

Preoperative Peripapillary Retinal Nerve Fiber Layer Thickness as the Prognostic Factor of Postoperative Visual Functions After Endoscopic Transsphenoidal Surgery for Pituitary Adenoma

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Purpose: To evaluate the prognostic ability of preoperative peripapillary retinal nerve fiber layer thickness (pRNFLT) for predicting postoperative visual functions, including the visual field index (VFI) and visual acuity (VA), of subjects with pituitary adenoma (PA) who were treated with endoscopic transsphenoidal surgery for pituitary adenoma (ETSS-PA) exclusively.

Subjects and Methods: This 11-year retrospective study was performed at a single institution in Thailand. Sixty-six eyes of 33 subjects who had a PA compressing the anterior visual pathway and were treated with ETSS-PA alone were included. The pRNFLT was measured globally and in the four quadrants preoperatively, using optical coherence tomography. Multivariable analysis and area under the curve (AUC) were used to demonstrate the prognostic ability of preoperative pRNFLT for postoperative visual functions (> 1 month but < 6 months after ETSS-PA).

Results: The mean postoperative VFI and median postoperative VA were $79.45\% \pm 24.24\%$ and 0.14 [interquartile range: 0.02, 0.40] logarithm of the minimum angle of resolution. Among the 56 eyes with a reliable postoperative VFI, thicker preoperative temporal (odds ratio, 1.18; $p = 0.024$) and inferior (odds ratio, 1.07; $p = 0.013$) pRNFLT values were associated with a postoperative VFI > 90%. The strongest association occurred with the preoperative temporal pRNFLT (AUC = 0.821, 95% CI: 0.720–0.923) with a cut-off value of 60 μm . Multivariable analysis for all 66 eyes showed that thicker preoperative inferior-quadrant pRNFLT (odds ratio, 1.05; $p = 0.001$) was associated with a postoperative VA of at least 20/25. The strongest performance was found with the preoperative inferior pRNFLT (AUC = 0.732, 95% CI: 0.615–0.849) with a cut-off value of 105 μm .

Conclusion: Preoperative pRNFLT offers clinical utility for predicting visual functions after ETSS-PA. Temporal pRNFLT $\geq 60 \mu\text{m}$ and inferior pRNFLT $\geq 105 \mu\text{m}$ predicted postoperative VFI > 90% and postoperative VA better than or equal to 20/25, respectively.

Keywords: optical coherence tomography, pituitary adenoma, peripapillary retinal nerve fiber layer, visual field, visual acuity, endoscopic transsphenoidal surgery

Introduction

Pituitary adenomas (PAs) accounts for 10% of intracranial neoplasms.¹ When the PA is larger than 10 mm high, patients may present with visual disturbances due to the compression of the optic chiasm, which located just above the tumor.^{2,3} PA, which is the most common cause of optic chiasm compression,⁴ causes axonal damage through disruption of conduction, decreasing axoplasmic flow, demyelination and ischemia from direct compression or stretching of the chiasmatic vessels.⁵ The most common indication for surgical treatment of PA is compressive optic chiasmopathy; endoscopic transsphenoidal surgery for pituitary adenoma (ETSS-PA) is the most common surgical technique used for resection of such a tumor.^{6–8}

The factors prognostic of visual recovery after surgical treatment of PA have been studied. Barzaghi et al reported that prognostic factors associated with visual field (VF) recovery after ETSS-PA were low preoperative mean-deviation absolute value, small craniocaudal tumor diameter (< 30 mm) and younger age at the time of surgery.⁹ Of ophthalmic structural parameters, the loss of peripapillary retinal nerve fiber layer thickness (pRNFLT), measured with optical coherence tomography (OCT), indicates loss of retinal ganglion cell axons resulting from chronic compression of the optic chiasm.¹⁰ There have been various studies supporting the use of pRNFLT as a prognostic factor for postoperative visual recovery after ETSS-PA.^{11–15} However, these studies did not evaluate the postoperative visual functions in terms of their actual values. Instead, they evaluated outcomes in terms of postoperative visual recovery, i.e. the *changes* in visual functions at after surgery, compared with preoperative visual functions.

