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TITLE : Comparison of glaucoma diagnostic ability of retinal nerve fibre layer thickness, ganglionic cell complex thickness and optic disc measurements made with the Spectral Domain Optical Coherence Tomography.

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ABSTRACT :

Purpose

To evaluate the diagnostic accuracy of retinal nerve fibre layer thickness (RNFLT), ganglion cell complex (GCC), and optic disc measurements made with the RTVue-100 Fourier-domain optical coherence tomography (OCT) to detect glaucoma in an Asian population.

Methods

One randomly selected eye of 532 Asian patients (132 healthy, 112 ocular hypertensive, 134 preperimetric glaucoma, and 154 perimetric glaucoma eyes) was evaluated.

Results

Using the software-provided classification, the Total population sensitivity for GCC was 82.7% , RNFLT parameters did not exceed 73.6% and for the optic nerve head 62.8. Specificity was high (92.6–100%) for most RNFLT and GCC parameters, but low (74.0–76.4%) for the optic disc parameters. Positive predictive value (PPV) varied between 96.1 and 100% for the main RNFLT parameters, 94.6 and 100% for the 16 RNFLT sectors, 96.4 and 99.0% for the GCC parameters, but did not exceed 86.3% for any of the optic disc parameters. Positive likelihood ratio (PLR) was higher than 10 for average, inferior and superior RNFLT (28.5 to infinite), 12 of the 16 RNFLT sectors (14.6 to infinite), and three of the four GCC parameters (40.0 to 48.6). No optic disc parameter had a PLR higher than 2.0.

Conclusion

RNFLT and GCC parameters of the RTVue-100 Fourier-domain OCT showed moderate sensitivity but high specificity, positive predictive value and PLR for detection of glaucoma. The optic disc parameters had lower diagnostic accuracy than the RNFLT and GCC parameters.

Keywords

Retinal nerve fibre layer thickness; Ganglion cell complex; Optic disc; Fourier-domain optical coherence tomography; Glaucoma

Full Text

Introduction

RGC bodies residing in the inner nuclear layer are known to be ten to twenty-fold thicker than their axons [1,2]. Studies have consistently shown that both peripapillary retinal nerve fiber layer thickness (RNFLT) and macular volume are lower in glaucomatous eyes [2-6]. It can be speculated that improvement in the resolution of imaging technologies may increase segmentation in the macula, which can be useful for detection of glaucoma at earlier stages.

The RTVue-100 OCT (Optovue Inc., Fremont, CA, USA) is one of the new commercially available Fourier-domain OCT instruments [7-14] . Its axial resolution is approximately 5 μm and the scan speed is 26 000 A-scans per second. Thus the speed is 65 times higher than that of the Stratus OCT system, and the resolution is about twice as good as such time-domain OCT instruments. The RTVue optic nerve head map (ONH map) scan was developed for peripapillary retinal nerve fibre layer thickness (RNFLT) and two-dimension ONH measurements to detect glaucoma. As reduction of macular thickness, especially of the inner retinal layers, is an important OCT finding associated with glaucoma [15] the ganglion cell complex (GCC) scan of the RTVue system, which comprises tissue layers (the retinal nerve fibre layer, the retinal ganglion cell layer and the inner-plexiform layer) that are directly influenced by glaucomatous ganglion cell loss, may also have clinical importance. The instrument's software contains a normative database sufficient for statistical comparison for the different RNFLT, ONH and GCC parameters [16].

In this study, we investigated the diagnostic accuracy of the different RNFLT, GCC and ONH parameters of the RTVue-100 Fourier-domain OCT using the software-provided classifications for detection of glaucoma on 532 patients over a period of 18 months.

Materials and methods

For inclusion, all participants had to have, in the study eye, sufficient central vision for optimal fixation, image quality sufficient for optimal evaluation, no macular pathology except for a small number of hard drusen, on stereoscopic evaluation.

