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Journal
Ophthalmology Glaucoma, 4(2)

ISSN
2589-4234

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Publication Date
2021-03-01

DOI
10.1016/j.ogla.2020.08.012

Peer reviewed

HHS Public Access

Author manuscript

Ophthalmol Glaucoma. Author manuscript; available in PMC 2022 March 01.

Published in final edited form as:

Ophthalmol Glaucoma. 2021 ; 4(2): 209–215. doi:10.1016/j.ogla.2020.08.012.

Local Macular Thickness Relationships between Two OCT Devices

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Abstract

Purpose: To compare local ganglion cell/inner plexiform (GCIPL) thickness measurements between two OCT devices and explore factors that may influence the difference in measurements.

Design: Cross-sectional study.

Subjects: 69 glaucoma eyes (63 patients) with evidence of central damage or mean deviation of −6.0 dB or worse on 24–2 visual field.

Methods: Cirrus and Spectralis OCT macular volume scans were exported and data from the central 20° of both OCT devices were centered, aligned, and 50×50 arrays of 0.4°×0.4° superpixels were created. We estimated nonparametric (Spearman's) correlations and used Bland-Altman plots to compare GCIPL thickness measurements between the two OCTs at the superpixel level. Factors that may have influenced the differences between thickness measurements between the two devices were explored with linear mixed models.

Main Outcome Measures: Pooled and individual eye Spearman's correlation and agreement between thickness measurements from the two devices.

Results: The median (IQR) 24–2 visual field mean deviation was −6.8 (−4.9, −12.3) dB. The overall pooled Spearman's correlation between the two devices for all superpixels/eyes was 0.97 ($p<0.001$). The median (IQR) within-eye correlation coefficient was 0.72 (0.59–0.79). Bland-Altman plots demonstrated a systematic bias in most individual eyes with Spectralis GCIPL measurements becoming larger than Cirrus measurements with increasing superpixel thickness.

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The average superpixel thickness and distance to the fovea influenced the thickness difference between the two devices in multivariable models ($p<0.001$).

Conclusions: Local macular thickness measurements from the Spectralis and Cirrus devices are highly correlated but not interchangeable. Differences in thickness measurements between the two devices are influenced by the location of superpixels and their thickness.

Keywords

Optical Coherence Tomography; Macula; GCIPL thickness; superpixels

Introduction

Optical Coherence Tomography (OCT) has become a standard tool for glaucoma evaluation. [1,2] A significant proportion of the retinal ganglion cells (RGCs) reside in the macula, and structural damage to central RGCs can be measured with macular OCT imaging. [3,4] The three most commonly used OCT devices in the US, Cirrus high-definition OCT (HD-OCT), Spectralis OCT, and RTVue, each provide a different macular structural outcome measure and none of these measures has been proven to be clearly superior to others. [5–7]

Structural and functional measures play a significant role in glaucoma diagnosis and management.[8] Prior studies have reported that regional macular thickness measurements from different types of OCTs are not directly comparable, and that measurements from different OCTs cannot be used interchangeably in an individual due to different imaging and segmentation algorithms. [2,5,9] On the other hand, with the availability of DICOM images and patient mobility, it would be ideal if OCT images from various devices could be compared over time.[6]

The standardization of layer segmentation among various OCT devices has been previously explored. [6] There are no uniform approaches for combining macular structural measurements originating from different OCT devices with central VF measurements. Models for evaluating structure-function relationships require local OCT data in order to be able to provide one-to-one correspondence with central visual field test locations. [7,10]

The goal of the current study is to: 1) compare GCIPL thickness measurements between Spectralis and Cirrus OCTs at the superpixel level; 2) investigate factors such as age, axial length, disease severity or eccentricity that may influence differences in GCIPL measurements.

Methods

Sixty-nine eyes of 63 patients from the Advanced Glaucoma Progression Study (AGPS), an ongoing longitudinal prospective study at Stein Eye Institute, were included in this study. The study was performed in accordance with the tenets of the declaration of Helsinki and the Health Insurance Portability and Accountability Act (HIPAA) and was approved by the Human Research Protection Program at the University of California Los Angeles. Inclusion criteria for the enrolled eyes were: 1) clinical diagnosis of primary open-angle glaucoma, primary angle-closure glaucoma, pseudoexfoliative glaucoma, and pigmentary glaucoma; 2)

age between 40–80 years; 3) best-corrected visual acuity ≥20/50; 4) good quality macular OCT cubes with both Spectralis and Cirrus OCTs defined as quality factor >15 and signal strength >6, respectively, and absence of artifacts or significant segmentation issues on macular B-scans or confounding macular pathology such as epiretinal membrane, diabetic retinopathy, or age-related macular degeneration among others based on a subjective review of the images; 5) 24–2 VF mean deviation of −6.0 dB or worse, or evidence of central VF involvement defined as the presence of ≥2 test locations with $p < 0.05$ on the pattern deviation plot within the central 10 degrees on the 24–2 standard achromatic VFs; and 6) no significant confounding retinal or neurological disease. All study patients underwent a thorough eye examination at baseline and macular imaging with Spectralis OCT (Heidelberg Engineering®, Heidelberg, Germany) and Cirrus HD-OCT (Carl Zeiss Meditec®).

