Diagnosis of Early-Stage Glaucoma by Grid-Wise Macular Inner Retinal Layer Thickness Measurement and Effect of Compensation of Disc-Fovea Inclination

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PURPOSE. To evaluate grid-wise analyses of macular inner retinal layer thicknesses and effect of compensation of disc-fovea inclination for diagnosing early-stage glaucoma.

METHODS. Spectral-domain optical coherence tomography measurements over a 6.0 × 6.0-mm macular area were prospectively obtained in 104 eyes of 104 patients with early-stage glaucoma with a mean deviation of −1.8 ± 1.9 dB and 104 eyes of 104 age- and refraction-matched normal subjects. Macular retinal nerve fiber layer (mRNFL), ganglion cell-inner plexiform layer (GCIPL) combined, and ganglion cell complex (GCC) thickness of the entire area and each subdivided macular grid were determined to compare diagnostic capability for glaucoma using receiver operating characteristic curves and various normal cutoff values for each layer thickness and number of grids flagged as abnormal. Diagnostic capability was then compared with that of circumpapillary RNFL (cpRNFL) measurements. Effects of compensation of inclination of disc-fovea line by reconfiguration of the macular grid were also studied.

RESULTS. Macular inner retinal layer analyses using 8 × 8 grids generally yielded higher diagnostic capability. Only the 8 × 8 grid GCC analyses using the various normal cutoff values yielded a sensitivity ≥0.90 with specificity ≥0.95 under several conditions in discriminating the glaucoma eyes. In glaucoma and normal eyes with both reliable cpRNFL and macular measurements, the best sensitivity/specificity were 0.98/0.95 for the 8 × 8 grid-mRNFL analysis and 0.93/0.96 for the 8 × 8 grid GCC analysis using various normal cutoff values, which were better than that (0.78/0.95) for clock-hour cpRNFL analysis (P = 0.001). Compensation of the disc-fovea inclination did not improve the diagnostic capability.

CONCLUSIONS. Grid-wise analysis of macular GCC—especially using 8 × 8 grids and normative data-based cutoff values—was very useful for diagnosing early-stage glaucoma, though compensation of the disc-fovea inclination had little effect. Keywords: glaucoma, optical coherence tomography, inner retinal layers, grid

Optical coherence tomography (OCT) effectively detects glaucomatous optic neuropathy with early visual field damage.1–7 Optical coherence tomography–based glaucoma diagnosis is based mainly on analyzing the circumpapillary retinal nerve fiber layer (cpRNFL) thickness and/or optic disc morphology.8–12 Major retinal vessels in the circumpapillary area, however, may limit detection of early glaucomatous changes. Moreover, reliable and automatic determination of the anatomical disc margin or Bruch membrane’s opening, which is an important benchmark for cpRNFL measurements, may be difficult.13 On the other hand, analysis of detailed structure-function relationships is possible in the macular area, which contains ≥50% of the whole retinal ganglion cells.14 Measurements of OCT are less affected by retinal vessels and automatic determination of the fovea as the center of the analysis area is technically easier in the macular area without manifest pathological changes.

Current spectral-domain (SD)-OCT devices are equipped with software that provides automatic segmentation and thickness measurements of macular inner retinal layers, including the macular retinal nerve fiber layer (mRNFL), ganglion cell layer (GCL) + inner plexiform layer (GCIPL), and the mRNFL + GCIPL (ganglion cell complex, GCC).15–17 Several SD-OCT studies report significant decreases in the thicknesses of these layers in eyes with early-stage glaucoma, even in those lacking manifest visual field defects (VFD) in standard static automated perimetry.21,22

The diagnostic capability of macular GCIPL or GCC has been studied based on the thickness of the layers over the whole macula,19,20,23 hemifield, or sectorial macular area,24–26 and macular GCIPL or GCC measurements have similar glaucoma
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<table>
<thead>
<tr>
<th>Table 1. Characteristics of the Subjects</th>
</tr>
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<tbody>
<tr>
<td>Glaucomatous Damage</td>
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<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Number of subjects, eyes</td>
</tr>
<tr>
<td>Women/men*</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Refraction, D</td>
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<tr>
<td>Mean deviation, dB†</td>
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</tbody>
</table>

Refraction indicates spherical equivalent of the subject’s eye. Mean deviation indicates mean deviation of a central 24-2 test program of Humphrey Field Analyzer. Intergroup difference was significant at *p = 0.023, χ²-test and /p < 0.001, Mann-Whitney U test.