One randomly selected eye of each 532 Asian individuals underwent RNFLT, GCC, and ONH measurements made with the RTVue-100 Fourier-domain OCT between 1 January 2012 and 30th June2013, was enrolled in the study. All patients underwent the same diagnostic protocol, which comprised a detailed slit-lamp evaluation, stereoscopic ONH photography and evaluation by a glaucoma specialist , stereoscopic evaluation of the macula, repeated White on white automated perimetry with the Humphrey Visual Field Analyser 750 24-2 Sita Standard visual field testing, and daytime intraocular pressure phasing made with Goldman applanation tonometry within 1 month from the RTVue-100 OCT imaging. The final clinical classification based on the results of these tests was made a Senior Consultant at the Glaucoma Service . Any image with a Signal Strength Index (SSI) of lower than 40 was discarded. The patient population comprised of 132 healthy subjects with no ONH damage, reliable and reproducible normal visual field tests with normal mean defect (MD), that is, MD less than 2 dB, and intraocular pressure consistently below 21 mm Hg, based on daytime phasing (five measurements between 0008 and 1600 hours); 112 ocular hypertensive subjects with normal ONH, visual field with MD less than

2 dB and untreated intraocular pressure consistently above 21 mm Hg; 134 preperimetric glaucoma patients characterized with definite glaucomatous neuroretinal rim loss (diffuse or localised neuroretinal rim thinning) and reliable and reproducible normal visual field with MD less than 2 dB; and 154 perimetric glaucoma patients characterized with glaucomatous neuroretinal rim loss and reliable and reproducible visual field defect typical for glaucoma (inferior and/or superior paracentral or arcuate scotomas, nasal step, hemifield defect or generalised depression with MD higher than 2 dB). Severity of glaucomatous visual field damage was classified according to the modified Bascom Palmer staging system [17]. The demographics of the participants are shown in Table I.

Table I : Demographic characteristics of the participants and eyes analysed in the study

Total number of eyes (*n*)	532 (100%)
Male/Female (*n*/*n*)	236/296
Best-corrected visual acuity (mean±SD)	0.9±0.2
Refractive error (*D*) (mean±SD, range)	−0.7±2.9 (−14.00+8.00)
Prevalence of healthy eyes	132/532 (24.8%)
Prevalence of OHT eyes	112/532(21.0%)
Prevalence of glaucoma eyes	288/532 (54.1%)
Preperimetric	114/288 (39.5%)
Perimetric	174/288 (60.4%)

Type of glaucoma	
Primary open-angle glaucoma	146/288 (51.2%)
Juvenile open-angle glaucoma	6/288 (2.0%)
Normal-pressure glaucoma	8/288 (2.7%)
Chronic angle closure glaucoma	4/288 (1.3%)
Pseudoexfoliative glaucoma	2/288 (0.69%)
Pigment glaucoma	4/288 (1.3%)
Other secondary glaucomas	4/288 (1.3%)
Mean defect (dB) (mean±SD)	
- Healthy eyes	0.4±1.4
- OHT eyes	−0.1±1.3
- Preperimetric glaucoma eyes	0.1±1.6
- Perimetric glaucoma eyes	7.8±6.9
Distribution of disease severity in the perimetric glaucoma group [a]	
Stage 1	31/288 (10.76%)
Stage 2	94/288 (32.6%)

Stage 3	81/288 (28.1%)
Stage 4	74/288 (25.6%)
Stage 5	8/288 (2.7%)
Age (years) (mean±SD)	
Healthy eyes	55.9±14.9
OHT eyes	50.5±14.5
Preperimetric glaucoma eyes	54.6±12.8
Perimetric glaucoma eyes	55.2±14.4
Untreated maximal IOP of the OHT eyes (mm Hg) (mean±SD)	27.1±7.9

Fourier domain OCT

OCT was performed through undilated pupil with the RTVue-100 Fourier-domain OCT instrument (Optovue Inc.) with software version 4.0. Macular Inner retinal Layer (MIRL) thickness using the GCC scan protocol and RNFL thickness employing two scanning modes, NHM4 and RNFL 3.45, were measured. The GCC scan covered a 7 × 7-mm scan area centered on the fovea. RNFL thickness was determined by both NHM4 (RNFL1) and RNFL 3.45 modes (RNFL2).

