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Original article

Can diagnostic accuracy for early glaucoma be improved in Japanese? A trial with a potential new parameter of the RTVue OCT

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Abstract

Aim: To evaluate the diagnostic accuracy of the ratio of circumpapillary retinal nerve fiber layer thickness (cpRNFLT) to macular outer retinal thickness (R/O ratio) and the ratio of ganglion cell complex (GCC) thickness to outer retinal thickness (G/O ratio) measured with the RTVue-100 Fourier-domain optical coherence tomograph for detecting early glaucoma in Japanese eyes.
Methods: Forty-seven healthy control, 31 preperimetric and 70 early perimetric glaucoma eyes. We used cpRNFLT and macular retinal thickness measurements to calculate new ratio parameters, and to compare their diagnostic accuracy to those of the manufacturer-provided parameters of the RTVue-100. The ability of each parameter to diagnose glaucoma was examined by comparing the area under the receiver-operating characteristics curve (AUROC).
Results: AUROC values for the healthy vs. preperimetric glaucoma comparison were 0.842, 0.859, and 0.925 for average cpRNFLT, average R/O ratio, and average G/O ratio, respectively. For the healthy vs. early perimetric glaucoma comparison the AUROC values were 0.927, 0.933, and 0.979 for cpRNFLT, R/O ratio, and G/O ratio, respectively. Diagnostic accuracy of the R/O ratio and cpRNFLT did not differ significantly ($P > 0.05$). Diagnostic accuracy for the G/O ratio was significantly greater than the cpRNFLT in early glaucoma ($P < 0.05$).
Conclusions: Use of the G/O ratio is recommended for the detection of early glaucoma in Japanese eyes.

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Key words: ganglion cell complex, outer retinal thickness, ratio, preperimetric glaucoma, retinal nerve fiber layer thickness

1. Introduction

In the last decade, Fourier-domain optical coherence tomography (FD-OCT) has gained importance for detecting glaucoma.[1-3] A decrease in the circumpapillary retinal nerve fiber layer thickness (cpRNFLT) is frequently detected in the early stages of glaucoma,[4-6] although the normal cpRNFLT range is wide: it varies between 79.[5] and 131.4 µm, and its overlap with cpRNFLT in preperimetric glaucoma (reported range: 60.2 to 114.4 µm) is considerable.[7] The variability of cpRNFLT in normal eyes is likely influenced by the axial length, refractive error, age, disc size, image quality, and race.[8-13] In addition, it has been shown that various manufacturer-provided and investigator-generated FD-OCT parameters perform differently in Japanese and Caucasian eyes.[10,14,1] Japanese eyes, like many Asian eyes, are have higher axial length and therefore they are typically more myopic than Caucasian eyes.[16] This can be considered as a reason of the different relationship between macular ganglion cell complex (GCC) thickness and macular outer retina thickness (OR) thickness in Japanese and Caucasian eyes: GCC and OR thickness correlate significantly in Japanese eyes, but they do not correlate Caucasian eyes.[14] Therefore, to further increase the diagnostic value of FD-OCT for detecting early glaucoma in Japanese patients, we investigated novel FD-OCT parameters and parameter ratios with smaller normal ranges[17] and compared them with the standard FD-OCT parameters for clinical usefulness. We recently reported that the GCC to total retinal thickness ratio (the G/T ratio) is useful for diagnosing perimetric glaucoma in Japanese eyes with myopia.[17] Furthermore, since GCC thickness correlated significantly with OR thickness in normal eyes and glaucoma, the GCC to OR thickness ratio (the G/O ratio) is a suitable parameter to account for variation in the OR thickness, and the G/O ratio has a smaller normal range.[17,18] These parameters are not affected by the axial length.[18] Since cpRNFLT and GCC thickness decrease in glaucoma and OR thickness is not affected by the glaucomatous ganglion cell and axon loss,[17,18,20,21] in the present study, we investigated whether the thickness ratio of cpRNFLT and OR (R/O ratio) and the G/O ratio offer an advantage over the existing manufacturer-provided FD-OCT parameters for detecting preperimetric and early perimetric glaucoma.