Given the effects of race and ethnicity on pRNFLT,^{16,17} the ability to generalize prior studies' results from populations of different races and ethnicities is limited. To-date, there have been few studies that have identified pRNFLT as predictive of postoperative visual recovery or visual functions after ETSS-PA for Asian individuals. For example, a study conducted in South Korea reported that preoperative global pRNFLT ≥ 23.6 μm was associated with better postoperative VF defect recovery after ETSS-PA.¹⁴ Moreover, there were also other limitations in the previous studies.^{10,13} First, they included both transsphenoidal and transcranial approaches in the cohorts without separate analysis on either condition.¹⁰ In addition, they included individuals with PA who had undergone tumor resection and/or radiotherapy prior to enrollment.¹³

Therefore, the primary goal of our study was to evaluate the utility of preoperative pRNFLT for predicting postoperative visual functions in terms of their actual values among Thai subjects with PA who were treated with ETSS-PA alone.

Materials and Methods

This study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of the Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand (IRB number: COA. MURA2021/838), which waived the need for written informed consent from the subjects due to the retrospective nature of the study. All data were kept confidentially in our database. Electronic medical records were reviewed to identify all subjects with PA who underwent ETSS-PA in Ramathibodi Hospital, Mahidol University, Bangkok, Thailand from 1 April, 2011, to 31 December, 2021.

Subjects/Eyes Selection

Included were subjects who met all of the following criteria: 1) PA with associated compression of the anterior visual pathways confirmed by magnetic resonance imaging; 2) underwent ETSS-PA in Ramathibodi Hospital during the relevant period; 3) tissue diagnosis of PA confirmed by histopathology; 4) had both preoperative visual acuity (VA) and VF assessments, as well as pRNFLT measured with OCT within 3 months prior to ETSS-PA; and 5) had both VA and VF assessments > 1 month but < 6 months after ETSS-PA. Exclusion criteria included the following: 1) age < 18 years at the time of ETSS-PA; 2) history of previous treatments for PA, such as tumor resection, hormonal therapy, radiotherapy or chemotherapy; and 3) presence of postoperative complications, including intracranial hemorrhage, cerebrospinal fluid leakage and postoperative infection. Furthermore, eyes with one or more of the following were excluded: 1) presence of visually significant cataracts and/or diseases other than PA that could affect VA and/or VF; and 2) spherical refractive error outside the range of > 5 diopters, or > 2 diopters of astigmatism.

Demographic Data, Visual Functions Assessment, and Preoperative pRNFLT Measurement

Demographic data (age at ETSS-PA, sex and spherical equivalent refraction) and visual function assessments, including VA and VFs within 3 months prior to ETSS-PA and again between 1 and 6 months after ETSS-PA, were reviewed. VA was assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. Postoperative VA was categorized into 2 groups, “good VA” (i.e. postoperative VA better than or equal to 20/25), and “worse than 20/25 VA”. VF

assessment was performed using the 24–2 SITA program (Humphrey Field Analyzer, Carl-Zeiss Meditec, Dublin, CA). Eyes with an unreliable VF assessment, which was defined as > 33% false positive, > 33% false negative or > 20% fixation loss, were excluded from the VF analysis. The visual field index (VFI) was used as a proxy for the degree of VF defect (the greater the VF defect, the lower the VFI percentage). “Favorable VF” was defined as a postoperative VFI > 90%, whereas “unfavorable VF” was defined as postoperative VFI ≤ 90%. The preoperative pRNFLT measurement was performed using the Cirrus HD-OCT Model 4000 (Carl-Zeiss Meditec) within 3 months prior to ETSS-PA. The optic nerve head cube 200×200 scan protocol was used. OCT images of low signal strength (signal strength < 6) or with segmentation error(s) were excluded. The mean thickness of the pRNFLT was measured both globally, and separately in all four quadrants (superior, temporal, inferior and nasal).

Statistical Analysis

Continuous variables were expressed using mean or median, with normally distributed results shown as mean ± standard deviation (SD) and non-normally distributed results shown as median and interquartile range (IQR). Categorical variables were expressed as frequency and percentage. Age at ETSS-PA and preoperative pRNFLT (globally and in all four quadrants) were compared between groups using independent *t*-tests. Sex was compared between groups using a Chi-squared test. Spherical equivalent refraction was compared between groups using the Wilcoxon rank sum test. For multivariable analysis, logistic regression was applied, to simultaneously regress postoperative visual functions with variables (age at ETSS-PA, sex and preoperative pRNFLT). The likelihood ratio test was applied to select and retain only significant variables in the final equation. All analyses were performed using STATA 17.0 (StataCorp LLC, College Station, TX). *P*-values of < 0.05 were considered statistically significant. The optimal cut-off values were identified using the maximal Youden’s index value.¹⁹ ETDRS VA values were converted to logarithm of the minimum angle of resolution (logMAR) values for statistical analysis. VA categories of counting fingers, hand motion, light perception and no light perception were converted to 2.6, 2.7, 2.8 and 2.9 logMAR, respectively.^{20,21}

