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Diagnostic Capability of Peripapillary Retinal Thickness in Glaucoma Using 3D Volume Scans

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Abstract

Purpose—To determine the diagnostic capability of spectral domain optical coherence tomography (SD-OCT) peripapillary retinal thickness (RT) measurements from 3-dimensional (3D) volume scans for primary open angle glaucoma (POAG).

Design—Cross-sectional study.

Setting—Institutional

Study population—156 patients (89 POAG and 67 normal subjects)

Observation procedures—One eye of each subject was included. SD-OCT peripapillary RT values from 3D volume scans were calculated for four quadrants of three different sized annuli. Peripapillary retinal nerve fiber layer (RNFL) thickness values were also determined.

Main outcome measures—Area under the receiver operating characteristic curve (AUROC) values, sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios.

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Results—The top five RT AUROCs for all glaucoma patients and for a subset of early glaucoma patients were for the inferior quadrant of outer circumpapillary annulus of circular grid (OCA) 1 (0.959, 0.939), inferior quadrant of OCA2 (0.945, 0.921), superior quadrant of OCA1 (0.890, 0.811), inferior quadrant of OCA3 (0.887, 0.854), and superior quadrant of OCA2 (0.879, 0.807). Smaller RT annuli OCA1 and OCA2 consistently showed better diagnostic performance than the larger RT annulus OCA3. For both RNFL and RT measurements, best AUROC values were found for inferior RT OCA1 and OCA2, followed by inferior and overall RNFL thickness.

Conclusion—Peripapillary RT measurements from 3D volume scans showed excellent diagnostic performance for detecting both glaucoma and early glaucoma patients. Peripapillary RT values have the same or better diagnostic capability compared to peripapillary RNFL thickness measurements, while also having fewer algorithm errors.

Introduction

Glaucoma is the leading cause of irreversible blindness worldwide, and it results in a characteristic optic neuropathy with corresponding visual field defects. Clinical evaluation of the optic nerve head (ONH) and retinal nerve fiber layer (RNFL) is highly observer dependent and is primarily limited by large inter-observer variation.¹ Because nerve tissue loss in glaucoma is irreversible and up to 50% of nerve tissue may be lost by the time there is evidence of visual field damage,² there is a need to better assess nerve tissue loss more objectively and quantitatively both for diagnosing glaucoma and for evaluating glaucoma progression.

Imaging devices can assess nerve tissue objectively and quantitatively, and optical coherence tomography (OCT) is the most widely used imaging technology for the evaluation of the ONH, RNFL, and ganglion cell region in glaucoma. The Spectralis machine (Heidelberg Engineering, Inc., Heidelberg, Germany) is one of the many commercially available spectral domain (SD) OCT instruments, and it acquires 40,000 A scans per second with an axial resolution of 7 μ m, a lateral resolution of 14 μ m, and a scan depth of 1.8 mm.³ SD-OCT machines can measure glaucomatous nerve damage by evaluating different structural parameters, which including the following: RNFL thickness, ganglion cell layer thickness, macular thickness, and ONH parameters (e.g. rim area, rim volume, cup volume).^{4–12} The most popular glaucoma parameter in commercially available SD-OCT machines is RNFL thickness, and thinning of the RNFL is a strong indicator of glaucoma.^{5, 13, 14}

The reliability of OCT RNFL measurements decreases in glaucoma where the RNFL is thinner.^{15, 16} Since the coefficient of variation is reciprocally related to reliability, the coefficient of variation is greater in glaucoma patients.¹⁶ One of the main reasons for inaccurate OCT RNFL measurements in glaucoma is that the reflectivity of the RNFL decreases in glaucoma,¹⁷ which makes it difficult for segmentation algorithms to differentiate the normally highly reflective RNFL layer from the underlying tissue. Also, it is difficult to assess for glaucomatous RNFL thinning in myopic patients, because nearly half of myopic patients without glaucoma are classified as abnormal.^{18, 19} Another factor that affects RNFL thickness measurements is peripapillary atrophy (PPA). Complete loss of

the retinal pigment epithelium occurs in patients with β -zone PPA, and some of the other retinal layers may also terminate in the region of β -zone PPA, before reaching the disc margin.²⁰ Although the continuity of the RNFL is not disturbed in PPA, diagnostic performance of RNFL thickness within PPA is decreased.^{21, 22} Both PPA and myopia are increased in prevalence in glaucoma.^{23, 24} Asrani et al²⁵ reported that artifacts for RNFL measurements can occur in 19.9% of images. Misalignment artifacts for RNFL measurements can occur in as much as 46.7% of SD-OCT images.²⁶ In addition, the rate of false positives using RNFL thickness for the diagnosis of glaucoma has been reported to be between 18 and 39%.^{22, 27}

Because of the inherent difficulties in measuring RNFL thickness in glaucoma patients (due to decreased RNFL reflectivity, myopia, and PPA), we believe that peripapillary retinal thickness (RT) may provide improved diagnostic performance for glaucoma and may be more easily measured in a greater percentage of glaucoma patients. Although peripapillary RT is a useful metric in diabetic retinopathy and radiation optic neuropathy,^{28, 29} and although the effect of acute intraocular pressure elevation on peripapillary RT in monkeys has been evaluated,³⁰ the diagnostic capability of peripapillary RT in glaucoma patients has not yet been studied using 3D volume scans. Past publications by our group have suggested that RT may be useful in glaucoma diagnosis.^{31–33} Therefore, in this study, we evaluated the diagnostic capability of peripapillary RT from SD-OCT volume scans of the peripapillary region in primary open-angle glaucoma (POAG) patients, who were imaged with the Spectralis machine.

Materials and Methods

PARTICIPANTS AND EXAMINATIONS

All study subjects were recruited from the Glaucoma Service at the Massachusetts Eye and Ear Infirmary between January 2009 and July 2013, as part of the prospective SIG (Spectral Domain OCT in Glaucoma) Study which was approved by the Massachusetts Eye and Ear Infirmary institutional review board. Informed consent form was obtained from all the subjects participating in the study. All methods adhered to the tenets of the Declaration of Helsinki for research involving human subjects, and the study was conducted in accordance with Health Insurance Portability and Accountability Act regulations. All study subjects underwent a complete eye examination by a glaucoma specialist (T.C.C.), and this included history, visual acuity testing, refraction, Goldmann applanation tonometry, slit-lamp biomicroscopy, gonioscopy, ultrasonic pachymetry, dilated ophthalmoscopy, stereo disc photography (Visucam Pro NM; Carl Zeiss Meditec, Inc.), visual field (VF) testing (Swedish Interactive Threshold Algorithm 24–2 test of the Humphrey visual field analyzer 750i; Carl Zeiss Meditec, Inc.), and volume scans using Spectralis OCT (HRA/Spectralis software version 5.4.8.0, Heidelberg Engineering GmbH, Heidelberg, Germany).

Patients were included if they had a spherical equivalent between -5.0 and $+5.0$ diopters and a best-corrected visual acuity of 20/40 or better. Only patients with reliable VF testing were included, with less than 33% fixation losses, less than 20% false-positive results, and less than 20% false-negative results. Patients were excluded if they had discernible congenital anomalies of the anterior chamber, corneal scarring or opacities, diabetic proliferative or

severe non-proliferative retinopathy, VF loss attributable to a non-glaucoma condition, or a dilated pupil diameter of less than 2 mm.

Glaucoma patients were defined as having characteristic changes of the ONH with corresponding abnormal VF defects. The VF was considered to be abnormal if 3 or more contiguous test locations in the pattern standard deviation plot were depressed significantly at the $p < 0.05$ level with at least 1 at the $p < 0.01$ level on the same side of the horizontal meridian and if the VF defect corresponded to the optic nerve appearance.¹³ Only POAG patients were included. VF abnormalities were classified as early (mean deviation [MD] > -6 decibels [dB]), moderate ($-12 \text{ dB} < \text{MD} \leq -6 \text{ dB}$), or severe ($\text{MD} \leq -12 \text{ dB}$).

