Intereye Comparison of Cirrus OCT in Early Glaucoma Diagnosis and Detecting Photographic Retinal Nerve Fiber Layer Abnormalities

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Glaucoma is characterized by progressive changes in the neuroretinal rim, retinal nerve fiber layer (RNFL), and visual field (VF). In many instances, structural changes in the neuroretinal rim and RNFL precede VF defects in the early stages of glaucoma. Therefore, detection of structural changes is important in terms of early glaucoma diagnosis. Although thinning of the RNFL is difficult to detect during clinical examination, optical coherence tomography (OCT) currently provides reliable and reproducible measurements useful in glaucoma diagnosis. Recent high-speed, high-resolution imaging of the RNFL using spectral-domain OCT has afforded even more detailed information that can be used to detect glaucoma. Of the several available models of spectral-domain OCTs, the Cirrus OCT (Zeiss, Dublin, CA, USA) can construct various ocular maps. The Deviation map and Thickness map are more sensitive when used to detect photographically localized RNFL defects than the Quadrant and Clock-hour maps. However, variations in axial length and disc size cause false-positive errors.

Glaucoma is often bilateral, but may be symmetric. A difference in the cup-to-disc ratios between eyes is an early sign of glaucomatous damage. “Intereye” comparisons of other structural measures may detect early damage. We compared the ability of various Cirrus OCT-derived maps, including the “intereye comparison” of the temporal superior nasal inferior temporal (TSNIT) map to detect localized RNFL defects similar with those seen in red-free fundus photographs.

METHODS

Participants

Open-angle glaucoma patients with localized RNFL defects, and healthy control participants from the glaucoma clinic of Seoul St. Mary’s Hospital (Seoul, Korea), were consecutively enrolled in the study from January 2010 to August 2013. Localized RNFL defects were considered to be present in the red-free fundus photography if their width at a 1-disc diameter distance from the edge of the disc was larger than a major retinal vessel and if they diverged in an arcuate or wedge shape reaching the edge of the disc with clear margins. The control group was composed of patients referred for routine visual acuity examinations; these patients had no ocular disease. The study was conducted in accordance with the ethical standards of the...
Declaration of Helsinki and with the approval of the institutional review board of Seoul St. Mary’s Hospital.

On initial work-up, each patient underwent a complete ophthalmic examination, including a review of medical history, measurement of best-corrected visual acuity and refraction, slit lamp biomicroscopy, gonioscopy, Goldmann application perimetry, measurement of central corneal thickness using ultrasound pachymetry (Tomey Corporation, Nagoya, Japan), measurement of axial length using ocular biometry (IOL Master; Carl Zeiss Meditec, Dublin, CA, USA), dilated stereoscopic examination of the optic disc, disc and red-free fundus photography (Canon, Tokyo, Japan), Heidelberg Retina Tomography (HRT; Heidelberg Engineering GmbH, Heidelberg, Germany), Cirrus OCT (Carl Zeiss Meditec), and Humphrey VF examination using the Swedish interactive threshold algorithm (SITA) Standard 24-2 test (Carl Zeiss Meditec). All studies were done within a 1-month period.

Study participants met the following inclusion criteria: best-corrected visual acuity of greater than 20/30, with a spherical equivalent between −6.0 and +4.0 diopeters (D) and a cylinder correction within +3.0 D; and reliable VF test results with a false-positive error less than 15%, a false negative error less than 15%, and a fixation loss less than 20%. Subjects were excluded if they met any of the following criteria: (1) mean deviation of the VF worse than −6.0 dB, (2) a history of any retinal disease, (3) a history of ocular trauma or surgery, including trabeculectomy or glaucoma tube shunt surgery, with the exception of uncomplicated cataract surgery, (4) any optic nerve disease other than glaucoma, and (5) a history of systemic medication use or a cerebrovascular event that could affect the VF. In patients in whom both eyes were eligible for the study, the eye with more advanced glaucoma or with a higher mean deviation of the VF was chosen for inclusion.

