Published in final edited form as:

Ophthalmology. 2011 July ; 118(7): . doi:10.1016/j.ophtha.2010.11.029.

Comparison of the diagnostic accuracies of Spectralis, Cirrus and RTVue optical coherence tomography devices in glaucoma

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Abstract

Purpose—To compare the diagnostic accuracies of retinal nerve fiber layer (RNFL) thickness measurements obtained with Spectralis (Heidelberg Engineering, Dossenheim, Germany), Cirrus (Carl Zeiss Meditec, Dublin, CA) and RTVue (Optovue Inc, Fremont, CA) for the detection of glaucoma.

Design—Diagnostic, case-control study

Participants—Two hundred thirty three eyes (107 healthy, 126 glaucomatous) of 149 participants from the longitudinal Diagnostic Innovations in Glaucoma Study (DIGS) and from the African Descent and Glaucoma Evaluation Study (ADAGES).

Methods—All participants underwent retinal nerve fiber layer (RNFL) thickness imaging with Spectralis, Cirrus and RTVue in the same visit. Receiver operating characteristic (ROC) curves adjusted for age and race were obtained for quadrants (superior, nasal, inferior, temporal) and global RNFL thickness for all instruments. Areas under ROC (AUC) and sensitivities at fixed specificities (80% and 95%) were calculated and compared.

Main Outcome measure—Comparison of diagnostic accuracy using AUCs and sensitivities at fixed specificities of 80% and 95%.

Results—The RNFL thickness parameter with the largest AUCs was the superior quadrant for the Spectralis (0.88) and the global RNFL thickness for the Cirrus (0.88) and the RTVue (0.87). The pair-wise comparison among the ROC curves showed no statistical difference for all parameters except for the nasal quadrant, which had significantly larger AUC in Spectralis and RTVue compared to Cirrus ($P < 0.03$ for both comparisons). There were no significant differences in sensitivities among the best parameters from each instrument ($P > 0.05$). The superior quadrant thickness measured with Spectralis had sensitivity of 81.9% at a fixed specificity of 80% and 70% at a fixed specificity of 95%. The global thickness measured by the Cirrus had a sensitivity of 80.3% at a fixed specificity of 80% and 65.6% at a fixed specificity of 95%. For the RTVue, the

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Meeting presentation: This study has been accepted as a paper presentation at the 2010 AAO meeting.

Conflicts of interest: MT Leite, none; HL Rao, none; RN Weinreb, Carl Zeiss Meditec, Inc., (C,F); Heidelberg Engineering, GmbH, (F); Optovue, Inc., (C, F); Topcon Medical Systems, Inc., (F, R). LM Zangwill, Carl Zeiss Meditec, Inc. (F), Heidelberg Engineering, GmbH (F), Optovue, Inc. (F), Topcon Medical Systems, Inc. (F); FA Medeiros, Alcon Laboratories, Inc. (C, F, R), Allergan, Inc. (C, R), Carl Zeiss Meditec, Inc. (F, R), Pfizer, Inc. (C, F, R), Reichert, Inc.(R).

global thickness had a sensitivity of 77.9% at a fixed specificity of 80% and 62.1% at a fixed specificity of 95%.

Conclusion—Although the spectral-domain OCTs have different resolution and acquisition rates, their ability to detect glaucoma was similar.

INTRODUCTION

Evaluation of the retinal nerve fiber layer (RNFL) plays an essential role in the diagnosis and follow-up of glaucomatous patients. However, its clinical examination is often difficult and subjective.¹ Several imaging technologies, such as optical coherence tomography (OCT), have been developed to objectively measure the thickness of the parapapillary RNFL in a non-invasive manner. The recent introduction of spectral-domain OCT (SD-OCT) has greatly enhanced scan resolution and reduced acquisition time, providing more reproducible images compared to older versions of this technology.²⁻⁹

Unlike time-domain OCT, SD-OCT technology is commercially available from several different companies. Three of the commonly used SD-OCTs are the Spectralis (Heidelberg Engineering, Dossenheim, Germany), the Cirrus (Carl Zeiss Meditec, Dublin, CA) and the RTVue (Optovue Inc, Fremont, CA). The working principles are similar for all these devices and involve a diode laser scan that collects three-dimensional images of the parapapillary region from which information about the RNFL thickness can be obtained. The instruments differ in acquisition speed and resolution and, possibly, in diagnostic ability. Several studies have addressed the diagnostic accuracy of the SD-OCTs individually or compared them to time-domain technology,^{3-7, 10-14} however, no previous study has evaluated and compared the diagnostic abilities of these instruments using the same population.