Normal subjects were those without ocular disease, except for mild cataract, and those with normal VF test results, as defined by a pattern standard deviation of more than 5% and glaucoma hemifield test results within normal limits.³⁴ If both eyes were eligible for the study, 1 eye was selected randomly by using RANDBETWEEN(min,max) function in Microsoft® Office Excel 2007. We defined “1” for the “min” and “2” for the “max”. We ran the command = RANDBETWEEN(1,2) for every row of patients whose both eyes were eligible. We picked the right eye for the result “1” and left eye for the result “2”.

SPECTRALIS OPTICAL COHERENCE TOMOGRAPHY PERIPAPILLARY RETINAL VOLUME SCAN

After pupillary dilation, all SD-OCT imaging was performed with the Spectralis OCT machine which utilizes an 870-nm superluminescent diode laser source. Additional details of the SD-OCT technique have been described elsewhere.^{35, 36} Spectralis OCT provides an automatic real-time (ART) function with an eye-tracking system that can increase image quality. With the ART function activated, multiple frames of the same scanning location are obtained. These data then are averaged for noise reduction, and eye-motion artifacts are reduced. As suggested by the manufacturer, scans with signal strength of less than 15dB (range, 0 to 40) were excluded from the analysis.³⁷ In addition, the criteria for determining adequate scan quality were as follows: a clear fundus image with good optic disc and scan area visibility before and during image acquisition, overlay of volume scan visible and without interruptions, and a continuous scan pattern without missing or blank areas. The Spectralis OCT software enables volume scans, which are performed with a 20×20 degree field and which are centered on the ONH. One-hundred ninety-three sections were taken with the high speed rate and 3 frames for ART. All 193 B-scans for each subject were checked for algorithm artifacts and errors.

Analysis of the volume scans was performed using the Heidelberg Eye Explorer version 1.7.0.0 (Heidelberg Engineering GmbH, Heidelberg, Germany). The scan area overlay was lowered to zero, and the circular grid pattern was centered on the ONH by one of the authors (H.S.). The mean retinal thickness, determined by an internal program algorithm, was recorded in regions we term Circumpapillary Annuli. For these Circumpapillary Annuli, mean retinal thickness values are shown in black (Figure 1 bottom left). For this paper, we only analyzed the outer annulus for each of the circular grid scan options (gray areas, Figure 2), because the inner circular region and inner annulus covered portions of the optic nerve. The outer annuli (gray areas, Figure 2) were further subdivided by quadrant: superior,

temporal, inferior and nasal. For Circumpapillary Annulus 1 (Figure 1 top left, Figure 2 left), the inner area is bounded by circles of diameters 1.00 mm and 2.00 mm, and the outer area by circles of diameters 2.00 mm and 3.00 mm (gray area OCA1, Figure 2 left). For Circumpapillary Annulus 2 (Figure 1 top middle, Figure 2 center), the inner area is bounded by circles of diameters 1.00 mm and 2.22 mm, and the outer area by circles of diameters 2.22 mm and 3.45 mm (gray area OCA2, Figure 2 center). For Circumpapillary Annulus 3 (Figure 1 top right, Figure 2 right), the inner area was bounded by circles of diameters 1.00 mm and 3.00 mm, and the outer area by circles of diameters 3.00 mm and 6.00 mm (gray area OCA3, Figure 2 right). Throughout the rest of the paper, the outer Circumpapillary Annuli of circular grids 1, 2 and 3 will be called OCA1, OCA2, and OCA3, respectively. If parts of OCA1, OCA2 or OCA3 extended outside the 20×20 degree field, these areas were also excluded from the final data analysis.

The average RNFL thickness values for the overall RNFL (360 degrees), for each 90-degree quadrant (superior, temporal, inferior and nasal), and for each sector (superior-temporal [TS], superior nasal [NS], inferior-temporal [TI], and inferior-nasal [NI]) were recorded from the Spectralis OCT RNFL printouts.

STATISTICAL ANALYSIS

All of the calculations in this article were performed using MedCalc for Windows, version 11.4.2 (MedCalc Software, Ostend, Belgium). Demographic characteristics of the normal and glaucoma groups were compared using chi-square tests for categorical variables and non-paired 2-tailed Student's *t* tests for continuous variables. Receiver operating characteristic (ROC) curves were created, and areas under the receiver operating characteristic (AUROC) curves were calculated for the retinal volume scans of the 4 quadrants (i.e. superior, temporal, inferior, and nasal) for each of the OCA1, OCA2 and OCA3. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), and negative likelihood ratio (NLR) were calculated. The cut off value for each variable is calculated by the statistical program automatically, depending on the maximum value of the *Youden index (J)* which is equal to the maximum of $[Sensitivity + Specificity - 1]$. This value corresponds with the point on the ROC curve furthest from the diagonal line. Pairwise comparisons of ROC curves were performed to determine which quadrant had higher accuracy in the diagnosis of glaucoma. False positive and false negative values were evaluated with respect to the cut-off value. Normal subjects who had RT values smaller than the cut off value were counted as false positives, and POAG patients who had RT values larger than the cut off were counted as false negatives. The effects of PPA on false positive and false negative determinations were calculated by chi-square tests.

ROC curves for RNFL thickness values were created, and AUROC curves were calculated for overall RNFL, the 4 quadrants, and the 4 sectors. Sensitivity, specificity, PPV, NPV, PLR, and NLR were calculated as described above. Pairwise comparisons of ROC curves were performed for the best AUROC curve values for RT and RNFL thickness measurements both for all POAG patients and for the early POAG patient subset. Differences were considered significant at *p* values <0.05.

Results

There were 156 study patients, with 67 normal subjects and 89 POAG subjects. Of the 89 POAG subjects, 33 of them had early glaucoma (37.1%), 24 of them had moderate glaucoma (27.0%), and 32 of them had severe glaucoma (36.0%), which represents an equal distribution. Demographics of the study population are shown in Table 1. All 193 B-scans for each subject were checked for algorithm artifacts and errors, and no segmentation errors were noted for any of the automated RT determinations. For all quadrants of RT annuli OCA1, OCA2 and OCA3, POAG and early POAG patients had thinner retinas compared to normal patients ($p < 0.0001$ and $p < 0.01$, respectively, Table 2).

When analyzing OCA1 and OCA2, there were no subjects who were excluded due to OCA1 and OCA2 being outside the 20×20 degree field scan area. When analyzing OCA3, 38 of 156 subjects (23.7%) were excluded from the analysis, because the 20×20 degree scan area did not fully cover the ringed area for OCA3. Twenty-one of these incomplete scanned regions were in the superior quadrant, 24 of them were in nasal quadrant, 6 of them were in the temporal quadrant, and 3 of them were in the inferior quadrant (Figure 1).

Table 3 shows the AUROC curve values and the RT cut-off values which are associated with the highest sensitivity and specificity values for distinguishing normal patients from POAG and early POAG patients. The highest two AUROC curves for distinguishing between normal and both POAG and early POAG patients were both associated with the inferior region [i.e. inferior OCA1 (0.959, 0.939) and inferior OCA2 (0.945, 0.921)]. Pairwise comparisons of ROC curves also revealed that inferior OCA1 and inferior OCA2, which were the highest two ranked AUROC curves, had statistically better diagnostic performance than other quadrants of OCAs for both POAG and early POAG patients.

In quadrant-based pairwise comparisons of ROC curves of normal versus POAG patients, OCA1 had better diagnostic capability than OCA3 for all quadrants. ($p_{\text{superior}} = 0.0051$, $p_{\text{temporal}} = 0.0020$, $p_{\text{inferior}} = 0.0001$ $p_{\text{nasal}} = 0.0031$). OCA2 had better diagnostic capability than OCA3 for all quadrants ($p_{\text{superior}} = 0.0031$, $p_{\text{temporal}} = 0.0028$, $p_{\text{inferior}} < 0.0001$ and $p_{\text{nasal}} = 0.0012$). AUROC curve values are higher in OCA1 than OCA2. There is no difference found between ROC curves of OCA1 and OCA2 except in the nasal quadrant ($p_{\text{superior}} = 0.0723$, $p_{\text{temporal}} = 0.3718$, $p_{\text{inferior}} = 0.0537$ and $p_{\text{nasal}} = 0.0113$).

