

# Influence of optic disc size on the diagnostic performance of macular ganglion cell complex and peripapillary retinal nerve fiber layer analyses in glaucoma

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**Aim:** To evaluate the influence of optic disc size on the diagnostic accuracy of macular ganglion cell complex (GCC) and conventional peripapillary retinal nerve fiber layer (pRNFL) analyses provided by spectral domain optical coherence tomography (SD-OCT) in glaucoma.

**Methods:** Eighty-two glaucoma patients and 30 healthy subjects were included. All patients underwent GCC (7 × 7 mm macular grid, consisting of RNFL, ganglion cell and inner plexiform layers) and pRNFL thickness measurement (3.45 mm circular scan) by SD-OCT. One eye was randomly selected for analysis. Initially, receiver operating characteristic (ROC) curves were generated for different GCC and pRNFL parameters. The effect of disc area on the diagnostic accuracy of these parameters was evaluated using a logistic ROC regression model. Subsequently, 1.5, 2.0, and 2.5 mm<sup>2</sup> disc sizes were arbitrarily chosen (based on data distribution) and the predicted areas under the ROC curves (AUCs) and sensitivities were compared at fixed specificities for each.

**Results:** Average mean deviation index for glaucomatous eyes was  $-5.3 \pm 5.2$  dB. Similar AUCs were found for the best pRNFL (average thickness = 0.872) and GCC parameters (average thickness = 0.824;  $P = 0.19$ ). The coefficient representing disc area in the ROC regression model was not statistically significant for average pRNFL thickness ( $-0.176$ ) or average GCC thickness (0.088;  $P \geq 0.56$ ). AUCs for fixed disc areas (1.5, 2.0, and 2.5 mm<sup>2</sup>) were 0.904, 0.891, and 0.875 for average pRNFL thickness and 0.834, 0.842, and 0.851 for average GCC thickness, respectively. The highest sensitivities – at 80% specificity for average pRNFL (84.5%) and GCC thicknesses (74.5%) – were found with disc sizes fixed at 1.5 mm<sup>2</sup> and 2.5 mm<sup>2</sup>.

**Conclusion:** Diagnostic accuracy was similar between pRNFL and GCC thickness parameters. Although not statistically significant, there was a trend for a better diagnostic accuracy of pRNFL thickness measurement in cases of smaller discs. For GCC analysis, an inverse effect was observed.

**Keywords:** glaucoma, retinal nerve fiber layer, optical coherence tomography, ganglion cell complex

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## Introduction

Morphological changes of the optic nerve head (ONH) and peripapillary retinal nerve fiber layer (pRNFL) often precede the development of visual field (VF) loss in glaucoma. Therefore, a precise structural evaluation is essential for early diagnosis of the disease.<sup>1,2</sup> Clinical examination combined with stereophotograph evaluation is still the most commonly used method to assess structural damage in glaucoma. However, several

objective imaging devices have become available over the past few years, improving diagnosis of the disease and disease follow-up.<sup>3,4</sup>

Since the introduction of time-domain optical coherence tomography (TD-OCT), studies have consistently shown the usefulness of pRNFL thickness measurement for glaucoma diagnosis.<sup>5-7</sup> However, as a diagnostic parameter, total macular thickness measurement using TD-OCT has not been nearly as accurate as pRNFL.<sup>8,9</sup> With the advent of spectral-domain optical coherence tomography (SD-OCT), a significant improvement in imaging resolution was achieved, allowing segmentation of the macular region and better identification of each layer.<sup>10-12</sup> The RTVue-100 OCT (Optovue Inc, Fremont, CA) is one of the commercially available SD-OCT devices. With an axial resolution of 5  $\mu\text{m}$  in tissue and a scan speed of 26,000 A-scans/second (compared with an axial resolution of 8 to 10  $\mu\text{m}$  and a scan speed of 400 A-scans/second from TD-OCT), the RTVue-100 OCT provides a segmented evaluation of the macular inner retinal layers (MIRL).<sup>13</sup> This specific analysis is called ganglion cell complex (GCC) scan, and consists of three layers: the RNFL, ganglion cell layer, and inner plexiform layer.<sup>13</sup> Recent studies have demonstrated GCC thickness as a useful parameter for glaucoma diagnosis.<sup>14,15</sup>