To be diagnosed with glaucoma, patients had to meet the following criteria: a glaucomatous optic disc abnormality (such as diffuse or localized rim thinning, a notch in the rim, or a vertical cup-to-disc ratio higher than that of the other eye by more than 0.2); and glaucomatous VF loss (<3 significant [P < 0.05], nonedge contiguous points with values ≥1 at the P < 0.01 level on the same side of the horizontal meridian in the pattern deviation plots of two qualifying VFs) confirmed by two glaucoma specialists (H-YLP and CKP); and an open-angle on gonioscopic examination. Glaucomatous eyes with normal Humphrey test using the SITA Standard 24-2 test was considered to have preperimetric glaucoma. Healthy control eyes were defined as eyes with optic discs of normal appearance, with an absence of any RNFL defect in red-free fundus photographs, that yielded normal results upon VF testing, and that had an IOP of 21 mm Hg or lower.

Measurement of Retinal Nerve Fiber Layer Defects on Red-Free Fundus Photographs

The the location and the width of each RNFL defect identified on red-free fundus photographs were measured in degrees using a previously reported technique. First, a circle of diameter 3.46 mm centered on the optic nerve head (ONH) was drawn on the red-free image. Next, a line was drawn from the center of the ONH to each point where the borders of RNFL defects met the circle. Next, the angle between each pair of lines, representing the temporal-most clock hour sector for both the right and left eyes.

Optical Coherence Tomography

Retinal nerve fiber layer thickness was measured using the optic disc cube protocol of a Cirrus OCT running version 6.0 software. The Optic Disc Cube protocol scans a 6 × 6-mm² area centered on the ONH and collects 200 × 200 axial scans containing 40,000 points. The RNFL thickness at each pixel was measured and an RNFL thickness map was generated. A calculation circle, 3.46 mm in diameter consisting of 256 A-scans, was automatically positioned around the optic disc. Abnormal RNFL measurements in the 6-mm² parapapillary area were noted and displayed in each RNFL thickness deviation map. This map was composed of 50 × 50 superpixels (each superpixel contained 4 × 4 pixels). Images exhibiting involuntary saccade, misalignment, or blinking artifacts, and those of signal strength less than 6, were discarded. Images featuring algorithm segmentation failure were also excluded, after careful visual inspection.

In the present study, an abnormal finding in an OCT map that matched the location of an RNFL defect observed in a red-free fundus photograph was defined as detection of a photographic RNFL defect (Fig. 1A). The RNFL Thickness map does not feature comparison of derived data with those in a normative database. In the Thickness map, areas with thick RNFLs are shown in red/white and those with thin RNFLs in blue/black. We defined detection of a photographic RNFL defect in the Thickness map as the presence of a blue/black area that corresponding to the RNFL defect area evident in the red-free fundus photograph (Fig. 1B).8,17

Cirrus OCT results derived by comparison of RNFL thickness data with those in the normative database were coded using a stoplight color or color scheme. A result was considered abnormal when the measured value was lower than that of a nominated percentile of the intrinsic normative database information; thus, below the 5% or 1% levels. In each RNFL thickness Deviation map, areas with RNFL thicknesses occurring in less than 5% of age-matched controls were colored yellow, and areas with RNFL thicknesses occurring in less than 1% of age-matched controls red. Absence of color indicated normal RNFL thickness. An abnormal finding on the Deviation map was presented as a greater than or equal to 10-superpixel sized, wedge-shaped color pattern (yellow or red) across the calculation circle 3.46 mm in diameter, with greater than or equal to 3 superpixels within the circle (Fig. 1C). The width of the wedge-shaped color pattern in the Thickness and Deviation map was measured by determining the angle between the two lines from the center of the disc to the points at which the color pattern and the 3.46-mm calculation circle converged. In the Quadrant and Clock-hour maps, RNFL thicknesses within the normal range were shown in green, those abnormal at the 5% level in yellow, and those abnormal at the 1% level in red. Quadrant and Clock-hour maps with greater than or equal to 1 yellow or red sector were considered abnormal (Fig. 1D).