In quadrant-based pairwise comparisons of ROC curves of normal versus early POAG patients, although OCA1 had higher AUROC curve values than OCA2, there was no statistically significant difference between ROC curves ($p_{\text{superior}} = 0.5986$, $p_{\text{temporal}} = 0.5469$, $p_{\text{inferior}} = 0.0850$ and $p_{\text{nasal}} = 0.0799$). OCA1 had higher AUROC curve values than OCA3 in all quadrants. After comparing ROC curves of OCA1 and OCA3, the diagnostic capability of OCA1 was statistically better than OCA3 for temporal and inferior quadrants ($p_{\text{temporal}} = 0.0342$ and $p_{\text{inferior}} = 0.0005$). The superior and nasal quadrants of OCA1 and OCA3 had the similar ROC curves ($p_{\text{superior}} = 0.4784$ and $p_{\text{nasal}} = 0.1827$). After comparing ROC curves of OCA2 and OCA3, OCA2 had better ROC curve than OCA3 in the temporal and inferior quadrants ($p_{\text{temporal}} = 0.0216$ and $p_{\text{inferior}} = 0.0008$) but there was no difference between the superior and nasal quadrants ($p_{\text{superior}} = 0.5454$ and $p_{\text{nasal}} = 0.3667$).

The diagnostic performance of RT parameters with the best sensitivity and specificity values for distinguishing normal versus POAG patients is shown in Table 4. The diagnostic performance of RT parameters with the best sensitivity and specificity values for distinguishing normal versus early POAG patients is shown in Table 5.

We evaluated images for the presence of PPA, because we wanted to determine if PPA was associated with higher rates of false positive or false negative diagnoses of glaucoma. In OCA1 (Figure 2, gray area, left image), β -zone PPA was detected in a total of 34.0% of patients (53 of 156 subjects). In OCA2 (Figure 2, gray area, center image), β -zone PPA was detected in 21.2% of patients (33 of 156 patients). There were no patients who had PPA that extended into OCA3 (Figure 2, gray area, right image). For each of the three scan patterns, a total of 624 quadrants (156 subjects $\times$ 4 quadrants) were analyzed. Table 6 shows that PPA was noted in 16.5% (103 of 624) of the OCA1 quadrants. The presence of PPA was not significantly correlated with a misdiagnosis of glaucoma, on the basis of false positive and false negative results ($p=0.709$, $p=0.239$). In OCA2, PPA was noted in 8.5% (53 of 624) of quadrants. The presence of PPA again was not significantly associated with an inaccurate glaucoma diagnosis ($p=0.419$, $p=0.640$). Detailed information about PPA with false positive and negative rates is shown in Table 6.

Tables 7 and 8 depict the diagnostic capability of RNFL thickness parameters. Best sensitivity and specificity values for distinguishing normal from POAG patients are shown in Table 7 and for distinguishing normal from early glaucoma patients in Table 8.

The best RNFL thickness AUROC curve values were associated with the inferior quadrant and overall RNFL thickness (0.930, 0.909 for all POAG patients; 0.922, 0.899 for early POAG patients; Tables 7 and 8). Therefore, inferior and overall RNFL thickness measurements were used for pairwise comparisons with inferior OCA1 and inferior OCA2 RT measurements. When comparing best RNFL to RT parameters for normal versus all POAG patients, inferior OCA1 RT was significantly better than overall RNFL ($p=0.03$). Other pairwise comparisons of best RNFL to RT parameters showed similar diagnostic capability [inferior OCA1 RT versus inferior RNFL AUROC curves ($p=0.10$), inferior OCA2 RT versus inferior RNFL ($p=0.50$), inferior OCA2 RT versus overall RNFL ($p=0.17$)].

When comparing best RNFL to RT parameters for normal versus early POAG patients, pairwise comparisons showed similar diagnostic capability for RNFL and RT parameters [inferior OCA1 RT versus inferior RNFL AUROC curves ($p=0.61$), inferior OCA2 RT versus inferior RNFL ($p=0.73$), for inferior OCA1 RT versus overall RNFL ($p=0.18$), inferior OCA2 RT versus overall RNFL ($p=0.62$).

Discussion

Our study shows that SD-OCT peripapillary RT values may be utilized as a diagnostic tool for differentiating glaucoma from normal patients, because both glaucoma patients as well as a subset of early glaucoma patients have thinner RT values compared to normal patients (Table 2). Best AUROC curves and diagnostic values were noted for the inferior quadrants

for the regions which were closer to the optic nerve head (i.e. OCA1 and 2) and for both glaucoma patients and a subset of early glaucoma patients (Table 3). Also, we found that the inferior quadrant RT measurements were best for diagnosing glaucoma, followed by the superior quadrant, and then the temporal and nasal quadrants (Table 3); and this pattern is similar to RNFL measurements which have best diagnostic ability for the superior and inferior quadrants.^{4, 5, 10} This principle that inferior quadrant RT values are best for diagnosing glaucoma, followed by the superior, and then temporal and nasal quadrants, is also true for both glaucoma patients (Table 4) and a subset of early glaucoma patients (Table 5).

While making within quadrant comparisons of OCA1,2 and 3 on the basis of AUROC values, RT measurements closer to the ONH (i.e. OCA1 and OCA2) have better diagnostic capability than regions further from the ONH (i.e. OCA3; Table 3). This is consistent with the fact that RT measurements closer to the ONH have an increased proportion of RNFL to total RT,⁴¹ and that the RNFL is the retinal layer that is preferentially affected by glaucoma disease. Therefore, we believe that the diagnostic performance of RT values is largely dependent on the change in RNFL thickness. Moreover, RNFL tissue loss increasingly affects total RT as the ONH is approached due to the higher proportion of RNFL there. For the subset of early glaucoma patients, RT measurements closer to the ONH (i.e. OCA1 and OCA2) also have better diagnostic performance than the more peripheral OCA3 (Table 3).

We analyzed RNFL thickness data in order to determine if RT or RNFL thickness were better for diagnosing glaucoma. Although reports suggest that RNFL thickness has good diagnostic capability, it is not known whether RNFL or RT is better for glaucoma diagnosis. Many studies support that best RNFL thickness parameters have good diagnostic capability, with AUROC curves ranging between 0.884 and 0.970.^{6, 12, 42–43} Our group also demonstrated good diagnostic capability using Spectralis RNFL thickness measurements.¹³ All these studies have suggested that overall and inferior RNFL thickness measurements provide the best diagnostic capability.^{6,12, 13, 42, 43} When we calculated AUROC curve values for both RNFL and RT measurements, best AUROC curve values were found for the inferior OCA1 and OCA2 RT annuli, followed by inferior and overall RNFL thickness. Pairwise comparisons of these 4 best RT and RNFL AUROC curves showed that inferior OCA1 RT had significantly better diagnostic potential than overall RNFL thickness ($p=0.03$). Other comparisons between best RNFL and RT parameters were all not statistically significant ($p>0.05$). Therefore, this study showed that RT has, at least, the same diagnostic capability as RNFL thickness measurements; and that some RT parameters (inferior OCA1 and inferior OCA2) had better diagnostic capability compared to best RNFL thickness parameters.

