperative visual field test varied. However, this interval was not significantly correlated with the magnitude of MD change after the operation. Second, the cpRNFLT reduction does not directly reflect the loss of RGCs. A previous study reported that ganglion cell complex (GCC) measurements were significantly correlated with postoperative MD better than with cpRNFLT(19). In addition, measurement of GCC by OCT can make it easier to detect macular changes with vertical step (20). Analysis of GCC may also reveal the correlation between preoperative changes detected by OCT and the perioperative course of visual acuity. We did not take into account the interval between appearance of symptoms and the operation.

186 **Conclusions**

187 Cystic tumors enlarge more rapidly than solid tumors. The visual field in patients with cystic tumors
188 showed significantly greater improvements than that in patients with solid tumors.

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190 **Acknowledgement**

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248

249 Table 1. Characteristics of patients

	Total
Patients/eyes	18/32
Age, years	58.04 ± 11.81
Sex (male/ female)	16 / 16
Eye (Right / Left)	16 / 16
Preoperative visual acuity (logMAR)	0.15 ± 0.42
Postoperative visual acuity (logMAR)	-0.06 ± 0.20
Preoperative mean deviation, dB	-11.34 ± 10.02
Postoperative mean deviation, dB	-6.51 ± 7.78
Period until postoperative HFA assessment, days	428.81 ± 544.43
Change in mean deviation, dB	4.83 ± 8.42
cpRNFLT, μm	81.75 ± 15.45
Maximum diameter of the tumor, mm	27.26 ± 6.94

250 cpRNFLT, circumpapillary retinal nerve fiber layer thickness; HFA, Humphrey field analyzer.

251 Table 2. Univariate and multivariate regression analysis using the general estimating equation to evaluate the factors influencing postoperative mean
252 deviation

	Univariate regression		Multivariate regression	
	β (95% CI)	<i>P</i> value	β (95% CI)	<i>P</i> value
cpRNFLT	0.34 (0.14 to 0.53)	<0.001	0.20 (0.070 to 0.33)	0.0025
Preoperative MD	0.50 (0.14 to 0.86)	0.0065	0.28 (-0.038 to -0.61)	0.083
Age at operation	0.25 (-0.044 to 0.55)	0.095	0.13 (-0.028 to 0.28)	0.11
Sex (male = 0, female = 1)	-0.41 (-6.5 to 5.6)	0.89	-0.75 (-4.6 to 3.1)	0.7
Maximum tumor diameter	-0.16 (-0.58 to 0.26)	0.46	0.22 (0.004 to 0.43)	0.046
Preoperative visual acuity (logMAR)	-10.5 (-19.5 to -1.51)	0.022	-1.1 (-6.3 to 4.08)	0.68

253 CI, confidence interval; cpRNFLT, circumpapillary retinal nerve fiber layer thickness; MD, mean deviation

254 Table. 3 Characteristics of patients in the cystic tumor and solid tumor groups

	Total	Cystic	Solid	<i>P</i> value
Age, years	58.04 ± 11.81	59.03 ± 12.54	56.92 ± 11.27	0.41
Sex				
Male	16	11	5	0.16
Female	16	6	10	
Eye				
Right	17	8	8	1
Left	14	9	7	
Preoperative visual acuity (logMAR)	0.15 ± 0.42	0.33 ± 0.50	-0.05 ± 0.16	0.004
Postoperative visual acuity (logMAR)	-0.06 ± 0.20	-0.02 ± 0.26	-0.12 ± 0.07	0.17
Preoperative mean deviation, dB	-11.34 ± 10.02	-16.87 ± 9.51	-5.08 ± 6.32	<0.001
Postoperative mean deviation, dB	-6.51 ± 7.78	-7.94 ± 9.58	-4.90 ± 4.88	0.29
Period until postoperative HFA assessment, days	428.81 ± 544.43	470.06 ± 659.19	382.07 ± 394.10	0.77
Change in mean deviation, dB	4.83 ± 8.42	8.93 ± 7.85	0.18 ± 6.56	0.002
Preoperative cpRNFLT, μm	81.75 ± 15.45	78.00 ± 18.34	86.00 ± 10.37	0.23
Maximum tumor diameter, mm	27.68 ± 6.94	31.13 ± 6.78	22.79 ± 3.78	0.003

255 cpRNFLT, circumpapillary retinal nerve fiber layer thickness; HFA, Humphrey field analyzer

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Figure 1. Relationships of maximum tumor diameter with postoperative mean deviation and circumpapillary retinal fiber layer