We recruited self-reported healthy volunteers ≥ 20 years of age. The following ocular examinations were performed at the first visit: refraction and corneal curvature (ARK-900; NIDEK, Tokyo, Japan), best-corrected visual acuity, axial length (IOL Master; Carl Zeiss Meditec, Dublin, CA, USA), and OCT images (HFA; Carl Zeiss Meditec, Dublin, CA, USA).29 Thus, subdividing the macula further, as in the central 10-2 visual field test, may yield better diagnostic capability for detecting early glaucomatous abnormalities. A recent study reported that cluster analysis of mRNFL or GCCP thickness divided into 10 × 10 grids over the macula produced better sensitivity than mean thickness of these structures over the whole or hemiretinal macula.28 Moreover, compensation for the inclination of disc center-fovea line, that is, the difference between the anatomical horizontal line and the horizontal line on the fundus photograph, might increase the diagnostic capability of SD-OCT circumpapillary or macular inner layer parameters.13

We investigated the diagnostic capability of analytical methods by further subdividing the macula into gridwise square areas in eyes with early-stage glaucoma. Effects of compensation of the inclination of disc-fovea line on the diagnosis were also studied.

**MATERIALS AND METHODS**

**Subjects**

Data for normal subjects and open-angle glaucoma (OAG) patients were prospectively acquired from four institutes in Japan using the same selection criteria: the University of Tokyo (Tokyo, Japan), Kanazawa University (Kanazawa, Japan), Kyoto University (Kyoto, Japan), and Tajimi Municipal Hospital (Gifu, Japan). The study protocol was approved by each institution’s institutional review board and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from each subject after explanation of the study protocol.

We recruited self-reported healthy volunteers ≥ 20 years of age. The following ocular examinations were performed at the first visit: refraction and corneal curvature (ARK-900; NIDEK, Tokyo, Japan), best-corrected visual acuity, axial length (IOL Master; Carl Zeiss Meditec, Inc.), biomicroscopy, intraocular pressure (IOP; Goldmann applanation tonometry), dilated funduscopy, and VF test (HFA 24-2 SITA standard program). Exclusion criteria were: contradication to pupil dilation; IOP ≥ 22 mm Hg; best-corrected visual acuity ≤ 20/25; refractive error ≤ −6.0 diopters (D) or ≥ +3.0 D; unreliable HFA results (fixation loss, false-positive, or false-negative > 20%); VFDs suggestive of glaucoma according to Anderson and Patella’s criteria; history of intraocular or refractive surgery or ocular or systemic diseases that could affect the OCT results, including cataract or macular degeneration; and optic nerve or retinal abnormalities.

Open-angle glaucoma patients fulfilling the following criteria were consecutively enrolled in each institute and underwent the same examinations as above. Inclusion criteria were: 1) accustomed to VF testing and producing reliable and reproducible VF test results with mean deviation (MD) of ≤ −6.0 dB; 2) apparent glaucomatous changes in the optic disc with or without apparent RNFL defects confirmed by glaucoma specialists (MA, AI) according to stereo-fundus photographs and digitally constructed red-free photographs. Apparent glaucomatous changes in the optic disc referred to here are a rim notch with a remaining rim ≤ 0.1 of the disc diameter or a vertical cup-to-disc ratio > 0.7 in one eye with that of the fellow eye smaller by ≥0.2 not explained by differences in disc size. Glaucomatous VFDs were not a concern when apparent disc findings and/or RNFL defects were wider than the major retinal vessel diameter at the disc margin; 3) eyes with refractive error > −6.0 D and < 3.0 D; and 4) no history of any other ocular pathologic changes that could affect the results of HFA or OCT examinations, including incisional intraocular surgeries or refractive surgeries. The Humphrey field analyzer 24-2 SITA standard program results were obtained within 3 months of the OCT examination, and glaucomatous VFDs were defined by 1) a cluster of ≥ 3 points in the pattern deviation plot in a single hemifield (superior/inferior) with P < 0.05, one of which must have been P < 0.01, 2) glaucoma hemifield test result outside of normal limits, or 3) abnormal pattern standard deviation with P < 0.05.30 If both eyes of a subject were eligible, we included the eye with better data quality in the SD-OCT examination.