In addition to RT parameters having the same or better diagnostic capability compared to RNFL thickness values, RT measurements appear to have the advantage of having fewer algorithm errors and artifacts compared to RNFL thickness measurements. In this study, all 193 B-scans for each subject were checked for algorithm artifacts and errors, and no segmentation errors were noted for any of the automated RT determinations. In contrast, errors in RNFL thickness measurements have been reported to range from 18.0% to 46.7%.^{22, 25–27} Accurate RNFL thickness measurements are more difficult to obtain in

glaucoma patients, because glaucomatous disease causes not only RNFL thinning but also RNFL reflectivity loss. When there is a decrease in RNFL reflectivity, it is more difficult for automated OCT algorithms to differentiate the posterior RNFL border from the less reflective underlying structures. Therefore, delineating the posterior RNFL border is especially difficult in moderate and severe glaucoma patients, who have more significant loss of RNFL reflectivity.¹⁷ There is no evidence in the literature to suggest that glaucoma disease causes a loss of reflectivity in the RPE/Bruch's membrane complex, which comprises the RT posterior border. In summary, compared to RNFL thickness, RT is consistently easier to measure accurately in glaucoma patients, especially in those with moderate to severe glaucoma.

Peripapillary RT measurements in glaucoma may have some other possible advantages over RNFL measurements, especially if there are conditions which may decrease the accuracy of RNFL measurements, such as myopia, PPA, and severe glaucoma.^{15, 16, 18, 21, 44} In this study, we specifically looked at PPA, in order to determine if PPA affects the diagnostic capability of RT measurements. With PPA, there is an absence of certain retinal layers. For example, the cross-sectional composition of β -zone PPA was determined with SD-OCT in 90 eyes.²⁰ In β -zone PPA, the RPE/Bruch's membrane complex and the inner and outer segment junction of the photoreceptors were absent in all subjects. Moreover, with β -zone PPA, the external limiting membrane was absent in 85% of subjects, the outer plexiform layer was absent in 34% of patients, the inner plexiform layer was absent in 29% of subjects, and the ganglion cell layer was absent in 27% of subjects.²⁰ Because of the absence of retinal layers in PPA, it is difficult to distinguish and measure the RNFL when there is PPA. Kim et al²¹ found that the diagnostic performance of RNFL thickness in glaucoma patients with PPA is worse than in patients without PPA. For OCT retinal thickness determinations, the absence of the RPE/Bruch's membrane complex in subjects with PPA may theoretically cause inaccurate retinal thickness measurements, because the lower measurement boundary is no longer well-defined over the analyzed region. We investigated whether the presence of PPA decreased the efficacy of peripapillary RT as a diagnostic parameter for glaucoma. We tested this hypothesis in Table 6, by analyzing the rates of a false positive or false negative diagnosis, with and without PPA. The presence of PPA did not significantly affect the rates of false positives or false negatives. Our findings are preliminary since the sample size was small, and no quantitative grading of the degree of PPA was attempted. Further larger studies are needed to clarify the precise effect of PPA on RT measurements.

Despite careful centering of the pre-set Heidelberg software circular grid on the optic disc, the pre-set circular grid area sometimes extended beyond the square scanned region, so we sometimes had to exclude from the analysis the peripheral RT circular grid areas that extended beyond the square scanned region. This problem occurred with the largest RT annulus OCA3. Since this decreased the number of subjects analyzed for RT annulus OCA3, this may partly explain why the diagnostic capability of OCA3 is less than that of OCA1 and OCA2. It is possible that if OCA3 could have been analyzed for all patients, OCA3, which is furthest from the ONH, may have had better diagnostic value. However, because the RNFL component of the total RT is so small that far from the ONH, we hypothesize that increasing the scanned area and scan time would not have significantly increased the diagnostic capability of RT in OCA3 over that of OCA1 and OCA2.

Evaluating 3D volume scans for peripapillary RT determinations in glaucoma patients had not been tested before, because past studies evaluated RT measurements using 2 dimensional imaging technology. For example, Schuman et al⁴⁵ measured mean RT using time domain OCT circular grids centered on the ONH with scan diameters of 2.9 mm, 3.4mm, and 4.5 mm away from the optic disc. In their study, RT in normal patients were thicker at 303 μ m, 286 μ m, and 256 μ m, respectively, for all 3 scan diameter sizes, compared to thinner RT values in glaucoma patients at 270 μ m, 262 μ m, and 240 μ m, respectively. Although they measured RT in only circular scans not volume scans, they did noted that RT decreases as one is further from the optic disc, which is similar to our results.

One of the limitations of this study is that all our POAG patients had VF defects. So, our paper can only conclude that RT has diagnostic value for perimetric glaucoma. Further studies will be required to evaluate the diagnostic capability of RT in pre-perimetric glaucoma. Another potential limitation of using total retinal thickness is that measurements would include the outer retina which is not affected in glaucoma. This may theoretically decrease the sensitivity of retinal thickness measurements for glaucoma diagnosis in patients with concomitant diseases that may affect the outer retina. Another limitation of this study is the large proportion of eyes excluded using the OCA3 protocol. Since OCA1 and OCA2 have better diagnostic potential than OCA3, the high number of OCA3 areas excluded may incorrectly suggest that larger RT annuli have less diagnostic value than smaller RT annuli, but another study needs to be done to fully evaluate this hypothesis. Nevertheless, since the current ETDRS Heidelberg retinal thickness software necessitated exclusion of many OCA3 areas, this underscores the need for new software specifically designed for glaucoma parameters and not diabetic retinopathy data.

SD-OCT has been shown to be a reliable tool for retinal thickness measurements of the macular region using the ETDRS circular grid.^{38, 39} Ghasia et al⁴⁰ presented excellent reproducibility of retinal thickness measurements of the macular region in normal and glaucoma subjects in both the adult and pediatric study group. However, future studies are needed to investigate the reproducibility of peripapillary RT parameters.

In conclusion, the diagnostic capability of RT is excellent for both POAG and early POAG patients. RT parameters are either the same or better than RNFL parameters for diagnosing glaucoma, and OCT RT measurements appear to be less prone to algorithm errors compared to RNFL measurements in glaucoma patients. Assessment of peripapillary RT may also be useful for detecting the progression of glaucoma.

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References

1. Tielsch JM, Katz J, Quigley HA, Miller NR, Sommer A. Intraobserver and interobserver agreement in measurement of optic disc characteristics. *Ophthalmology*. 1988; 95(3):350–356. [PubMed: 3174002]