The purpose of this study was to compare the diagnostic accuracies of the Spectralis, Cirrus and RTVue SD-OCTs for the detection of patients with glaucomatous visual field loss in a single population.

METHODS

Participants

In this observational case-control study, individuals were recruited from the longitudinal Diagnostic Innovations in Glaucoma Study (DIGS) and the African Descent And Evaluation Study (ADAGES) conducted at the Hamilton Glaucoma Center (University of California, San Diego). Informed consent was obtained from all participants. The University of California San Diego Human Subjects Committee approved all protocols and the methods described adhered to the tenets of the Declaration of Helsinki.

Each participant underwent a comprehensive ophthalmologic examination including review of medical history, best-corrected visual acuity, slit lamp biomicroscopy, intraocular pressure measurement, gonioscopy, dilated funduscopic examination with a 78-D lens, stereoscopic optic disc photography and automated perimetry with the 24-2 Swedish Interactive Threshold Algorithm (SITA; Carl Zeiss Meditec, Inc.).

To be included, subjects had to have best corrected visual acuity of 20/40 or better, spherical refraction within ± 5.0 D, cylinder correction within ± 3.0 D, and open angles on gonioscopy. Eyes with coexisting retinal disease, uveitis, or non-glaucomatous optic neuropathy were excluded from the investigation.

Glaucomatous eyes had to have at least two consecutive, reliable and repeatable standard automated perimetry (SAP) examinations with either a pattern standard deviation (PSD)

outside the 95% normal limits or a glaucoma hemifield test (GHT) result outside the 99% normal limits. Healthy subjects were recruited from the general population and had IOP<22mmHg with no history of elevated IOP and with at least two reliable normal visual fields, defined as a PSD within 95% confidence limits and a GHT result within normal limits. All visual fields were reviewed by the VisFACT (Visual Field Assessment CenTer) visual field reading center. VisFACT checked for the presence of artifacts such as lid and rim artifacts, fatigue effects, inattention or inappropriate fixation. In addition, visual field loss location in consecutive exams was evaluated to ensure repeatability.

Instrumentation

Measurements of the parapapillary RNFL thickness were obtained during the same visit using the Spectralis, Cirrus and RTVue SDOCTs.

Spectralis OCT (Spectralis HRA+OCT; software version 5.2.0.3) uses a dual beam SD-OCT and a confocal laser scanning ophthalmoscope (CSLO) that works by emitting a superluminescent diode light with a center wavelength of 870nm and a infrared scan to simultaneously provide images of ocular microstructures. Spectralis OCT incorporates a real-time eye tracking system that couples CSLO and SD-OCT scanners to adjust for eye movements and to ensure that the same location of the retina is scanned over time. The instrument uses 1024 A-scan points from a 3.45mm circle centered on the optic disc. The examiner is required to manually place the scan around the optic disc. The acquisition rate of the device is 40,000 a-scans per second at an axial resolution of 3.9 μ m. The instrument requires scan averaging to reduce noise, thus increasing the effective acquisition time. To be included, all images were reviewed for non-centered scans and had to have a signal strength >15dB.

The Cirrus (software version 4.5, Carl Zeiss Meditec Inc., Dublin, CA) uses a superluminescent diode scan with a center wavelength of 840nm and an acquisition rate of 27,000 A-scans per second at an axial resolution of 5 μ m. The protocol used for RNFL thickness evaluation was the optic disc cube. This protocol is based on a three-dimensional scan of a 6 $\times$ 6 mm² area centered on the optic disc where information from a 1024 (depth) $\times$ 200 $\times$ 200-point parallelepiped is collected. Then, a 3.46mm diameter circular scan is automatically placed around the optic disc and the information about parapapillary RNFL thickness is obtained. Because information from the whole region is obtained, it is possible to modify the position of the scan after the exam is taken. To be included, all images were reviewed for non-centered scans and had to have a signal strength >6, the absence of movement artifacts and good centering around the optic disc.

The RTVue (software version 4.0.5.39) uses a superluminescent diode scan with a center wavelength of 840nm to provide high-resolution images. The ONH (optic nerve head map) protocol was used in this study. This protocol generates a RNFL thickness map that is measured along a circle 3.45 mm in diameter centered on the optic disc. After the RNFL map is obtained, the RNFL thickness parameters are estimated by assessing a total of 2,325 data points between the anterior and posterior RNFL borders. The instrument is able to collect 26,000 a-scans per second with an axial resolution of 5 μ m. Only good quality images, as defined by a signal strength index of ≥ 30 were used for analysis.