Macular OCT imaging

The Posterior Pole Algorithm of Spectralis SD-OCT acquires 61 horizontal B-scans, approximately 120 μm apart, extending across a 30°×25° area, parallel to the axis connecting the center of the fovea to the centroid of the Bruch's membrane opening (BMO). Each scan consists of 768 A-scans. The acquisition of B-scans is repeated 9–11 times to decrease speckle noise. The Glaucoma Module Premium Edition (GMPE) software was used to segment the individual retinal layers. We extracted the raw OCT data as XML files containing 61×768 matrices for the ganglion cell layer (GCL) and inner plexiform layer (IPL). The GCL and IPL data were then summed to calculate GCIPL thickness measurements. Left eye data were converted to the right eye format.

The Macular Cube 200×200 of Cirrus HD-OCT consists of 40,000 A-scans in a 6×6mm area, centered on the fovea. Segmentation of the macular cube data was performed by Carl Zeiss Meditec's proprietary software, and a 200×200 matrix of GCIPL thickness measurements was provided by the company. All left eye data were converted into right eye format.

Spectralis OCT segmentation errors were corrected where applicable. The images were reviewed by experienced observers in our research laboratory who were instructed to correct any areas of obviously incorrect segmentation but not to intervene if they were not certain to be able to improve the segmentation. Since this capability is not available with Cirrus HD-OCT, eyes with obvious artifacts or issues with segmentation were excluded from the study sample.

Reformatting raw data

Current Spectralis OCT macular cubes span a 30°×25° area centered on the fovea whereas Cirrus HD-OCT provides GCIPL measurements in approximately the central 20°×20° of the macula. To match cube data from the 2 devices, we extracted the central 20°×20° of raw data for Spectralis OCT centered on the fovea. We interpolated thickness measurements between the sequential B-scans linearly to create a square thickness matrix. Thickness measurements were then averaged to create 50×50 arrays of 0.4°×0.4° superpixels for the macular OCT cube. Cirrus 200×200 Macular Cube GCIPL matrices were also averaged to create 50×50 arrays of 0.4°×0.4° superpixels to match the reformatted Spectralis OCT data (Figure1).

Rotational matching of Cirrus and Spectralis OCT macular cubes

The Posterior Pole algorithm of Spectralis OCT acquires B-scans with respect to the axis connecting the BMO centroid and the fovea (FoBMO axis); however, the macular cube of the Cirrus HD-OCT is acquired parallel to the horizontal acquired image frame (AIF). To take this difference into account, the Spectralis data matrices were counter-rotated by the angle offset between the AIF and the FoBMO, the FoBMO axis angle. For each eye, this angle offset was carried out by aligning the en face infrared fundus image of the Spectralis with the scanning laser ophthalmoscope (SLO) fundus image of the Cirrus HD-OCT. The alignment was performed by the i2k Retina software (i2k Retina Pro, Version: 2.5.0, DualAlign, LLC, Clifton Park, NY) based on a Dual-Bootstrap algorithm.[11]

Statistical analyses

We estimated nonparametric correlations (Spearman's correlation coefficients) between GCIPL thickness at superpixels derived from the two OCTs. We also used Bland-Altman plots to explore the agreement in superpixel measurements within eyes and for all eyes pooled together to detect potential bias in the corresponding measurements. Proportional bias is considered to be present if the measurement difference and average of measurements by the two devices are significantly correlated. We used linear mixed models to investigate the potential influence of covariates such as age, axial length, visual field mean deviation, GCIPL thickness or eccentricity on the difference in measurements by the two devices. Superpixels were divided into 3 eccentricities based on the distance from the fovea consisting of inner, middle and outer rings, 0°–4°, 4°–12° and 12°–20° from the fovea, respectively (Figure1).

