

# Performance of Optical Coherence Tomography for Distinguishing between Normal Eyes, Glaucoma Suspect and Glaucomatous Eyes

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**Objective:** Evaluate the diagnostic performance of spectral-domain optical coherence tomography (OCT) parameters to distinguish between healthy, glaucoma suspect, and glaucomatous eyes.

**Material and Method:** Forty-eight eyes of glaucoma, 48 glaucoma suspect eyes, and 35 healthy eyes were included. The circumpapillary and macular retinal nerve fiber layer (RNFL) thickness were measured using the Cirrus™ OCT (Carl Zeiss Meditec, Inc., Dublin, CA, USA). One-way analysis of variance was used to compare the different parameters among groups. Calculating areas under receiver operating characteristic (AROC) curves evaluated the discriminating power of each parameter.

**Results:** The average circumpapillary RNFL thickness in normal, glaucoma suspects, and glaucomatous eyes were  $100.31 \pm 7.69 \mu\text{m}$ ,  $90.27 \pm 9.22 \mu\text{m}$ , and  $71.40 \pm 13.08 \mu\text{m}$ , respectively ( $p < 0.001$ ). The largest AROC curve among the circumpapillary parameters was the inferior quadrant thickness (0.974,  $p < 0.001$ ). The macular volume had the largest AROC curves (0.898,  $p < 0.001$ ) of all macular parameters. For glaucoma suspect eyes versus early glaucomatous eyes, the best value of circumpapillary parameters was inferior quadrant thickness (0.835,  $p < 0.001$ ). Among the macular parameters, the best value was the macular cube volume (0.766,  $p < 0.001$ ).

**Conclusion:** Circumpapillary parameters have better diagnostic performance than macular parameters especially the inferior quadrant thickness that has the best discriminating power.

**Keywords:** Spectral-domain, Optical coherence tomography, Discrimination, Glaucoma suspect, Glaucoma

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Glaucoma manifests clinically as retinal nerve fiber layer (RNFL) thinning and optic disc cupping with corresponding functional visual field loss. RNFL thinning has been accepted as the glaucomatous structural change that precedes achromatic visual field (VF) defects<sup>(1)</sup>. RNFL thickness measurements in the circumpapillary and macular areas offer early glaucoma detection<sup>(2)</sup>.

Because of the subjective and qualitative manner of the standard stereoscopic optic disc photography, several tissue-imaging techniques have been developed<sup>(3,4)</sup>. Optical coherence tomography (OCT) facilitates objective, quantitative, and reproducible assessment for glaucoma diagnosis. Several studies confirmed the diagnostic performance

of time-domain OCT (TD-OCT) for early glaucoma detection with excellent reproducibility<sup>(5,6)</sup>. The introduction of a spectral-domain OCT (SD-OCT) has offered higher quality RNFL imaging<sup>(7,8)</sup>.

The purpose of the present study was to evaluate the diagnostic performances of the Cirrus™ OCT (Carl Zeiss Meditec, Inc., Dublin, CA, USA) parameters in the circumpapillary and the macular areas for distinguishing between healthy, glaucoma suspect and glaucomatous eyes.

## Material and Method

A prospective cross-sectional study was carried out between September 2009 and April 2010. The research followed the Declaration of Helsinki guidelines. After the Ethics Committee of Prince of Songkla University approved the present study, written informed consent was obtained from each subject. A complete ophthalmic examination was performed, including visual acuity (VA), refractive error, intraocular pressure (IOP) measurement by applanation

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tonometer and stereoscopic disc and macular examination.

For all subjects, the inclusion criteria included age 18 to 80 years, best-corrected VA not less than 20/60, refractive error within  $\pm 5.0$  diopters sphere and  $\pm 3.0$  diopters cylinder, normal anterior segments, open angles, and normal posterior segments. The subjects that had any other intraocular or neurologic diseases that affected the circumpapillary RNFL (cpRNFL) at the optic disc and macular region, secondary causes for increased IOP, previous ocular trauma, previous intraocular surgery or laser surgery, unqualified VF testing, and poor signal strength OCT were excluded. After a complete ophthalmic examination, all subjects underwent pupil dilation using a drop of 1% tropicamide. A pupil diameter of at least 5 mm was required for good signal strength. Cirrus OCT software version 3.0.0.64 (Carl Zeiss Meditec, Inc., Dublin, CA, USA) was used for RNFL thickness measurement in this study. All scans were performed in the same visit for all patients.

