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ORIGINAL ARTICLE

Cirrus High-definition Optical Coherence Tomography Versus Spectral Optical Coherence Tomography/Scanning Laser Ophthalmoscopy in the Diagnosis of Glaucoma

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ABSTRACT

Purpose: This study was performed to compare the positive predictive value of peripapillary retinal nerve fiber layer (RNFL) thickness measurements obtained using Cirrus high-definition optical coherence tomography (Cirrus HD-OCT; Carl Zeiss Meditec, Dublin, CA) and spectral OCT/scanning laser ophthalmoscopy (SLO) (OPKO/OTI, Miami, FL) in the diagnosis of glaucoma.

Methods: A total of 50 eyes of 50 healthy subjects and 60 eyes of 60 subjects with glaucoma were included. All participants underwent RNFL thickness measurement using Cirrus HD-OCT and spectral OCT/SLO on the same day. Average, quadrant, clock-hour RNFL thicknesses, area under the receiver operating characteristic curve (AUC), and sensitivities at fixed specificities (80% and 95%) were calculated for comparison.

Results: RNFL thickness as measured by spectral OCT/SLO was greater than that measured using Cirrus HD-OCT ($p < 0.001$). For both the Cirrus HD-OCT and spectral OCT/SLO, the parameter with the largest AUC was average RNFL thickness (0.954 and 0.944, respectively). The AUCs of RNFL thickness for the discrimination of glaucoma did not differ significantly between the devices ($p > 0.05$), with the exception of RNFL thickness in the nasal area (nasal quadrant, clock-hour sectors 3 and 4); in these areas, spectral OCL/SLO yielded greater AUCs than Cirrus HD-OCT ($p < 0.05$). Sensitivities varied similarly to AUCs.

Conclusions: RNFL thicknesses measures using Cirrus HD-OCT and spectral OCT/SLO were not interchangeable. The utility of RNFL thickness measurements in the diagnosis of glaucoma was similar for both the devices.

Keywords: Glaucoma, optical coherence tomography, retinal nerve fiber layer, scanning laser ophthalmoscopy, spectral-domain

INTRODUCTION

Progressive thinning of the peripapillary retinal nerve fiber layer (RNFL) is a key finding associated with glaucoma.[1–6] Optical coherence tomography (OCT) imaging devices can quantitatively analyze RNFL thickness with high resolution and excellent reproducibility.[1–9] Recently, spectral-domain technology has been introduced in this field. The utility of peripapillary RNFL thickness measurements obtained using spectral-domain OCT devices in the diagnosis of glaucoma was compared among several devices.[4,9–13] Cirrus high-definition OCT (Cirrus HD-OCT; Carl Zeiss Meditec, Dublin, CA) and spectral OCT/scanning laser ophthalmoscopy (SLO) (OPKO/OTI, Miami, FL) are spectral-domain OCTs commonly used for the evaluation of glaucoma. To our knowledge, no study has compared the peripapillary RNFL thickness measurements obtained using these two devices in terms of utility in the diagnosis of glaucoma. This study compared the RNFL thickness measurements obtained using a

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Cirrus HD-OCT to those obtained using spectral OCT/SLO.

MATERIALS AND METHODS

Participants

This study was approved by the Institutional Review Board of Kim's Eye Hospital in Seoul, Korea. All procedures conformed to the Declaration of Helsinki. Participants seen by a glaucoma specialist (Y.H.H.) were recruited consecutively during the period from May 2012 to October 2012 at the glaucoma clinic at Kim's Eye Hospital. Each subject underwent a full ophthalmic examination, which included the assessment of visual acuity, determination of refractive error by using a model TX-20 P autorefractokeratometer (Canon, Tokyo, Japan), measurement of intraocular pressure (IOP) with a Goldmann applanation tonometer, optic nerve head (ONH) evaluation and fundus examination with a 90-diopter lens, red-free fundus photography performed using a Kowa Nonmyd7 fundus camera (Kowa, Tokyo, Japan), 24-2 Swedish Interactive Threshold Algorithm standard automated visual field (VF) test (Humphrey Visual Field Analyzer; Carl Zeiss Meditec), and two sets of peripapillary RNFL thickness measurements obtained using the Cirrus HD-OCT and spectral OCT/SLO on the same day.