Results

We included 69 eyes of 63 glaucoma patients. Table 1 describes the demographic and clinical characteristics of the study sample. Seventy percent of the study sample (48 eyes) had primary open-angle glaucoma. The median (IQR) visual field mean deviation (MD) of 24–2 VFs in the study sample was −6.8 (−4.9, −12.3) dB. The median (IQR) GCIPL thickness was significantly different between Cirrus and Spectralis OCTs at all 3 eccentricities as follows for Cirrus vs. Spectralis OCTs: 23.5 (20.7, 26.3) vs. 20.2 (16.6, 24.1) μm at 0°–4°eccentricity, 29.9 (26.2, 35.8) vs. 27.6 (22.8, 34.5) μm at 4°–12° eccentricity, and 26.4 (18.5, 35.7) vs. 23.7 (17.3, 31.9) μm at 12°–20° eccentricity, respectively ($p < 0.001$). The correlation coefficient between Spectralis and Cirrus OCT average superpixel thickness measurements was 0.97 ($p < 0.001$) when all superpixels in all eyes were pooled (Figure 2). The median (IQR) within-eye correlation coefficient was 0.72 (0.59–0.79). Figure 3 demonstrates the frequency distribution of correlation coefficients between Spectralis and Cirrus macular GCIPL measurements at 0.4°×0.4° superpixels for individual eyes. Figure 4 displays the Bland-Altman plot for the entire study sample. The concordance correlation coefficient (agreement between two devices) was 0.66 (CI: 0.66–0.67, $p < 0.001$). The average (±SD) thickness difference at superpixels was −2.8 (± 6.1) μm (95% limits of agreement: −14.7 to 9.1 μm). A review of Bland-Altman plots for individual eyes revealed that most eyes tended to show a systematic bias towards an increasing difference in thickness measurements with increasing superpixel thickness (Figure 5), i.e.

Spectralis measurements tended to become larger than Cirrus measurements. The agreement between the two devices and the 95% limits of agreement for the average GCIPL thickness at different eccentricities are displayed in Figure 6. Figure 7 demonstrates the frequency distribution of the slopes of Bland-Altman plots of all individual eyes.

A multivariable linear mixed model including intraocular pressure, visual field MD, and spherical equivalent, a larger average GCIPL thickness (i.e., average of thickness measurements from the two devices), shorter distance to the fovea, and a more negative MD were associated with a more positive Spectralis OCT measurement ($p < 0.001$ for all).

Discussion

We used a superpixel-based approach to compare local macular thickness measurements from two devices. While the present study found that the GCIPL measurements from Spectralis and Cirrus OCT devices demonstrated a strong correlation ($\rho = 0.97$) at the superpixels level, Bland-Altman plots showed a systematic bias, depending on the GCIPL thickness and the distance from the fovea. Although these devices use similar technology, important differences in measurements regardless of eccentricity indicates that the devices should not be used interchangeably. To our knowledge, this is the first study to compare local macular thickness measurements at the level of superpixels between two OCT devices in glaucoma patients. Our approach could be used as a to compare data from macular cubes acquired with different OCT devices and may also be used as a unifying approach for combining macular structural and functional data cross-sectionally and longitudinally with different OCT devices.

Several previous studies have analyzed the agreement and comparability of the retinal and peripapillary nerve fiber layer thickness measurements from Cirrus and Spectralis OCTs. Although measurements were highly repeatable for each device, a significant difference was reported between the two devices for the retinal nerve fiber layer (RNFL) thickness in glaucoma patients,[12–14] full macular thickness (FMT) in healthy subjects,[1] and FMT and GCIPL thickness in eyes with diabetic macular edema. [15] Such differences among newer generation spectral domain OCTs could be challenging with regard to monitoring of glaucoma patients. [14]

We compared GCIPL thickness measurement from Spectralis and Cirrus in a group of 69 glaucomatous eyes with central or moderate to severe glaucoma damage at the level of 0.4°×0.4° superpixel. Given the vertical distance between sequential horizontal B-scans of Spectralis' imaging protocol (about 120 μ), this is the lowest useful resolution for the superpixel size for such comparisons. The correlation between GCIPL thickness measurements from the two OCT devices was overall strong (0.97 for the entire sample; $p < 0.001$); however, a fair amount of within-eye variability was observed when thickness correlations were investigated within individual eyes with a median (IQR) ρ of 0.72 (0.61–0.79). This is consistent with prior recommendation that the two devices may not be used interchangeably in individual eyes and casts doubt on the feasibility of a universal formula for converting measurements from one OCT device to another. [15] Mitsch et al. found that the global Pearson correlation coefficient for neuroretinal rim width (NRW) between Cirrus and

Spectralis OCTs was 0.78 ($p < 0.01$) in glaucoma patients. [5] Interestingly, they found a higher correlation between NRW width among healthy subjects (0.95; $p < 0.01$). Faghihi and colleagues reported a high correlation between Spectralis and Cirrus peripapillary RNFL thickness measurements ($r = 0.912$, $p < 0.001$) in eyes with suspected or established glaucoma. [14] Lammer and associates reported Pearson's correlation coefficients >0.7 among various OCT devices, including Spectralis SD-OCT, Cirrus HD-OCT, 3D OCT-1000, and Stratus OCT when assessing full retinal thickness in eyes with diabetic macular edema. [16] A study by Leite et al. comparing average RNFL thickness between Cirrus HD-OCT and Spectralis OCT reported a systematic bias with a tendency towards higher measurements with Spectralis OCT with increasing thickness. [1] In our study, while no significant fixed bias was observed on the Bland-Altman plots for pooled data, review of the plots for individual eyes revealed a small fixed bias between the two OCT measurements with Cirrus HD-OCT measurements being on average higher than those for Spectralis OCT ($p < 0.001$) at the level of 0.4°×0.4° superpixels. Prior studies showed that Spectralis thickness measurements were higher than Cirrus thickness values when measuring GCIPL thickness in eyes with diabetic macular edema, macular and GCIPL thickness in glaucomatous patients, or central retinal thickness and FMT in neovascular age-related macular degeneration. [2,15,17]

