Wide 3-Dimensional Macular Ganglion Cell Complex Imaging with Spectral-Domain Optical Coherence Tomography in Glaucoma

Satoshi Morooka, Masanori Hangai, Masayuki Nukada, Noriko Nakano, Kobei Takayama, Yugo Kimura, Tadamichi Akagi, Hanako Obashi Ikeda, Atsushi Nonaka, and Nagabisa Yoshimura

PURPOSE. To determine whether measurement of ganglion cell complex (GCC) thickness over a wide area (8-mm diameter) can improve the glaucoma-discriminating ability of spectral-domain optical coherence tomography (SD-OCT) compared to that in the standard macular area (6-mm diameter).

METHODS. Ninety-three subjects were enrolled, including 46 healthy eyes of 46 volunteers and 47 eyes of 47 glaucoma patients (23 eyes with preperimetric glaucoma [PPG] and 24 eyes with early glaucoma [EG]). All patients underwent SD-OCT raster scanning over a 9 mm × 9 mm square area centered on the fovea. Areas under the receiver operating characteristic curves (AROCs) were compared between wide sector (1–8-mm ring) and standard-size sector (1–6-mm ring) charts.

RESULTS. AROCs for average GCC thickness in the wide chart were significantly greater than those of the standard chart in eyes with PPG (0.928 vs. 0.891; P = 0.038), EG (0.912 vs. 0.861; P = 0.003), and both (0.920 vs. 0.876; P = 0.004). Overall, the AROCs of regional GCC thicknesses were nearly comparable between the middle ring (4–6 mm) and outer ring (6–8 mm). Coefficients of variation were 0.68% and 0.97% in the standard and wide sector charts, respectively, in eyes with PPG, and 0.45% and 0.72% in the standard and wide sector charts, respectively, in eyes with EG.

CONCLUSIONS. Addition of the GCC thickness outside the macula to the standard macular GCC thickness significantly increased the glaucoma-discriminating ability of SD-OCT. (Invest Ophthalmol Vis Sci. 2012;53:4805–4812) DOI:10.1167/iovs.12-9870

Glaucomatous structural damage stems from retinal ganglion cell (RGC) loss, which is thought to be caused by damage to axons within the optic nerve head (ONH). The loss of RGC axons results in the thinning of the neuroretinal rim of the ONH and retinal nerve fiber layer (RNFL). Damage to the RGC axons eventually causes RGC soma loss, particularly in the macula, with subsequent thinning of the ganglion cell layer (GCL). Many earlier studies have determined how accurately measurements of the ONH and retinal structures can distinguish between glaucomatous and normal eyes.

The development of various optical imaging technologies, such as confocal scanning laser tomography (Heidelberg Retina Tomograph, Heidelberg Engineering, Heidelberg, Germany), scanning laser polarimetry (GDx-VCC, Carl Zeiss Meditec, Dublin, CA), and optical coherence tomography (OCT; Stratus OCT, Carl Zeiss Meditec) has enabled measurement of ONH topography and circumpapillary RNFL (cpRNFL) thickness. Among these imaging technologies, OCT has also enabled measurements of retinal thickness in the macula, which have demonstrated glaucoma-discriminating ability.7–15 Advance in OCT detection technology into spectral domain (SD) combined with a broader-wavelength light source has permitted the development of SD-OCT instruments with drastically improved imaging speed and axial resolution. SD-OCT instruments allow automated measurement of the ganglion cell complex (GCC = RNFL + GCL + inner plexiform layer),16–20 which more directly reflects RGC loss than retinal thickness in the macula.16–22 cpRNFL thickness should theoretically reflect global RNFL damage, because all RGC axons assemble in the ONH. By contrast, GCC analysis is currently limited to the macular area (6 × 6 mm square or circle of 6 mm in diameter). Thus, this method does not reflect loss of all RGCs, because only approximately 50% of RGCs are present within the macula, with the remainder outside the macula. Regardless of the limited area for macular GCC (mGCC) analysis, the glaucoma-discriminating ability of mGCC was reportedly comparable to that of cpRNFL.15–20 However, we often see patients with early glaucoma who present RNFL defects outside the macular area. Thus, GCC analysis including an area wider than the macula may further improve glaucoma-discriminating ability.