The parapapillary RNFL sectors evaluated in this study were superior quadrant (46°-135°), inferior quadrant (226°-315), temporal quadrant (316°-45°), nasal quadrant (136°-225°) and global (360°) RNFL thickness.

Statistical Analysis

Descriptive statistics included mean and standard deviation for normally distributed variables and median, first quartile, third quartile for non-normally distributed variables.

To evaluate the ability of the instruments to differentiate eyes with glaucomatous visual field loss from healthy eyes, receiver operating characteristic (ROC) curves were built and the area under the ROC curves (AUC) was calculated to summarize the diagnostic accuracy for each parameter. An AUC equal to 1 represents perfect discrimination while an AUC of 0.5 represents chance discrimination.

Initially, we reported AUCs and 95% confidence intervals for each parameter adjusting for age and race. A bootstrap resampling procedure ($n=1000$ resamples) was used to derive these confidence intervals.¹⁵ Race and age adjustment was performed using a ROC regression model.¹⁶ The model is able to adjust for the differences in variables between control and cases by fitting a linear regression of the marker distribution on the adjustment variables among controls. Standardized residuals based on this fitted linear model are used in place of the marker values for cases and controls.¹⁷ The pair-wise comparison of the AUCs was performed for each parameter using a method proposed by Pepe et al.¹⁸ We also calculated the sensitivities at fixed specificities (80% and 95%) for each parameter. To account for the potential correlation between eyes, the cluster of data for the study subject was considered as the unit of resampling when calculating standard errors. This procedure has been previously used to adjust for the presence of multiple correlated measurements from the same unit.^{15, 19}

All statistical analyses were performed with commercially available software (Stata version 10; StataCorp, College Station, Tx). The alpha level (type I error) was set at 0.05.

RESULTS

This study included 233 eyes (107 healthy, 126 glaucomatous) from 149 patients (58 healthy, 91 glaucomatous). Table 1 shows demographics and ocular characteristics. The mean ages of glaucomatous patients and healthy subjects were 50 and 70 years old, respectively ($P<0.001$). No difference in gender was found between glaucomatous and healthy participants ($P=0.205$). African-American ancestry was more prevalent in the glaucomatous group compared to the healthy group ($P=0.019$). Glaucomatous eyes had an average MD of -5.85dB (median = -3.71dB) and an average PSD of 5.36dB (median= 3.52dB).

Table 2 shows the AUC adjusted for race and age for the different parameters of each instrument. The parameters average thickness, superior thickness and inferior thickness had the largest AUCs for all 3 instruments, with small differences among parameters. For the average thickness parameter, areas under the ROC curves were 0.88, 0.88 and 0.87 for Spectralis, Cirrus and RTVue, respectively. The statistical comparison of AUCs between instruments was not able to find significant differences for any of the parameters (Table 2), except for nasal quadrant thickness, which showed significantly larger AUCs for Spectralis (0.73) and RTVue (0.71) compared to Cirrus (0.60; $P < 0.03$ for both comparisons). Figures 1, 2 and 3 show the race and age-adjusted ROC curves for the different instruments for the average, inferior and superior RNFL thickness parameters, respectively.

Table 3 shows sensitivities for fixed specificities at 80% and 95% for the different parameters of each instrument. The parameter with the highest sensitivity obtained using the Spectralis was the superior quadrant thickness with a sensitivity of 81.9% at a fixed specificity of 80% and 70% at a fixed specificity of 95%. For the Cirrus, the parameter with

the highest sensitivity was the global thickness with a sensitivity of 80.3% at a fixed specificity of 80% and 65.6% at a fixed specificity of 95%. The parameter with the highest sensitivity using the RTVue was the global thickness with a sensitivity of 77.9% at a fixed specificity of 80% and 62.1% at a fixed specificity of 95%. There were no statistically significant differences in sensitivities among the best parameters from each instrument ($P>0.05$ for all comparisons). Also, values of sensitivities for fixed specificities were very similar for the average thickness, superior thickness and inferior thickness for all 3 devices.

DISCUSSION

In the present study, we demonstrated that the Spectralis, the Cirrus and the RTVue had similar performances for the discrimination of eyes with glaucomatous visual field loss from healthy subjects. To our knowledge, this is the first study to compare the diagnostic accuracies of these three different SD-OCTs in the same population of glaucomatous and healthy eyes.