The inclusion criteria for glaucoma patients (glaucoma group) were best-corrected visual acuity of 20/30 or better; a normal anterior segment on slit-lamp examination; an ONH with glaucomatous changes (i.e. increased cup-disc ratio and narrowing of the neuroretinal rim); RNFL defects on red-free fundus photography (i.e. a dark wedge-shaped area with its apex touching the optic disc border in the brightly striated pattern of the surrounding RNFL[14] or a generalized loss of RNFL visibility in the upper or lower retina);[15] and glaucomatous VF defects (i.e. a cluster of three points with probabilities of <5% on the pattern deviation map in at least 1 hemifield, including at least one point with a probability of <1% or a cluster of two points with a probability of <1%, or glaucomatous hemifield test results outside of normal limits, or a pattern standard deviation beyond 95% of normal limits[16]) as confirmed by at least two reliable examinations (false positive/negatives <15%, fixation losses <15%). The exclusion criteria were the presence of concurrent retinal disease (i.e. secondary to a vascular disorder, macular degeneration), optic nerve disease other than glaucoma, or a brain disorder that could influence VF results.

Healthy subjects (control group) matched to glaucoma patients for age, sex and refractive error were recruited from among the subjects who visited our clinic during the enrollment period for an annual health examination. The inclusion criteria for the control group consisted of a best-corrected visual acuity of 20/30 or better; IOP < 21 mm Hg; a normal anterior chamber and open angle, a normal ONH without glaucomatous changes; no RNFL defect on red-free fundus photography; and normal reliable VF test results (false positive/negatives <15%, fixation losses <15%, no significant pattern standard deviation at the <5% level, and normal results on the glaucoma hemifield test).

OCT Measurements

A 200×200 cube Optic Disc Scan was obtained using the Cirrus HD-OCT for RNFL measurements. This raster scan measures $200 \times 200 \times 1024$ points within a $6\,\text{mm} \times 6\,\text{mm} \times 2\,\text{mm}$ volume scanned at 27,000 A-scans/s, which yields 40,000 A-scans acquired in 1.48 s.[13] The Cirrus HD-OCT algorithm automatically identifies the center of the ONH and calculates circumpapillary RNFL thickness on a circle of 3.46-mm diameter consisting in 256 A-scans.[13] When using the spectral OCT/SLO, peripapillary RNFL thickness measurements were obtained with the scan circle centered on the optic disc. The spectral OCT/SLO uses a circular scan with a diameter of 3.46 mm, with 512 A-scans acquired in 1.50 s.[9] Using the built-in algorithms of each device, the RNFL thicknesses were obtained over the entire area, 4 quadrants, and 12 clock-hour sectors. All OCT data were aligned according to the orientation of the right eye: clock-hour 9 of the scan represented the temporal side of the optic disc in both eyes. Images with signal strength ≥ 6 and without motion artifacts were included. Large parapapillary atrophy (PPA) may affect the circumpapillary RNFL thickness measurement by OCT. Therefore, in the present study, we excluded eyes with a PPA area extending outside of the OCT scan circle centered on the ONH. In addition, eyes with media opacity were excluded to ensure that we acquired images with sufficient quality.

Statistical Analyses

The distributions of all variables were examined for normality using the Kolmogorov–Smirnov one-sample test. The unpaired *t*-test, Mann–Whitney *U* test, or Fisher's exact test was performed to compare clinical characteristics and RNFL thickness between the control and glaucoma groups. RNFL thicknesses obtained by Cirrus HD-OCT and spectral OCT/SLO were compared using the paired *t*-test. The percentage of RNFL thickness in each quadrant relative to the overall average RNFL thickness was calculated for control group and compared between devices by using a paired *t*-test.[12] This ratio was not calculated for glaucomatous eyes because of variability in the

amount of RNFL deterioration among quadrants.[12] The agreement of average RNFL thickness between the devices was assessed using the Bland–Altman plot.

To evaluate the diagnostic utility of average, quadrant, and clock-hour RNFL thickness in diagnosing glaucoma, areas under the receiver operating characteristics curves (AUCs) were calculated and compared. The AUC was classified as follows: 0.9 to 1.0 = excellent, 0.80 to 0.89 = good, 0.70 to 0.79 = fair, 0.60 to 0.69 = poor and 0.50 to 0.59 = worthless.[17] Sensitivities at a fixed specificity of 80% and 95% were calculated based on the receiver operating characteristics curves. Significant differences between AUCs were assessed as described previously.[18] A P value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 12.0 (SPSS, Chicago, IL) and MedCalc version 11.6.1.0 (MedCalc Software bvba, Mariakerke, Belgium).