2. Materials and methods

In total, 148 consecutive Japanese subjects (47 normal patients and 101 patients with primary open-angle glaucoma) examined between October 2009 and March

2013 at the Toho University Ohashi Medical Center Department of Ophthalmology (Tokyo, Japan) were retrospectively selected from a research database. One eye in each subject was randomly selected as the study eye. The Toho University Ohashi Medical Center Institutional Review Board for Human Research approved the study protocol (No.12-87), and the study conduct adhered to the tenets of the Declaration of Helsinki.

All study participants underwent a complete ophthalmologic examination that included visual acuity testing (with determination of refractive error), slit-lamp biomicroscopy, gonioscopy, Goldmann applanation tonometry, and dilated stereoscopic fundus examination. Noncycloplegic refraction was measured using an auto-refracto/keratometer (ARK-530A; Nidek, Aichi, Japan). Refraction data were converted to the spherical equivalent, defined as the spherical power (in diopters) plus half the cylindrical power. Visual fields were considered reliable when fixation losses were < 20% and false-positive and false-negative rates were < 15%. An abnormal visual field result was defined as an abnormal range on the glaucoma hemifield test, a pattern standard deviation of < 5%, or three abnormal points (< 5% probability of being normal), with one point having a pattern deviation of < 1%.

To be included in the normal eye group, healthy control subjects had to have normal intraocular pressure (IOP; < 21 mmHg) and normal optic nerve head (ONH) appearance, open anterior chamber angles, a normal and reliable visual field test result on the Swedish interactive threshold algorithm (SITA) 24-2 standard test of the Humphrey Field Analyzer (HVF, Humphrey-Zeiss Systems, Dublin, CA), a best-corrected visual acuity of 20/20 or better, a refractive spherical error between +3.00 and -6.00 diopters, and a refractive cylindrical error of < 3.0 diopters. An eye was considered to have a normal optic nerve head if the stereoscopic fundus examination revealed a vertical cup-to-disc ratio of < 0.7 (although in Japanese eyes the disc area is similar to that in European eyes, the cup-to-disc ratio of healthy Japanese eyes is usually higher than that of healthy Caucasian eyes10), a uniform neuroretinal rim, no retinal nerve fiber layer (RNFL) defects, and no optic nerve abnormalities (e.g., diffuse or localized rim thinning, disc hemorrhage, or an interocular difference in vertical cup-to-disc ratio > 0.2). The subjects were not included if they had a possible history of elevated IOP (*e.g.*, iridocyclitis, trauma), intraocular eye disease, or any other condition that may have affected the visual field (*e.g.*, pituitary lesions, demyelinating diseases, diabetic retinopathy). Subjects were also excluded if they had a history of intraocular surgery or retinal laser procedures.

For inclusion in the early perimetric glaucoma group, patients had to have a best-corrected visual acuity of 20/20 or better, a refractive spherical error between +3.00 and -6.00 diopters, a refractive cylindrical error of < 3.0 diopters, open anterior chamber angles (determined with gonioscopy), glaucomatous optic neuropathy (GON) and corresponding HVF abnormalities (mean deviation (MD) value up to -6 dB) on reliable and reproducible SITA 30-2 test, and the diagnosis of primary open-angle glaucoma or normal-tension glaucoma. GON was defined as neuroret-

inal rim narrowing at the optic disc margin with notching, excavation, or a visible RNFL defect.

For inclusion in the preperimetric glaucoma group, patients had to have a best-corrected visual acuity of 20/20 or better, a refractive spherical error between +3.00 and -6.00 diopters, a refractive cylindrical error of < 3.0 diopters, open anterior chamber angles (determined with gonioscopy), and GON and normal HVF results on reliable and reproducible SITA 30-2 test. Both preperimetric and perimetric glaucoma patients were excluded if they had any retinal pathology, neurological disease, diabetes, or a history of retinal laser or intraocular procedures. We included patients with glaucoma who had already commenced treatment with ocular hypotensive drugs.

2.1. Macula and retinal nerve fiber layer imaging

The FD-OCT measurements were performed using the RTVue-100 OCT (software version 4.0.5.39; Optovue Inc., Fremont, CA, USA), which employs a scan beam with a wavelength of 840 ± 10 nm. After pupil dilation, a well-trained operator obtained high-quality OCT images. Only scans with a signal strength index of > 45 were included in analyses. Measurements of cpRNFLT and macular parameters in each participant were obtained on the same day.