Both eyes of each subject were scanned using the optic disc cube and macular cube algorithms. An experienced ophthalmic photographer performed all OCT imaging in the same session. A good quality OCT image was defined as an image with generalized signal distribution, no missing sections, and a signal strength score of at least 7<sup>(8,9)</sup>.

An optic disc cube algorithm was used for cpRNFL thickness assessment. The acquired data were displayed as an RNFL thickness map, RNFL thickness deviation, and RNFL TSNIT plot. The global or average thickness, the thickness in each quadrant and the thickness in each clock-hour sector were reported.

A macular cube algorithm was used for the thickness assessment at the macula. The instruments then reported the RNFL thickness map in regions according to the Age Related Eye Disease Study (AREDS) subfields. The Cirrus software also calculated a macular cube volume and a macular cube average thickness.

VFs were tested with achromatic automated static perimetry with the Swedish Interactive Threshold Algorithm (SITA) standard 24-2 mode of the Humphrey Field Analyzer (Humphrey Field Analyzer; Humphrey Instrument, Dublin, CA). The qualifying VF was defined as the result that had fewer than 20% fixation loss and fewer than 33% false negative and false positive responses in at least two tests. The VF that had a better pattern standard

deviation (PSD) was selected for analysis. Two consecutive VF examinations were accomplished within three months after OCT examinations. A single well-trained operator did all the tests. Only one eye of each subject was randomly chosen for division into three major diagnostic groups: normal, glaucoma suspect and glaucoma.

The subjects were classified as normal when they had an IOP  $< 21$  mmHg, open angle, normal stereoscopic optic disc appearance, and a normal result on VF testing that was defined as mean deviation (MD) and PSD values within a 95% confidence limit and a normal result in the Glaucoma Hemifield Test (GHT). The subjects were classified as glaucoma when they had both glaucomatous optic neuropathy and corresponded VF defects. A glaucomatous optic neuropathy was defined as including one of the following criteria: a vertical cup-to-disc ratio that was  $> 0.6$  or an asymmetrical vertical cup-to-disc ratio that was  $> 0.2$ , as compared with the contralateral eye, or a visible RNFL defect. A glaucomatous VF defect was defined in a SITA standard 24-2 program as including at least one of the following criteria: a cluster of three or more contiguous points with a sensitivity loss of p-value less than 0.5, one of which must have a p-value of less than 0.01 in a single hemifield of a pattern deviation map or a PSD that was outside the 95% normal confidence limits or an abnormal result in a GHT. The preceding defect, if repeatable on at least two consecutive VFs, was considered a glaucomatous field defect. Glaucoma subjects were subdivided into mild, moderate and severe glaucoma according to the Hodaap-Parrish-Anderson criteria.

The subjects were classified as glaucoma suspect based on optic disc appearances that suspected having glaucomatous optic neuropathy with a normal result on VF testing and an IOP  $< 21$  mmHg.

One eye of each subject in each group was randomly chosen for analysis. The receiver operating characteristic (ROC) curves were obtained by calculating the sensitivity and specificity of a test at every possible cut-off point. In determining the optimal cut-off point that best differentiated subjects with the disease and those without the disease, the best point for balancing the sensitivity, and specificity of a test was the point on the curve closest to the (0,1) point. The minimum value of the expression  $(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$  was used as the best point<sup>(10)</sup>. The area under the ROC (AROC) and 95% confidence interval (95% CI) of the AROC were used to assess the capability of discrimination. A likelihood ratio of

each test parameter was also calculated. Statistical analyses were performed using SPSS version 14.0 (SPSS Inc., Chicago, IL) and MedCalc version 9. A p-value of <0.05 was considered as statistically significant.