2. Quigley HA, Addicks EM, Green WR. Optic nerve damage in human glaucoma. III. Quantitative correlation of nerve fiber loss and visual field defect in glaucoma, ischemic neuropathy, papilledema, and toxic neuropathy. *Arch Ophthalmol*. 1982; 100(1):135–146. [PubMed: 7055464]
3. Spectralis, Spectralis HRA+OCT, Spectralis HRA. Heidelberg Engineering G. Spectralis OCT Hardware Operating Instructions, Version 0001 ed. 2007. p. 22
4. Nakatani Y, Higashide T, Ohkubo S, Takeda H, Sugiyama K. Evaluation of macular thickness and peripapillary retinal nerve fiber layer thickness for detection of early glaucoma using spectral domain optical coherence tomography. *J Glaucoma*. 2011; 20(4):252–259. [PubMed: 20520570]
5. Schulze A, Lamparter J, Pfeiffer N, Berisha F, Schmidtmann I, Hoffmann EM. Diagnostic ability of retinal ganglion cell complex, retinal nerve fiber layer, and optic nerve head measurements by Fourier-domain optical coherence tomography. *Graefes Arch Clin Exp Ophthalmol*. 2011; 249(7): 1039–1045. [PubMed: 21240522]
6. Kita Y, Kita R, Takeyama A, Takagi S, Nishimura C, Tomita G. Ability of optical coherence tomography-determined ganglion cell complex thickness to total retinal thickness ratio to diagnose glaucoma. *J Glaucoma*. 2013; 22(9):757–762. [PubMed: 22668980]
7. Hwang YH, Kim YY. Glaucoma diagnostic ability of quadrant and clock-hour neuroretinal rim assessment using cirrus HD optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2012; 53(4): 2226–2234. [PubMed: 22410556]
8. Mwanza JC, Oakley JD, Budenz DL, Anderson DR. Cirrus Optical Coherence Tomography Normative Database Study G. Ability of cirrus HD-OCT optic nerve head parameters to discriminate normal from glaucomatous eyes. *Ophthalmology*. 2011; 118(2):241–248. [PubMed: 20920824]
9. Kotowski J, Folio LS, Wollstein G, et al. Glaucoma discrimination of segmented cirrus spectral domain optical coherence tomography (SD-OCT) macular scans. *Br J Ophthalmol*. 2012; 96(11): 1420–1425. [PubMed: 22914498]
10. Na JH, Sung KR, Baek S, Sun JH, Lee Y. Macular and retinal nerve fiber layer thickness: which is more helpful in the diagnosis of glaucoma? *Invest Ophthalmol Vis Sci*. 2011; 52(11):8094–8101. [PubMed: 21911590]
11. Sung KR, Na JH, Lee Y. Glaucoma diagnostic capabilities of optic nerve head parameters as determined by Cirrus HD optical coherence tomography. *J Glaucoma*. 2012; 21(7):498–504. [PubMed: 21637115]
12. Rao HL, Zangwill LM, Weinreb RN, Sample PA, Alencar LM, Medeiros FA. Comparison of different spectral domain optical coherence tomography scanning areas for glaucoma diagnosis. *Ophthalmology*. 2010; 117(9):1692–1699. [PubMed: 20493529]
13. Wu H, de Boer JF, Chen TC. Diagnostic capability of spectral-domain optical coherence tomography for glaucoma. *Am J Ophthalmol*. 2012; 153(5):815–826. [PubMed: 22265147]
14. Na JH, Sung KR, Lee JR, et al. Detection of glaucomatous progression by spectral-domain optical coherence tomography. *Ophthalmology*. 2013; 120(7):1388–1395. [PubMed: 23474248]
15. Gurses-Ozden R, Ishikawa H, Hoh ST, et al. Increasing sampling density improves reproducibility of optical coherence tomography measurements. *J Glaucoma*. 1999; 8(4):238–241. [PubMed: 10464731]
16. Wu H, de Boer JF, Chen TC. Reproducibility of retinal nerve fiber layer thickness measurements using spectral domain optical coherence tomography. *J Glaucoma*. 2011; 20(8):470–476. [PubMed: 20852437]
17. van der Schoot J, Vermeer KA, de Boer JF, Lemij HG. The effect of glaucoma on the optical attenuation coefficient of the retinal nerve fiber layer in spectral domain optical coherence tomography images. *Invest Ophthalmol Vis Sci*. 2012; 53(4):2424–2430. [PubMed: 22427540]
18. Leung CK, Mohamed S, Leung KS, et al. Retinal nerve fiber layer measurements in myopia: An optical coherence tomography study. *Invest Ophthalmol Vis Sci*. 2006; 47(12):5171–5176. [PubMed: 17122099]
19. Aref AA, Sayyad FE, Mwanza JC, Feuer WJ, Budenz DL. Diagnostic Specificities of Retinal Nerve Fiber Layer, Optic Nerve Head, and Macular Ganglion Cell-Inner Plexiform Layer Measurements in Myopic Eyes. *J Glaucoma*. 2014; 23(8):487–493. [PubMed: 23221911]

20. Lee KY, Tomidokoro A, Sakata R, et al. Cross-sectional anatomic configurations of peripapillary atrophy evaluated with spectral domain-optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2010; 51(2):666–671. [PubMed: 19850838]
21. Kim SY, Park HY, Park CK. The effects of peripapillary atrophy on the diagnostic ability of Stratus and Cirrus OCT in the analysis of optic nerve head parameters and disc size. *Invest Ophthalmol Vis Sci*. 2012; 53(8):4475–4484. [PubMed: 22618588]
22. Leal-Fonseca M, Rebolleda G, Oblanca N, Moreno-Montanes J, Munoz-Negrete FJ. A comparison of false positives in retinal nerve fiber layer, optic nerve head and macular ganglion cell-inner plexiform layer from two spectral-domain optical coherence tomography devices. *Graefes Arch Clin Exp Ophthalmol*. 2014; 252(2):321–330. [PubMed: 24337431]
23. Jonas JB, Nguyen XN, Gusek GC, Naumann GO. Parapapillary chorioretinal atrophy in normal and glaucoma eyes. I. Morphometric data. *Invest Ophthalmol Vis Sci*. 1989; 30(5):908–918. [PubMed: 2722447]
24. Mitchell P, Hourihan F, Sandbach J, Wang JJ. The relationship between glaucoma and myopia: the Blue Mountains Eye Study. *Ophthalmology*. 1999; 106(10):2010–2015. [PubMed: 10519600]
25. Asrani S, Essaid L, Alder BD, Santiago-Turla C. Artifacts in spectral-domain optical coherence tomography measurements in glaucoma. *JAMA Ophthalmol*. 2014; 132(4):396–402. [PubMed: 24525613]
26. Moreno-Montanes J, Anton A, Olmo N, et al. Misalignments in the retinal nerve fiber layer evaluation using cirrus high-definition optical coherence tomography. *J Glaucoma*. 2011; 20(9): 559–565. [PubMed: 21336154]
27. Kim NR, Lim H, Kim JH, Rho SS, Seong GJ, Kim CY. Factors associated with false positives in retinal nerve fiber layer color codes from spectral-domain optical coherence tomography. *Ophthalmology*. 2011; 118(9):1774–1781. [PubMed: 21550120]
28. Cho HY, Lee DH, Chung SE, Kang SW. Diabetic retinopathy and peripapillary retinal thickness. *Korean J Ophthalmol*. 2010; 24(1):16–22. [PubMed: 20157409]
29. Yousef YA, Finger PT. Optical coherence tomography of radiation optic neuropathy. *Ophthalmic Surg Lasers Imaging*. 2012; 43(1):6–12. [PubMed: 22251840]
30. Fortune B, Yang H, Strouthidis NG, et al. The effect of acute intraocular pressure elevation on peripapillary retinal thickness, retinal nerve fiber layer thickness, and retardance. *Invest Ophthalmol Vis Sci*. 2009; 50(10):4719–4726. [PubMed: 19420342]
31. Chen TC. Spectral domain optical coherence tomography in glaucoma: qualitative and quantitative analysis of the optic nerve head and retinal nerve fiber layer (an AOS thesis). *Trans Am Ophthalmol Soc*. 2009; 107:254–281. [PubMed: 20126502]
32. Yi K, de Boer J, Chen TC. Diagnosing Preperimetric Glaucoma with Modern Imaging Technology. *Ophthalmology Rounds*. 2009; 2(2):1–6.
33. Yi K, Mujat M, Sun W, Park BH, de Boer JF, Chen TC. Peripapillary Retinal Thickness Maps in the Evaluation of Glaucoma Patients: A Novel Concept. *ISRN Ophthalmology*. 2011; 2011:146813.10.5402/2011/146813 [PubMed: 24527226]
34. Gordon MO, Kass MA. The Ocular Hypertension Treatment Study: design and baseline description of the participants. *Arch Ophthalmol*. 1999; 117(5):573–583. [PubMed: 10326953]
35. Cense B, Nassif N, Chen T, et al. Ultrahigh-resolution high-speed retinal imaging using spectral-domain optical coherence tomography. *Opt Express*. 2004; 12(11):2435–2447. [PubMed: 19475080]
36. Chen TC, Cense B, Pierce MC, et al. Spectral domain optical coherence tomography: ultra-high speed, ultra-high resolution ophthalmic imaging. *Arch Ophthalmol*. 2005; 123(12):1715–1720. [PubMed: 16344444]
37. Spectralis HRA+OCT User Guide Software version 5.1. Heidelberg Engineering GmbH; Carlsbad, CA: 2009. p. 25
38. Giani A, Deiro AP, Staurengi G. Repeatability and reproducibility of retinal thickness measurements with spectral-domain optical coherence tomography using different scan parameters. *Retina*. 2012; 32(5):1007–1012. [PubMed: 22366899]