The ONH protocol was designed for measuring cpRNFLT. The total time required to acquire a single scan was 0.55 seconds. Using the OCT-generated fundus image (video baseline protocol), the ONH contours were manually traced. The cpRNFLT was then automatically measured by the instrument's software at a diameter of 3.45 mm around the center of the optic disc. A total of 775 A-scans were obtained along this circle. Subjects were excluded if peripapillary atrophy extended outside the OCT measurement circle. The cpRNFLT parameter represents the mean thickness of RNFLT measurements made around the 360° circle, and the superior hemisphere and inferior hemispheres, respectively.

The GCC scanning protocol was used to determine the GCC thickness (measured from the inner limiting membrane (ILM) to the outer inner plexiform layer (IPL) border), total retinal thickness (measured from ILM to the outer retinal pigment epithelium (RPE) border), OR thickness (measured from the outer IPL border to the outer RPE border), global loss volume (GLV), and focal loss volume (FLV) in the macula. The GCC protocol consisted of 15 vertical line scans over a 7×7-mm square region. To achieve optimum imaging coverage within the temporal region, the GCC protocol scan was centered one mm temporal to the center of the fovea. The area within a 0.75-mm radius from the center of the fovea was also excluded. During the scanning period, the GCC protocol captured 15,000 data points within 0.6 s. The GCC scan created a six-mm map corresponding to approximately 20° of HVF, and the average GCC thickness, total retinal thickness, and OR thickness were calculated over the three measurement regions (global, superior, and inferior hemisphere). GLV and FLV are two software-provided RTVue-100 OCT parameters calculated from

the GCC scan. Detailed descriptions of these analytic methods have been reported previously.[7,22] In brief, GLV measures the average amount of GCC loss over the entire GCC map and is based on the fractional deviation (FD) map. FLV measures the average focal loss over the entire GCC map and is based on both FD and pattern deviation maps. All HVF and OCT tests were conducted within a three-month period.

2.2. Ratio parameters

The G/O and G/T ratios were calculated using the following published formulas:[18]

$$\text{G/O ratio (\%)} = \left(\frac{\text{GCC thickness}}{\text{macular OR thickness}}\right) \times 100$$

$$\text{G/T ratio (\%)} = \left(\frac{\text{GCC thickness}}{\text{macular total retinal thickness}}\right) \times 100$$

The novel R/O ratio parameter was calculated using the following formula:

$$\text{R/O ratio (\%)} = \left(\frac{\text{cpRNFLT}}{\text{macular OR thickness}}\right) \times 100$$

2.3. Statistics

The demographic characteristics were compared between the groups with the $\chi 2$ test and with the Tukey-Kramer test. The RTVue-100 OCT measurements were compared between the groups using a combination of the analysis of variance and the Tukey-Kramer test. Pearson's correlation coefficients were used to characterize the relationships between the RTVue-100 OCT parameters and OR thickness and between the RTVue-100 OCT parameters and the refractive spherical equivalent. Receiver-operating characteristic (ROC) curves were used to determine whether each variable could differentiate between glaucomatous and normal eyes. The ROC curve describes the trade-off between sensitivity and specificity. An area under the ROC curve (AUROC) of 1.0 represents perfect discrimination, whereas an AUROC of 0.5 represents only chance discrimination. MedCalc (version 12.3.0, MedCalc Software, Mariakerke, Belgium) was used to draw and compare the ROC curves; all other statistical analyses were performed using SPSS statistical software (version 20.0, SPSS Inc., Chicago, IL, USA). Data are reported as the mean ± standard deviation (SD); the statistical significance was defined as $P < 0.05$.

3. Results

The normal group comprised 47 eyes of 47 healthy subjects. Thirty-one eyes of 31 patients and 70 eyes of 70 patients were included in the preperimetric and early perimetric glaucoma groups, respectively. The demographics of the participants are summarized in Table 1. There were no significant differences in sex distribution,

Table 1. Demographics and clinical characteristics of study subjects.