RESULTS

This study included 50 healthy eyes from 50 subjects (control group) and 60 glaucomatous eyes from 60 subjects (glaucoma group). The clinical characteristics of both groups are listed in Table 1. The eyes in the glaucoma group had a higher IOP (mean [standard deviation], 16.2 [3.9] mmHg) than those in the control group (14.1 [2.2] mmHg, $p = 0.002$). The eyes in the glaucoma group yielded worse VF test results than eyes in the control group ($p < 0.001$). Other parameters, including age, sex, and refractive error, did not differ significantly between the groups ($p > 0.05$).

When RNFL thickness measurements from both the devices were compared, RNFL thickness as measured using the spectral OCT/SLO was significantly greater than that measured using the Cirrus HD-OCT. This was true for each area measured in both groups ($p < 0.001$; Table 2). The Bland–Altman plot shows that average RNFL thickness differences between the two devices was greater in eyes with thicker average RNFL ($r^2 = 0.11$; $p < 0.001$; Figure 1).

The mean percentage (standard deviation) of superior, nasal, inferior, and temporal quadrant to average RNFL thickness was 30.5 (2.8), 18.2 (2.6), 31.3 (2.6), and 19.9 (3.0) for Cirrus HD-OCT and 29.5 (2.3), 20.2 (2.5), 30.4 (2.6), and 19.9 (3.3) for spectral OCT/SLO. Spectral OCT/SLO had a smaller proportion of occupation in superior and inferior quadrants ($p = 0.001$), a greater proportion of occupation in nasal quadrant ($p < 0.001$) compared with Cirrus HD-OCT; in temporal quadrant, no significant difference was found ($p = 0.889$).

Among the various RNFL parameters, average RNFL thickness (0.954), inferior quadrant RNFL thickness (0.945), and RNFL thicknesses of clock-hour sectors 6 (0.922) and 7 (0.916) showed the greatest AUCs for the Cirrus HD-OCT (Table 3). Spectral OCT/SLO average RNFL thickness (0.944), inferior quadrant RNFL thickness (0.938), and RNFL thicknesses of clock-hour sectors 6 (0.915) and 7 (0.918) showed the greatest AUCs. No significant difference was found when the AUCs of both the devices were compared ($p > 0.05$), with the exception of the nasal quadrant and clock-hour sectors 3 and 4. In these areas, spectral OCL/SLO yielded greater AUC than the Cirrus HD-OCT device ($p < 0.05$).

The RNFL thickness parameter with the highest sensitivity obtained using the Cirrus HD-OCT was the average RNFL thickness with a sensitivity of 96.0% at a fixed specificity of 80 and 76.7% at a fixed specificity of 95%. For the Spectral OCT/SLO, the RNFL thickness parameter with the highest sensitivity was the average RNFL thickness with a sensitivity of 95.0% at a fixed specificity of 80% and 74.0% at a fixed specificity of 95%. The RNFL thicknesses of both the

TABLE 1 Comparison of clinical characteristics between control and glaucoma groups (mean [standard deviation] and range for variables with normal distribution, median [1st and 3rd quartiles] and range for variables without normal distribution).

	Control group ($n = 50$)	Glaucoma group ($n = 60$)	p Value
Age (yrs)	58.5 (14.9) (30–81)	60.7 (13.9) (32–84)	0.433[a]
Female/male (n)	21/23	33/27	0.296[b]
Intraocular pressure (mmHg)	14.1 (2.2) (11–20)	16.2 (3.9) (11–20)	0.002[a]
Refractive error (diopter)	−1.18 (2.31) (−7.00–2.00)	−1.22 (2.45) (−9.00–1.00)	0.932[a]
Visual field			
Mean deviation (dB)	−0.23 (−0.46, 0.53) (−1.01, 1.00)	−7.64 (−10.69, −3.84) (−17.23, −0.24)	<0.001[c]
Pattern standard deviation (dB)	1.22 (0.83, 1.27) (0.40, 1.97)	6.92 (4.75, 8.81) (2.27, 15.52)	<0.001[c]

[a]Unpaired t test.
[b]Fisher's exact test.
[c]Mann–Whitney U test.

TABLE 2 Comparison of average, quadrant, and clock-hour peripapillary retinal nerve fiber layer (RNFL) thickness (μm) obtained by Cirrus high-definition optical coherence tomography (Cirrus HD-OCT) and spectral OCT/scanning laser ophthalmoscopy (SLO) (mean [standard deviation]).