Currently, only the RS5000 OCT device (Nidek, Gamagori, Japan), which enables the fastest image acquisition (53,000 A-scans/s), allows three-dimensional (3D) raster scanning (cube scan) over a 9 × 9 mm square region, providing a unique opportunity to investigate the glaucoma-discriminating ability of GCC in an area wider than the macula. The purpose of this study was to assess the glaucoma-discriminating ability of GCC thickness measured over a wider (8-mm diameter) area with 3D SD-OCT imaging.
Methods

Patients

Study subjects who met the eligibility criteria and underwent examination by RS3000 were enrolled from a database of patients who were examined for glaucoma between September 2009 and July 2010 at the Department of Ophthalmology, Kyoto University Hospital. Candidates for the study included patients with either preperimetric glaucoma (PPG) or early glaucoma (EG) and volunteers without glaucoma who had at least one eye with a best corrected visual acuity of 20/20 or better in Snellen equivalent, spherical refractive error greater than −6.00 diopters (D) and less than 3 D, a normal open anterior chamber angle, good quality of red-free photography, and reliable visual field tests. Subjects were assigned to the PPG, early EG, or normal control group. The PPG group demonstrated apparent glaucomatous optic disc appearance and normal standard automated perimetry (SAP) results. The EG group demonstrated apparent glaucomatous optic disc appearance associated with glaucomatous visual field defects with a mean deviation of greater than −6 dB. Glaucomatous disc appearance was defined as diffuse or localized neuroretinal rim thinning evaluated on stereo color fundus photographs. Volunteer eyes were assigned to the healthy control group when they demonstrated normal optic disc appearance, no visible RNFL defect on red-free RNFL photography, an intraocular pressure of 21 mm Hg or lower with no history of increased IOP, and no family history of glaucoma in a first-degree relative. Data for candidate control eyes were retrospectively collected from our database of normal volunteers who were determined by our department to have at least one normal eye and who agreed to undergo the examinations described in this study. In cases in which both eyes of a subject were eligible for the study, only one eye was randomly chosen for inclusion. Exclusion criteria for both groups were history of ocular surgery and evidence of vitreoretinal disease,uveitis, nonglaucomatous optic neuropathy or diabetes mellitus, or any other systemic disease that could affect the eye and visual field results. Patients for whom reliable OCT results could not be obtained were also excluded from the study.

A total of 95 subjects including 46 healthy eyes of 46 volunteers and 47 eyes of 47 patients with glaucoma (23 eyes with PPG and 24 eyes with EG) were enrolled.

All patients underwent a comprehensive ophthalmic examination, including measurement of uncorrected and best-corrected visual acuity using the 5-meter Landolt chart, slit-lamp examinations, IOP measurements using a Goldmann applanation tonometer, gonioscopy, dilated stereoscopic examination of the ONH, stereo disc photography with a 3-Dx simultaneous stereo disc camera (Nidek, Gamagori, Japan), red-free fundus photography using a Heidelberg Retina Angiogram 2 (HRA2, Heidelberg Engineering), SAP using a Humphrey Visual Field Analyzer (Carl Zeiss Meditec), and SD-OCT examination with the RS3000 system (Nidek).

All investigations in this study adhered to the tenets of the Declaration of Helsinki. This study was approved by the Institutional Review Board and Ethics Committee of the Kyoto University Graduate School of Medicine. Informed consent was obtained from the subjects after explanation of the nature and possible consequences of the study.

Visual Field Testing

Reliable visual field results (fixation loss ≤20%, false-positive ≤15%, and false-negative ≤33%) on SAP using the Humphrey 24-2 Swedish Interactive Threshold Algorithm (SITA) (HFA, Carl Zeiss-Meditec) were used. Abnormal visual field defects were defined using the 24-2 Swedish Interactive Threshold Algorithm standard program as (1) abnormal range on the glaucoma hemifield test; and (2) three abnormal points with P less than 5% probability of being normal, one abnormal point with P less than 1% by pattern deviation; or (3) pattern standard deviation (PSD) of less than 5% of the normal reference, confirmed on two consecutive tests.