Results

Demographic Data, Preoperative and Postoperative Visual Functions, and Preoperative pRNFLT Measurement

The study included data from 66 eyes of 33 subjects who underwent ETSS-PA. The mean age at ETSS-PA was 52.2 ± 15.3 years. Of the 33 subjects, 15 (45.5%) were female. The median spherical equivalent refraction was −0.38 (−0.75, 0.00) diopters. The median preoperative VA was 0.32 (0.12, 0.74) logMAR and median postoperative VA was 0.14 (0.02, 0.40) logMAR (*p* < 0.001). There were 56 eyes with both reliable preoperative VFI and reliable postoperative VFI. The mean preoperative VFI was 67.68% ± 29.51% and mean postoperative VFI was 79.45% ± 24.24% (*p* < 0.001). The preoperative global and quadrant pRNFLT measurements are shown in [Table 1](#).

Association Between Preoperative pRNFLT Measurement and Postoperative VFI

Based on postoperative VFI, the 56 eyes were categorized into a favorable-VF group and an unfavorable-VF group. The mean age at ETSS-PA was significantly younger in the favorable-VF group than the unfavorable-VF group (46.43 ± 14.22 versus 58.18 ± 13.85 years, respectively, *p* = 0.006). Compared with the unfavorable-VF group, the favorable-VF group had a higher proportion of females (71.43% versus 21.43%, *p* < 0.001). There was no significant difference in spherical equivalent refraction between the groups (*p* = 0.383). Preoperative pRNFLT measurements in the favorable-VF group were significantly thicker than those in the unfavorable-VF group globally, and in the superior, temporal and inferior quadrants ([Table 2](#)). Multivariable analysis revealed that female sex (odds ratio, 20.65; *p* = 0.014), and thicker preoperative temporal (odds ratio, 1.18; *p* = 0.024) and inferior (odds ratio, 1.07; *p* = 0.013) pRNFLT values were associated with favorable VF, as shown in [Table 3](#). The strongest association was observed for the preoperative temporal pRNFLT (area under the curve (AUC) = 0.821, 95% confidence interval (CI): 0.720–0.923) with a cut-off value of 60 μm. The sensitivity and specificity of this preoperative temporal pRNFLT cut-off value for predicting favorable VF after ETSS-PA were 85% and 78%, respectively.

Table 1 Demographic Data, Preoperative and Postoperative Visual Functions, and Preoperative pRNFLT Measurement

Variables	Values
Number of subjects	33
Number of eyes	66
Age at ETSS-PA, mean \pm SD, years	52.2 \pm 15.3
Female, number of subjects (%)	15 (45.5%)
Spherical equivalent refraction, median (IQR), diopters	-0.38 (-0.75, 0.00)
Preoperative VA, median (IQR), logMAR	0.32 (0.12, 0.74)
Preoperative VFI ^a , mean \pm SD, %	67.68 \pm 29.51
Preoperative pRNFLT, mean \pm SD, μ m	
Global	81.27 \pm 18.61
Superior	99.94 \pm 32.65
Temporal	60.02 \pm 16.62
Inferior	103.92 \pm 24.36
Nasal	60.98 \pm 13.32
Postoperative VA, median (IQR), logMAR	0.14 (0.02, 0.40) ^c
Postoperative VFI ^b , mean \pm SD, %	79.45 \pm 24.24 ^c

Notes: ^aReliable preoperative VFI values from 56 eyes were included. ^bReliable postoperative VFI values from 56 eyes were included. ^cP-value < 0.001 when compared with preoperative assessment.

Abbreviations: pRNFLT, peripapillary retinal nerve fiber layer thickness; ETSS-PA, endoscopic transsphenoidal surgery for pituitary adenoma; SD, standard deviation; IQR, interquartile range; VA, visual acuity; logMAR, logarithm of the minimum angle of resolution; VFI, visual field index.