	Control group ($n = 50$)			Glaucoma group ($n = 60$)		
	Cirrus HD-OCT	Spectral OCT/SLO	p Value[a]	Cirrus HD-OCT	Spectral OCT/SLO	p Value[a]
Average	91.70 (7.69)	106.11 (9.45)	<0.001	70.05 (10.10)	82.48 (11.64)	<0.001
Quadrant						
Superior	111.66 (13.89)	125.70 (13.89)	<0.001	87.40 (20.04)	104.23 (20.59)	<0.001
Nasal	66.45 (10.11)	85.84 (12.09)	<0.001	60.15 (8.69)	72.22 (12.79)	<0.001
Inferior	114.75 (13.84)	129.84 (16.12)	<0.001	76.68 (15.47)	91.00 (16.44)	<0.001
Temporal	72.95 (13.32)	84.93 (17.58)	<0.001	56.18 (12.51)	64.38 (11.52)	<0.001
Clock-hour sectors						
12	114.05 (23.18)	129.57 (19.98)	<0.001	88.25 (24.83)	109.10 (224.57)	<0.001
1	95.57 (17.01)	114.61 (17.70)	<0.001	85.52 (19.78)	103.05 (22.74)	<0.001
2	77.57 (12.97)	96.25 (14.61)	<0.001	70.33 (14.15)	84.20 (17.07)	<0.001
3	59.16 (10.74)	76.73 (11.90)	<0.001	54.53 (8.13)	64.50 (11.47)	<0.001
4	62.48 (11.97)	84.05 (13.72)	<0.001	55.67 (9.98)	67.95 (13.76)	<0.001
5	88.16 (12.53)	111.61 (16.68)	<0.001	71.18 (15.62)	86.65 (15.32)	<0.001
6	124.77 (22.40)	135.45 (21.87)	<0.001	80.00 (20.43)	95.60 (19.99)	<0.001
7	131.41 (23.99)	139.77 (25.66)	<0.001	78.80 (26.03)	90.97 (24.16)	<0.001
8	74.61 (16.77)	89.45 (22.09)	<0.001	56.42 (14.76)	67.28 (14.83)	<0.001
9	59.57 (9.51)	69.91 (14.09)	<0.001	47.97 (10.46)	54.90 (9.52)	<0.001
10	85.25 (17.16)	95.39 (19.14)	<0.001	62.12 (18.60)	70.70 (15.76)	<0.001
11	125.73 (19.17)	132.95 (16.11)	<0.001	88.58 (29.66)	100.62 (23.60)	<0.001

[a]Paired *t test*.

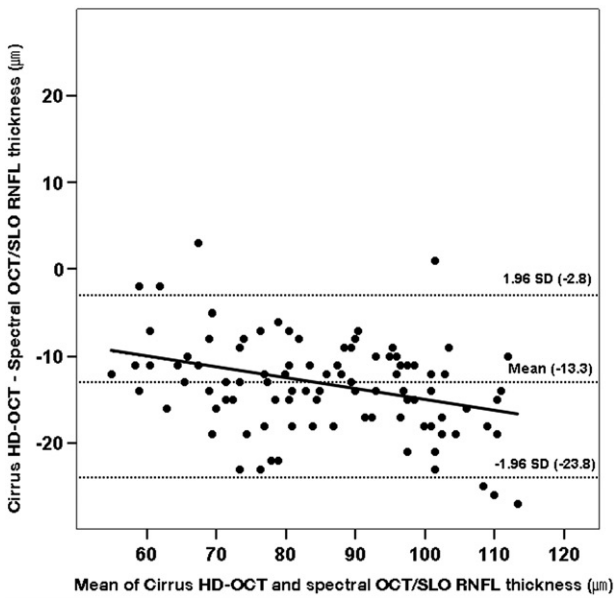

FIGURE 1 Bland–Altman plot showing agreement of average retinal nerve fiber layer (RNFL) thickness between Cirrus high-definition optical coherence tomography (Cirrus HD-OCT) and spectral OCT/scanning laser ophthalmoscope (SLO). Proportional bias was presented as a solid line ($y = -2.70 - 0.12x$; $r^2 = 0.11$; $p < 0.001$).

devices showed similar sensitivities for glaucoma detection, with the exception of nasal quadrant RNFL and RNFL thicknesses in clock-hour sectors 3 and 4, for which spectral OCT/SLO measurements had greater sensitivity than those of the Cirrus HD-OCT (Table 4).