While measuring MIRL thickness, the GCC protocol uses a  $7 \times 7$  mm macular grid centered 1 mm temporal to the fovea.<sup>14-16</sup> Based on a different method, the pRNFL protocol uses a circular scan (3.45 mm in diameter) concentric to the ONH to provide regional and global thickness measurements.<sup>2,3</sup> For all patients, a fixed disc diameter is adopted. A well-centered image is essential for accurate and reproducible pRNFL thickness measurements.<sup>3,4</sup> However, it is generally recognized that the optic disc area shows a high interindividual variability in normal and glaucomatous eyes, ranging between 0.8 and 6.0  $\text{mm}^2$ .<sup>1,13</sup> Using the same circular scan diameter for all eyes may result in pRNFL thickness measurements performed at different distances from the ONH margin.<sup>3</sup> Consequently, this would lead to over- or underestimated pRNFL measurements in eyes with small or large optic disc sizes, as it is well known that the pRNFL is thicker closer to the disc margin compared with more distant regions. It could be hypothesized that these altered pRNFL thickness measurements could affect the OCT's ability to discriminate between glaucomatous and healthy eyes.

In the present study, the influence of optic disc area on the diagnostic accuracy of pRNFL and GCC scan protocols provided by SD-OCT for glaucoma diagnosis were evaluated and compared.

## Methods

This prospective study followed the tenets of the Declaration of Helsinki and was approved by the institutional review board. Written informed consent was obtained from all participating patients.

## Patients

Glaucoma patients (glaucomatous optic neuropathy [GON] and reproducible VF loss) and healthy subjects were prospectively enrolled. Initially, all participants underwent a thorough ophthalmological examination. Exclusion criteria were: previous ocular surgery or trauma; spherical equivalent  $> \pm 4.0$  D; history of using oral or topical steroids; and any ocular disease other than glaucoma (for glaucomatous patients), including moderate or advanced cataract. All controls needed a normal ophthalmological examination, with intraocular pressure (IOP)  $< 21$  mmHg, normal VF testing and absence of GON on funduscopy and stereophotographic evaluation.

Characteristic GON was defined as a vertical cup:disc ratio (CDR)  $\geq 0.6$ , asymmetry of CDR  $\geq 0.2$  between eyes, presence of localized RNFL defects, and/or neuroretinal rim defects in the absence of any other abnormalities that could explain such findings. A glaucomatous VF defect in the standard automated perimetry (Humphrey SITA – Standard 24-2, Carl Zeiss Meditec, Dublin, CA) was defined as three or more points in clusters with a probability of  $< 5\%$  (excluding those on the edge of the field or directly above and below the blind spot) on the pattern deviation plot, a pattern standard deviation index with a probability of  $< 5\%$ , or a glaucoma hemifield test with results outside the normal limits.

## Procedures

Baseline data assessed were age, gender, self-described race, best-corrected visual acuity, VF mean deviation (MD) index, and Goldmann applanation tonometry (IOP). Initially, ONH area for each patient was determined by confocal scanning laser ophthalmoscopy using the Heidelberg Retina Tomograph III (HRT III) (Heidelberg Engineering, Heidelberg, Germany). In all cases, ONH was delineated manually by an experienced glaucomatologist, masked to patient condition. The mean value of three consecutive scans was considered for analysis. Then all patients underwent MIRL thickness measurement (GCC scan protocol) and pRNFL thickness measurement (using the RNFL 3.45 mm scan) with the RTVue-100 OCT. Differently from TD-OCT, which accumulates the information along the longitudinal direction over the course of the scan time

(using a mechanical moving part to perform the A-scan), SD-OCT acquires the information simultaneously (in an entire A-scan) by a CCD camera. Due to the nature of the mechanical moving speed, the scan time in TD-OCT is very slow, limiting its application in cases that require high repeatability and data-sampling rates. In SD-OCT, the A-scan acquisition rate is only limited by the CCD camera frame transfer rate and the computer calculation time to perform the Fourier transform of the CCD-acquired raw data into A-scan information. Because of the fast CCD camera frame transfer rate and fast Fourier transform algorithm, SD-OCT, like the RTVue, can perform 26,000 A-scans/second (65 times faster than TD-OCT).<sup>13</sup>

Global (average thickness) and regional (superior and inferior thicknesses) parameters of the two scan protocols (MIRL and pRNFL) were used for analysis. Images that had a signal strength index <40 or that were not well centered (subjective assessment) were excluded from the analysis. All images were acquired by the same experienced operator, who was masked for patient clinical data.