The normative database for diagnostic classification consists of 1800 healthy eyes of Indian ethnicity subjects, with ages ranging between 18 and 80 years. RNFLT values are found to correlate significantly with age of subject, ethnicity and with optic disc size, and adjustments for

these effects (using multiple linear regression equations) are implemented in the software to improve classification results. For RNFLT, GCC and ONH measurements the standard glaucoma protocol was used [8]. This includes a 3D optic disc scan for the definition of the disc margin on the basis of the computer-assisted determination of retinal pigment epithelium endpoints, an ONH scan to measure the optic disc parameters and RNFLT within an area of diameter 4 mm, centred on the pre-defined disc, and the standard GCC scan. Each ONH scan consists of 12 radial lines and six concentric rings, which are used to create an RNFLT map. The measuring circle (920 points) is derived from this map after the sample circle is adjusted to be centred on the optic disc. The measured RNFLT is automatically compared with the normative database for the total circle, the superior and inferior sectors, and each of the sixteen 22.5°-sized sectors of the measuring circle. In this investigation the following software-provided parameters were evaluated: (1) average RNFLT for the total 360° around the ONH; (2) superior quadrant RNFLT; (3) inferior quadrant RNFLT; (4) all 16 separate RNFLT sectors (abbreviations: TU; temporal upper, ST; supero-temporal, SN; supero-nasal, NU; nasal upper, NL; nasal lower, IN; infero-nasal, IT; infero-temporal, and TL; temporal lower), (5) superior GCC (thickness of all macular layers between the internal limiting membrane and the inner plexiform layer, in the area above the horizontal meridian); and (6) inferior GCC (thickness of all macular layers between the internal limiting membrane and the inner plexiform layer, in the area below the horizontal meridian); (7) average GCC; (8) GCC focal loss volume (FLV; the total sum of statistically significant GCC volume loss divided by the GCC map area, in percent); (9) cup area; (10) cup/disc area ratio; and (11) rim area. For these software calculated parameters an instrument provided classification is indicated in a colour coded manner: sectors with ‘within normal limits' classification (ie sectors for which the probability of there being no glaucomatous damage ⩾5%)

are printed in green, sectors with ‘borderline' classification (*P*<5 but ⩾1%) in yellow and sectors with ‘outside normal limits' classification (*P*<1%) in red. In the current investigation both the retinal pigment epithelium endpoints and the ONH contour line were determined by the same trained examiner .To be included in the analysis, images had to have a signal strength index >40. Overt misalignment of the surface detection algorithm on at least 10% of consecutive A-scans or 15% of cumulative A-scans or with overt decentration of the measurement circle location (assessed subjectively) were excluded from further analysis. Pharmacologic dilation was performed if the pupil was smaller than 3.0 mm. All images were acquired by a single well-trained operator who was masked to the diagnosis and other clinical findings, including location and severity of VF defect during the same patient visit. These RTVue-100 OCT examinations were not used for the clinical classification of the patients.

The SPSS 15.0 program package was used for statistical analysis (SPSS Inc., Chicago, IL, USA). ANOVA to compare age and the measured parameter values between the patient groups. Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio (PLR) and negative likelihood ratio of the software provided classification results were determined. *P*-values of <0.05 were considered as statistically significant.

Results

There was no statistically significant age difference between the patients of the various groups. All images met the pre-defined signal strength criterion and were analysed. Comparison of the different RNFLT, GCC and ONH values between the patient groups is shown in Table II A, B and C .

Tables II A : **Comparison of the different Ganglionic Cell Complex (GCC) parameters between the patient groups.**

GCC parameters														
	Healthy **1**		OHT **2**		Preperimet-ric **3**		Perimetric **4**		p values [b]					
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	1vs2	1vs3	1vs4	2vs3	2vs 4	3vs4
Average (ìm)	96.7	7.8	96.4	7.1	92.8	6.0	73.0	13.6	0.827	0.543	<0.001	0.987	<0.001	<0.001
Superior (ìm)	98.3	7.1	95.3	8.7	94.0	8.2	76.3	15.4	0.561	0.020	<0.001	0.465	<0.001	<0.001
Inferior (ìm)	97.5	7.7	98.2	7.2	91.5	6.4	70.6	14.6	0.566	0.005	<0.001	0.453	<0.001	<0.001
FLV (%)	1.0	1.4	1.8	2.6	1.6	1.6	7.4	4.6	0.364	0.812	<0.001	0.875	<0.001	<0.001