A TSNIT thickness map constructed by the Cirrus OCT shows the RNFL thicknesses of both eyes. A comparative thickness separation of more than 50 μm between both eyes was considered to represent an abnormal difference (Fig. 1E, black arrow). A separation of less than 50 μm was considered to be a normal variation (Fig. 1E, gray arrow). The reason for this 50-μm cut off value was that the provided y-axis of the TSNIT thickness map is graded in 50-μm intervals. Clinically, separation of TSNIT curve of both eyes more than 50 μm is the minimum value that we could identify from the Cirrus OCT printout. Abnormal difference values were calculated from the RNFL thicknesses of either eye at each of 256 points on the
least 1 separation of RNFL thickness curves more than 50 μm was considered to represent abnormal thinning (outside normal region in the TSNIT map). Separation of the TSNIT curves of either eye by less than 50 μm was considered to reflect normal variation (gray arrow). The intereye difference value from the TSNIT map was defined as the sum of the RNFL thickness differences of both eyes along 256 points on the 3.46-mm diameter scan circle. Each RNFL thickness difference was calculated by subtracting the RNFL thickness of the eye with the photographically identified RNFL defect from that of the opposite eye. At point 216 of the 256 points, the RNFL thicknesses were 169 μm for the right eye and 69 μm for the left eye. Differences were calculated for all positions at which significant TSNIT curve separation was evident.

This difference was defined as abnormal thinning (outside normal limits) when it was greater than 50 μm. Overall, the OCT thickness map, or (4) a separation (>50 μm) of the RNFL thickness curves of either eye in the TSNIT thickness map, the event was classified as misidentification of a photographic RNFL defect by Cirrus OCT. Optical coherence tomography images were interpreted by graders who were masked to the red-free RNFL photographs and VF results.

To compare the sensitivity of each map for detecting the RNFL defect, the RNFL defect detected was defined as abnormal thinning (outside normal) or a separation (>50 μm) of the RNFL thickness curves of either eye from the TSNIT thickness map in the sector that corresponded with the location of the RNFL defect on red-free fundus photography. To compare the sensitivity and specificity of the maps of Cirrus OCT for detecting glaucoma, glaucoma detected was defined as abnormal thinning (at least 1 outside normal region in the Clock-hour, Quadrant, Deviation, and Thickness maps or at least 1 separation of RNFL thickness curves more than 50 μm in the TSNIT map).

### Statistical Analysis

The paired t-test was used to compare differences between the eyes of patients in each group. Student’s t-test was used to compare differences in study eyes between groups. The χ² test was used as appropriate to compare frequencies. Areas under receiver operating characteristic (ROC) curves were measured to assess the ability of measures of RNFL thickness derived from various maps to detect localized RNFL defects. Overall sensitivities and specificities were evaluated by comparison of measurements with those of the OCT normative database, or by comparing data from either eye. The sensitivities and specificities of OCT maps were compared using the χ² test, and multiple comparisons were performed only after application of the Bonferroni correction. To explore whether the capability to detect localized RNFL defects was affected by the width of localized RNFL defects, as measured on RNFL photographs, the Mantel-Haenszel χ² test was applied to the entire dataset and the McNemar test was used to compare the data yielded by different maps. The relationships between the intereye difference values from the TSNIT map and the width of RNFL defects evident on RNFL photography, average RNFL thickness, and mean deviation of the VF were analyzed by Pearson’s correlation analysis. In addition, univariate and multivariate logistic regression analysis was performed. The dependent variable was misidentification of photographic RNFL defects when intereye difference from the TSNIT map was used. The independent variables were patient age, axial length, mean deviation of the VF, disc area, disc area and axial length difference between the study and opposite eye, and average RNFL thickness. Variables exhibiting significance values of P less than 0.20 upon univariate analysis were included in the multivariate model. A P value of less than 0.05 was considered to indicate statistical significance. Statistical analysis was performed using the SPSS statistical software package (SPSS, Chicago, IL, USA).
RESULTS

We enrolled 131 glaucoma patients and 56 healthy controls. Among the 131 study eyes, 48 were myopic (of axial length longer than 24.0 mm). Twenty-four (18.3%) from 131 eyes had unilateral glaucoma. We found no intergroup difference in terms of age, sex, spherical equivalent, axial length, central corneal thickness, or disc area (Table 1). Study eyes of the glaucoma group exhibited significantly poorer VF indices (mean deviation and pattern standard deviation) than those of the healthy control group ($P < 0.001$ and $P = 0.001$, respectively) and the opposite eyes of the glaucoma group ($P < 0.001$ and $P = 0.009$, respectively). In study eyes of the glaucoma group, the mean values of mean deviation (±SD) was $-2.27 (±1.85)$ dB and pattern standard deviation was $3.58 (±2.65)$ dB at the lower ends of the ranges defining mild VF loss. Of the 131 study eyes, 51 had preperimetric VF defects. The average RNFL thickness was significantly less in study eyes of the glaucoma group compared with the healthy control group ($P < 0.001$) and the opposite eyes of the glaucoma group ($P < 0.001$).