## Results

Forty-eight glaucomatous eyes, 48 glaucoma suspect eyes, and 35 normal healthy eyes were included in the final analysis. In the glaucoma group, 25 eyes had early glaucoma, 10 eyes had moderate glaucoma, and 13 eyes had severe glaucoma. The baseline demographic data showed no statistical significance between any of the parameters for the three groups, except for the vertical cup to disc ratio ( $p < 0.001$ ) and the MD on visual testing ( $p < 0.001$ ).

The average cpRNFL in normal, glaucoma suspect, and glaucomatous eyes were  $100.31 \pm 7.69 \mu\text{m}$ ,  $90.27 \pm 9.22 \mu\text{m}$ , and  $71.40 \pm 13.08 \mu\text{m}$ , respectively ( $p < 0.001$ ). The average cpRNFL thicknesses and thicknesses in each quadrant are summarized in Table 1. Comparing the quadrant parameters among the normal, glaucoma suspect and glaucoma group, all study groups were significantly different from each other ( $p < 0.001$ ) in the superior, inferior and temporal quadrants.

The average macular thickness in normal, glaucoma suspect and glaucomatous eyes were  $277.66 \pm 8.53 \mu\text{m}$ ,  $272.19 \pm 18.45 \mu\text{m}$ , and  $257.02 \pm 14.55 \mu\text{m}$ , respectively ( $p < 0.001$ ). The macular thicknesses at each OCT parameter are shown in Table 2. ANOVA and post hoc multiple comparisons tests were used to compare each parameter among the normal, glaucoma suspect and glaucoma group. The glaucoma group was significantly different from the other groups ( $p < 0.05$ ) in all-macular parameters.

The 2-best AROC values and their best cut-off points from both optic disc and macular algorithms for distinguishing between normal versus glaucomatous eyes and between glaucoma suspect versus early glaucomatous eyes are shown in Table 3 and 4, respectively. To discriminate between normal and glaucomatous eyes, the highest AROC value among the cpRNFL parameters was the inferior quadrant RNFL (IQ-RNFL) thickness parameter (0.974,  $p < 0.001$ ). The macular cube volume had the highest AROC value (0.898,  $p < 0.001$ ) of all macular parameters evaluated. For glaucoma suspect eyes versus early glaucomatous eyes, the best AROC value of cpRNFL parameters was the IQ-RNFL thickness (0.835,  $p < 0.001$ ). Among the macular parameters, the highest

**Table 1.** The results of circumpapillary RNFL thickness in average and each quadrant of OCT parameters in the normal group, glaucoma suspect group, glaucoma group, and glaucoma subgroup by severity

RNFL thickness (microns) mean (SD)	Normal	Glaucoma suspect	Glaucoma	p-value*		Glaucoma subgroup			p-value*
				Early (n = 25)	Moderate (n = 10)	Severe (n = 13)			
Average	100.31 (7.69)	90.27 (9.22)	71.40 (13.08)	<0.001 <sup>#</sup>	75.44 (11.67)	73.03 (13.22)	62.15 (11.70)	<0.001 <sup>+</sup>	
Quadrants									
Superior	129.17 (13.74)	109.29 (13.74)	85.83 (19.18)	<0.001	92.32 (15.64)	91.80 (21.24)	68.77 (13.43)	<0.001	
Inferior	135.63 (16.18)	116.71 (19.44)	83.60 (24.13)	<0.001	94.48 (20.38)	80.10 (25.16)	65.38 (18.94)	<0.001	
Temporal	69.63 (9.10)	65.13 (8.32)	57.40 (10.98)	<0.001	57.92 (9.71)	58.80 (7.58)	55.31 (15.28)	<0.001	
Nasal	68.00 (9.11)	68.00 (9.21)	61.92 (8.65)	0.001	63.24 (8.67)	61.60 (8.26)	59.62 (9.06)	0.006	

RNFL = retinal nerve fiber layer; OCT = optical coherence tomography; SD = standard deviation

\* Analysis of variance (Scheffe post-hoc test)

<sup>#</sup> Each group is significantly different from each other

<sup>+</sup> Each glaucoma subgroup is significantly different from each other

**Table 2.** The results of RNFL thickness at macular area in each OCT parameters in the normal group, glaucoma suspect group, glaucoma group, and glaucoma subgroup by severity