Finally, macular OCT images fulfilling the criteria described below were obtained in 104 early-stage OAG eyes of 104/181 initially enrolled OAG patients. From all normal subjects meeting the inclusion criteria, we selected those matched to glaucoma patients in terms of age and refraction (within 1 year of age and 1 D of spherical equivalent). Thus, 104 age- and refraction-matched normal eyes of 104/261 normal subjects were selected (Table 1).

**OCT Measurements**

Optimal coherence tomography scanning was performed using a three-dimensional (3D) OCT-1000 Mark II (Topcon, Inc., Tokyo, Japan) after pupillary dilation with 1% tropicamide. Spectral-domain OCT datasets were obtained with the raster-scan protocol in which data were obtained in 6.0 × 6.0-mm² areas (128 scan lines each comprised of 512 A-scans) centered on the fixation point within approximately 2.5 seconds. The magnification effect was corrected according to the manufacturer-provided formula based on refractive error, corneal radius, and axial length. Registration of fundus photographs and OCT images was automatically confirmed using an OCT projection image and localization of major retinal vessels. Measurements in the macula were repeated three times at several second intervals.

A similar raster scan was performed centered on the optic disc, and repeated three times. The disc center was determined as the barycenter of the closed spline curve fitted to seven manually determined points on the disc edge in a simultaneously obtained color fundus photograph by the non-mydriatic fundus camera function of the instrument used, and extrapolated in all OCT images thereafter.

Data influenced by eye movements, involuntary blinking, or saccade, indicated by breaks or shifting of the images or a straight line across the image, or those with a quality factor < 60% were discarded. Data with the best quality factor (given by the SD-OCT apparatus based on signal intensity) were adopted.
within each grid (Fig. 1).

were calculated as the mean thickness over all sampling point.

illustrated in Figure 2.

adjacent to the fovea were excluded from the analyses of the

3 and the layer thicknesses were determined at each sampling

confirmed on all B-scan images by an experienced examiner (MH),

hemiretina, 4

layer and GCIPL were automatically segmented

acquisition area were excluded. Macular retinal nerve fiber

fusus photograph as described above and we calculated the

exceed the data acquisition area (6.0 x 6.0 mm), and grids

peripheral grids exceeded the data acquisition area (6.0 x 6.0

changed from 5.5 x 5.5 mm to 4.8 x 4.8 mm, so that the most

5.5-mm analysis area in a sample eye (right eye with early-stage

OCT image as the sampling point with the thinnest retinal

The optic disc center and fovea (Fig. 3b). When any of the most

The normative data based on the 0.5th, 1st, 2.5th, 5th, or

percentile cutoff values after correction of the inclination

were separately constructed using data from the normal

eyes for which the analysis area exceeded the edge of the 6.0

mRNFL, GCIPL, or GCC (mRNFL + GCIPL)

were calculated as the mean thickness over all sampling point

within each grid (Fig. 1).