	Normal eyes (n = 47)	**Preperimetric glaucoma (n = 31)**	**Early perimetric glaucoma (n = 70)**	**P value**
Gender				0.07[a]
Male (subjects)	26	10	26	
Female (subjects)	21	21	44	
Age (years)	52.4 ± 11.1	57.4 ± 9.8	55.5 ±12.1	0.114[b]
Spherical equivalent (D)	-1.30 ± 1.91	-1.68 ± 2.23	-2.09 ± 2.45	0.177[b]
IOP (mmHg)	14.8 ± 2.7	13.4 ± 2.4	16.1 ± 3.5	< 0.001[†b]
MD in HFA (dB)	0.35 ± 1.06	0.10 ± 1.08	-2.83 ± 1.80	< 0.001*[b]
PSD in HFA (dB)	1.42 ± 0.25	1.88 ± 0.27	6.95 ± 3.10	< 0.001*[b]

Data are presented as mean ± standard deviation. [a] indicates χ^2 test; [b] indicates variance with the Tukey-Kramer test; [†] indicates preperimetric glaucoma vs. early glaucoma, $P < 0.001$; * indicates normal vs. early glaucoma, $P < 0.001$, preperimetric glaucoma vs. early glaucoma, $P < 0.001$; D = diopter; IOP = intraocular pressure; MD = mean deviation; HFA= Humphrey Field Analyzer; PSD = pattern standard deviation.

age, or refraction among the groups. The early perimetric glaucoma group had a significantly higher IOP than the preperimetric glaucoma group, and significant differences in the visual field MD and pattern standard deviation were observed among the groups.

The standard RTVue-100 OCT parameter values and ratio parameter results are summarized in Tables 2 and 3, respectively. No significant difference was observed between the groups for the average OR thickness (P = 0.895). In contrast, the GCC thickness, total retinal thickness, and average cpRNFLT decreased with increasing disease severity. FLV, GLV, the G/O ratio, the G/T ratio, and the R/O ratio all significantly differed among the study groups (P < 0.001). The OR thickness correlated significantly with cpRNFLT in normal eyes (r = 0.401, P = 0.005) but not in preperimetric and early perimetric glaucoma eyes (Table 4). Significant correlations were observed between the spherical refractive equivalent and cpRNFLT (r = 0.343, P = 0.018) and between the spherical refractive equivalent and R/O ratio (r = 0.364, P = 0.012). In contrast, no correlation was observed between the spherical refractive equivalent and OR thickness (r = 0.006, P = 0.968).

Table 2. Optical coherence tomography parameters in each study group.

	Normal eyes	**Preperimetric glaucoma**	**Early perimetric glaucoma**	**P value (ANOVA)**
GCC thickness (µm)				
Average	94.9 ± 7.6	83.7 ± 5.4	78.8 ± 6.6	< 0.001†
Superior hemisphere	94.8 ± 7.9	86.6 ± 7.4	83.2 ± 9.3	< 0.001#
Inferior hemisphere	95.0 ± 7.7	80.7 ± 6.5	74.5 ± 10.2	< 0.001†
Total retinal thickness (µm)				
Average	264.7 ± 14.2	253.9 ± 8.4	248.7 ± 11.4	< 0.001#
Outer retinal thickness (µm)				
Average	169.8 ± 8.7	170.4 ± 5.4	169.9 ± 6.8	0.895
Superior hemisphere	171.6 ± 8.7	171.9 ± 5.4	171.1 ± 7.4	0.826
Inferior hemisphere	168.0 ± 8.9	168.9 ± 5.6	168.6 ± 6.9	0.854
FLV (%)	0.85 ± 0.94	4.41 ± 2.36	8.72 ± 3.83	< 0.001†
GLV (%)	6.65 ± 4.73	15.68 ± 5.09	20.29 ± 6.15	< 0.001†
cpRNFLT (µm)				
Average	102.0 ± 8.9	89.7 ± 8.2	84.4 ± 8.1	< 0.001†
Superior hemisphere	102.4 ± 10.6	91.3 ± 11.6	87.7 ± 13.3	< 0.001#
Inferior hemisphere	101.6 ± 9.0	88.1 ± 8.7	81.1 ± 8.4	< 0.001†

Data presented as mean ± standard deviation. † normal vs. preperimetric glaucoma group and preperimetric glaucoma vs. early glaucoma group statistically different (Tukey-Kramer test); # normal vs. preperimetric glaucoma group statistically different and preperimetric glaucoma group vs. early glaucoma group not statistically different (Tukey-Kramer test); ANOVA = analysis of variance; cpRNFLT = circumpapillary retinal nerve fiber layer thickness; FLV = focal loss volume; GCC = macular ganglion cell complex; GLV = global loss volume.