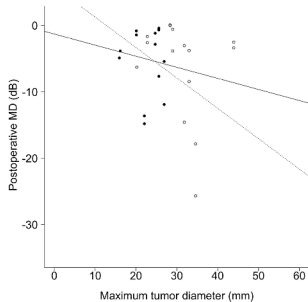
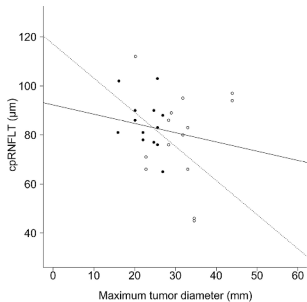
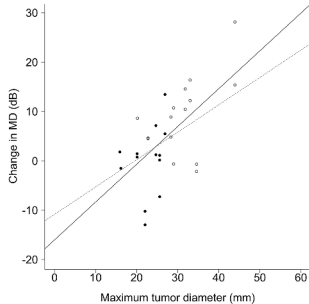
(A) Maximum tumor diameter was not correlated significantly with postoperative mean deviation ($r = -0.18$, $p = 0.46$, solid line). When we excluded two eyes with maximum tumor diameter greater than 40 mm, the maximum tumor diameter was negatively correlated with postoperative MD but not significantly ($r = -0.37$, $p = 0.18$, dotted line).

(B) Maximum tumor diameter was not correlated significantly with circumpapillary retinal nerve fiber layer thickness ($r = -0.17$, $p = 0.44$, solid line). When we excluded two eyes with maximum tumor diameter more than 40 mm, the maximum tumor diameter was negatively correlated significantly with circumpapillary retinal nerve fiber layer thickness ($r = -0.48$, $p = 0.04$, dotted line).

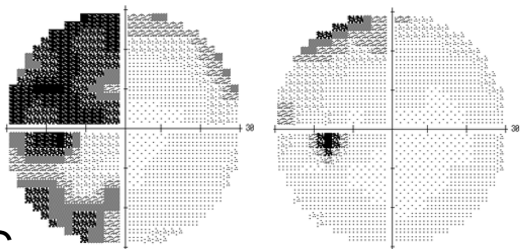
(C) Maximum tumor diameter was correlated significantly with change in mean deviation ($r = 0.61$, $p = 0.0089$, solid line). When we excluded two eyes with maximum tumor diameter more than 40 mm, the maximum tumor diameter was also negatively correlated with change in mean deviation but not significantly ($r = 0.40$, $p = 0.10$, dotted line).

Each dot in the scatter plots represents one eye. White circle indicates cystic tumors and black indicates solid tumors.

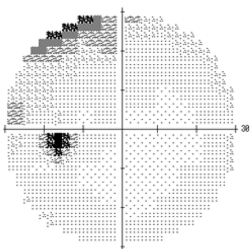
274 Figure 2. Humphrey field analyzer (HFA) and optical coherence tomography (OCT) in a case showing
275 improvement in cystic tumor. Preoperative HFA findings (A). Postoperative HFA findings (B).
276 Preoperative OCT findings (C).
277 HFA and OCT findings in a case showing a little improvement in solid tumor. Preoperative HFA
278 findings (D). Postoperative HFA findings (E). Preoperative OCT findings (F).
279 Brain coronal MRI findings. Cystic tumor (G). Solid tumor (H).
280

A**B****C**

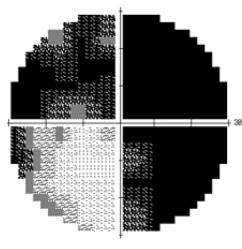
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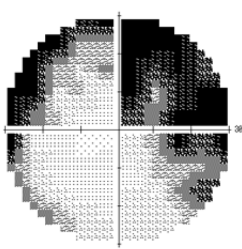
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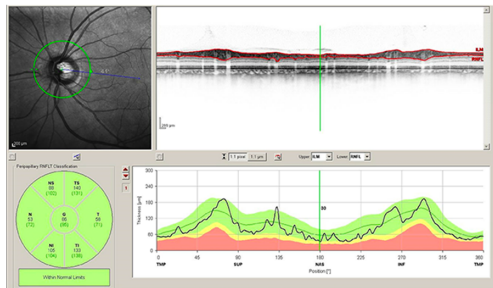
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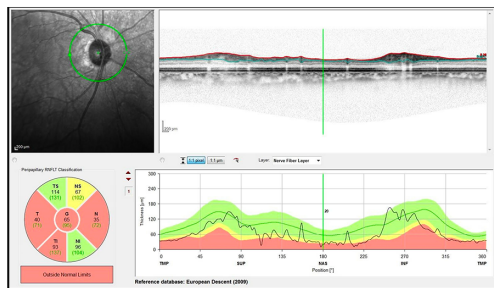
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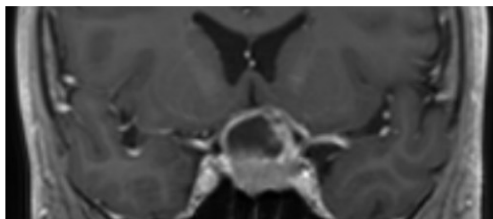
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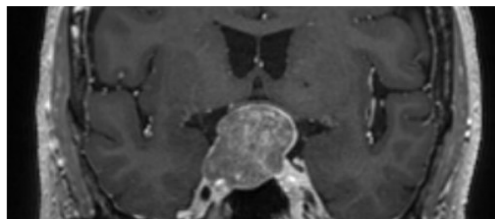
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Influence of tumor characteristics on visual field outcomes after pituitary adenoma surgery