39. Menke MN, Dabov S, Knecht P, Sturm V. Reproducibility of retinal thickness measurements in healthy subjects using spectralis optical coherence tomography. *Am J Ophthalmol*. 2009; 147(3): 467–472. [PubMed: 19026403]
40. Ghasia FF, El-Dairi M, Freedman SF, Rajani A, Asrani S. Reproducibility of Spectral-Domain Optical Coherence Tomography Measurements in Adult and Pediatric Glaucoma. *J Glaucoma*. 2013;10.1097/IJG.0b013e31829521db.2013.05.29
41. Varma R, Skaf M, Barron E. Retinal nerve fiber layer thickness in normal human eyes. *Ophthalmology*. 1996; 103(12):2114–2119. [PubMed: 9003346]
42. Oddone F, Centofanti M, Tanga L, et al. Influence of disc size on optic nerve head versus retinal nerve fiber layer assessment for diagnosing glaucoma. *Ophthalmology*. 2011; 118(7):1340–1347. [PubMed: 21474186]
43. Mwanza JC, Durbin MK, Budenz DL, et al. Glaucoma diagnostic accuracy of ganglion cell-inner plexiform layer thickness: comparison with nerve fiber layer and optic nerve head. *Ophthalmology*. 2012; 119(6):1151–1158. [PubMed: 22365056]
44. Qiu KL, Zhang MZ, Leung CK, et al. Diagnostic classification of retinal nerve fiber layer measurement in myopic eyes: a comparison between time-domain and spectral-domain optical coherence tomography. *Am J Ophthalmol*. 2011; 152(4):646–653 e642. [PubMed: 21726842]
45. Schuman JS, Pedut-Kloizman T, Hertzmark E, et al. Reproducibility of nerve fiber layer thickness measurements using optical coherence tomography. *Ophthalmology*. 1996; 103(11):1889–1898. [PubMed: 8942887]

Biographies

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chapters. Drs. Johannes de Boer and Teresa Chen were the first to image an eye with video-rate 3-dimensional spectral domain optical coherence tomography.

Figure 1.

The three scan protocols used for peripapillary retinal thickness analysis in glaucoma using 3D volume scans. This figure shows the infrared reflectance (IR) image of the 3D volume scans of the optic nerve and peripapillary region (top left, middle, and right), a sample average retinal thickness map (bottom left), a sample retinal thickness topography map (bottom middle), and a sample B-scan image (bottom right). The horizontal green arrow in the IR image represents the 97th of 193 B-scan measurements, and 97/193 is shown in green at the top left corner of the images (top left, middle, and right). Scanned regions are depicted by the green translucent square areas in the IR images which are centered over the optic nerve (top left, middle, and right). The diameters of the blue circular grids of the top row are 1mm, 2mm, and 3mm (top left), 1 mm, 2.22 mm, and 3.45 mm (top middle), and 1 mm, 3 mm, and 6mm (top right). The black-white small squares in the top row in the IR images show the retinal thickness values at the place called Marker whose value is shown in the left bottom image of the figure. The 97th frame of the 193 B scans is shown in the bottom left image of the figure. In the average thickness map (bottom left), retinal thickness values are written in black and retinal volume parameters are written in red. Thickness and volume parameters are only shown for the outer circumpapillary annulus of the circular grid region.

Figure 2.

Schematic representation of the three circular grids used for peripapillary retinal thickness determinations using 3D volume scans. The first scan grid has diameters of 1 mm, 2 mm and 3 mm (left), the second scan grid has diameters of 1 mm, 2.22 mm, and 3.45 mm (center), and the third scan grid has diameters of 1 mm, 3 mm, and 6 mm (right). The gray areas represent the outer circumpapillary annuli of circular grids (OCA) 1 (left), OCA2 (center), and OCA3 (right).

Table 1

Demographics of the normal and primary open angle glaucoma study population.

	Normal	POAG	p*	Early POAG	p**
Number of eyes	67	89		33	
Number of right eyes/left eyes	37/30	51/38	0.871	22/11	0.190
Mean age (years $\pm$ SD)	62.6 $\pm$ 11.6	66.0 $\pm$ 10.6	0.055	67.1 $\pm$ 7.9	0.051
Refractive error (D)					
Sphere	0.008 $\pm$ 1.41	0.04 $\pm$ 1.23	0.878	-0.19 $\pm$ 1.01	0.500
Cylinder	-0.57 $\pm$ 0.74	-0.45 $\pm$ 0.81	0.371	-0.74 $\pm$ 0.57	0.095
Spherical equivalent	-0.28 $\pm$ 1.52	-0.19 $\pm$ 1.18	0.678	1.52 $\pm$ 1.01	0.828
VF					
Mean deviation (dB)	-1.92 $\pm$ 1.99	-11.20 $\pm$ 7.92	<0.0001	-3.97 $\pm$ 1.50	<0.001
Pattern standard deviation (dB)	1.84 $\pm$ 0.70	7.01 $\pm$ 3.35	<0.0001	4.40 $\pm$ 1.77	<0.001

POAG: primary open angle glaucoma. SD: standard deviation, D: diopter, VF: visual field, dB: decibel.

Results are expressed as the mean $\pm$ standard deviation unless otherwise indicated.

* Normal versus POAG

** Normal versus early POAG

Table 2

Mean Retinal Thickness Measurements for Normal and Primary Open Angle Glaucoma Patients, Using 3 Different Diameter Scan Regions of the Peripapillary Retina Using 3D Volume Scans.

		Normal Mean±SD (µm)	POAG* Mean±SD (µm)	Early POAG [†] Mean±SD (µm)
OCA1	Superior	356.0±47.3	289.4±38.0	311.15±32.74
	Temporal	308.7±28.9	264.4±32.9	275.42±33.51
	Inferior	352.7±28.8	278.0±31.2	292.39±23.14
	Nasal	303.4±26.8	270.3±29.0	283.91±20.50
OCA2	Superior	344.9±45.2	288.3±31.3	304.55±28.81
	Temporal	306.1±26.1	270.7±26.2	279.52±26.70
	Inferior	341.5±26.2	278.7±27.1	290.24±22.42
	Nasal	297.8±24.1	272.7±26.6	282.21±19.90
OCA3	Superior	295.2±23.5	265.2±21.9	269.80±19.08
	Temporal	290.5±31.0	266.6±25.3	273.52±27.41
	Inferior	290.8±21.4	255.0±19.6	261.36±17.49
	Nasal	285.0±29.7	262.8±28.6	264.17±24.79

*
p<0.0001 for all

[†]
p<0.01 for all

POAG: primary open angle glaucoma, SD: standard deviation, µm: micrometers or microns, OCA1: outer circumpapillary annulus of circular grid 1, OCA2: outer circumpapillary annulus of circular grid 2, OCA3: outer circumpapillary annulus of circular grid3.

Table 3

Areas Under the Receiver Operating Characteristic Curves and Cut-Off Values for Best Sensitivities And Specificities For Normal Versus Primary Open Angle Glaucoma Patients of Peripapillary Retinal Thickness Using 3D Volume Scans in Glaucoma Diagnosis

		Normal versus POAG		Normal versus early POAG	
		AUROC (SE)	Cut-off μm ()	AUROC (SE)	Cut-off μm ()
OCA1	Superior	0.890(0.0283)	318	0.811 (0.0464)	344
	Temporal	0.842(0.0336)	292	0.777 (0.0500)	292
	Inferior	0.959(0.0176)	318	0.939 (0.0234)	322
	Nasal	0.806(0.0368)	295	0.725 (0.0512)	292
OCA2	Superior	0.879(0.0296)	320	0.807 (0.0463)	310
	Temporal	0.832(0.0346)	293	0.765 (0.0516)	293
	Inferior	0.945(0.0203)	309	0.921 (0.0290)	322
	Nasal	0.758(0.0402)	288	0.693 (0.0539)	304
OCA3	Superior	0.835(0.0346)	289	0.799 (0.0455)	288
	Temporal	0.727(0.0420)	268	0.659 (0.0585)	268
	Inferior	0.887(0.0287)	268	0.854 (0.0414)	267
	Nasal	0.717(0.0452)	270	0.717 (0.0590)	270

POAG: primary open angle glaucoma, AUROC: area under the receiver operating characteristic curve, SE: standard error, μm : micrometers or microns, OCA1: outer circumpapillary annulus of circular grid 1, OCA2: outer circumpapillary annulus of circular grid 2, OCA3: outer circumpapillary annulus of circular grid 3.