Table 3. Ratio parameter values in the three study groups.

	Normal eyes	**Preperimetric glaucoma**	**Early perimetric glaucoma**	**P value (ANOVA)**
G/O ratio (%)				
Average	55.91 ± 3.69	49.13 ± 3.15	46.41 ± 3.54	< 0.001[†]
G/T ratio (%)				
Average	35.82 ± 1.50	32.94 ± 1.46	31.66 ± 1.67	< 0.001[†]
R/O ratio (%)				
Average	60.09 ± 4.94	52.72 ± 5.58	49.78 ± 4.99	< 0.001[†]
Superior hemisphere	59.68 ± 5.79	53.22 ± 7.42	51.36 ± 7.87	< 0.001[#]
Inferior hemisphere	60.53 ± 5.27	52.33 ± 5.76	48.20 ± 5.25	< 0.001[†]

Data presented as mean ± standard deviation. [†] normal vs. preperimetric glaucoma and preperimetric glaucoma vs. early glaucoma statistically different (Tukey-Kramer test); [#] normal vs. preperimetric glaucoma statistically different and preperimetric glaucoma vs. early glaucoma not statistically different (Tukey-Kramer test); ANOVA = analysis of variance; G/O ratio = ganglion cell complex (GCC) thickness/outer retinal (OR) thickness ratio; G/T ratio = GCC thickness/total retinal thickness ratio; average R/O ratio = average circumpapillary retinal nerve fiber layer thickness (cpRNFLT)/average OR thickness ratio; superior hemisphere R/O ratio = superior hemisphere cpRNFLT /superior OR thickness; inferior hemisphere R/O ratio = inferior hemisphere cpRNFLT/inferior OR thickness.

Table 4. Correlation between macular outer retinal thickness and circumpapillary retinal nerve fiber layer thickness measurements.

	Normal eyes		**Preperimetric glaucoma**		**Early perimetric glaucoma**	
	r	*P*	r	*P*	r	*P*
Average outer retinal thickness						
Average cpRNFLT	0.401	0.005	-0.225	0.224	0.058	0.634
Superior outer retinal thickness						
Superior hemisphere cpRNFLT	0.363	0.012	-0.229	0.214	0.066	0.585
Inferior outer retinal thickness						
Inferior hemisphere cpRNFLT	0.337	0.021	-0.153	0.411	0.019	0.875

Values printed in bold are statistically significant ($P < 0.05$). GCC = macular ganglion cell complex; cpRNFLT = circumpapillary retinal nerve fiber layer thickness; r =Pearson correlation coefficient.

Table 5 summarizes the AUROC results for the established global RTVue-100 OCT parameters and the R/O ratio. The highest AUROC values were observed for FLV (0.941, 0.996, and 0.979 for preperimetric, early perimetric glaucoma, and all glaucoma, respectively). The G/O ratio also favorably discriminated the groups (the AUROC values for preperimetric, early perimetric glaucoma, and all glaucoma were 0.925, 0.979, and 0.962, respectively). The AUROC for FLV was significantly greater than that for cpRNFLT in both glaucoma groups. In the early perimetric glaucoma group and for all glaucoma eyes the AUROCs for the G/O ratio and G/T ratio were significantly greater than those for cpRNFLT and the R/O ratio ($P < 0.05$). At a specificity of ≥ 90%, GLV had the highest sensitivity in the preperimetric group, and FLV had the highest sensitivity in the early perimetric glaucoma group. The G/O and G/T ratios had the second highest sensitivity at a specificity of ≥ 90% in the preperimetric group. AUROCs for the hemisphere cpRNFLT and the corresponding R/O ratios are shown in Table 6.

Table 5. Area under receiver operating characteristic curves and sensitivity at a fixed specificity.