Optic Disc Evaluation

The appearance of the optic nerve head on fundus photographs, including the stereoscopic photographs, was independently evaluated by three glaucoma specialists (M.H., H.O.I., and A.N.) who were masked to all other data about the eyes. Images of each eye from both healthy and PPG candidates were displayed on a monitor. If the decisions of all three examiners were not in agreement, consensus was reached by group review and discussion of the fundus color photographs and stereophotographs.

Wide Area Three-Dimensional Spectral-Domain Optical Coherence Tomography Imaging

The RS-3000 system (software version 2.0.0) was used to perform 3D SD-OCT imaging. This instrument includes a confocal scanning laser ophthalmoscope to monitor fundus images and SD-OCT equipment to obtain tomographic images. The OCT equipment has a 5-μm depth resolution in tissue and 20-μm transverse resolution. Each A-scan of this instrument had a depth of 2 mm and comprised 512 pixels, providing a digital depth sampling of 3.9 μm per pixel. For wide-area 3D imaging in the posterior pole, raster scanning over a 9 × 9-mm square area centered on the foveal center was conducted with a scan density of 512 A-scans (horizontal) × 128 B-scans (vertical). For cpRNFL imaging, raster scanning over a 6 × 6-mm square area centered on the optic disc center was conducted with a scan density of 512 A-scans (horizontal) × 128 B-scans (vertical). It took 1.6 seconds to obtain a single 3D data set. Imaging was performed by a well-trained examiner after pupillary dilation, with the examiner rejecting any scans with motion artifacts (discontinuous jump), poor centration, incorrect segmentation, poor focus, or missing data and accepting only good-quality images, defined as those with “Signal Strength Index” scores (as assigned by the RS3000) of at least 6/10 (as suggested by the manufacturer).

Measurements

Automated measurements of GCC and cpRNFL thickness were performed, and thickness and significance maps for GCC and cpRNFL thickness were generated using in-built software of the RS3000. The GCC thickness was measured between the internal limiting membrane and the outer boundary of the inner plexiform layer (IPL). cpRNFL thickness was measured in a circle 3.45 mm in diameter consisting of 256 A-scans, which were positioned automatically around the optic disc in each 3D data set.

Wide Sector Chart

For this study, we used a modified glaucoma sector chart (GSC), which was originally used by Wollstein et al. to investigate the relationship between total macular thickness and visual field defects in eyes with glaucoma. The GSC was created by rotating the Early Treatment Diabetic Retinopathy Study (ETDRS) chart centered on the fovea by 45 degrees. The ETDRS chart was originally designed for evaluating diabetic macular edema and is not optimized for glaucoma detection. This chart includes four sectors that cross the horizontal meridian, which does not appear to reflect the anatomy of the RNFL. The GSC layout, which divides the macula by vertical and horizontal lines through the central fovea into superior, inferior, temporal, and nasal quadrants, better represented glaucomatous damages compared with the ETDRS. Our wide macular sector chart based on the GSC layout divides the macula into inner, middle, and outer rings, with the inner ring 1 to 4 mm from the foveal center, the middle ring being from 4 to 6 mm from the foveal center, and the outer ring 6 to 8 mm from the foveal center (Fig. 1). Because the 8-mm circle sometimes overlaps
the optic disc, we removed the nasal part of the outer ring within 60
degrees (Fig. 1B).

**Statistical Analysis**

The statistical significance of differences in the continuous data between
two groups was evaluated with the Mann-Whitney test and among three
groups by ANOVA followed by post hoc test (Bonferroni). Levels of $P$
less than 0.05/3 = 0.0166 were considered statistically significant for
Bonferroni, and those of $P$ less than 0.05 for other statistical analyses. To
assess the ability of GCC thickness in various sectors to discriminate eyes
with glaucoma from normal eyes, the area under the receiver operating
characteristic curve (AROC) was calculated for each measurement. An
AROC displays the relationship between sensitivity and 1 – specificity for
the result of a given diagnostic test. An AROC of 1.0 indicates that the
test perfectly discriminates between the presence or absence of the
condition, whereas an AROC of 0.5 represents chance discrimination.
Commercially available software (MedCalc version 9.3.8.0, Med Calc
Software, Mariakerke, Belgium) was used to compare AROCs. The
coefficient of variation (CV, 100 × SD/overall mean) and intraclass
correlation coefficient (ICC) were calculated from measurements
obtained from three imaging sessions at the same visit.