One important finding of our study was that despite accounting for the average superpixel thickness, the systematic bias observed between Cirrus and Spectralis GCIPL measurements varied as a function of eccentricity (Figures 6 and 7). The slope of the observed systematic bias was positive for the two eccentricities closer to the fovea (0°–4° and 4°–12° zones), whereas it was negative for the 12°–20° zone. A closer look at Figure 6C suggests that this negative slope may be driven by superpixels with very low GCIPL thickness, implicating possible poor segmentation and measurement accuracy in the peripheral macula as the cause.

Similar to the pooled data, most individual eyes demonstrated a positive systematic bias in measurements, i.e., as average GCIPL measurements increased, the differences tended to reverse and Spectralis GCIPL thickness measurements became larger than those of Cirrus HD-OCT (Figure 5). The fact that this pattern was not observed in all eyes could be a function of the range of GCIPL measurements in an individual eye. Alternatively, this might be a reflection of the lower measurement floor of Spectralis OCT compared with Cirrus HD-OCT.[18]

While there is no evidence in the literature on the ideal size of superpixels, the 0.4°×0.4° superpixels in our study represent a compromise between the larger 3°×3° superpixels provided by Spectralis OCT and the much smaller superpixels of Cirrus HD-OCT, which consist of the averaged thickness within a grid of 4×4 pixels. While there is no evidence to support the optimal size for macular superpixels, it is expected that with decreasing size of superpixels, the amount of variability would increase; at the same time, larger superpixels could dilute information due to averaging of data (Thung E, Knipping S, Caprioli J, Nouri-Mahdavi K. Global and Regional Intrasession Test-Retest Variability of Macular Thickness Measurements with Spectral-domain Optical Coherence Tomography with and without Tracking. Poster presentation at 2013 Annual meeting of the Association for Research in Ophthalmology and Vision Science). The 0.4°×0.4° superpixels used in this study provide a

compromise with regard to the local information acquired vs. magnitude of noise; this issue needs to be formally explored.

We tested the influence of various confounding factors on the difference between superpixel thickness measurements from the two devices. We found that only eccentricity (distance from foveal center), mean GCIPL thickness, and to a much smaller extent a worse MD influenced this outcome ($p < 0.001$ for all). Leite et al. reported that the agreement between RNFL measurements from Spectralis and Cirrus OCTs was affected by longer axial length ($p = 004$), more negative spherical equivalent ($p < 0.001$) and worse visual field mean deviation ($p = 0.001$).[1] In our models, visual field MD was a much weaker predictor of the difference in GCIPL thickness measurements between the two devices compared to eccentricity and mean GCIPL thickness . Since the predicted outcome measure was estimated at the level of superpixels, it was expected that the GCIPL thickness measurements at the level of superpixels would be a much stronger local proxy for glaucoma damage.

We provide an approach to match OCT superpixels derived from different devices and imaging algorithms that can be used to compare and unify such measurements. This approach could be used to reformat structural data from various OCT devices so that matching of macular structure-function data can be implemented in a uniform way both cross-sectionally and over time. [19] The availability of such software could significantly improve the study of longitudinal structure-function relationships in glaucoma patients and is expected to improve monitoring of glaucoma patients.

One limitation of our study is that we only compared the GCIPL thickness in a cross-sectional group of glaucoma eyes. The results cannot be generalized to other macular parameters or to healthy eyes. Given that study eyes had central or moderate to severe glaucomatous damage, there was a wide range of observed GCIPL measurements and the results, therefore, should be generalizable to patients over a wide range of glaucoma severity. We had 6 out of 63 patients who had both eyes included in this study. Methods for accounting for clustering of data are not well-developed for nonparametric correlations used in this study. To address this issue indirectly, we calculated the correlation coefficient for corresponding superpixel thickness measurements between left and right eyes for each device to verify if this was indeed an issue that could confound the results. The correlation coefficients (ρ) were 0.02 ($p = 1.0$) and 0.14 ($p = 0.80$) for between-eye correlations of superpixel thickness measurements with Cirrus and Spectralis OCTs, respectively.