The RNFL thickness parameter with the largest AUC for the Spectralis was the superior quadrant followed by global RNFL thickness. In a study evaluating the diagnostic performance of the Spectralis, Leung et al.¹³ reported the global thickness parameter as having the largest AUC. Compared to our results, their study showed larger AUC values for all parameters, up to 0.958. In their study, however, glaucomatous eyes had more severe disease as indicated by the average MD of -10.36dB , compared to -5.85dB from our study. For the Cirrus, the parameter with the largest AUCs was the global thickness, followed by superior and inferior quadrant. These results are similar to those by Park et al.¹² and Leung et al.⁵ who reported the inferior, average and superior quadrant as having the best diagnostic performances using the Cirrus. Both studies have found larger AUCs than the present study. Differences in disease severity and in the definition of glaucomatous damage contribute to this apparent discrepancy. For the RTVue, the parameters with the largest AUCs were superior quadrant and global RNFL thickness. Our results are similar to those reported by Sehi et al.,¹¹ who found that the inferior, average and superior quadrant thickness were the parameters with the best performances. It is important to note that no statistical difference was found between the superior, inferior and global RNFL thickness parameters for the detection of glaucoma in any of the devices; thus, it is likely that, on average, these parameters perform similarly for all three devices.

For all instruments, the performance of the nasal and temporal quadrants for the detection of glaucoma was lower than the performance obtained from the other quadrants. We obtained AUCs ranging from 0.60 to 0.73 for the nasal quadrant and ranging from 0.69 to 0.72 for the temporal quadrant. The greater amount of RNFL loss detected by SD-OCTs in the superior and inferior quadrants compared to the nasal and temporal ones corresponds to the expected pattern of optic nerve damage in patients with early glaucoma.^{11, 12, 20} Another potential explanation for the poor performance of the nasal sector in all instruments could be related to the angle of incidence of the laser beam, which may influence image acquisition and measurements of RNFL thickness in that sector.²¹ The poor performance of the temporal quadrant may be explained by the early glaucomatous damage in our population, in which the papillomacular bundle is likely to be spared. In fact, in a population with more severe glaucoma, Leung et al.²² reported AUCs of 0.88 for the temporal quadrant using the Spectralis versus 0.69 obtained from our study.

Sensitivities at fixed specificities of 80% and 95% were similar among the instruments. For the average thickness parameter, the sensitivities were 81.1% for the Spectralis, 80.3% for the Cirrus and 77.9% for the RTVue for specificity fixed in 80%. Fixing specificity in 95%, we obtained sensitivities of 68.6% for the Spectralis, 65.6% for the Cirrus and 62.1% for the

RTVue. It is interesting to note that even with differences in axial resolution (Spectralis: 3.9 μ m, Cirrus: 5 μ m, RTVue: 5 μ m) and in acquisition time (Spectralis: 40,000 a-scans per second, Cirrus: 27,000 a-scans per second, RTVue: 26,000 A-scans per second) the overall performance was equivalent. Reports comparing SD-OCTs with time-domain OCT have also not found significant differences in the diagnostic performance between these technologies.^{5, 8, 11} Therefore, it is likely that, at least for the cross-sectional detection of eyes with glaucomatous visual field loss, higher resolution is not as beneficial as expected. However, the higher resolution and better reproducibility of SD-OCTs compared to TDOCT may be advantageous for detection of longitudinal change. In addition, different scan protocols, such as the macular ganglion cell complex currently available on the RTVue, may increase the sensitivity of these devices in detecting glaucoma.^{23, 24} Future studies with longitudinal design and testing different protocols should be conducted to address these matters.

In addition to age and race, other covariate may influence the performance of the SD-OCTs, notably, signal strength. Previous studies have shown a significant association between the magnitude of signal strength and RNFL thickness.^{25, 26} To minimize this effect, all images were reviewed for quality and only images with acceptable signal strength were included. Although glaucomatous patients had, on average, lower signal strength compared to healthy eyes, no significant effect of signal strength was found on the diagnostic ability of the instruments after adjusting for age. Furthermore, we found a significant association between age and signal strength, therefore, it is likely that lower signal strength may be explained by advancing age.

Our study has limitations. To be considered glaucomatous, all of our patients had repeatable abnormal visual fields, while our healthy subjects had no evidence of visual field loss. Diagnostic studies using a case-control design such as the one employed on our study may overestimate the performance of the test.^{27, 28} In fact, diagnostic studies are used in clinical practice to evaluate patients suspected of having disease, not individuals with confirmed signs of damage, such as presence of visual field loss. However, due to the absence of a perfect reference standard that can be applied for cross-sectional diagnosis of disease in suspects, diagnostic accuracy studies enrolling these subjects require longitudinal follow-up^{29, 30} which is not yet available with the recently introduced SD-OCTs. Nevertheless, information on the ability of these instruments to detect eyes with visual field damage is essential for initial validation of the tests and assessment of their performance as a screening tool for detection of patients with more advanced signs of disease. Our study did not consider the potential effects of disease severity on the diagnostic abilities of the instruments. Diagnostic tests tend to be more sensitive when the disease is more advanced and studies have confirmed this effect for the SD-OCTs.³¹⁻³⁴ Therefore, different results may be obtained when evaluating the instrument in different clinical settings.