DISCUSSION

Thus far, this is the only study comparing the glaucoma diagnostic ability of RNFL thickness as determined by Cirrus HD-OCT and spectral OCT/SLO. The results showed that RNFL thicknesses as measured by Cirrus HD-OCT and spectral OCT/SLO were not interchangeable. The glaucoma diagnostic ability of the RNFL thickness measurements was similar for both the devices.

Previous studies comparing RNFL thicknesses as determined by various spectral-domain OCTs reported significant differences were found among the devices.[4,9–13] In the present study, RNFL thickness values were greater when obtained using spectral OCT/SLO than Cirrus HD-OCT. Pierro et al.[9] also reported a thicker RNFL in healthy eyes when measured using spectral OCT/SLO than using Cirrus HD-OCT. The mean difference in average RNFL thickness in Pierro et al.'s study (13.5 μm; 90.1 μm by Cirrus HD-OCT and 103.6 μm by spectral OCT/SLO) was similar to the results of the control group in our study (14.4 μm; 91.7 μm by Cirrus HD-OCT and 106.1 μm by spectral OCT/SLO).[9] Although both the devices use spectral-domain technology, there may be differences in segmentation algorithms that affect delineation of the outer border of the RNFL, scan pattern (raster scan for Cirrus HD-OCT versus circular scan for spectral OCT/SLO), signal strength, or scan circle placement.[9,13] The differences in RNFL thickness measurements may be attributable to these technical differences.

TABLE 3 Area under receiver operating characteristics curves (95% confidence interval) of average, quadrant, and clock-hour peripapillary retinal nerve fiber layer (RNFL) thickness obtained by Cirrus high-definition optical coherence tomography (Cirrus HD-OCT) and spectral OCT/scanning laser ophthalmoscopy (SLO).

	Cirrus HD-OCT	Spectral OCT/SLO	*p* Value
Average	0.954 (0.916–0.991)	0.944 (0.900–0.989)	0.493
Quadrant			
Superior	0.827 (0.751–0.904)	0.794 (0.710–0.877)	0.189
Nasal	0.680 (0.577–0.783)	0.784 (0.696–0.871)	0.015
Inferior	0.945 (0.896–0.995)	0.938 (0.889–0.988)	0.456
Temporal	0.818 (0.740–0.897)	0.851 (0.779–0.922)	0.160
Clock-hour sectors			
12	0.763 (0.674–0.852)	0.732 (0.637–0.827)	0.358
1	0.655 (0.551–0.760)	0.659 (0.556–0.763)	0.921
2	0.662 (0.556–0.767)	0.707 (0.607–0.807)	0.255
3	0.608 (0.499–0.716)	0.780 (0.691–0.870)	0.002
4	0.675 (0.571–0.779)	0.812 (0.732–0.892)	0.002
5	0.828 (0.749–0.907)	0.868 (0.800–0.936)	0.124
6	0.922 (0.866–0.977)	0.915 (0.855–0.975)	0.581
7	0.918 (0.865–0.971)	0.916 (0.859–0.974)	0.898
8	0.796 (0.712–0.879)	0.819 (0.739–0.899)	0.367
9	0.781 (0.689–0.874)	0.823 (0.744–0.902)	0.132
10	0.817 (0.739–0.896)	0.846 (0.773–0.919)	0.245
11	0.838 (0.763–0.914)	0.862 (0.793–0.932)	0.270

TABLE 4 Sensitivities for specificities set at 80 and 95% according to the average, quadrant, and clock-hour peripapillary retinal nerve fiber layer (RNFL) thickness obtained by Cirrus high-definition optical coherence tomography (Cirrus HD-OCT) and spectral OCT/scanning laser ophthalmoscopy (SLO).

	Cirrus HD-OCT		Spectral OCT/SLO	
	Specificity at 80%	Specificity at 95%	Specificity at 80%	Specificity at 95%
Average	96.0%	76.7%	95.0%	74.0%
Quadrant				
Superior	70.0%	55.3%	61.3%	48.3%
Nasal	40.0%	12.7%	52.3%	30.8%
Inferior	93.3%	87.7%	91.7%	78.7%
Temporal	60.7%	55.0%	69.7%	49.3%
Clock-hour sectors				
12	58.3%	50.2%	58.0%	40.0%
1	43.0%	25.8%	45.0%	33.3%
2	40.0%	18.7%	45.0%	25.3%
3	36.0%	17.3%	50.7%	34.3%
4	40.0%	19.7%	60.7%	47.7%
5	71.3%	51.7%	83.3%	58.3%
6	90.0%	78.3%	86.7%	76.8%
7	90.0%	71.0%	84.7%	66.7%
8	65.0%	55.3%	67.7%	42.8%
9	61.2%	39.4%	69.3%	31.0%
10	66.0%	50.0%	70.0%	48.3%
11	70.0%	63.3%	73.3%	66.7%