Tables II B : **Comparison of the different retinal nerve fibre layer thickness (RNFLT) values between the patient groups.**

RNFLT parameters (ìm)					
	Healthy	OHT	Preperimetri	Perimetric **4**	p values [b]

	1		**2**		c **3**									
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	1vs2	1vs3	1vs4	2vs3	2vs 4	3vs4
Average	104.5	9.2	104.0	10.4	95.9	11.2	74.9	12.0	0.162	<0.001	<0.001	0.021	<0.001	<0.001
Temporal	76.6	9.4	74.8	10.3	67.8	9.7	53.7	13.4	0.863	0.001	<0.001	0.049	<0.001	<0.001
Superior	136.6	15.2	126.5	15.4	112.4	19.5	93.7	16.7	0.033	<0.001	<0.001	0.062	<0.001	<0.001
Nasal	82.0	10.1	76.3	13.2	72.3	11.5	61.3	11.9	0.472	0.106	<0.001	0.995	<0.001	<0.001
Inferior	138.2	15.6	132.6	17.9	122.2	18.6	92.1	14.9	0.538	<0.001	<0.001	0.034	<0.001	<0.001

Tables II C : **Comparison of the different Optic Nerve Head (ONH) parameters between the patient groups.**

Optic nerve Head parameters														
	Healthy **1**		OHT **2**		Preperimetric **3**		Perimetric **4**		p values [b]					
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	1vs2	1vs3	1vs4	2vs3	2vs 4	3vs4
Cup area	0.853	0.550	0.821	0.520	1.436	0.493	1.50	0.56	0.97	<0.001	<0.001	<0.001	<0.001	0.700

(mm2)							3	6	0					
Cup/disc area ratio	0.425	0.243	0.517	0.224	0.696	0.121	0.839	0.167	1.000	<0.001	<0.001	<0.001	<0.001	0.005
Rim area (mm2)	1.123	0.438	0.932	0.314	0.627	0.275	0.434	0.414	0.140	<0.001	<0.001	<0.001	<0.001	<0.01

Abbreviations: FLV, focal loss volume; OHT – Ocular Hypertension

b: ANOVA<0.01 for all parameters

RNFLT, GCC and ONH parameters differed significantly between the groups, showing decreasing RNFLT, GCC thickness and rim area values, and increasing cup area and cup/disc area ratio with increasing disease severity categories.

Diagnostic performance is shown in Table III for each disease category and parameter, respectively. When borderline and outside normal limits classifications were grouped together (both considered abnormal), specificity was high (94.6–100%) for most RNFLT and GCC parameters, and low (72.0–76.3%) for the ONH parameters, in all analyses. For detection of perimetric glaucoma, GCC FLV showed the best sensitivity (92.8%).

Table III : Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR) and negative likelihood ratio (NLR) of the software provided classification for detection of glaucoma in the total study population (*n*=532), for each parameter, respectively.

	Normal vs OHT, preperimetric and perimetric glaucoma

	Sensitivity (%) (95% CI)	***Specificity (%) (95% CI)***	***PPV (%) (95% CI)***	***NPV (%) (95% CI)***	***PLR (95% CI)***	***NLR (95% CI)***
Main RNFLT parameters (μm)						
Average	82.0 (80.8–84.8)	96.0 (94.0–98.0)	94.0 (96.0–92.0)	53.4 (43.4–63.2)	Infinite	0.4 (0.3–0.5)
Superior	86.0 (85.5–87.5)	94.0 (92.0–96.0)	98.0 (96.0–100.0)	52.0 (41.9–61.8)	Infinite	0.4 (0.4–0.6)
Inferior	82.9 (80.4–.841)	97.8 (92.4–99.4)	98.1 (93.4–99.5)	51.1 (41.0–61.1)	25.5 (6.3–103.2)	0.5 (0.4–0.6)
GCC parameters						
Average (μm)	84.2 (88.3–86.2)	99.4. (99.2–99.8)	98.9 (94.2–99.8)	47.6 (37.7–57.8)	44.3 (6.2–318.3)	0.5 (0.4–0.6)
Superior (μm)	82.5 (82.4–84.2)	98.9 (94.1–100.0)	98.8 (93.6–99.8)	45.5 (35.7–55.7)	40.0 (5.6–288.6)	0.6 (0.5–0.7)
Inferior (μm)	82.8 (82.2–78.3)	99.9 (99.1–100.0)	99.0 (94.7–99.8)	50.0 (39.9–60.1)	48.6 (6.8–348.2)	0.5 (0.4–0.6)
FLV (%)	84.7 (82.8–86.8)	99.1 (98.6–100.0)	98.4 (98.2–100.0)	53.2 (42.5–63.7)	5.8 (3.1–10.9)	0.4 (0.3–0.5)