Table 4

Diagnostic Performance of Peripapillary Retinal Thickness in Primary Open Angle Glaucoma Using 3D Volume Scans. Table of Best Sensitivity and Specificity Values for 3 Different Diameter Scan Regions.

	Sensitivity (CI)	Specificity (CI)	PLR (CI)	NLR (CI)	PPV (CI)	NPV (CI)
Superior	79.78 (69.9–87.6)	85.07 (74.3–92.6)	5.34 (4.6–6.2)	0.24 (0.1–0.5)	87.7 (78.4–94.0)	76.0 (64.7–85.1)
Temporal	83.91 (74.5–90.9)	76.12 (64.1–85.7)	3.51 (3.0–4.1)	0.21 (0.1–0.4)	82.0 (72.5–89.4)	78.5 (66.5–87.7)
Inferior	93.18 (85.7–97.5)	88.06 (77.8–94.7)	7.80 (7.0–8.7)	0.077 (0.03–0.2)	91.1 (83.2–96.1)	90.8 (80.9–96.6)
Nasal	83.53 (73.9–90.7)	65.67 (53.1–76.8)	2.43 (2.0–3.0)	0.25 (0.1–0.4)	75.5 (65.6–83.8)	75.9 (62.7–86.2)
Superior	85.39 (76.3–92.0)	77.61 (65.8–86.9)	3.81 (3.3–4.5)	0.19 (0.10–0.4)	83.5 (74.2–90.5)	80.0 (68.2–88.9)
Temporal	83.53 (73.9–90.7)	77.61 (65.8–86.9)	3.73 (3.2–4.4)	0.21 (0.1–0.4)	82.6 (72.8–89.9)	78.8 (66.9–88.0)
Inferior	88.64 (80.1–94.4)	89.55 (79.7–95.7)	8.48 (7.6–9.5)	0.13 (0.05–0.3)	91.8 (83.7–96.6)	85.7 (75.3–92.9)
Nasal	77.65 (67.3–86.0)	62.69 (50.0–74.2)	2.08 (1.7–2.6)	0.36 (0.2–0.6)	72.5 (62.1–81.4)	68.9 (55.7–80.1)
Superior	90.24 (81.7–95.7)	63.64 (50.9–75.1)	2.48 (2.0–3.0)	0.15 (0.07–0.3)	75.5 (65.8–83.6)	84.0 (70.7–92.9)
Temporal	59.52 (48.3–70.1)	77.61 (65.8–86.9)	2.66 (2.1–3.3)	0.52 (0.3–0.9)	76.9 (64.7–86.5)	60.5 (49.3–70.8)
Inferior	79.78 (69.9–87.6)	85.07 (74.3–92.6)	5.34 (4.6–6.2)	0.24 (0.1–0.5)	87.7 (78.4–94.0)	76.0 (64.7–85.1)
Nasal	68.49 (56.6–78.9)	71.67 (58.6–82.5)	2.42 (1.9–3.0)	0.44 (0.3–0.7)	74.6 (62.5–84.5)	65.2 (52.4–76.5)

CI: 95% confidence interval, PLR: positive likelihood ratio, NLR: negative likelihood ratio, PPV: positive predictive value, NPV: negative predictive value, OCA1: outer circumferential annulus of circular grid 1, OCA2: outer circumferential annulus of circular grid 2, OCA3: outer circumferential annulus of circular grid 3.

Table 5

Diagnostic Performance Of Peripapillary Retinal Thickness in Early Primary Open Angle Glaucoma Using 3D Volume Scans. Table of Best Sensitivity and Specificity Values for 3 Different Diameter Scan Regions.

	Sensitivity (CI)	Specificity (CI)	PLR (CI)	NLR (CI)	PPV (CI)	NPV (CI)
Superior	87.88 (71.8–96.6)	62.69 (50.0–74.2)	2.36 (1.9–2.9)	0.19 (0.07–0.5)	53.7 (39.6–67.4)	91.3 (79.2–97.6)
Temporal	72.73 (54.5–86.7)	76.12 (64.1–85.7)	3.05 (2.4–3.9)	0.36 (0.2–0.7)	60.0 (43.3–75.1)	85.0 (73.4–92.9)
Inferior	93.94 (79.8–99.3)	85.07 (74.3–92.6)	6.29 (5.5–7.2)	0.071 (0.02–0.3)	75.6 (59.7–87.6)	96.6 (88.2–99.6)
Nasal	72.73 (54.5–86.7)	67.16 (54.6–78.20)	2.21 (1.7–2.9)	0.41 (0.2–0.8)	52.2 (36.9–67.1)	83.3 (70.7–92.1)
Superior	63.64 (45.1–79.6)	86.57 (76.0–93.7)	4.74 (3.6–6.2)	0.42 (0.2–0.9)	70.0 (50.6–85.3)	82.9 (71.9–90.9)
Temporal	69.70 (51.3–84.4)	77.61 (65.8–86.9)	3.11 (2.4–4.0)	0.39 (0.2–0.8)	60.5 (43.4–76.0)	83.9 (72.3–92.0)
Inferior	90.91 (75.7–98.1)	83.58 (72.5–91.5)	5.54 (4.8–6.4)	0.11 (0.03–0.4)	73.2 (57.1–85.8)	94.9 (85.7–99.0)
Nasal	87.88 (71.8–96.6)	49.25 (36.8–61.8)	1.73 (1.3–2.3)	0.25 (0.10–0.6)	46.0 (33.4–59.1)	89.2 (74.3–97.0)
Superior	86.67 (69.3–96.2)	63.64 (50.9–75.1)	2.38 (1.9–3.0)	0.21 (0.08–0.6)	52.0 (37.4–66.3)	91.3 (79.0–97.6)
Temporal	51.52 (33.5–69.2)	77.61 (65.8–86.9)	2.30 (1.6–3.3)	0.62 (0.4–1.1)	53.1 (34.7–70.9)	76.5 (64.6–85.9)
Inferior	84.85 (68.1–94.9)	79.10 (67.4–88.1)	4.06 (3.4–4.9)	0.19 (0.08–0.5)	66.7 (50.5–80.4)	91.4 (80.9–97.2)
Nasal	75.86 (56.5–89.7)	71.67 (58.6–82.5)	2.68 (2.1–3.5)	0.34 (0.2–0.7)	56.4 (39.6–72.2)	86.0 (73.3–94.2)

CI: 95% confidence interval, PLR: positive likelihood ratio, NLR: negative likelihood ratio, PPV: positive predictive value, NPV: negative predictive value, OCA1: outer circumferential annulus of circular grid 1, OCA2: outer circumferential annulus of circular grid 2, OCA3: outer circumferential annulus of circular grid 3.

Table 6

Frequency of Peripapillary Atrophy and Its Impact on Diagnostic Accuracy of Peripapillary Retinal Thickness in Primary Open Angle Glaucoma Using 3D Volume Scans. Table Includes Data from All 156 Subjects (67 Normal and 89 Primary Open Angle Glaucoma Subjects).