	Normal vs. preperimetric glaucoma		**Normal vs. early perimetric glaucoma**		**Normal vs. all glaucoma**	
	AUROC	Sn/Sp (Sp ≥ 90%)	AUROC	Sn/Sp (Sp ≥ 90%)	AUROC	Sn/Sp (Sp ≥ 90%)
Average GCC thickness	0.896 ± 0.04	74.19/ 91.49	0.961 ± 0.02	91.43/ 91.49	0.941 ± 0.02	86.14/ 91.49
FLV	0.941 ± 0.02†	74.19/ 91.49	0.996 ± 0.003#	98.57/ 95.74	0.979 ± 0.009#	91.09/ 91.49
GLV	0.907 ± 0.04	80.65/ 91.49	0.967 ± 0.02	97.14/ 91.49	0.949 ± 0.02 †	92.08/ 91.49
Average G/O ratio	0.925 ± 0.03	77.42/ 91.49	0.979 ± 0.01§	95.71/ 91.49	0.962 ± 0.01§	90.10/ 91.49
Average G/T ratio	0.921 ± 0.03	77.42/ 91.49	0.979 ± 0.01§	95.71/ 91.49	0.961 ± 0.01§	90.10/ 91.49
Average cpRNFLT	0.842 ± 0.05	41.94/ 91.49	0.927 ± 0.02	75.71/ 91.49	0.901 ± 0.03	65.35/ 91.49
Average R/O ratio	0.859 ± 0.05	67.74/ 91.49	0.933 ± 0.02	80.00/ 91.49	0.910 ± 0.02	76.24/ 91.49

Data presented as mean ± standard error. † $P < 0.05$ for average cpRNFLT comparison; # $P < 0.01$ for average cpRNFLT and R/O ratio comparisons; § $P < 0.05$ for average cpRNFLT and R/O ratio comparisons; AUROC = area under receiver operating characteristic curve; Sn = sensitivity; Sp = specificity; GCC = macular ganglion cell complex; FLV = focal loss volume; GLV = global loss volume; cpRNFLT = circumpapillary retinal nerve fiber layer thickness; G/O ratio = GCC thickness to outer retinal thickness ratio; G/T ratio = GCC thickness to total retinal thickness ratio; R/O ratio = cpRNFLT to outer retinal thickness ratio.

Table 6. Comparison of area under receiver operating characteristic curves between the corresponding sector cpRNFLT and R/O ratio parameters.

	Normal vs. preperimetric glaucoma			**Normal vs. early perimetric glaucoma**		
	cpRNFLT	R/O ratio	*P*	cpRNFLT	R/O ratio	*P*
Average	0.842 ± 0.05	0.859 ± 0.05	0.466	0.927 ± 0.02	0.933 ± 0.02	0.659
Superior hemisphere	0.770 ± 0.06	0.774 ± 0.06	0.838	0.806 ± 0.04	0.798 ± 0.04	0.646
Inferior hemisphere	0.865 ± 0.04	0.861 ± 0.04	0.854	0.949 ± 0.02	0.956 ± 0.02	0.417

Area under the receiver operating characteristic curve data presented as mean ± standard error. cpRNFLT = circumpapillary retinal nerve fiber layer thickness; R/O ratio = cpRNFLT to outer retinal thickness ratio.

4. Discussion

In the present study, we evaluated a potential novel RTVue-100 OCT parameters, the R/O ratio and the G/O ratio, for its diagnostic accuracy in preperimetric and early perimetric glaucoma in Japanese eyes. This investigation was conducted because the detection of early perimetric and particularly preperimetric glaucoma, with the FD-OCT instruments, has been consistently reported as suboptimal, for various populations.[22-25] In very early stages of glaucoma, the decrease of cpRNFLT, the most frequently used OCT parameter in glaucoma diagnostics, is relatively small, and therefore cpRNFLT may remain within the corresponding normal range. In order to increase the discrimination between normal eyes and eyes with early structural damage more sensitive parameters are needed. It has been shown that OCT parameter ratios have narrower normal ranges than non-ratio type parameters.[17] This is why in the current investigation R/O and G/O ratios were evaluated for their diagnostic accuracy in early and preperimetric glaucoma.