## Statistical analysis

Initially, receiver operating characteristic (ROC) curves were generated for different GCC and pRNFL parameters. Then a ROC logistic regression model was built to evaluate the effect of disc size on the diagnostic performance of each parameter. This model has been described in detail elsewhere;<sup>17,18</sup> briefly, the modeling technique allows the evaluation of the effect of covariates on the whole ROC curve. Also, it is possible to calculate areas under ROC for arbitrary levels of the covariate. Subsequently, 1.5, 2.0, and 2.5 mm<sup>2</sup> disc sizes were arbitrarily chosen (based on the distribution of the data) and the predicted areas under the ROC curves (AUCs) and sensitivities at fixed specificities for each of them were compared. Whenever both eyes were

eligible, one was randomly selected for analysis. Statistical significance was set at  $P < 0.05$ .

## Results

A total of 82 glaucoma patients (mean age  $67.5 \pm 10.4$  years) and 30 healthy subjects (mean age  $60.5 \pm 11.3$  years) were included. Average MD for glaucomatous eyes was  $-5.3 \pm 5.2$  dB. Baseline characteristics of study patients are summarized in Table 1.

The AUCs for average, superior, and inferior GCC thickness were not significantly different at 0.824, 0.823, and 0.791, respectively ( $P \geq 0.13$ ). The AUCs for average, superior, and inferior pRNFL thickness were also similar at 0.872, 0.816, and 0.845, respectively ( $P \geq 0.09$ ). Finally, similar AUCs were found for the best pRNFL (average thickness = 0.872) and GCC parameters (average thickness = 0.824;  $P = 0.19$ ) (Figure 1).

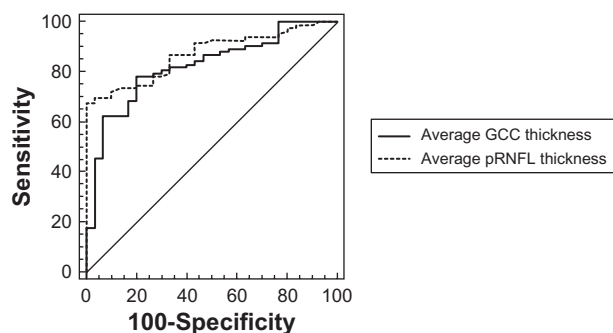
Regarding the influence of optic disc size on the diagnostic accuracy of the SD-OCT parameters analyzed, the coefficient representing disc area in the ROC regression model was not statistically significant for average pRNFL thickness ( $-0.176$ ) or average GCC thickness ( $0.088$ ;  $P \geq 0.56$ ). However, a trend for a better diagnostic accuracy of pRNFL thickness and a worse performance of GCC thickness measurement was observed in smaller disc cases, based on the comparisons of AUCs and sensitivities at 80% specificity. AUCs for fixed disc areas (1.5, 2.0, and 2.5 mm<sup>2</sup>) were 0.904, 0.891, and 0.875 for average pRNFL thickness, and 0.834, 0.842, and 0.851 for average GCC thickness, respectively. The highest sensitivities at 80% specificity for average pRNFL (84.5%) and average GCC thicknesses (74.5%) were found with disc sizes fixed at 1.5 mm<sup>2</sup> and 2.5 mm<sup>2</sup>, respectively. All sensitivity values according to each fixed disc area are provided in Table 2.

**Table 1** Baseline characteristics of study patients

Variables	Glaucoma patients (n = 82)	Controls (n = 30)
Mean age (years)	67.5 ± 10.4	60.5 ± 11.3
Average visual field mean deviation index (dB)	-5.3 ± 5.2	0.1 ± 1.5
Average ONH area (mm <sup>2</sup> ; determined by HRT)	2.15 ± 0.64	1.61 ± 0.36
Average pRNFL thickness (μm)	105.9 ± 18.3	133.1 ± 15.1
Average superior pRNFL thickness (μm)	103.5 ± 19.4	127.5 ± 16.7
Average inferior pRNFL thickness (μm)	108.4 ± 21.3	138.7 ± 18.9
Average GCC thickness (μm)	83.1 ± 11.4	96.3 ± 8.6
Average superior GCC thickness (μm)	82.5 ± 12.9	96.1 ± 9.4
Average inferior GCC thickness (μm)	83.8 ± 13.1	96.6 ± 8.1

**Note:** Data are given as mean ± standard deviation.

**Abbreviations:** ONH, optic nerve head; HRT, Heidelberg Retina Tomograph; pRNFL, peripapillary retinal nerve fiber layer; GCC, ganglion cell complex.