**RESULTS**

**Subjects**

All of the enrolled subjects were Japanese. Subject demographics
and visual field mean deviation (MD) of the three groups are
shown in Table 1. No statistically significant differences in age,
sex, or spherical equivalent of refractive errors were observed
among the three groups. Visual field MD values did significantly
differ among the three groups.

**Case Showing Retinal Nerve Fiber Layer Defects
Outside the Standard Sector Chart**

Figure 2 shows a case of PPG, in which abnormal thinning
(<1% of confidence intervals of normative data base) of the
GCC corresponding to a RNFL defect was detected in the wide
sector chart but not in the standard sector chart. The color disc
photograph shows localized thinning in the superotemporal
neuroretinal rim associated with an RNFL defect. The red-free
photograph shows a wedge-shaped localized RNFL defect near
the superotemporal vascular arcade, which appears to be
located outside the macula. The significance map of GCC
thickness demonstrated a wedge-shaped arcuate area with red
color (<1%) outside the macula (standard chart [1–6-mm
ring]). A large portion of the arcuate area was located within
the outer ring (6–8 mm).

**Comparison of Ganglion Cell Complex and
Circumpapillary Retinal Nerve Fiber
Layer Thicknesses**

Average GCC thickness in the standard (1–6-mm ring) and
wide (1–8-mm ring) sector charts and average cpRNFL
thickness significantly differed among the three groups (Table
2). All thickness parameters were significantly smaller in the
PPG and EG groups compared with the healthy control group,
whereas no statistical differences in these parameters were
observed between the PPG and EG groups.

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**Table 1. Subject Demographics**

<table>
<thead>
<tr>
<th></th>
<th>Healthy</th>
<th>PPG</th>
<th>EG</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>46</td>
<td>23</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Age, y Range</td>
<td>29–76</td>
<td>31–71</td>
<td>28–73</td>
<td>0.372*</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>54.6 ± 12.8</td>
<td>56.8 ± 9.4</td>
<td>51.9 ± 12.2</td>
<td>0.436†</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>21/25</td>
<td>7/16</td>
<td>11/13</td>
<td></td>
</tr>
<tr>
<td>SE (D), Mean ± SD</td>
<td>−0.89 ± 1.94</td>
<td>−1.77 ± 2.48</td>
<td>−1.07 ± 2.25</td>
<td>0.282*</td>
</tr>
<tr>
<td>MD on SAP (dB), Mean ± SD</td>
<td>0.03 ± 1.26</td>
<td>−0.63 ± 1.10</td>
<td>−2.60 ± 1.47</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

SE, spherical equivalent refractive errors.

* ANOVA.
† Chi-square test.
Comparison of Areas under Receiver Operating Characteristic Curves for Ganglion Cell Complex Thickness between Standard and Wide Sector Charts

The AROCs for average GCC thickness in the wide chart (1–8-mm ring) were significantly greater than those of the standard chart (1–6-mm ring) in eyes with PPG, EG, and both (Table 3, Fig. 3). The AROCs for average GCC thickness in the wide chart were more than 0.9 in eyes with PPG, EG, or both, whereas those of average cpRNFL thickness were less than 0.9 in eyes with PPG. The AROCs for average GCC thickness in the wide chart area and average cpRNFL thickness did not significantly differ in eyes with PPG, EG, or both.