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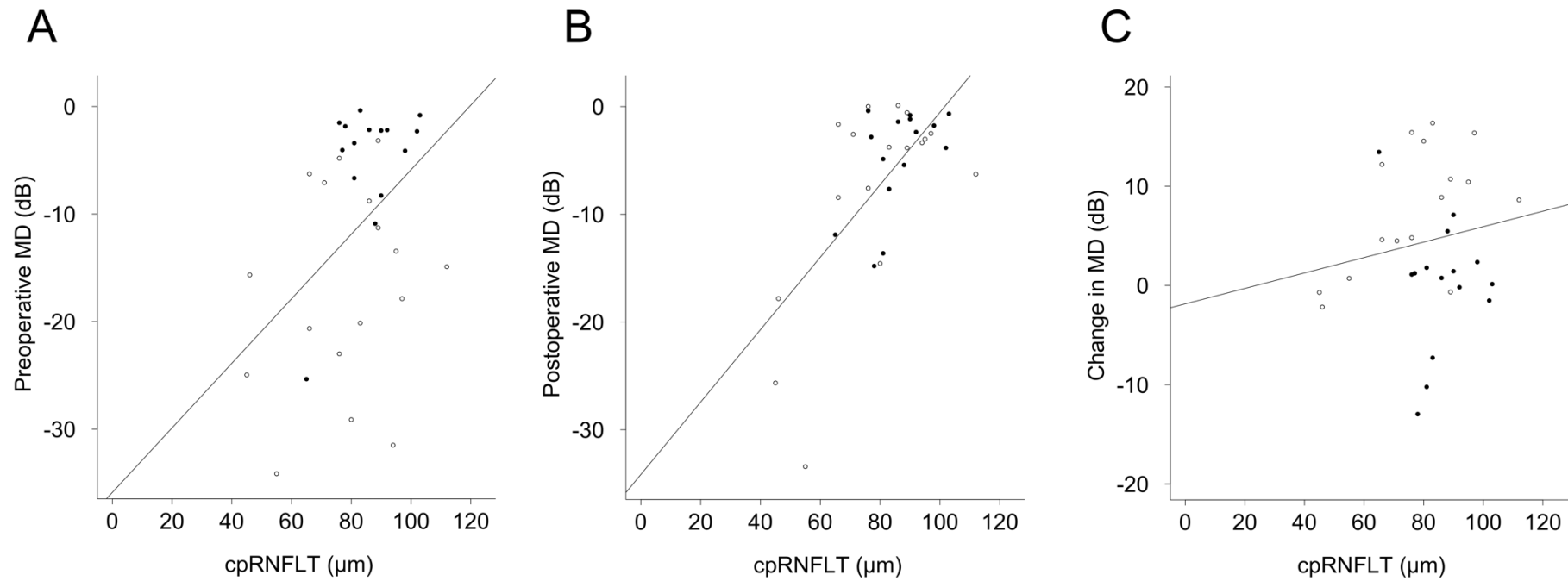
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Supplementary Table 1. Univariate and multivariate analysis using the general estimating equation to evaluate the factors influencing postoperative MD after excluding two eyes with maximum tumor diameter more than 40 mm as outliers

	Univariate regression		Multivariate regression	
	β (95% CI)	p value	β (95% CI)	p value
cpRNFLT	0.34 (0.14 to 0.54)	<0.001	0.18 (0.049 to 0.30)	0.0065
Preoperative MD	0.61 (0.3 to 0.91)	<0.001	0.34 (-0.0066 to 0.69)	0.055
Age at operation	0.25 (-0.047 to 0.54)	0.01	0.13 (-0.022 to 0.29)	0.093
Sex (Male = 0, Female = 1)	-0.9 (-7.3 to 5.5)	0.78	-1.46 (-5.28 to 2.37)	0.45
Maximum tumor diameter	-0.4 (-0.98 to 0.18)	0.18	0.147 (-0.182 to 0.477)	0.38
Preoperative visual acuity (logMAR)	-13 (-22 to -4)	0.005	-1.37 (-7.04 to 4.3)	0.64

CI, confidence interval; cpRNFLT, circumpapillary retinal nerve fiber layer thickness; MD, mean deviation



Supplementary Figure 1. Correlations between circumpapillary retinal fiber layer thickness (cpRNFLT) and mean deviations of Humphrey field analyzer

White circle indicates cystic tumors and black indicates solid tumors. (A) Circumpapillary retinal nerve fiber layer thickness (cpRNFLT) was correlated significantly with the preoperative MD ($r = -0.37$, $p = 0.004$). Each dot in the scatter plots represents one eye. (B) cpRNFLT was correlated significantly with the postoperative mean deviation (MD; $r = -0.66$, $p < 0.001$). (C) cpRNFLT was not correlated significantly with the magnitude of the change in MD postoperatively ($r = 0.16$, $p = 0.36$).