It has been shown that cpRNFLT decreases during glaucomatous ganglion cell and axon loss, while OR thickness remains uninfluenced by glaucoma.[17,18,20,21] Therefore, we hypothesized that in case a positive correlation between cpRNFLT and OR thickness is observed in normal eyes, a decrease of the normal range of R/O ratio can be expected for preperimetric and early perimetric glaucoma, and this may potentially be applicable for the detection of early glaucoma.

In fact, we observed a statistically significant moderate positive correlation between cpRNFLT and OR thickness in the healthy control group and no correlation either in the preperimetric or the early perimetric glaucoma group. Although the OR thickness did not differ between the groups, despite its wide normal range,[7-9] cpRNFLT was significantly lower in preperimetric glaucoma eyes than in normal eyes, and in the early perimetric glaucoma group than in the other groups. As expected, we observed a significantly smaller R/O ratio for the preperimetric and perimetric glaucomatous groups than the healthy control eyes. Therefore, to further evaluate the R/O ratio, we compared its diagnostic accuracy to that of the manufacturer-provided standard RTVue-100 OCT parameters and the ratio parameters that showed a favorable diagnostic accuracy in Japanese eyes in our earlier studies.[17,18]

We observed that the R/O ratio did not perform better than the best discriminating manufacturer-provided parameters (GLV and FLV) or the ratio parameters (average G/O ratio, average G/T ratio) shown by us in our previous studies.[17,18] This can be explained with our present result that refractive error has a significant effect on the R/O ratio. Previously, it has been shown that cpRNFLT, GCC thickness, FLV, and GLV are all influenced by the axial length.[26] This influence was confirmed in the present study by a significant relationship between cpRNFLT and refractive error. Our results suggest that myopia, which is highly prevalent in East Asia,[16] negatively influences the diagnostic accuracy of the previously established parameters and the R/O ratio. To compare the diagnostic accuracy of the various cpRNFLT parameters and the spatially corresponding R/O ratios, we compared the corresponding hemisphere AUROC values. Although the average R/O ratio had a higher AUROC value than the average cpRNFLT for both the preperimetric and the early perimetric glaucoma groups, this advantage was not observed when the AUROC curves of the hemisphere cpRNFLT parameters and the corresponding R/O ratio parameters were compared. Overall, though the R/O ratio performed relatively well in discriminating between healthy and preperimetric or early perimetric glaucoma, its diagnostic accuracy did not exceed that of the established RTVue-100 OCT parameters.

Previously, we reported that G/T ratio is useful for diagnosing glaucoma.[17] Furthermore, although refractive error significantly affects FLV and GLV, the G/O ratio and G/T ratio does not influence the refractive error.[26] Therefore, G/O ratio and G/T ratio provide better specificity for diagnosing glaucoma with myopia. In the current study, the AUROC for G/O ratio and G/T ratio were significantly greater than that of the cpRNFLT. This is of particular importance in preperimetric glaucoma, when functional (visual field) testing is by definition unable to support the diagnostic process. This suggests that these parameters may have a place among the software-provided parameters of the RTVue OCT, for detecting early glaucoma. FLV had a higher AUROC value than the G/O ratio and G/T ratio, though the differences were not statistically significant. Since FLV is a parameter that is specific for the RTVue-OCT, but parameters similar to RTVue-OCT GCC thickness, OR thickness and total retinal thickness can be measured with various other OCT

systems, it is possible that G/O-like and G/T-like ratios can be applied also on other FD-OCT systems. Therefore further investigations on the potential applicability and clinical usefulness of these ratio parameters on other FD-OCT instruments for diagnosing early glaucoma in Japanese eyes is proposed.

Ethnic differences are known to exist in GCC thickness; the GCC thickness is significantly thinner in African-derived populations that in other ethnic groups.[10] Previously we found no significant difference in the G/T ratio between Japanese and European eyes.[14] These data suggest that further investigations are necessary to compare the G/T ratio between all main ethnic groups, and to evaluate whether the G/T ratio has a potential to improve glaucoma diagnostics in other East-Asian populations such as Koreans and Chinese.

In conclusion, although our study was limited by the relatively small number of patients and the absence of pathological myopia cases, our results suggest that the G/O and G/T ratios can be proposed as a potential novel OCT parameters for the detection of early perimetric glaucoma in Japanese eyes.

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