Table 2. Comparison of Average Ganglion Cell Complex and Circumpapillary Retinal Nerve Fiber Layer Thicknesses between Standard and Wide Sector Charts

<table>
<thead>
<tr>
<th></th>
<th>Healthy</th>
<th>PPG</th>
<th>EG</th>
<th>P Value*</th>
<th>P1†</th>
<th>P2†</th>
<th>P3†</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCC (1–6 mm)</td>
<td>108.2 ± 5.5 (98.9–122.5)</td>
<td>96.0 ± 8.8 (73.3–109.1)</td>
<td>94.9 ± 10.8 (72.6–114.6)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>1.000</td>
</tr>
<tr>
<td>GCC (1–8 mm)</td>
<td>101.7 ± 5.3 (93.3–114.7)</td>
<td>88.2 ± 8.3 (70.7–100.3)</td>
<td>86.9 ± 9.5 (72.0–104.9)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>1.000</td>
</tr>
<tr>
<td>cpRNFL</td>
<td>104.8 ± 8.6 (82.6–127.0)</td>
<td>87.2 ± 7.8 (75.6–98.7)</td>
<td>87.0 ± 11.4 (71.4–110.2)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Values are mean ± SD of thickness (µm) with ranges in parentheses.

* ANOVA.
† Post hoc test (Bonferroni).
Comparison of Areas under the Receiver Operating Characteristic Curves for Regional Average Ganglion Cell Complex Thickness in Wide Sector Chart

To determine the diagnostic power of regional average GCC thickness in the wide sector chart, we compared AROCs in each sector between the middle ring (4–6 mm) and outer ring (6–8 mm). Overall, the AROCs of regional GCC thicknesses were nearly comparable; the middle and outer sectors statistically significantly differed only in the temporal inferior sector for eyes with PPG (Table 4).

Measurement Variability and Reproducibility in Standard and Wide Sector Charts

CVs were 0.68% and 0.97% in the standard and wide sector charts, respectively, in eyes with PPG, and 0.45% and 0.72% in the standard and wide sector charts, respectively, in eyes with EG. ICCs were 0.983 and 0.978 in the standard and wide sector charts, respectively, in eyes with PPG, and 0.998 and 0.994 in the standard and wide sector charts, respectively, in eyes with EG.

Regional Measurement Variability and Reproducibility of the Wide Sector Chart

The CVs and ICCs in all of the sectors in the wide sector chart are summarized in Table 5. The CVs in the outer ring (6–8 mm) tended to be greater compared with the inner ring (1–4 mm) and middle ring (4–6 mm); they are particularly large (>4.0) in the temporal inferior sectors of the outer ring. Low ICCs were observed in the temporal inferior (PPG and EG) and temporal superior sectors (PPG) in the outer ring, and the temporal superior sector in the middle ring (PPG). The ICCs in all other sectors were greater than 0.9.

**Discussion**

Macular GCC thickness has been shown to be comparable and complementary to cpRNFL thickness in glaucoma-discriminating ability. However, we do not need to limit the area for the measurement of GCC thickness to the macula (6 mm in diameter) for glaucoma diagnosis. In fact, we often see patients with RNFL defects outside the macula, as shown in Figure 2. However, the glaucoma-discriminating ability of GCC thickness outside the macula has not been previously reported. The current study demonstrated that, although variability was slightly greater and reproducibility somewhat worse outside the macula (outer ring [6–8 mm]), inclusion of the GCC thickness in the outer ring to the standard mGCC analysis significantly increased glaucoma-discriminating ability.

Anatomical characteristics of the GCL and RNFL may underlie this finding. The GCL thickness increases steeply as a function of distance from the central fovea, with a peak around 1 mm, and then gradually decreases with greater distance from the fovea. This thickness pattern stems from the RGC density topographic pattern. By contrast, RNFL thickness in the posterior pole is smallest around the fovea and gradually increases with greater distance from the fovea in the superior, nasal, and inferior regions. The RNFL thickness appears to contribute to the diagnostic utility of GCC thickness, particularly in the extramacular region. In fact, circumpapillary RNFL thickness peaks in the superotemporal and inferotemporal quadrants, referred to as double humps. The “double humps,” which are the arcuate bundles of the thickest RNFL and not just double humps, are reportedly located between 120° and 135° in the superotemporal and 270° and 285° in the inferotemporal region, a large part of which is located outside the macula (6-mm diameter circle).