		PPA present			Percent of Normals with a False Positive Diagnosis of Glaucoma		p*	Percent of Glaucoma Patients with a False Negative Diagnosis of Glaucoma		p**
		Percentage of all 156 subjects	Number of all 156 subjects	Normal	POAG	PPA absent	PPA present	PPA absent	PPA present	
OCA1 Quadrant	Superior	14.1%	22	7	15	13.3%	28.6%	21.6%	6.7%	1
	Temporal	27.5%	43	10	33	17.5%	50.0%	23.2%	3.0%	0.114
	Inferior	16.0%	25	8	17	8.5%	37.5%	6.9%	5.9%	1
	Nasal	8.3%	13	3	10	35.9%	0.0%	16.4%	10.0%	1
OCA1 All Quadrants		16.5%	103	28	75	19.2%	35.7%	16.7%	6.7%	0.239
OCA2 Quadrant	Superior	7.1%	11	3	8	21.9%	0.0%	14.8%	12.5%	1
	Temporal	16.0%	25	6	19	21.3%	33.3%	18.6%	5.3%	0.697
	Inferior	6.4%	10	3	7	7.8%	0.0%	19.5%	28.6%	0.324
	Nasal	4.5%	7	2	5	27.7%	0.0%	25.0%	0.0%	0.595
OCA2 All Quadrants		8.5%	53	14	39	19.7%	14.3%	9.6%	10.3%	0.640

PPA: peripapillary atrophy, POAG: primary open angle glaucoma.

OCA1: outer circumpapillary annulus of circular grid 1, OCA2: outer circumpapillary annulus of circular grid 2.

* p values comparing rates of a false positive diagnosis between subjects with and without PPA

** p values comparing rates of a false negative diagnosis between subjects with and without PPA

Table 7

Areas Under the Receiver Operating Characteristic Curves and Diagnostic Capability of Retinal Nerve Fiber Layer Thickness (RNFL) in Glaucoma. Table of Best Sensitivity and Specificity Values of Overall RNFL, RNFL Quadrants, and RNFL Sectors.

	AUROC (SE)	Sensitivity (CI)	Specificity (CI)	PLR (CI)	NLR (CI)	PPV (CI)	NPV (CI)
Overall	0.909 (0.0252)	88.89 (80.0 – 94.8)	83.61 (71.9 – 91.8)	5.42 (3.1 – 9.6)	0.13 (0.07 – 0.2)	87.8 (78.6 – 94.0)	85.0 (73.4 – 92.9)
Superior	0.862 (0.0309)	69.14 (57.9 – 78.9)	93.55 (84.3 – 98.2)	10.72 (4.1 – 28.0)	0.33 (0.2 – 0.5)	93.3 (83.8 – 98.2)	69.9 (58.8 – 79.5)
Temporal	0.821 (0.0366)	70.37 (59.2 – 80.0)	83.61 (71.9 – 91.8)	4.29 (2.4 – 7.7)	0.35 (0.2 – 0.5)	85.1 (74.2 – 92.7)	68.0 (56.2 – 78.3)
Inferior	0.930 (0.0219)	91.36 (83.0 – 96.5)	85.48 (74.2 – 93.1)	6.29 (3.4 – 11.6)	0.10 (0.05 – 0.2)	89.2 (80.3 – 94.9)	88.3 (77.4 – 95.2)
Nasal	0.778 (0.0390)	86.08 (76.5 – 92.8)	56.45 (43.3 – 69.0)	1.98 (1.5 – 2.7)	0.25 (0.1 – 0.4)	71.6 (61.3 – 80.4)	76.1 (61.0 – 87.5)
TS	0.837 (0.0336)	62.50 (51.0 – 73.1)	93.55 (84.3 – 98.2)	9.69 (3.7 – 25.4)	0.40 (0.3 – 0.5)	92.6 (82.1 – 97.9)	65.9 (55.0 – 75.7)
NS	0.809 (0.0367)	83.95 (74.1 – 91.2)	66.13 (53.0 – 77.7)	2.48 (1.7 – 3.6)	0.24 (0.1 – 0.4)	76.4 (66.2 – 84.8)	75.9 (62.2 – 86.6)
TI	0.887 (0.0295)	83.95 (74.1 – 91.2)	83.87 (72.3 – 92.0)	5.20 (2.9 – 9.3)	0.19 (0.1 – 0.3)	87.2 (77.6 – 93.7)	80.0 (68.2 – 88.9)
NI	0.831 (0.0347)	83.95 (74.1 – 91.2)	72.58 (59.8 – 83.1)	3.06 (2.0 – 4.6)	0.22 (0.1 – 0.4)	80.0 (69.9 – 87.9)	77.6 (64.7 – 87.5)

AUROC: area under receiver operating characteristic curve, SE: standard error, CI: 95% confidence interval, PLR: positive likelihood ratio, NLR: negative likelihood ratio, PPV: positive predictive value, NPV: negative predictive value, TS: temporal superior sector, NS: nasal superior sector, TI: temporal inferior sector, NI: nasal inferior sector

Table 8

Areas Under the Receiver Operating Characteristic Curves and Diagnostic Capability of Retinal Nerve Fiber Layer Thickness (RNFL) in Early Glaucoma. Table of Best Sensitivity and Specificity Values of Overall RNFL, RNFL Quadrants, and RNFL Sectors.

	AUROC (SE)	Sensitivity (CI)	Specificity (CI)	PLR (CI)	NLR (CI)	PPV (CI)	NPV (CI)
Overall	0.899 (0.0320)	88.24 (72.5 – 96.7)	83.61 (71.9 – 91.8)	5.38 (3.0 – 9.6)	0.14 (0.06 – 0.4)	75.0 (58.6 – 87.4)	92.7 (82.4 – 98.0)
Superior	0.822 (0.0469)	64.71 (46.5 – 80.3)	88.71 (78.1 – 95.3)	5.73 (2.7 – 12.0)	0.40 (0.3 – 0.6)	75.9 (56.5 – 89.7)	82.1 (70.8 – 90.4)
Temporal	0.760 (0.0532)	70.59 (52.5 – 84.9)	72.13 (59.2 – 82.9)	2.53 (1.6 – 4.0)	0.41 (0.2 – 0.7)	58.5 (41.9 – 73.9)	81.5 (68.4 – 90.8)
Inferior	0.922 (0.0295)	94.12 (80.3 – 99.3)	85.48 (74.2 – 93.1)	6.48 (3.5 – 11.9)	0.069 (0.02 – 0.3)	78.0 (62.2 – 89.6)	96.4 (87.5 – 99.6)
Nasal	0.692 (0.0565)	78.79 (61.1 – 91.0)	56.45 (43.3 – 69.0)	1.81 (1.3 – 2.5)	0.38 (0.2 – 0.8)	49.1 (34.9 – 63.3)	83.3 (68.6 – 93.0)
TS	0.762 (0.0559)	51.52 (33.5 – 69.2)	93.55 (84.3 – 98.2)	7.98 (2.9 – 21.8)	0.52 (0.4 – 0.7)	81.0 (58.1 – 94.6)	78.4 (67.2 – 87.2)
NS	0.758 (0.0519)	85.29 (68.9 – 95.0)	62.90 (49.7 – 74.8)	2.30 (1.6 – 3.3)	0.23 (0.1 – 0.5)	55.8 (41.3 – 69.5)	88.6 (75.4 – 96.2)
TI	0.861 (0.0414)	82.35 (65.5 – 93.2)	83.87 (72.3 – 92.0)	5.11 (2.8 – 9.2)	0.21 (0.1 – 0.4)	73.7 (56.6 – 86.7)	89.7 (78.8 – 96.1)
NI	0.832 (0.0423)	91.18 (76.3 – 98.1)	72.58 (59.8 – 83.1)	3.33 (2.2 – 5.1)	0.12 (0.04 – 0.4)	64.6 (49.5 – 77.8)	93.7 (82.8 – 98.7)

AUROC: area under receiver operating characteristic curve, SE: standard error, CI: 95% confidence interval, PLR: positive likelihood ratio, NLR: negative likelihood ratio, PPV: positive predictive value, NPV: negative predictive value, TS: temporal superior sector, NS: nasal superior sector, TI: temporal inferior sector, NI: nasal inferior sector