Additionally, intereye difference values yielded by the TSNIT map were significantly greater for the glaucoma than the healthy control group ($P < 0.001$). The intereye difference value from the TSNIT map was $803.52 (±358.22) \mu m$ in the healthy control group, which increased to $1742.20 (±895.27) \mu m$ in the glaucoma group. The intereye difference value from the TSNIT map correlated modestly with the angular widths of RNFL defects evident in red-free fundus photographs ($R = 0.558, P < 0.001$), average RNFL thickness ($R = -0.425, P < 0.001$), and VF mean deviation ($R = -0.596, P < 0.001$; Fig. 2).

The distributions of the widths and locations of 131 RNFL defects identified in red-free fundus photographs of the 131 study eyes are shown in Table 2. Retinal nerve fiber layer defects were found most commonly in inferotemporal areas (70.2%). The width of RNFL defects less than 20° were 43.5% among all study eyes, since early glaucoma patients were mainly enrolled.

Table 3 shows the sensitivities and specificities of the Cirrus OCT in terms of glaucoma detection using the criteria described above. The overall sensitivities of OCT maps used to detect localized RNFL defects identified with the aid of the RNFL normative database, or by analysis of intereye differences, differed significantly from one another ($P < 0.001$). Use of intereye differences from the TSNIT maps afforded superior sensitivity (98.0%) compared with that of any other map, for all glaucomatous eyes (all $P < 0.001$). Subanalyses of the preperimetric and perimetric groups yielded similar results. The intereye difference from the TSNIT map among preperimetric eyes afforded a detection sensitivity superior (97.7%) to that of all other maps (all $P < 0.001$). The overall specificities afforded by the various OCT maps did not significantly differ when either all glaucomatous or preperimetric eyes were analyzed.

The sensitivities of the Cirrus OCT maps in terms of detection of an RNFL defect were compared with reference to the angular widths of the defects (Table 4). We analyzed all glaucomatous eyes, and the subset of preperimetric eyes. In all

![Figure 2](image-url)  
**Figure 2.** Relationships between intereye difference value from TSNIT map and angular widths of RNFL defects evident in red-free fundus photographs, average RNFL thickness, and mean deviation of VF test.
glaucomatous eyes, all of the Quadrant, Clock-hour, Deviation, and Thickness maps exhibited significant differences in terms of detecting RNFL defects (abnormal thinning) when the width of the RNFL defect varied (all $P$ values < 0.0001). However, the intereye difference from the TSNIT map detected RNFL defects of varying widths with equal sensitivities ($P = 0.087$). Of photographic RNFL defects of width less than 20°, 96% were detected using intereye difference from the TSNIT map. The detection rate of RNFL defects was higher using intereye difference from the TSNIT map compared with the Thickness map (McNemar test, $P = 0.003$). In preperimetric glaucoma, all of the Quadrant, Clock-hour, and Deviation maps differed significantly in terms of detecting RNFL defects (abnormal thinning) by the width of the RNFL defect. However, the Thickness map and intereye difference from the TSNIT map afforded similar RNFL defect detection rates as the width of the defect varied ($P = 0.115$ and $P = 0.929$, respectively). Intereye difference from the TSNIT map detected 97% of photographic RNFL defects of width less than 20°. The detection rate of RNFL defects was higher when intereye differences from the TSNIT map were used, compared with the Thickness map (McNemar test, $P < 0.001$).

In univariate logistic regression analysis, Cirrus OCT misidentification of photographic RNFL defects when using intereye difference from the TSNIT map was associated with larger differences in between-eye disc area ($P = 0.046$) and the smaller width of the RNFL defect ($P = 0.001$; Table 5). Of these two factors, considerable difference in disc area between the study and opposite eye ($P = 0.017$), and the width of the RNFL defect ($P < 0.001$), were both significantly associated with misidentification of photographic RNFL defects upon multivariate logistic regression analysis. Myopia had no significant effect on misidentification of photographic RNFL defects.