In summary, we propose a method for overlaying macular thickness measurements from various OCT devices within the central macula. We demonstrate that despite the high correlation of GCIPL thickness measurements between two commonly used devices, such measurements are not interchangeable or easily convertible given the presence of both fixed and systematic bias between the measurements, influenced by GCIPL thickness and eccentricity. Our proposed approach could be used as a unified platform for formatting data from different OCT devices and would facilitate the comparison of OCT devices.

Acknowledgments

This study was supported by an NIH R01 grant (R01-EY029792, KNM), an unrestricted Departmental Grant from Research to Prevent Blindness and an unrestricted grant from Heidelberg Engineering (KNM).

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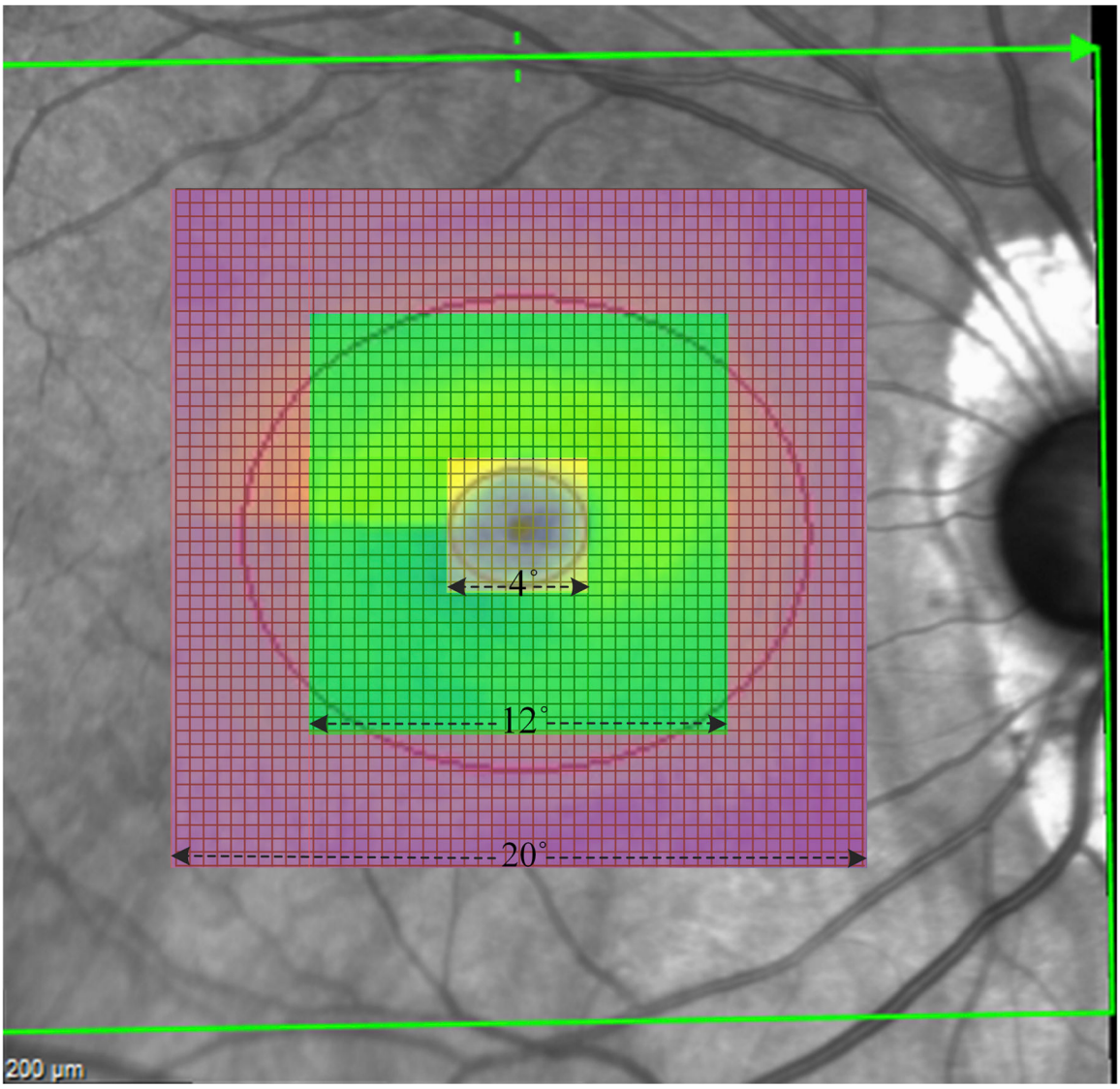

Figure1.

The region of interest from Cirrus and Spectralis OCT macular volume scans consisted of 50×50 arrays of 0.4°×0.4° superpixels divided into 3 eccentricities: 0°–4° eccentricity (yellow), 4°–12°(green), and 12°–20° eccentricity (purple).