Table 2 Comparison of Demographic Data and Preoperative pRNFLT Measurements Between Eyes with Favorable and Unfavorable VF

Variables	Favorable VF	Unfavorable VF	P-value
Number of eyes	28	28	
Age at ETSS-PA, mean \pm SD, years	46.43 \pm 14.22	58.18 \pm 13.85	0.006*
Female, number of eyes (%)	20 (71.43%)	6 (21.43%)	< 0.001*
Spherical equivalent refraction, median (IQR), diopters	-0.90 (-1.19, 0.00)	-0.57 (-1.15, +0.25)	0.383
Preoperative pRNFLT, mean \pm SD, μ m			
Global	91.82 \pm 14.01	69.18 \pm 15.98	< 0.001*
Superior	117.82 \pm 25.71	79.50 \pm 28.46	< 0.001*
Temporal	71.79 \pm 12.45	50.04 \pm 14.43	< 0.001*
Inferior	117.32 \pm 18.52	88.82 \pm 21.18	< 0.001*
Nasal	61.79 \pm 11.50	56.14 \pm 16.85	0.152

Note: *Statistically significant ($p < 0.05$).

Abbreviations: pRNFLT, peripapillary retinal nerve fiber layer thickness; VF, visual field; ETSS-PA, endoscopic transsphenoidal surgery for pituitary adenoma; SD, standard deviation; IQR, interquartile range.

Table 3 Factors Associated with Favorable VF After ETSS-PA

Variables	Univariable Analysis		Multivariable Analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age at ETSS-PA (years)	0.94 (0.09–0.98)	0.006*	0.93 (0.86–1.02)	0.107
Sex (female)	9.17 (2.71–31.03)	< 0.001*	20.65 (1.84–232.16)	0.014*
Preoperative pRNFLT (μm)				
Global	1.10 (1.05–1.16)	< 0.001*		
Superior	1.06 (1.03–1.09)	< 0.001*		
Temporal	1.14 (1.06–1.23)	< 0.001*	1.18 (1.02–1.35)	0.024*
Inferior	1.07 (1.03–1.10)	< 0.001*	1.07 (1.02–1.14)	0.013*
Nasal	1.02 (0.98–1.06)	0.152		

Note: *Statistically significant ($p < 0.05$).

Abbreviations: VF, visual field; ETSS-PA, endoscopic transsphenoidal surgery for pituitary adenoma; OR, odds ratio; CI, confidence interval; pRNFLT, peripapillary retinal nerve fiber layer thickness.

Table 4 Comparison of Demographic Data and Preoperative pRNFLT Measurement Between Eyes with Postoperative VA Better Than or Equal to 20/25 versus Worse Than 20/25

Variables	Postoperative VA Better Than or Equal to 20/25	Postoperative VA Worse Than 20/25	P-value
Number of eyes	27	39	
Age at ETSS-PA, mean \pm SD, years	47.63 \pm 13.76	55.38 \pm 15.50	0.040*
Female, number of eyes (%)	15 (55.56%)	15 (38.46%)	0.173
Spherical equivalent refraction, median (IQR), diopters	-0.63 (-1.00, 0.00)	-0.71 (-1.25, 0.00)	0.979
Preoperative pRNFLT, mean \pm SD, μm			
Global	88.56 \pm 19.00	76.23 \pm 16.78	0.007*
Superior	115.89 \pm 30.62	88.90 \pm 29.59	< 0.001*
Temporal	65.74 \pm 15.20	56.05 \pm 16.59	0.019*
Inferior	117.26 \pm 18.99	94.69 \pm 23.55	< 0.001*
Nasal	62.11 \pm 17.56	60.20 \pm 13.75	0.623

Note: *Statistically significant ($p < 0.05$).

Abbreviations: pRNFLT, peripapillary retinal nerve fiber layer thickness; VA, visual acuity; ETSS-PA, endoscopic transsphenoidal surgery for pituitary adenoma; SD, standard deviation; IQR, interquartile range.

Association Between Preoperative pRNFLT Measurement and Postoperative VA

The mean age at ETSS-PA was significantly younger in the good-VA group than in the worse than 20/25 VA group (47.63 \pm 13.76 versus 55.38 \pm 15.50 years, respectively, $p = 0.040$). There was no significant difference in terms of sex or spherical equivalent refraction ($p = 0.173$ and $p = 0.979$, respectively). Eyes in the postoperative good-VA group had significantly thicker preoperative pRNFLT measurements globally and in the superior, temporal and inferior quadrants (Table 4). The multivariable analysis revealed that thicker preoperative inferior-quadrant pRNFLT (odds ratio, 1.05; $p = 0.001$) was associated with good postoperative VA, as shown in Table 5. The maximal predictive performance was found

Table 5 Factors Associated with Postoperative VA Better Than or Equal to 20/25 After ETSS-PA

Variables	Univariable Analysis		Multivariable Analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age at ETSS-PA (years)	0.94 (0.09–0.98)	< 0.001*	0.96 (0.93–1.00)	0.066
Sex (female)	2.00 (0.74–5.42)	0.173	0.94 (0.28–3.13)	0.920
Preoperative pRNFLT (μm)				
Global	1.04 (1.01–1.07)	0.011*		
Superior	1.03 (1.01–1.05)	0.002*		
Temporal	1.04 (1.01–1.07)	0.024*		
Inferior	1.05 (1.02–1.07)	0.001*	1.05 (1.02–1.08)	0.001*
Nasal	1.01 (0.98–1.04)	0.500		

Note: *Statistically significant ($p < 0.05$).