Recently, Garvin et al. established a correlation map between RNFL thickness in peripapillary wedge sectors of superotemporal and inferotemporal quadrants (15 degrees in
each sector) and GCL thickness in macular grid regions as measured with SD-OCT in patients with glaucoma and suspected glaucoma. This map showed that the top-most or bottom-most two wedge sectors (corresponding to 30 degrees) had highest correlations with only a few superior or inferior macular peripheral grids. This structure-structure correlation model may support the validity of our hypothesis that the sampling on RGC axons outside the macular region en route to the optic disc enhances the glaucoma discriminating ability.

Lee et al. reported that photographic RNFL defects were most commonly identified in the 7 and 11 o’clock sectors, and in some eyes in the 6 and 12 o’clock sectors, indicating that RNFL defects occur at variable locations and cannot all be detected by macular-area GCC analysis. Leung et al. reported that 75% to 80% of glaucoma patients demonstrated tomographic RNFL loss evident at the inferotemporal meridians between 90° and 72°, with a peak at 76° as measured from the temporal horizontal line. Because RNFL at this angle assembles from almost outside the macula, it is possible that some regions outside the macula exist in which GCC thickness has high glaucoma-discriminating ability. In fact, in our study, the outer ring (6–8 mm) demonstrated comparable AROC values to the middle ring in eyes with preperimetric and early glaucoma. Thus, glaucomatous structural damages are often located outside the macula, which may be responsible for our finding that inclusion of the extramacular area to the standard mgGCC thickness chart significantly increased glaucoma-discriminating ability.

Table 4. Comparison of AROCs for Regional Average GCC Thickness between Middle and Outer Sectors in Wide Sector Chart (1–8-mm Ring)

<table>
<thead>
<tr>
<th>Region</th>
<th>Healthy vs. PPG</th>
<th>Healthy vs. EG</th>
<th>Healthy vs. PPG+EG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4–6 mm</td>
<td>6–8 mm</td>
<td>P1</td>
</tr>
<tr>
<td>Nasal inferior</td>
<td>0.863</td>
<td>0.874</td>
<td>0.789</td>
</tr>
<tr>
<td>Nasal superior</td>
<td>0.722</td>
<td>0.681</td>
<td>0.475</td>
</tr>
<tr>
<td>Temporal inferior</td>
<td>0.921</td>
<td>0.848</td>
<td>0.018</td>
</tr>
<tr>
<td>Temporal superior</td>
<td>0.826</td>
<td>0.757</td>
<td>0.092</td>
</tr>
<tr>
<td>Total</td>
<td>0.887</td>
<td>0.880</td>
<td>0.837</td>
</tr>
</tbody>
</table>

P1, Healthy control versus PPG; P2, Healthy control versus EG; P3, Healthy control versus PPG+EG.

The measurement variability in the outer ring (6–8 mm) and its sectors was relatively high compared with those of the middle (4–6 mm) and inner (1–4 mm) rings and their sectors. A possible reason for the higher measurement variability in the outer ring is that some eyes included larger blood vessels, such as the arcade vessels and their first branch vessels in the outer ring (Fig. 1C). Larger blood vessels likely interfere with the accuracy of boundary segmentation, consequently increasing the measurement variability of GCC. In general, high variability in thickness measures decreases AROC values. Another possible cause for measurement variability is the deviation from the preset scan pattern on the posterior pole due to involuntary ocular movements. This can occur because it took 1.6 seconds to obtain a single 3D data set. However, we discarded the images with apparent motion artifacts during OCT examination. Therefore, the effects of the deviations would be minimal. Moreover, it is uncertain whether the effects of the deviations are largest particularly in the outer ring because the changes in the GCC thickness as a function from the fovea are rather largest in the inner ring.

Regardless of the higher measurement variability in the outer ring compared with those in the middle and inner rings, the addition of the outer ring (wide sector chart [1–8 mm]) to the standard sector chart (1–6 mm) significantly increased the AROCs, and the AROCs of the outer ring were comparable to those of the middle ring in eyes with EG and PPG. The reason for these seemingly contradictory results is uncertain. One possibility is that the outer ring (6–8 mm) can cover the RNFL over a wider area compared with middle and inner rings. The