RNFL thickness (microns) mean (SD)	Normal	Glaucoma suspect	Glaucoma	p-value*	Glaucoma subgroup			p-value*
					Early (n = 25)	Moderate (n = 10)	Severe (n = 13)	
<b>Areas</b>								
Superior	277.97 (12.99)	271.13 (13.68)	256.85 (18.32)	<0.001	259.00 (17.16)	264.90 (20.69)	246.54 (15.03)	<0.001
Inferior	265.31 (11.08)	261.42 (12.14)	244.52 (18.85)	<0.001	251.24 (15.06)	242.50 (18.05)	233.15 (21.35)	<0.001
Temporal	260.94 (9.73)	257.29 (11.40)	246.65 (19.88)	<0.001	251.76 (21.69)	251.30 (16.24)	233.23 (11.94)	<0.001
Nasal	294.40 (18.68)	292.54 (12.66)	276.73 (19.06)	<0.001	280.96 (17.06)	282.30 (23.90)	264.31 (13.50)	<0.001
<b>Macular cube</b>								
Cube average thickness	277.66 (8.53)	272.19 (18.45)	257.02 (14.55)	<0.001	262.04 (12.86)	260.60 (16.07)	244.62 (8.63)	<0.001
Cube volume (mm <sup>3</sup> )	10.03 (0.32)	9.68 (1.29)	9.23 (0.51)	<0.001	9.41 (0.45)	9.37 (0.57)	8.80 (0.29)	<0.001

RNFL = retinal nerve fiber layer; OCT = optical coherence tomography; SD = standard deviation

\* Analysis of variance

AROC value was the macular cube volume (0.766,  $p < 0.001$ ).

## Discussion

OCT allows direct measurement of RNFL thickness by in vivo visualization of the retina and RNFL. Objective methods for measuring the RNFL thickness may aid physicians in making an early diagnosis of glaucoma. A good correlation has been found between the in vivo RNFL thickness and histomorphometric measurements<sup>(11)</sup>.

AROC values have been reported according to the area and parameters in evaluating the capacity of cpRNFL parameters. The present study also confirmed that the highest AROC value was the IQ-RNFL thickness with a specificity of 100% and sensitivity of 87.5%, followed by average and superior quadrant RNFL (SQ-RNFL) thicknesses. Several studies reported that the IQ-RNFL parameter had the best diagnostic performance in discriminating between normal eyes and glaucomatous eyes. The best AROC ranged from 0.820-0.971<sup>(12-15)</sup>.

Leite et al evaluated the performance of SD-OCT according to severity staging based on a VF index. The largest pooled AROC was for an average cpRNFL thickness (0.892) followed by IQ-RNFL thickness (0.881) and SQ-RNFL thickness (0.874)<sup>(16)</sup>. It was difficult to compare the present results with this study because the staging of glaucoma in the study was based on a MD value. However, the 3-best cpRNFL parameters were the same as our results.

A reason why the IQ-RNFL thickness had the greatest capacity, even in early glaucomatous damage, might be explained by the study of Leung et al. They used a Cirrus SD-OCT to analyze the RNFL defect pattern. A defect at the inferotemporal meridian accounted for 75% to 80% of the glaucoma patients. This indicated that the inferior quadrant area might be most vulnerable for glaucomatous damage and may explain the results in the study and why the three best parameters were IQ-RNFL, the average cpRNFL and SQ-RNFL. They showed that the most common pattern of early glaucomatous RNFL loss was the diffuse loss in the inferior quadrant. In moderate to advanced glaucoma, diffuse loss involving both the inferior and superior quadrants was the most common pattern. This might explain why the temporal and nasal quadrant parameters had less diagnostic capacity than the inferior or superior quadrants<sup>(17)</sup>.