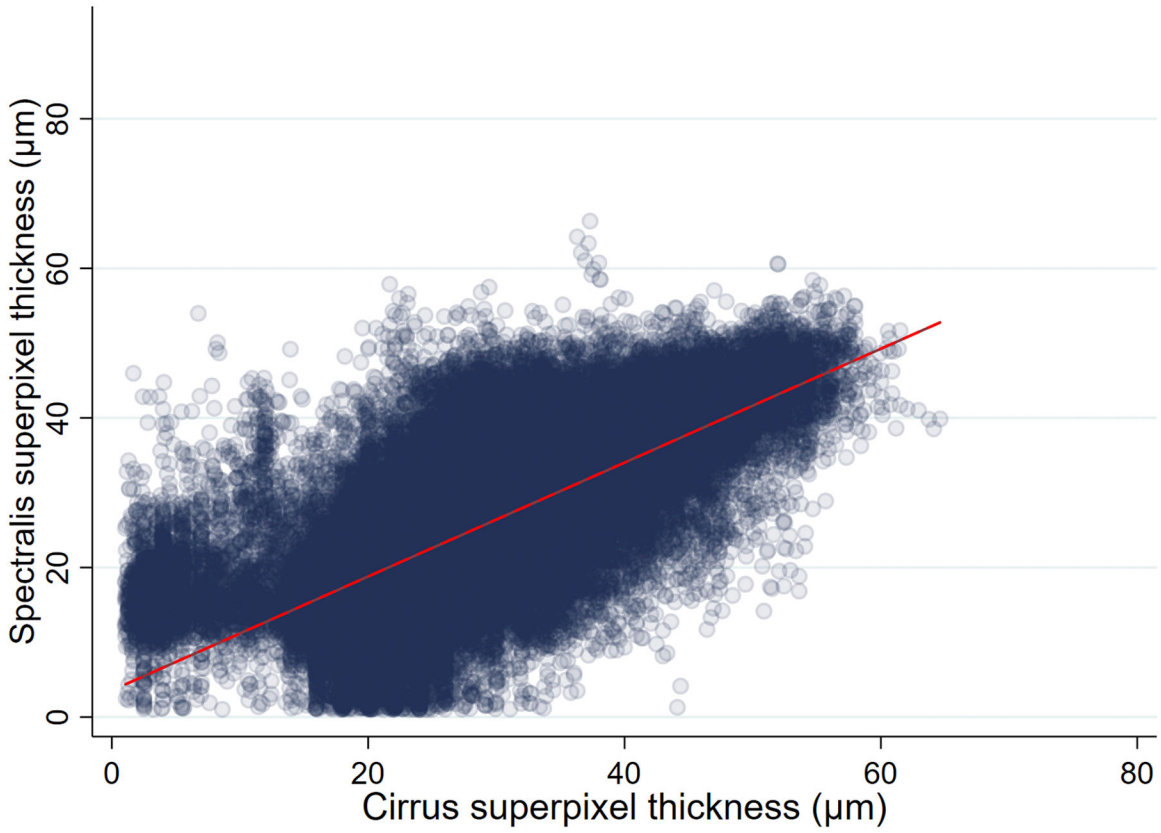

Figure 2.
Bivariate plot of Cirrus and Spectralis GCIPL measurements at 0.4°×0.4° superpixels located within 20° of the fovea.