The diagnostic capabilities of intereye difference values derived from TSNIT maps are shown in Table 6. The intereye difference value yielded the highest area under the curve for discrimination of glaucomatous from normal eyes (0.924), especially myopic eyes (0.909). Diagnostic ability in terms of discriminating preperimetric glaucomatous eyes from healthy eyes was greatest for inferior RNFL thickness (0.861), followed by the intereye difference value from the TSNIT map (0.846).

### Table 2. Distribution of Width and Location of RNFL Defects of the Study Eye From Glaucoma Group Evaluated by Red-Free Fundus Photographs

<table>
<thead>
<tr>
<th>Width, deg</th>
<th>Inferotemporal Area</th>
<th>Superotemporal Area</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>34 (56.7%)</td>
<td>21 (38.2%)</td>
<td>55 (42.0%)</td>
</tr>
<tr>
<td>20–29</td>
<td>22 (78.6%)</td>
<td>6 (21.4%)</td>
<td>28 (21.4%)</td>
</tr>
<tr>
<td>30–39</td>
<td>10 (55.6%)</td>
<td>8 (44.4%)</td>
<td>18 (13.7%)</td>
</tr>
<tr>
<td>≥40</td>
<td>26 (80.7%)</td>
<td>4 (13.3%)</td>
<td>30 (22.9%)</td>
</tr>
<tr>
<td>Total</td>
<td>92 (70.2%)</td>
<td>39 (29.8%)</td>
<td>131 (100%)</td>
</tr>
</tbody>
</table>

Data shown as n (%). Inferotemporal area, 6 to 8 clock-hour sectors; superotemporal area, 10 to 12 clock-hour sectors, with 9 o’clock hour presenting the temporal-most clock-hour sector for both right and left eyes.

### Table 3. Overall Sensitivity and Specificity of Each Maps of Cirrus OCT Based on Normative Database or Intereye Comparison for Detecting Localized RNFL Defects

<table>
<thead>
<tr>
<th></th>
<th>Quadrant Map</th>
<th>Clock-Hour Map</th>
<th>Deviation Map</th>
<th>Thickness Map</th>
<th>Intereye Difference From TSNIT Map</th>
</tr>
</thead>
<tbody>
<tr>
<td>All, $n = 131$</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>65.3 (51.5–72.4)</td>
<td>67.4 (53.5–76.7)</td>
<td>77.2 (60.2–81.4)</td>
<td>88.7 (82.4–90.9)</td>
<td>98.0 (87.9–99.8)</td>
</tr>
<tr>
<td>Specificity</td>
<td>85.3 (68.1–94.4)</td>
<td>85.3 (65.8–93.6)</td>
<td>82.5 (65.3–91.5)</td>
<td>81.8 (63.3–91.4)</td>
<td>81.5 (61.6–90.3)</td>
</tr>
<tr>
<td>Hit ratio</td>
<td>75.3</td>
<td>79.9</td>
<td>85.35</td>
<td>85.25</td>
<td>89.85</td>
</tr>
<tr>
<td>Preperimetric group, $n = 51$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>54.5 (45.7–63.2)</td>
<td>59.1 (50.2–67.5)</td>
<td>66.7 (57.8–74.5)</td>
<td>78.0 (63.1–85.1)</td>
<td>97.7 (92.9–99.4)</td>
</tr>
<tr>
<td>Specificity</td>
<td>78.2 (65.7–91.7)</td>
<td>75.9 (63.3–90.9)</td>
<td>73.8 (62.7–89.5)</td>
<td>71.1 (60.1–88.4)</td>
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<td>Hit ratio</td>
<td>66.35</td>
<td>69.5</td>
<td>73.7</td>
<td>78.55</td>
<td>83.92</td>
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<td>Perimetric group, $n = 80$</td>
<td></td>
<td></td>
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<tr>
<td>Sensitivity</td>
<td>75.6 (64.6–84.1)</td>
<td>78.0 (67.2–86.1)</td>
<td>85.4 (75.4–91.8)</td>
<td>92.5 (82.6–94.5)</td>
<td>98.7 (92.4–99.9)</td>
</tr>
<tr>
<td>Specificity</td>
<td>91.6 (81.0–99.5)</td>
<td>91.0 (79.3–95.6)</td>
<td>90.2 (77.6–92.4)</td>
<td>87.8 (72.4–90.7)</td>
<td>85.4 (70.9–89.4)</td>
</tr>
<tr>
<td>Hit ratio</td>
<td>83.6</td>
<td>84.5</td>
<td>87.3</td>
<td>87.15</td>
<td>88.55</td>
</tr>
</tbody>
</table>

Data are expressed in % (95% confidence intervals). The hit ratio was defined as the accuracy rate: the ratio of true positives to true negatives of all cases.