Diagnostic Capability of mRNFL, GCIPL, and GCC

Receiver operating characteristic (ROC) curve analyses were

performed to study the capability of mRNFL, GCIPL, and GCC
to discriminate current glaucoma eyes from age- and

refraction-matched normal eyes. The area under the ROC

curve (AUC) was calculated for the whole analysis area, upper

or lower hemiretina, or each of the 4 x 4 and 8 x 8 grids with

varied cutoff levels of mRNFL, GCIPL, or GCC thickness. The

area or grid with the greatest AUC was determined and

sensitivity was calculated when specificity was 0.95 in the

ROC curve. Then sensitivity/specificity of glaucoma detection

was calculated by normative data-based cutoff values of

mRNFL, GCIPL, or GCC thickness using single or contiguous

multiple grids. An eye was diagnosed with glaucoma if the

thickness was lower than the 0.5th, 1st, 2.5th, 5th, or 10th

percentile of the normative database in the whole macula,

one or both of the hemiretinas, or one or multiple contiguous

grids in 4 x 4 or 8 x 8 grids in the same hemiretina. The

Japanese age-specific normative database was established in

another group of 272 normal eyes.33,34 The central four grids

adjacent to the fovea were excluded from the analyses of the

8 x 8 grids of the mRNFL. The procedure of analyses is

illustrated in Figure 2.

Comparison of cpRNFL and Macular Inner Retinal Layer Thickness Measurements

Results for mRNFL, GCIPL, or GCC were compared with those

for cpRNFL in eyes of the same cohort of the subjects where

eligible data for both macular and circumpapillary areas were

obtained. Thickness of RNFL along a 3.4-mm diameter circle

centered on the optic disc center was obtained from the raster

scan data and averaged along the whole circumference or in

sectors, each accounting for upper or lower 180°, 90°, or 30°,

and the sector with the greatest AUC was determined and

sensitivity was calculated when specificity was 0.95 in the ROC

curve. Then the sensitivity/specificity was determined based on

the number of abnormal sectors and normal data-based
cutoff values (percentiles: 0.5th, 1st, 2.5th, 5th, or 10th

percentile) of cpRNFL thickness established in a separate

group of normal eyes35 similar to the analysis in the macular

area.

Effects of the Compensation of Inclination of Disc-Fovea Line on Grid-Wise Analyses of Macular Inner Retinal Layer Thicknesses

The optic disc center and fovea were determined on the

fundus photograph as described above and we calculated the

angle between the line connecting those two points and the

horizontal line, and positive angle indicates fovea is located

below the horizontal line (Fig. 5a). The analysis area was then

changed from 5.5 x 5.5 mm to 4.8 x 4.8 mm, so that the most

peripheral grid locating at a corner of the square did not

exceed the data acquisition area (6.0 x 6.0 mm), and grids

were reconfigured in parallel with the line connecting the

optic disc center and fovea (Fig. 5b). When any of the most

peripheral grids exceeded the data acquisition area (6.0 x 6.0

mm), the eye was excluded from analysis.

The normative data based on the 0.5th, 1st, 2.5th, 5th, or

10th percentile cutoff values after correction of the inclination

were separately constructed using data from the normal

eyes for mRNFL, GCIPL and GCC, and sensitivity/ specificity was calculated in the same manner as above.

Statistical Analysis

All statistical analyses were performed using (IBM SPSS

Statistics 19; IBM Software, Japan, Tokyo) or the statistical

programming language R (ver. 2.15.1; The R Foundation for

Statistical Computing, Vienna, Austria).

Demographic data were compared between normal and

OAG eyes by χ²-test or Mann-Whitney U test because their

normal distribution was rejected by the Kolmogorov-Smirnov

test. Sensitivities and specificities were compared using

McNemar’s test. We used the AUC to evaluate the clinical

usefulness of each condition, as suggested in a previous

paper.36 Comparison of multiple AUCs was carried out using

DeLong’s method.37 Values of P less than 0.05 were considered

significant.

RESULTS

Analyses Using mRNFL, GCC, and GCIPL

Finally, 104 eyes of 104 OAG patients among 181 initially

enrolled OAG patients were enrolled. Sixteen of 181 eyes

(8.8%) were excluded because the analysis area exceeded the
data acquisition area, and the other eyes were excluded

because of inadequate image data quality due to several factors,
including blinking, eye movements or obvious segmentation error.