Regarding the role of RNFL thickness in the diagnosis of glaucoma, average RNFL thickness (AUC, 0.954 for Cirrus HD-OCT and 0.944 for spectral OCT/SLO) and inferior quadrant RNFL thickness (AUC, 0.945 for Cirrus HD-OCT and 0.938 for spectral OCT/SLO) showed the greatest diagnostic ability for both the devices. This result is in agreement with those of previous studies obtained using Cirrus HD-OCT (AUC, 0.88–0.962 for average RNFL thickness, 0.87–0.963 for inferior quadrant RNFL thickness) or spectral OCT/SLO (AUC, 0.96–0.969 for average RNFL thickness, 0.84–0.893 for inferior quadrant RNFL thickness).[1–6] In the present study, superior quadrant RNFL thickness showed relatively lower utility in the diagnosis of glaucoma (AUC, 0.827 for Cirrus HD-OCT and 0.794 for spectral OCT/SLO) as compared to the results reported in previous studies (AUC, 0.81–0.963 for Cirrus HD-OCT and 0.9–0.936 for spectral OCT/SLO).[1–6] This discrepancy may be explained by differences in topographic RNFL defect distribution and severity of disease between our study population and other study populations; if a study population has less frequent or milder RNFL abnormalities in the superior area compared with other populations, the diagnostic ability of superior RNFL measurements may be lower than those reported in studies of other populations. Our study results showed that nasal and temporal RNFL thickness had lower glaucoma diagnostic ability than RNFL thickness measurements in other areas. Given that glaucomatous RNFL defects are mainly found supero- or inferotemporally, this finding is not remarkable.

Measurements of nasal quadrant RNFL thickness had greater positive predictive value when obtained using spectral OCT/SLO than using Cirrus HD-OCT. The corresponding AUCs were 0.680 for Cirrus HD-OCT and 0.784 for spectral OCT/SLO. Previous studies also reported that nasal RNFL thickness measurements had good or fair glaucoma diagnostic

ability when obtained using spectral OCT/SLO (AUC, 0.797–0.89).[5,6] This finding may be explained in part by differences in the weightage given to nasal measurements in calculations of overall RNFL thickness. For spectral OCT/SLO, nasal quadrant RNFL thickness contributes 20.2% of average RNFL; the nasal proportion accounts for 18.2% of Cirrus HD-OCT measurements. Differences in scan placement or incidence angle of the illuminating beam may contribute to this discrepancy. Although glaucomatous RNFL changes are less commonly found in the nasal area, other RNFL abnormalities caused by neurologic disorders or drugs are commonly found in the nasal quadrant.[19,20] The good or fair glaucoma diagnostic ability of nasal RNFL thickness as determined by spectral OCT/SLO suggests that nasal RNFL thickness measurements by spectral OCT/SLO may be useful for RNFL assessment in patients with neurologic disorders or drug toxicity issues.

In the present study, only RNFL thickness parameters determined by the 3.46-mm-diameter scan circle area were investigated. This was because spectral OCT/SLO provides only RNFL thicknesses as measured by the 3.46-mm-diameter scan. On the other hand, Cirrus HD-OCT additionally provides RNFL deviation and thickness maps based on the 6 mm × 6 mm × 2 mm cube scan data. Recently, Hwang et al.[21] reported that when RNFL defects are evaluated using the clock-hour sector RNFL thickness normative classification provided by the Cirrus HD-OCT, 28.1% of RNFL defects are identified incorrectly. However, only 9.2% were misidentified when using the RNFL deviation map, and no defects were misidentified when using the RNFL thickness map. In addition, Leung et al.[22] reported that when glaucoma progression was assessed based on changes in RNFL thickness as measured by OCT, RNFL changes were most likely to be noted in the inferotemporal meridian 2.0 mm away from the optic disc center, which is outside of the 3.46-mm-diameter scan area. Therefore, when evaluating RNFL thickness with spectral OCT/SLO, the possibility of RNFL abnormalities or changes outside of a 3.46-mm-diameter scan field should be considered.

In conclusion, the RNFL thickness values measured using Cirrus HD-OCT and spectral OCT/SLO were not interchangeable. The glaucoma diagnostic ability of RNFL thickness measurements was similar for both the devices.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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