Abbreviations: VA, visual acuity; ETSS-PA, endoscopic transsphenoidal surgery for pituitary adenoma; OR, odds ratio; CI, confidence interval; pRNFLT, peripapillary retinal nerve fiber layer thickness.

with preoperative inferior pRNFLT (AUC = 0.732, 95% CI: 0.615–0.849) with a cut-off value of 105 μm . The sensitivity and specificity of this preoperative inferior pRNFLT cut-off value for predicting good VA postoperatively after ETSS-PA were 68% and 79%, respectively.

Discussion

We evaluated the performance of preoperative pRNFLT, both as a global measure and in each of the four quadrants, for predicting postoperative visual functions among subjects with PA who underwent ETSS-PA. We found that the prognostic performance of pRNFLT in predicting favorable VF postoperatively was best in the temporal quadrants. This finding is comparable with previous study conducted in South Korea, which demonstrated that preoperative temporal pRNFLT $\geq 58 \mu\text{m}$ was associated with better postoperative VF defect recovery after ETSS-PA.¹⁸ We also found that the prognostic performance of pRNFLT in predicting good VA (VA better than or equal to 20/25) postoperatively was best in the inferior quadrant. Only a few studies have identified preoperative pRNFLT as the prognostic factor of postoperative VA after ETSS-PA. Iqbal et al reported that recovery in VA occurred after ETSS-PA postoperatively only when preoperative global pRNFLT was greater than 85 μm .¹⁵ Nevertheless, this study did not measure preoperative pRNFLT separately in each of the four quadrants. In addition to prior studies, in which preoperative pRNFLT has been investigated as a prognostic factor for postoperative visual recovery after ETSS-PA,^{15,18} our results provide better insight into postoperative visual functions in terms of their actual values.

Of interest, our study found an association between female sex and favorable VF status (odds ratio, 20.65; $p = 0.014$). An earlier medical attention seeking due to PA-related menstrual cycle interruption in females, compared with males, who do not seek medical attention until they have severe hypogonadism or problems due to space-occupying lesions or hypopituitarism, might explain this finding.²²

Our study comprehensively established the potential preoperative pRNFLT cut-off values in predicting postoperative VFI > 90% and good postoperative VA within the Thai population. These proposed cut-off values can give ophthalmologists and neurosurgeons enhanced information on postoperative visual prognoses and might, accordingly, help improve preoperative counseling before ETSS-PA. Furthermore, there were significant improvements in postoperative VFI compared with preoperative VFI and postoperative VA compared with preoperative VA. These significant improvements in postoperative VFI and VA after ETSS-PA are consistent with the findings in previous studies.^{18,23}

Our study had several strengths. First, to the best of our knowledge, this is the first study among the Thai population to establish an association between preoperative pRNFLT and postoperative visual functions after ETSS-PA. Second, our

study included both VFI and VA, measured pre- and postoperatively. Third, this study included a large number of subjects with PA who had no history of previous treatments for PA, such as tumor resection, hormonal therapy, radiotherapy or chemotherapy, and who were treated with ETSS-PA exclusively. Fourth, this study reports the cut-off values of preoperative pRNFLT for favorable VF and postoperative good VA. Finally, we used multivariable analysis to quantify the preoperative pRNFLT effect on the probability of favorable VF and postoperative good VA after regressing these postoperative visual functions with subject age at ETSS-PA and sex.

There were some limitations in this study. First, we did not evaluate other components of visual function, such as color vision or contrast sensitivity. Second, this study did not evaluate the thickness of the macular ganglion cell layer and the inner plexiform layer. Finally, postoperative visual functions were not assessed beyond 6 months after surgery.

Conclusions

Postoperative VFI greater than 90% is more likely to be found if the preoperative temporal pRNFLT is greater than or equal to 60 μm , and postoperative VA better than or equal to 20/25 is more likely to be found if preoperative pRNFLT in the inferior quadrant is greater than or equal to 105 μm . These findings provide greater clarity regarding the potential clinical utility of preoperative pRNFLT for predicting postoperative visual functions after ETSS-PA.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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