Results of ROC analyses with specificity equal to 0.95 and those using variant normative data–based cutoff values yielding the highest sensitivity with specificity \( \geq 0.95 \) under the given conditions are listed in Tables 2, 3, and 4 for the analyses of RNFL, GCIPL, or GCC, respectively.

For macular RNFL, the highest sensitivity with a specificity \( \geq 0.95 \) (sensitivity/specificity \( \approx 0.88/0.95 \)) was obtained using three or four contiguous 8 \( \times \) 8 grids outside the normative data–based 1st or 2.5th-percentile cutoff, respectively (Table 2).

For ganglion cell-inner plexiform layer, the highest sensitivity with specificity \( \geq 0.95 \) (sensitivity/specificity \( \approx 0.80/0.96 \)) was obtained using five contiguous 8 \( \times \) 8 grids outside the 2.5th percentile cutoff (Table 3).

For ganglion cell complex, only analyses using 8 \( \times \) 8 grids and normative data–based cutoff values yielded sensitivity \( \geq 0.90 \) associated with specificity \( \geq 0.95 \). That is, sensitivity/specificity equal to 0.90/0.96 was obtained using two or three contiguous 8 \( \times \) 8 grids outside the 0.5th or 1st percentile cutoff, respectively (Table 4). Further, sensitivity/specificity equal to 0.88 or 0.89/0.95 to 0.98 was obtained under several conditions using 8 \( \times \) 8 grids. The sensitivities/specificities obtained using the normative data-based 0.5th, 1st, 2.5th, 5th, and 10th percentile cutoff values for 8 \( \times \) 8 grids of GCC are plotted in Figure 4.

Adoption of 8 \( \times \) 8 grids yielded the highest sensitivity with specificity \( \geq 0.95 \) for each macular inner layer, but only analyses using GCC attained sensitivity \( \geq 0.90 \) with specificity \( \geq 0.95 \) in the current subjects.

**Comparison Between cpRNFL and Macular Inner Retinal Layer Thickness Measurements**

Analyses using cpRNFL were performed in 86/104 OAG eyes and 77/104 normal eyes (Table 5), because cpRNFL measurement results satisfying the inclusion criteria were not obtained in 18 OAG and 27 normal eyes, probably because the cpRNFL measurements were performed after three repeated macular measurements.

Results of ROC analyses are shown in Table 6. The highest AUC (0.920) was obtained with inferotemporal 30° sector (seven o’clock in right eye orientation), which was not significantly different from those obtained with global average (0.892, \( P = 0.32 \)), inferior 180° sector (0.883, \( P = 0.11 \)), inferior 90° sector (0.891, \( P = 0.18 \)). The highest sensitivity of 0.78 was obtained with specificity \( \geq 0.95 \) using the 7 o’clock 30° sector. All sectors, including nerve fibers projecting the macular area, temporal 90° and 30° sectors located at 8, 9, or 10 o’clock, showed significantly smaller AUCs (0.662, 0.705, 0.564, and 0.626, respectively; \( P < 0.01 \)) than that of global mean of cpRNFL (0.892).
The analyses using variant normative data-based cutoff values yielding the highest sensitivity with specificity \( \geq 0.95 \) under the given conditions are also listed in Table 6. The highest sensitivity with specificity \( \geq 0.95 \) obtained using various normative data-based cutoff values was 0.63 using 180° sectors. The largest sensitivity/specificity of 0.76/0.94 was obtained using at least one 30° sector outside the first-percentile cutoff, though specificity did not reach to 0.95.

On the other hand, the highest sensitivity with specificity \( \geq 0.95 \) obtained using mRNFL in the same eyes was 0.98 (sensitivity/specificity = 0.98/0.95) using three contiguous 8 × 8 grids outside the 2.5th-percentile cutoff, while those obtained using GCC and GCIPL in the same eyes were 0.93/0.96 using three contiguous 8 × 8 grids outside the first-percentile cutoff and 0.83/0.95 with three contiguous 8 × 8 grids outside the first-percentile cutoff, respectively.