Concerning the macular area, the thickness of the macula has been shown to be less than that of

**Table 3.** The area under the receiver operating characteristic curves and the best cut-off point for the 2-best parameters from optic disc and macular algorithm for distinguishing between the normal and glaucomatous eyes

Parameters	AROCs (SE)	95% CI	p-value	Best cut-off point				
				Value	Sensitivity	Specificity	PLR	NLR
Optic disc algorithm								
Inferior quadrant	0.974 (0.01)	0.95-0.99	<0.001	111.0	87.50	100.00	∞	0.13
Average	0.964 (0.02)	0.93-0.99	<0.001	85.0	89.58	100.00	∞	0.10
Macular algorithm								
Cube volume	0.898 (0.03)	0.83-0.97	<0.001	9.4	72.92	100.00	∞	0.27
Cube average	0.880 (0.04)	0.80-0.96	<0.001	262.0	72.92	100.00	∞	0.27

AROCs = areas under the receiver operating characteristic curves; 95% CI = 95% confidence interval; SE = standard error; PLR = positive likelihood ratio; NLR = negative likelihood ratio

**Table 4.** The area under the receiver operating characteristic curves and the best cut-off point for the 2-best parameters from optic disc and macular algorithm for distinguishing between the glaucoma suspect and early glaucomatous eyes

Parameters	AROCs (SE)	95% CI	p-value	Best cut-off point				
				Value	Sensitivity	Specificity	PLR	NLR
Optic disc algorithm								
Inferior quadrant	0.835 (0.05)	0.74-0.93	<0.001	107.0	80.00	81.25	4.27	0.25
Average	0.833 (0.05)	0.73-0.94	<0.001	85.0	84.00	72.92	3.10	0.22
Macular algorithm								
Cube volume	0.766 (0.06)	0.64-0.89	<0.001	9.3	60.00	89.58	5.76	0.45
Cube average	0.765 (0.06)	0.64-0.89	<0.001	259.0	60.00	89.58	5.76	0.45

AROCs = areas under the receiver operating characteristic curves, 95% CI = 95% confident interval, SE = standard error, PLR = positive likelihood ratio, NLR = negative likelihood ratio

healthy eyes even in the early stages of the disease<sup>(18)</sup>. In addition, a significant correlation was found between the macular thickness obtained by OCT and VF loss in glaucomatous eyes<sup>(19)</sup>. However, any changes in the macula in glaucoma were mostly not detected clinically. For this reason, several investigators used OCT and showed the capacity of macular volume analysis in glaucoma diagnosis<sup>(12,20,21)</sup>. Naithani et al found that the best macular parameter was the temporal area (AROC = 0.790)<sup>(14)</sup>. In the present study, the macular volume as well as all the thicknesses in different macular areas of glaucomatous eyes were shown to be significantly lower than that of healthy and glaucoma suspect eyes. The macular cube volume was the best among the macular parameters with an AROC of 0.898 ( $p < 0.001$ ), a sensitivity of 72.92% for 100% specificity. The inferior thickness, however, was the fourth-best parameter with an AROC of 0.807 ( $p < 0.001$ ). These differences from previous studies might be due to differences in race and OCT technology.

According to the present study results, the macular parameters had less discriminating power

than the cpRNFL parameters, similar to what has been reported in the aforementioned studies. Guedes et al also reported that the maximal AROC among macular parameters was only 0.770 for distinguishing glaucomatous from healthy eyes. The maximal AROC among the cpRNFL parameter, however, was 0.940<sup>(22)</sup>. Recently, Mori et al used the RTvue-100 (Optovue, Fremont, CA, USA) SD-OCT and specifically measured the volume of the ganglion cell complex (GCC). The AROC of the GCC volume (0.922) was significantly greater than the AROC of the total macular volume (0.857). The AROC of the GCC volume was still less than the AROC of the cpRNFL thickness (0.971), however, the difference was statistically insignificant ( $p = 0.112$ )<sup>(23)</sup>.

The present study had certain limitations. First, the sample size was small and patient ages tended toward an increasing age with glaucoma. Second, the difference in our AROC values from other studies could be due to several factors, one of which was ethnicity. All patients in the present study were Thai. The results cannot be applied confidently to other ethnic groups.