**Figure 1** ROC curves for SD-OCT thickness parameters. Similar AUCs were found for average pRNFL thickness (0.872) and average GCC thickness (0.824;  $P = 0.19$ ). **Abbreviations:** pRNFL, peripapillary retinal nerve fiber layer; GCC, ganglion cell complex; AUC, area under the ROC curve; SD-OCT, spectral domain optical coherence tomography.

## Discussion

The use of OCT for glaucoma detection and follow-up has been well established as a useful tool for the management of the disease. Understanding possible factors that could affect the diagnostic performance of the device is important while interpreting its results. Evaluating the influence of optic disc size on the discrimination ability of the conventional pRNFL analysis and on the relatively new GCC scan protocol provided by SD-OCT, slightly different diagnostic performances were found depending on the optic disc size. Interestingly, opposite effects were observed for the two different protocols analyzed.

In this study, it was demonstrated that the diagnostic accuracy was similar between pRNFL and GCC thickness parameters. Few studies have investigated the usefulness of the different parameters provided by the RTVue-100 SD-OCT in glaucoma patients; the findings of the present study are in agreement with all of these. In these studies, in which patients with different disease stages were evaluated, macular GCC thickness and pRNFL thickness also showed similar diagnostic performance for glaucoma detection.<sup>13–15</sup>

Evaluating the influence of optic disc size on the diagnostic performance of GCC and pRNFL scans, a trend for a better diagnostic performance of the pRNFL protocol in cases

**Table 2** Sensitivities at 80% specificity according to each fixed optic disc size

Optic disc area	Average pRNFL thickness	Average GCC thickness
1.5 mm <sup>2</sup>	84.5%	71.8%
2.0 mm <sup>2</sup>	82.3%	73.2%
2.5 mm <sup>2</sup>	79.9%	74.5%

**Abbreviations:** pRNFL, peripapillary retinal nerve fiber layer; GCC, ganglion cell complex.

of smaller discs and better performance of the macular GCC protocol in cases of larger discs was observed, based on the comparisons of AUCs and sensitivities at fixed specificities (the coefficient representing disc area in the ROC regression model was not statistically significant). Although these findings might not be important for patients with optic disc sizes within the normal range, they are probably relevant for those with small or large optic discs and should be considered when evaluating these patients. There is scant information in the literature about this topic. Rao et al,<sup>19</sup> conducting a similar study, found no correlation between optic disc size and sensitivity and specificity values provided by SD-OCT. In that study, disease severity was included as a covariate, and significantly influenced the diagnostic accuracies of RTVue scanning protocols. This fact might partially explain the different outcomes observed in these two studies.

It is important to stress some specific characteristics and limitations of this study. First, the control group had a relatively small average disc size (and also a limited range), which may have influenced the results. Second, not all SD-OCT parameters available in the RTVue-100 were investigated, such as global loss volume and focal loss volume. Finally, the correlation between disease severity and SD-OCT diagnostic performance was not investigated, as the study population had a narrow range of disease severity (based on functional loss), and only a small percentage of patients with advanced damage. A study with a wider range of disease severity would be able to investigate this association more appropriately.

## Conclusion

In summary, diagnostic accuracies were similar between conventional pRNFL and macular GCC protocols. Although not statistically significant, there was a trend for a better diagnostic performance of pRNFL thickness measurements in cases of smaller discs. For the GCC analysis, an inverse effect was observed. These findings should be taken into consideration while interpreting SD-OCT results for glaucoma diagnosis.

## Prior publication

This paper was presented in part at the Annual Meeting of the Association for Research in Vision and Ophthalmology, Fort Lauderdale, FL, May 2010.

## Disclosure

The authors report no conflicts of interest in this work.

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