Table 5. Regional Measurement Variability and Reproducibility

<table>
<thead>
<tr>
<th>Region</th>
<th>%CVs of Repeated Measures</th>
<th>ICCs of Repeated Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1–4 mm</td>
<td>4–6 mm</td>
</tr>
<tr>
<td>Nasal inferior</td>
<td>PPG 0.55</td>
<td>1.89</td>
</tr>
<tr>
<td></td>
<td>EG 0.91</td>
<td>1.51</td>
</tr>
<tr>
<td>Nasal superior</td>
<td>PPG 0.49</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>EG 0.50</td>
<td>0.67</td>
</tr>
<tr>
<td>Temporal inferior</td>
<td>PPG 1.07</td>
<td>3.09</td>
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<tr>
<td></td>
<td>EG 0.74</td>
<td>1.55</td>
</tr>
<tr>
<td>Temporal superior</td>
<td>PPG 0.84</td>
<td>1.95</td>
</tr>
<tr>
<td></td>
<td>EG 0.79</td>
<td>1.06</td>
</tr>
<tr>
<td>Total</td>
<td>PPG 0.48</td>
<td>1.44</td>
</tr>
<tr>
<td></td>
<td>EG 0.54</td>
<td>0.85</td>
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</table>
retinal nerve fibers that pass the macula (≈ middle ring + inner ring) also pass the outer ring, whereas those that pass the outer ring do not necessarily pass the middle or inner rings. The RS3000, which currently enables the fastest image acquisition (53,000 A-scans/s), allows 3D raster scanning (cube scan) over a 9 × 9-mm square region in 1.6 seconds. However, we did not use the 8- to 9-mm ring area for this analysis, first, because the GCC measurements in sectors of this ring demonstrated high variability (%CV, 1.64%-7.36%, data not shown). This variability is probably attributable to the inclusion of larger vessels, which could increase the measurement variability, as already mentioned.35 In addition, the 9-mm circle includes a larger part of the optic disc (Fig. 2), where the GCC cannot be measured. We also did not use the 8- to 9-mm ring area because the 3D raster-scan protocol bounded by the 9 × 9-mm square does not actually cover the entire region of the 9-mm circle chart area for measurement, when the central points of the 9 × 9-mm square scan area and the 9-mm circle area do not match exactly. In such cases, the thickness of the peripheral areas of the 8- to 9-mm ring area that was outside the 9 × 9-mm square cannot be measured.

In our study, the average GCC thickness in the standard (1-6 mm) or wide (1-8 mm) sector chart did not have significantly higher AROCs compared with cpRNFL. Although the AROC to distinguish between healthy and PPG eyes for cpRNFL thickness was even smaller than that for GCC thickness in the standard sector chart, no significant difference was found for AROCs between cpRNFL thickness and GCC thickness in the wide sector chart. This is probably attributable to the relatively large confidence intervals of the AROCs for cpRNFL. Our result is consistent with previous studies16-20 and has been attributed to the anatomical characteristics of mGCC and cpRNFL. A cpRNFL scan samples nearly all axons arising from RGCs, whereas an mGCC scan covers only the macular area. However, the mGCC scan samples macular damage better than the cpRNFL scan because the GCC includes the GCL, and it may be able to more sensitively detect glaucomatous changes where macular loss occurs early or predominantly. Even if the measurement area is enlarged from a 6-mm to 8-mm circle, the anatomical relationship between cpRNFL and GCC remains. A limitation of this study is that we tested only one in-built segmentation algorithm of the RS3000 instrument. Measurement variability was relatively high in the extramacular area compared with macular areas, and in the temporal inferior area compared with other areas. The latter may be attributable to the smaller thickness of the GCC as a result of glaucomatous damage. The inferotemporal area is the most frequent to suffer from glaucomatous damages.16,21 The accuracy and variability of GCC segmentation in these areas depends most on segmentation algorithm. Reducing the variability of segmentation in these areas could further improve glaucoma-discriminating ability.

Regardless of these limitations, our study successfully demonstrated that addition of extramacular GCC measurements to standard macular GCC analysis improved glaucoma-discriminating ability. Currently, widening of the 3D raster scan area is limited by the imaging speed of SD-OCT. As OCT technology advances in imaging speed, our findings may become more useful for enhancing the applicability of GCC analysis for glaucoma diagnosis.

References