The highest sensitivities of the mRNFL and GCC analyses were significantly higher than that of the cpRNFL analysis (0.98 vs. 0.78, \( P = 0.001 \) and 0.93 vs. 0.78, \( P = 0.001 \), respectively), while the same or a bit higher specificity of 0.95 or 0.96.
### Table 3. Diagnostic Capability of Macular GCIPL

<table>
<thead>
<tr>
<th>Macular Area</th>
<th>Greatest-Smallest AUC (SE)</th>
<th>Sensitivity/Specificity (With 95% CI; Sensitivity at Fixed Specificity of 0.95)</th>
<th>Analyses Based on ROC Curves in Each Single Area or Grid</th>
<th>Analyses Based on Variant Normative Data-Based Cutoff Values in Single or Multiple Contiguous Grids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole area</td>
<td>0.912 (0.019)</td>
<td>0.47 (0.37-0.57)/0.95 (0.89-0.98)</td>
<td>2.5th percentile, the whole area 0.42 (0.33-0.52)/0.98 (0.93-1.00)</td>
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<tr>
<td>Upper or lower hemiretina</td>
<td>0.869 (0.025)-0.695 (0.037)</td>
<td>0.55 (0.45-0.65)/0.95 (0.89-0.98)</td>
<td>2.5th percentile, at least one hemiretina 0.50 (0.40-0.60)/0.96 (0.90-0.99)</td>
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<tr>
<td>4 × 4 grids</td>
<td>0.884 (0.023)-0.580 (0.041)</td>
<td>0.56 (0.46-0.66)/0.95 (0.89-0.98)</td>
<td>0.5th percentile, at least one hemiretina 0.75 (0.66-0.83)/0.96 (0.90-0.99)</td>
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</tr>
<tr>
<td>8 × 8 grids</td>
<td>0.898 (0.022)-0.545 (0.041)</td>
<td>0.58 (0.48-0.67)/0.95 (0.89-0.98)</td>
<td>2.5th percentile, five contiguous grids 0.80 (0.71-0.87)/0.96 (0.90-0.99)</td>
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</tbody>
</table>

* Conditions where the eyes were flagged as glaucomatous with respect to the normative data-based cutoff values and numbers of abnormal grids.

### Table 4. Diagnostic Capability of Macular GCC

<table>
<thead>
<tr>
<th>Macular Area</th>
<th>Greatest-Smallest AUC (SE)</th>
<th>Sensitivity/Specificity (With 95% CI; Sensitivity at Fixed Specificity of 0.95)</th>
<th>Analyses Based on ROC Curves in Each Single Area or Grid</th>
<th>Analyses Based on Variant Normative Data-Based Cutoff Values in Single or Multiple Contiguous Grids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole area</td>
<td>0.912 (0.019)</td>
<td>0.71 (0.61-0.80)/0.95 (0.89-0.98)</td>
<td>5th percentile, the whole area 0.62 (0.51-0.71)/0.96 (0.90-0.99)</td>
<td></td>
</tr>
<tr>
<td>Upper or lower hemiretina</td>
<td>0.931 (0.018)-0.754 (0.054)</td>
<td>0.69 (0.59-0.78)/0.95 (0.89-0.98)</td>
<td>2.5th percentile, at least 1 hemiretina 0.74 (0.64-0.82)/0.99 (0.95-1.00)</td>
<td></td>
</tr>
<tr>
<td>4 × 4 grids</td>
<td>0.934 (0.017)-0.650 (0.038)</td>
<td>0.76 (0.67-0.84)/0.95 (0.89-0.98)</td>
<td>1st percentile, two contiguous grids 0.86 (0.77-0.92)/0.97 (0.92-0.99)</td>
<td></td>
</tr>
<tr>
<td>8 × 8 grids</td>
<td>0.936 (0.017)-0.595 (0.040)</td>
<td>0.78 (0.69-0.85)/0.95 (0.89-0.98)</td>
<td>0.5th percentile, two contiguous grids 0.90 (0.85-0.95)/0.96 (0.90-0.99)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1st percentile, three contiguous grids 0.90 (0.85-0.95)/0.96 (0.90-0.99)</td>
<td></td>
</tr>
</tbody>
</table>