Even in studies in other Asian populations, the results were different among different ethnicities. A study in a Japanese population by Ojima et al found that the performance of cpRNFL was better than the macular parameters. This is the same as our results. However, the average cpRNFL showed the largest AROC. The inferior segment was the best among the macular thicknesses and total macular volume was the second<sup>(18)</sup>. Thus, ethnicity should be taken into account. Third, ocular hypertension and preperimetric glaucoma patients whose achromatic visual fields were still normal were included in the glaucoma suspect group. Thus, the overlapping of subjects should be a concern when considering the capacity of SD-OCT in preperimetric glaucoma discrimination. Further investigations need to answer the question about the capability of SD-OCT parameters for progression prediction and for follow-up. The selective inner macular layers, GCC, should also be evaluated with a Cirrus SD-OCT to confirm a better diagnostic performance. In addition, larger studies with long-term follow-up are needed to validate our results.

In conclusion, the authors have confirmed that the overall best performing Cirrus SD-OCT parameter was the IQ-RNFL thickness. Even though the macular cube volume also served as the best macular parameter, the performance was less than the cpRNFL parameter. The SD-OCT has high-resolution optical imaging technology that can objectively discriminate healthy and glaucoma suspect eyes from glaucomatous eyes even in the early stages of the disease.

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#### Potential conflicts of interest

None.

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**สมรรถนะของเครื่องออฟติคอลลโคฮีเรนโทโมกราฟีในการแยกแยะระหว่างตาดปกติตาที่สงสัยเป็นต้อหินและตาที่เป็นต้อหิน**

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**วัตถุประสงค์:** เพื่อประเมินสมรรถนะการวินิจฉัยของเครื่องออฟติคอลลโคฮีเรนโทโมกราฟี ในการแยกแยะระหว่างตาดปกติ ตาสงสัยเป็นต้อหิน และตาที่เป็นต้อหิน

**วัสดุและวิธีการ:** ตาที่เป็นต้อหิน 48 ตา ตาที่สงสัยเป็นต้อหิน 48 ตา และตาดปกติ 35 ตา รับการคัดเข้าเพื่อวัดความหนาใยประสาทจอตารอบขั้วประสาทตาและจุดรับภาพ โดยใช้เครื่องออฟติคอลลโคฮีเรนโทโมกราฟี รุ่นเซอร์ริส ใช้การวิเคราะห์ความแปรปรวนแบบจำแนกทางเดียวเพื่อเปรียบเทียบแต่ละพารามิเตอร์ในแต่ละกลุ่ม คำนวณพื้นที่ใต้โค้ง receiver operating characteristic เพื่อประเมินกำลังการจำแนกของแต่ละพารามิเตอร์

**ผลการศึกษา:** ใยประสาทจอตารอบขั้วประสาทตาในกลุ่มตาดปกติ ตาที่สงสัยเป็นต้อหิน และตาที่เป็นต้อหิน มีความหนาเฉลี่ย  $100.31 \pm 7.69$ ,  $90.27 \pm 9.22$  และ  $71.40 \pm 13.08$  ไมครอน ตามลำดับ ( $p < 0.001$ ) พื้นที่ใต้โค้งที่มากที่สุดในกลุ่มพารามิเตอร์รอบขั้วประสาทตาคือความหนาส่วนเสี้ยวล่าง ( $0.974$ ,  $p < 0.001$ ) ปริมาตรจุดรับภาพมีพื้นที่ใต้โค้งมากที่สุดในกลุ่มพารามิเตอร์บริเวณจุดรับภาพ ( $0.898$ ,  $p < 0.001$ ) ในการจำแนกตาที่สงสัยต้อหินและตาที่เป็นต้อหินระยะแรกพบว่าในกลุ่มพารามิเตอร์รอบขั้วประสาทตาที่มีพื้นที่ใต้โค้งมากที่สุดคือความหนาส่วนเสี้ยวล่าง ( $0.835$ ,  $p < 0.001$ ) ส่วนในกลุ่มพารามิเตอร์บริเวณจุดรับภาพที่มีพื้นที่ใต้โค้งมากที่สุดคือปริมาตรจุดรับภาพ ( $0.766$ ,  $p < 0.001$ )

**สรุป:** พารามิเตอร์รอบขั้วประสาทตามีความสามารถในการวินิจฉัยดีกว่าพารามิเตอร์บริเวณจุดรับภาพ โดยเฉพาะอย่างยิ่งความหนาส่วนเสี้ยวล่างมีกำลังการแยกแยะดีที่สุด