### DISCUSSION

Although RNFL profiles are asymmetric between the eyes of an individual patient, and exhibit regional differences, the RNFL thickness of both eyes of the same subject have been reported to correlate strongly. One report found that a between-eye difference in average RNFL thickness of more than 9 to 12 µm may suggest the presence of early glaucomatous damage. Between-eye asymmetry of the nerve fiber layer index derived from scanning laser polarimetry has been identified as the most useful parameter for glaucoma diagnosis. Using a retinal thickness analyzer, Zeimer et al. found that a significant relationship existed between the extent of between-eye total retinal thickness asymmetry, and the extent of VF loss, in glaucoma patients. A recent study using Cirrus OCT found that a between-eye RNFL thickness difference of over 9 µm may indicate the presence of early glaucomatous damage. The advent of spectral-domain OCT has rendered it possible to quantify intereye differences in the precise location of the RNFL defect in one eye, rather than simply the overall difference in average RNFL thickness. Intereye difference data derived from TSNIT maps, examined in the present study reveal that such information may aid in detection of early RNFL defects and diagnosis of early-stage glaucoma. We have presented data from a representative case, in which an RNFL defect of width less than 20°, in an eye with very early-stage glaucoma, was not detected in the Deviation, Quadrant, or Clock-hour maps, and but barely detected in the Thickness map, but was clearly detected by comparing the RNFL thickness curves of the TSNIT maps of either eye (Fig. 3). Although precise comparative values are not currently provided by the Cirrus OCT software, it was possible to...
performed manual calculations in the present study. The difference value of greater than 50 μm was a practical cut off that could be used directly from the printouts of Cirrus OCT in clinical setting. Thus, separation of RNFL thickness curves by greater than 50 μm detected 98% of all RNFL defects.

Traditionally, bilateral asymmetry in the cup-to-disc ratios has been considered to be an early sign of clinical glaucomatous damage, and a predictor of future damage in patients with ocular hypertension.13,22 All large epidemiologic studies on glaucoma prevalence have used cup-to-disc ratio asymmetries of greater than or equal to 0.2 or greater than or equal to 0.3 to define glaucoma or to trigger referral for definitive diagnosis.27 An increase in disc cupping is greater in the right than the left eye, but other maps derived by Cirrus OCT showed near-normal findings. However, diffuse RNFL atrophy is evident in the red-free fundus photograph and the Thickness map of the right eye. Comparison of the two eyes clearly revealed the loss of RNFL in the superior and inferior region of the eye with early-stage glaucoma. Comparing the two eyes, with identifying of intereye difference, may be a valuable means by which to detect “loss” associated with glaucoma, because the onset of glaucoma in either eye is asymmetric.11,12 Usually, the two eyes are symmetric in terms of optical and anatomical characteristics, unless anisometropia is present.30 The opposite eye may serve as a useful reference for the glaucomatous eye in an individual patient. Such examination may enhance our ability to detect early-stage glaucomatous changes. Our approach is better than a simple comparison to the mean values of healthy eyes differing in terms of race, age, axial length, and disc size with the examined eye.

A smaller angular width of a localized RNFL defect evident on red-free fundus photography has been reported to be associated with a failure to detect the defect.31 A previous study found that the Deviation map of Cirrus OCT detected all RNFL defects in instances where red-free fundus photographs identified RNFL defects with angular widths over 20° to 30°, but failed to detect narrower, localized RNFL defects.32 Hwang et al.33 reported that the Deviation map and Thickness maps of Cirrus OCT misidentified photographic RNFL defects at rates of 9% and 0%, respectively. In that study, only 24.1% of eyes had RNFL defects of width less than 20°. In the present study, 24.1% of all RNFL defects were of width less than 20°, because
early-stage glaucomatous eyes were enrolled. The Deviation and Thickness maps misidentified photographic RNFL defects in 7% and 3% of cases, respectively, when the RNFL defects were over 20° in width. However, these maps misidentified photographic RNFL defects in 54% and 23% of eyes with RNFL defects less than 20° in width. Notably, intereye difference from TSNIT map misidentified photographic RNFL defects in only 4% of eyes with RNFL defects of width less than 20°. The detection rates afforded by the Deviation and Thickness maps were less in preperimetric eyes. However, the intereye difference from TSNIT map misidentified photographic RNFL defects in only 3% of preperimetric eyes with RNFL defects of width less than 20°. Thus, the good detection rate was maintained using intereye difference from the TSNIT map when preperimetric eyes were studied.