* Conditions where the eyes were flagged as glaucomatous in respect of the normative data-based cutoff values and numbers of abnormal grids.
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Effects of Compensation of Inclination of Disc-Fovea Line

The calculated inclination was $7.8^\circ \pm 3.2^\circ$ (mean $\pm$ SD) in normal eyes and $8.0^\circ \pm 2.7^\circ$ in glaucoma eyes ($n = 104$ each), with no significant difference between them ($P = 0.65$).

In some eyes, the peripheral $8 \times 8$ grids exceeded the data acquisition area edge after compensating for the inclination and were excluded from analysis. Valid data in a $4.8 \times 4.8$-mm macular area with and without compensation for inclination of disc-fovea line were obtained in $89$ normal and $88$ OAG eyes (Table 7). Performance of the optimum or suboptimum condition in detecting early-stage glaucoma was compared between with and without correction of inclination, but diagnostic capability was not significantly improved under any conditions. Representative results with the highest or the second highest sensitivity and specificity are summarized in Table 8. Almost identical sensitivity and specificity, approximately $0.95$, were obtained using reconstructed $8 \times 8$ grids of GCC or mRNFL in the $4.8 \times 4.8$-mm area and reconstructed normal data-based cutoff values after compensation of inclination of disc-fovea line.

DISCUSSION

Spectral-domain OCT allows for efficient analysis of the intraretinal layers in the macular region, and most previous studies report that GCC and GCIPL thicknesses yield reasonably reproducible measurements and are effective for diagnosing glaucoma, similar to cpRNFL analysis. In glaucoma, especially early-stage glaucoma, retinal thickness decreases in localized areas in the macular region and most previous studies report that GCC and GCIPL thicknesses yield reasonably reproducible measurements and are effective for diagnosing glaucoma, similar to cpRNFL analysis. In glaucoma, especially early-stage glaucoma, retinal thickness decreases in localized areas in the macular region and most previous studies report that GCC and GCIPL thicknesses yield reasonably reproducible measurements and are effective for diagnosing glaucoma, similar to cpRNFL analysis.
### Table 6. Diagnostic Capability of cpRNFL and Comparison With mRNFL and GCC

<table>
<thead>
<tr>
<th>Sector Width/Grid Pattern</th>
<th>Analyses Based on ROC Curves in Each Single Sector</th>
<th>Analyses Based on Variant Normative Data-Based Cutoff Values in Single or Multiple Contiguous Sectors/Grids</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity/Specificity (With 95% CI; Sensitivity at Fixed Specificity of 0.95)</td>
<td>Sensitivity/Specificity (With 95% CI; Highest Sensitivity at Specificity ≥ 0.95)</td>
</tr>
<tr>
<td></td>
<td>Greatest–Smallest AUC (SE)</td>
<td>Conditions*</td>
</tr>
<tr>
<td>cpRNFL</td>
<td></td>
<td>5th percentile, the whole circle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.5th percentile, at least one sector</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1st percentile, at least one sector</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.5th percentile, two contiguous sectors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.5th percentile, three contiguous grids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1st percentile, three contiguous grids</td>
</tr>
<tr>
<td>mRNFL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 × 8 grids</td>
<td></td>
<td></td>
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<tr>
<td>GCC</td>
<td></td>
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</tbody>
</table>

Analyses were performed in the eyes listed in Table 5.
* Conditions where the eyes were flagged as glaucomatous with respect to the normative data-based cutoff values and numbers of abnormal sectors or grid.