Optic nerve head parameters						
Cup area (mm 2)	70.0 (63.0–77.8)	76.3 (65.3–84.7)	86.3 (79.6–91.1)	56.8 (45.2–67.7)	3.0 (2.0–4.7)	0.4 (0.3–0.5)
Cup/disc area ratio	71.6 (64.8–79.1)	72.0 (60.3–81.4)	84.5 (77.7–89.6)	56.8 (44.9–68.0)	2.6 (4.7–3.9)	0.4 (0.3–0.5)
Rim area (mm 2)	70.0 (63.0–79.8)	76.3 (65.3–84.7)	86.3 (79.6–91.1)	56.8 (45.2–67.7)	3.0 (2.0–4.7)	0.4 (0.3–0.5)

Discussion

Evaluation of the diagnostic accuracy of the different protocols available in current Imaging devices is of clinical importance. In such investigations, for the best performing RNFLT and GCC parameters of the RTVue-100 OCT, the area under the receiver operating characteristic curve varied between 0.900 and 0.981 [18,19]. Other authors using other Fourier-domain OCT systems reported on similar values [4, 19]. These results suggest that under pre-defined circumstances the diagnostic accuracy of Fourier-domain OCT technology is higher than that of time-domain OCT technology [4,18,19]. The significance of this approach is that disease severity may have an influence on the diagnostic capability of the Fourier-domain OCT instruments [20], thus it needs to be considered in the evaluation. To evaluate the diagnostic capability of the instrument we used the software-provided classification, which is based on comparison between the measured values and the integrated normative database. As the RTVue-100 OCT has an age and disc size adjusted separate database for Asians, which was used by us for our patients, the age-related RNFLT and GCC difference between our healthy control and ocular hypertensive subjects and the perimetric glaucoma patients was corrected for.

As shown in Table II A,B and C, in the ocular hypertensive group, the difference from the healthy group was significant only for two parameters. In contrast, for all other groups several parameters showed significant damage compared with the healthy eyes, and the measured values showed more damage for the more severe disease categories, respectively.

Specificity was consistently high (94.6–100%); sensitivity was poor for detection of ocular hypertension and preperimetric glaucoma, and moderate to good (up to 82.8%) for detection of perimetric glaucoma. For our total unselected study population, most RNFLT and GCC

measurements had high specificity and positive predictive value (92.4–100%), and clinically useful PLR (>10 to infinite). No such favourable findings were obtained for the ONH parameters (cup area, cup/disc area ratio and rim area), which suggests that the Fourier-domain technology did not overcome the problems of ONH classification with the time-domain OCT technology [8,9,10].

Our results mean that in routine clinical practice a borderline or outside normal limits classification given for the main RNFLT parameters, RNFLT sectors or GCC parameters by the instrument's software, strongly suggests that the eye has lost retinal nerve fibres and macular ganglion cells. In contrast, because of the relatively low sensitivity and weak negative likelihood ratio, a within normal limits classification cannot exclude glaucoma.In conclusion, in our study population comprising healthy, ocular hypertensive, preperimetric and perimetric glaucoma patients for detection or exclusion of glaucoma, the RTVue-100 Fourier-domain OCT and its Asian normative database were found to be highly specific to detect glaucoma. The overall best-performing parameter was average GCC, but RNFLT parameters had favourable diagnostic accuracy.

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