An important finding of the present study is that neither axial length nor disc area significantly affected the diagnostic performance of intereye difference from the TSNIT map. The ROC value was highest when intereye differences of myopic eyes were compared. A longer axial length and a smaller disc area were previously reported to yield false-positives in terms of RNFL color codes, and to reduce the sensitivity of glaucoma detection.30,32,33 This may be because RNFL thickness profiles differ from those in the normative database if eyes with myopia are studied. A fixed circular scan yielding peripapillary RNFL measurements may potentially generate different measures in eyes with small optic discs.33,34 For this reason, the Deviation and Thickness maps may yield fewer false-positives than other maps because the Deviation map does not use data from a fixed circular scan and the Thickness map does not rely on comparisons with normative database values.8,10 The reference of the study eye using intereye differences from the TSNIT maps is the opposite eye and this also does not rely on data from a fixed circular scan does not feature any comparison with normative database values. The asymmetry in cup-to-disc ratio between both eyes depends on the disc size. Our findings suggest that RNFL thickness of one eye serves as a reference for the other eye regardless of axial length and disc size. Representative example of myopic eye is shown in Figure 5. Both eyes of this patient exhibit positive color codes in the inferior quadrants in the Clock-hour, Quadrant, and Deviation maps. The existence of a separation greater than 50 μm in the TSNIT map of the RNFL thickness curves of either eye reveals an RNFL defect in the left eye (a patient with glaucoma). The RNFL Quadrant and Clock Hour maps of the right eye may be flagged as ‘abnormal’ due to the anomalous nature of the optic disc and RNFL morphology by myopia.

Misidentification of photographic RNFL defects when using intereye difference from the TSNIT maps was associated only with the width of the RNFL defect, and the difference in disc area between the two eyes. Disc area difference between both eyes of a patient was related to misidentification of photographic RNFL defect using intereye difference from the TSNIT map, but not axial length difference between both eyes. This could be interpreted that the asymmetry of disc morphological changes between both eyes by myopia which is measured as asymmetry of disc size is important than myopia itself.35 Hood et al.36 reported that the local maxima in the RNFL profile is usually associated with blood vessels, and variations in the location of blood vessels are the most likely source of variations in the RNFL profiles. Disc morphological changes may result in changes of major vessel locations.37 In patients with difference RNFL profiles between both eyes due to different major vessel locations, using intereye difference from the TSNIT map may be limited.

Limitation of the present study should be acknowledged. First, caution should be made in generalizing our findings since only Koreans was involved. Second, there may be limitations for using intereye difference in patients who have glaucomatous change in both eyes or with advanced damage. The findings in this study would not be applicable to a more broad-based population of patients with bilateral glaucoma in which the severity of damage between fellow eyes is more symmetrical. Third, selecting patients with early glaucoma in this study may have resulted in potential selection bias. Unilateral or asymmetric disease may have favored the discriminating power to the intereye difference parameter. However, the frequency of unilateral disease in open-angle glaucoma is reported to be approximately 30% to 40%.58 The present study included 24 (18.3%) from 131 eyes with

Table 5. Characteristics of Eyes With Misidentification of Photographic RNFL Defects Using the Intereye Difference From TSNIT Map of Cirrus OCT