The present study has several limitations. The criteria used have limited capability to improve it by an approach other than recognizing up to 30° of macular inclinations. The macula may be divided by an approach other than recognizing the upper and lower hemimacula. The subject eyes were divided into three subgroups: (1) the relatively small degree of inclination (mean MD < 9.35 dB) might not be adequate to detect glaucomatous damage without reconstruction of the disc-fovea line. The angle without reconstruction of the disc-fovea line has little influence on the inclination of the disc-fovea line. This results in specificity in the normal eyes in the datasets. The criteria used have limited capability to improve it by an approach other than recognizing up to 30° of macular inclinations. The macula may be divided by an approach other than recognizing the upper and lower hemimacula. The subject eyes were divided into three subgroups: (1) the relatively small degree of inclination (mean MD < 9.35 dB) might not be adequate to detect glaucomatous damage without reconstruction of the disc-fovea line. The angle without reconstruction of the disc-fovea line has little influence on the inclination of the disc-fovea line. This results in specificity in the normal eyes in the datasets. The criteria used have limited capability to improve it by an approach other than recognizing up to 30° of macular inclinations. The macula may be divided by an approach other than recognizing the upper and lower hemimacula.
Table 8. Comparison of Sensitivity/Specificity for Glaucoma Detection With and Without Compensation of the Inclination of the Disc-Fovea Line

<table>
<thead>
<tr>
<th>Conditions (8 × 8 grids)</th>
<th>Macular Inner Retinal Layer</th>
<th>Compensation, –</th>
<th>Compensation, +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three contiguous grids outside the 0.5th percentile cutoff</td>
<td>GCC</td>
<td>0.94/0.94</td>
<td>0.94/0.94</td>
</tr>
<tr>
<td>Three contiguous grids outside the 1st percentile cutoff</td>
<td>GCC</td>
<td>0.92/0.97</td>
<td>0.91/0.96</td>
</tr>
<tr>
<td>Three contiguous grids outside the 1st percentile cutoff</td>
<td>mRNFL</td>
<td>0.93/0.94</td>
<td>0.93/0.94</td>
</tr>
<tr>
<td>Three contiguous grids outside the 2.5th percentile cutoff</td>
<td>mRNFL</td>
<td>0.97/0.96</td>
<td>0.95/0.94</td>
</tr>
</tbody>
</table>

Values indicate sensitivity/specificity. Compensation (–) indicates no compensation of inclination of disc-fovea line and compensation (+) indicates compensation of inclination of disc-fovea line.

and glaucoma eyes, and thus the clinical usefulness of the current optimum criterion requires further confirmation. Most of the current OAG patients had untreated normal IOP (normal tension glaucoma). Differences in the VFD pattern (i.e., differences in GCL damage distribution), between OAG patients with normal and elevated IOP, have been reported. Thus, the current optimum criterion may not be optimum in a group of OAG patients with elevated IOP. Comparison of the diagnostic capability between cpRNFL and macular inner retinal layers or effects of compensation of the inclination could only be studied in ~85% of the subjects. Although no significant difference was detected in the degree of glaucomatous damage or ocular and systemic factors between those included and not included (Tables 1, 5, and 7), this somewhat decreased the power of detection. Longitudinal and horizontal density of sampling points of the OCT apparatus was not equal (128 × 512) and its optimized rearrangement might have a significant effect on the results. In summary, the 5.5 × 5.5-mm macular area was subdivided in a grid-wise manner and measured by SD-OCT in up to 8 × 8 grids, and diagnostic capability for early-stage glaucoma (mean MD ~1.8 dB) was compared based on ROC analyses and various normative data–based cutoff values for mRNFL, GCIP, and GCC thickness in each grid and the number of abnormal grids. The 8 × 8 grid-GCC analysis yielded a sensitivity ≥ 0.90 and specificity ≥ 0.95 under two conditions, that is, two contiguous grids outside the 0.5th percentile cutoff or three contiguous grids outside first-percentile cutoff of normative data. Compensation of physiological inclination of disc-fovea line did not significantly affect diagnostic capability in the current subjects.

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