Although differences in axial resolution and acquisition time exist among the SD-OCTs, we demonstrated that the diagnostic performances of the Spectralis, the Cirrus and the RTVue were equivalent for detecting patients with glaucomatous visual field loss.

Acknowledgments

Financial support: Supported in part by NEI R01-EY08208 (FAM), NEI R01-11008 (LMZ), CAPES grant BEX1327/09-7 (MTL). Participant retention incentive grants in the form of glaucoma medication at no cost (Alcon Laboratories Inc., Allergan, Pfizer Inc., SANTEN Inc).

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Figure 1.

Age and race-adjusted receiver operating characteristic (ROC) curves for the global RNFL obtained with the Spectralis (Heidelberg Engineering, Dossenheim, Germany), Cirrus (Carl Zeiss Meditec, Dublin, CA), and RTVue (Optovue Inc., Fremont, CA). RNFL = retinal nerve fiber layer.

Figure 2. Age and race-adjusted receiver operating characteristic (ROC) curves for the inferior RNFL obtained with the Spectralis, Cirrus, and RTVue. RNFL = retinal nerve fiber layer.

Figure 3. Age and race-adjusted receiver operating characteristic (ROC) curves for the superior RNFL obtained with the Spectralis, Cirrus, and RTVue. RNFL = retinal nerve fiber layer.

Clinical and Ocular Characteristics of the Included Eyes Presented as Mean ($\pm$ Standard Deviation), Unless Indicated Otherwise

Table 1

Characteristics	Healthy Eyes (n = 107)	Glaucomatous Eyes (n 126)
Age (yrs)	50 ($\pm$ 19)	70 ($\pm$ 10)
Gender (% male)	36%	46%
Ancestry (% African-American)	25%	39%
MD (dB) [*]	0.32 (-0.36, 0.4, 0.97)	-5.85 (-7.59, -3.61, -2.
PSD (dB) [*]	1.48(1.27, 1.48, 1.68)	5.36 (2.15, 3.52, 7.95)

MD = mean deviation; PSD = pattern standard deviation.

^{*} Non-normally distributed variables represented as mean (first quartile, median, third quartile).

Table 2

Race and Age-Adjusted Areas Under Receiver Operating Characteristic Curves (95% Confidence Interval) for the Different Parameters of Each Instrument

Sector	Spectralis (Heidelberg Engineering, Dossenheim, Germany)	Cirrus (Carl Zeiss Meditec, Dublin, CA)	RTVue (Optovue Inc., Fremont, CA)	<i>P</i> Value [*]
Global thickness	0.88 (0.82–0.94)	0.88 (0.82–0.94)	0.87 (0.81–0.93)	0.34
Inferior thickness	0.85 (0.79–0.92)	0.87 (0.81–0.93)	0.86 (0.80–0.92)	0.28
Superior thickness	0.88 (0.83–0.94)	0.88 (0.82–0.93)	0.86 (0.79–0.92)	0.18
Nasal thickness	0.73 (0.64–0.81)	0.60 (0.51–0.71)	0.71 (0.62–0.81)	0.01 [†]
Temporal thickness	0.70 (0.61–0.80)	0.69 (0.58–0.79)	0.72 (0.63–0.81)	0.26

Largest areas under ROC curves for each instrument represented in bold.

^{*} Smallest *P* value obtained from the pairwise comparison between 2 instruments.

[†] The comparison between Spectralis and Cirrus (*P* = 0.01) and between RTVue and Cirrus (*P* = 0.03) reached statistical significance.

Table 3
Sensitivities for Specificities Set at 80% and 95% According to the Retinal Nerve Fiber Layer Thickness Parameter in Each Instrument

Parameters	Spectralis		Cirrus		RTVue	
	Specificity at 80%	Specificity at 95%	Specificity at 80%	Specificity at 95%	Specificity at 80%	Specificity at 95%
Global thickness	81.1%	68.6%	80.3%	65.6%	77.9%	62.1%
Inferior thickness	76.7%	61.8%	79.6%	65.9%	77.9%	61.7%
Superior thickness	81.9%	70%	79.3%	63.9%	77.8%	63.8%
Nasal thickness	54.8%	31.6%	34.4%	14.1%	55.1%	34.9%
Temporal thickness	47.6%	21.1%	41.7%	13.6%	48.9%	20.8%