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th></th>
<th>Multivariate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta (95% CI)</td>
<td>P Value</td>
<td>Beta (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Age</td>
<td>0.957 (0.910–1.006)</td>
<td>0.083</td>
<td>0.609 (0.547–1.111)</td>
<td>0.274</td>
</tr>
<tr>
<td>Axial length</td>
<td>1.438 (0.860–2.972)</td>
<td>0.141</td>
<td>1.800 (0.896–2.926)</td>
<td>0.362</td>
</tr>
<tr>
<td>Axial length difference with opposite eye</td>
<td>1.017 (0.910–1.831)</td>
<td>0.396</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean deviation</td>
<td>1.809 (0.395–1.660)</td>
<td>0.564</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disc area</td>
<td>0.622 (0.299–3.233)</td>
<td>0.652</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disc area difference with opposite eye</td>
<td>1.254 (1.081–2.633)</td>
<td>0.046</td>
<td>1.364 (1.191–2.716)</td>
<td>0.017</td>
</tr>
<tr>
<td>Width of RNFL defect</td>
<td>0.826 (0.730–0.947)</td>
<td>0.001</td>
<td>0.819 (0.722–0.942)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Average RNFL thickness</td>
<td>0.949 (0.889–1.015)</td>
<td>0.416</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The variables that retained significance at P < 0.20 in the univariate analysis were included in the multivariate model. Beta, regression coefficient; CI, confidence intervals.

Table 6. Area Under ROC Curve Values Among Healthy Eyes and Eyes With Photographic RNFL Defects

<table>
<thead>
<tr>
<th></th>
<th>Normal vs. All</th>
<th>Normal vs. Preperimertic Glaucoma</th>
<th>Normal vs. All in Myopic Eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intereye difference value from TSNIT map</td>
<td>0.924 (0.880–0.967)</td>
<td>0.846 (0.780–0.911)</td>
<td>0.909 (0.857–0.960)</td>
</tr>
<tr>
<td>Average RNFL thickness</td>
<td>0.864 (0.801–0.928)</td>
<td>0.832 (0.765–0.918)</td>
<td>0.850 (0.765–0.934)</td>
</tr>
<tr>
<td>Inferior RNFL thickness</td>
<td>0.898 (0.848–0.948)</td>
<td>0.861 (0.804–0.918)</td>
<td>0.900 (0.840–0.960)</td>
</tr>
</tbody>
</table>
FIGURE 3. A glaucomatous eye with an inferotemporal RNFL defect that is barely visible in the red-free fundus photograph ([A], white arrow). The inferotemporal RNFL defect was also barely visible in the Thickness map ([B], black arrow) and was not identified at all in the Deviation (C) or the Quadrant/Clock-hour maps (D). However, separation of the RNFL thickness curves of either eye, by over 50 µm, was apparent in the TSNIT map ([E], black arrow). This eye has an early glaucomatous VF defect in the corresponding region to the RNFL defect (F).

FIGURE 4. A glaucomatous eye with a diffuse RNFL defect embracing both the superior and inferior regions, evident upon red-free fundus photography (white arrow). Maps showing loss of retinal ganglion cells identified the diffuse RNFL defect; such maps included the Thickness map and intereye difference from the TSNIT map (black arrow). However, maps that measure residual retinal ganglion cells and define an abnormality via comparison with a normative database did not adequately identify the RNFL defect. The inferior RNFL defect is but poorly identified in the Deviation and Quadrant maps. The superior RNFL defect is missed in all of the Deviation, Quadrant, and Clock-hour maps.
unilateral glaucoma, which is less than the reported frequency. Finally, our findings may be only applied to patients with early damage (mean of mean deviation of approximately $-2.27 \text{ dB}$). This might have resulted in some selection bias of the study. Disease could be more asymmetric during the onset and initial stage of glaucoma. Our data clearly shows the advantage of this parameter in diagnosing early glaucoma, especially preperimetric glaucoma.

In summary, among various maps obtained with Cirrus OCT, comparing the RNFL thickness curves of the both eyes in the TSNIT map showed the best diagnostic ability and sensitivity in detecting photographic RNFL defects. Although the present software of Cirrus OCT does not provide the exact RNFL thickness difference values, simple examination of the separation of the two RNFL thickness curves of both eyes of a patient in the TSNIT map is diagnostically useful to find preperimetric and early-stage glaucoma. Test performance using intereye difference from the TSNIT map was not affected by myopia and disc size.

Acknowledgments

Disclosure: H.-Y.L. Park, None; H.-Y. Shin, None; J.-Y. Yoon, None; Y. Jung, None; C.K. Park, None

References