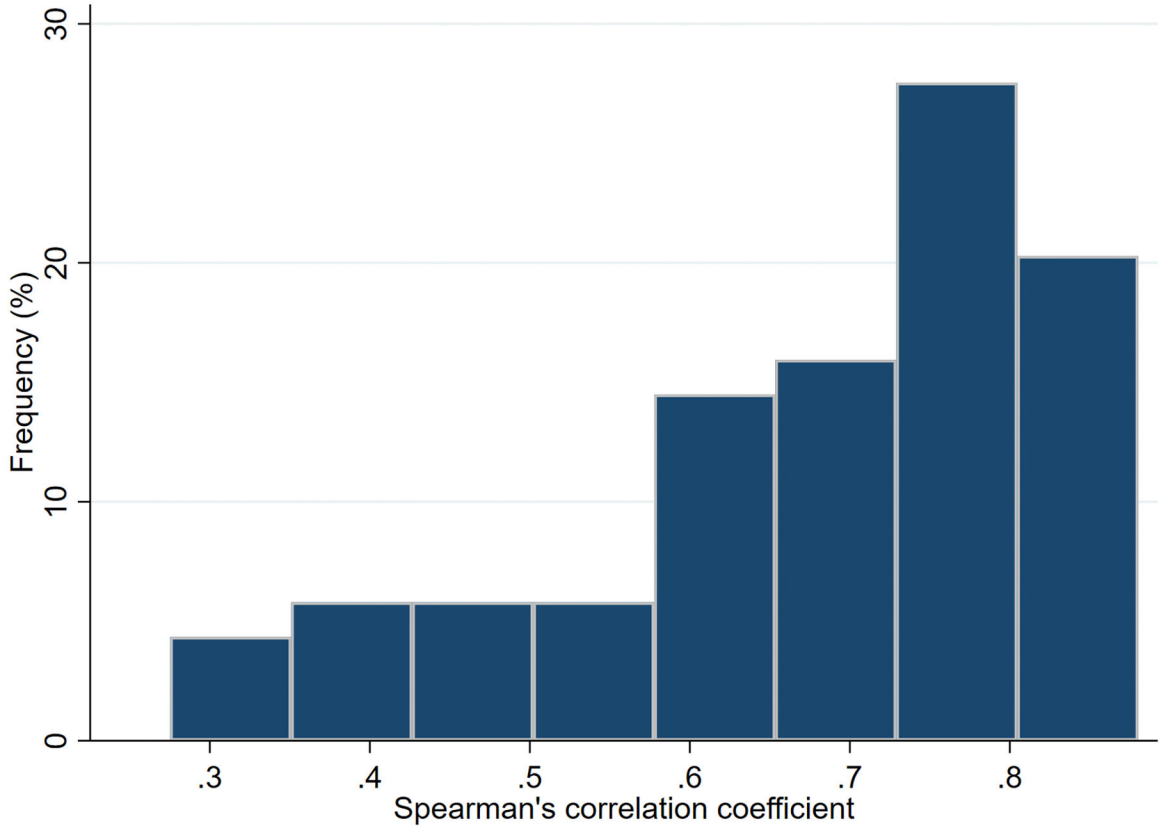

Figure 3.

Frequency distribution of Spearman's correlation coefficients for correlation of GCIPL thickness measurements within 0.4°×0.4° macular superpixels in individual eyes derived from Spectralis and Cirrus OCTs.

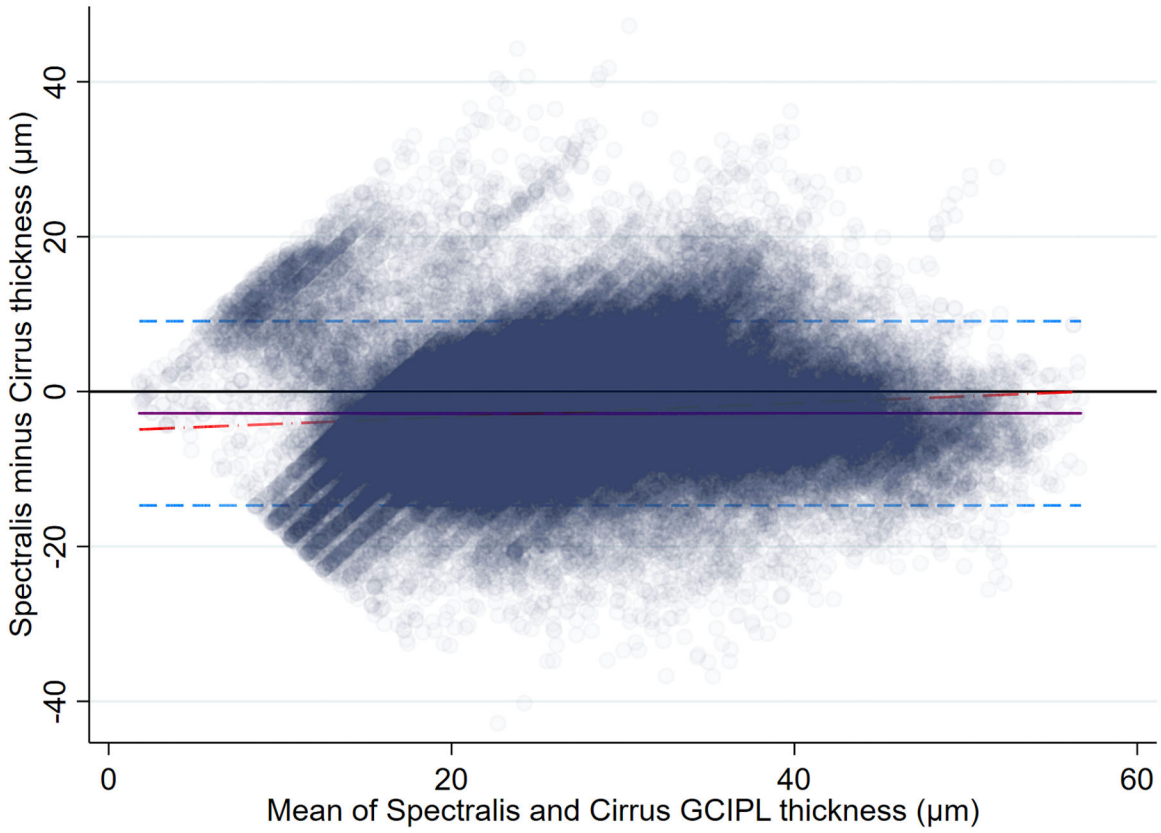

Figure 4.

The Bland-Altman plot for the pooled superpixel data demonstrates the relationship between Spectralis and Cirrus GCIPL thickness measurements at 0.4°×0.4° superpixels for all study eyes. Blue lines: 95% limits of agreement (−14.7, 9.1 µm), purple line: observed average (± SD) offset between the two devices (−2.8 ± 6.1 µm), dashed red line: fitted regression line demonstrating possible systematic bias, β =0.08, p <0.001; intercept: −5.1 µm).

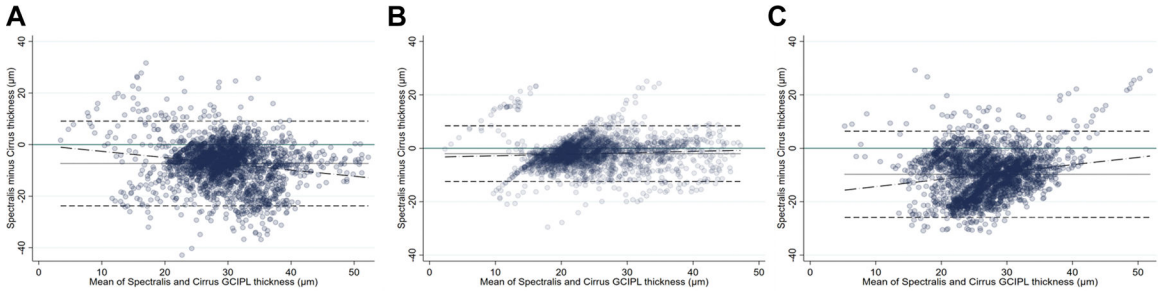

Figure 5.

Examples of Bland-Altman plots for individual eyes. **(A)** ρ_C = −0.24, slope of the fitted regression line: −0.24, p <0.001; intercept = −0.21 µm, average difference (± SD): −7.3 (± 8.4) µm, 95% limits of agreement: −23.8, 9.1 µm; **(B)** ρ_C =0.7 , slope of the fitted regression line: 0.05, p <0.001; intercept =−3.4 µm, average difference (± SD): −2.0 (± 5.3), 95% limits of agreement: −12.5 , 8.4 µm; **(C)** ρ_C =0.13, slope of the fitted regression line: 0.27, p <0.001; intercept = −17.1, average difference (± SD): −9.8 (± 8.2), 95% limits of agreement: −25.9, 6.4 µm. Abbreviations: ρ_C, concordance correlation coefficient.

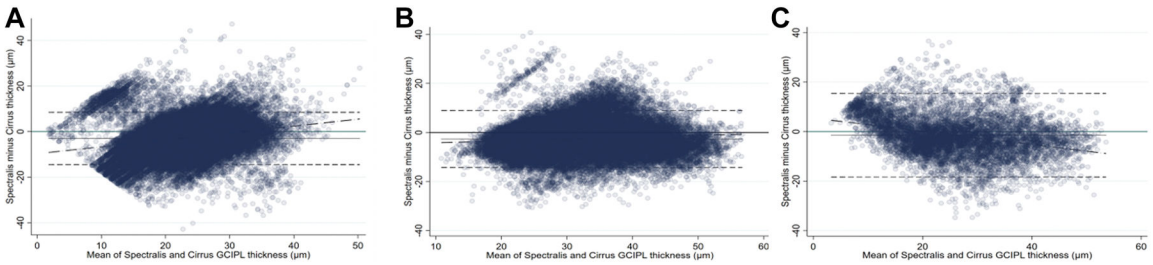

Figure 6.

Bland-Altman plot for the pooled superpixel data demonstrates the varying relationship between Spectralis and Cirrus GCIPL thickness measurements at 3 different eccentricities. **(A) 0°–4° eccentricity:** ρ_C =0.4, slope of the fitted regression line: 0.3, p <0.001; intercept = −9.7 µm, average difference (± SD): −3.0 (± 5.9) µm, 95% limits of agreement: −14.5, 8.5 µm; **(B) 4°–12° eccentricity:** ρ_C =0.68, slope of the fitted regression line: 0.08, p <0.001; intercept = −4.97 µm, average difference (± SD): −2.7 (± 5.9) µm, 95% limits of agreement: −14.3, 8.9 µm; **(C) 12°–20° eccentricity:** ρ_C =0.68, slope of the fitted regression line: −0.27, p <0.001; intercept = 5.45 µm, average difference (± SD): −1.5 (± 8.6) µm, 95% limits of agreement: −18.4 , 15.4 µm. Abbreviations: ρ_C, concordance correlation coefficient.

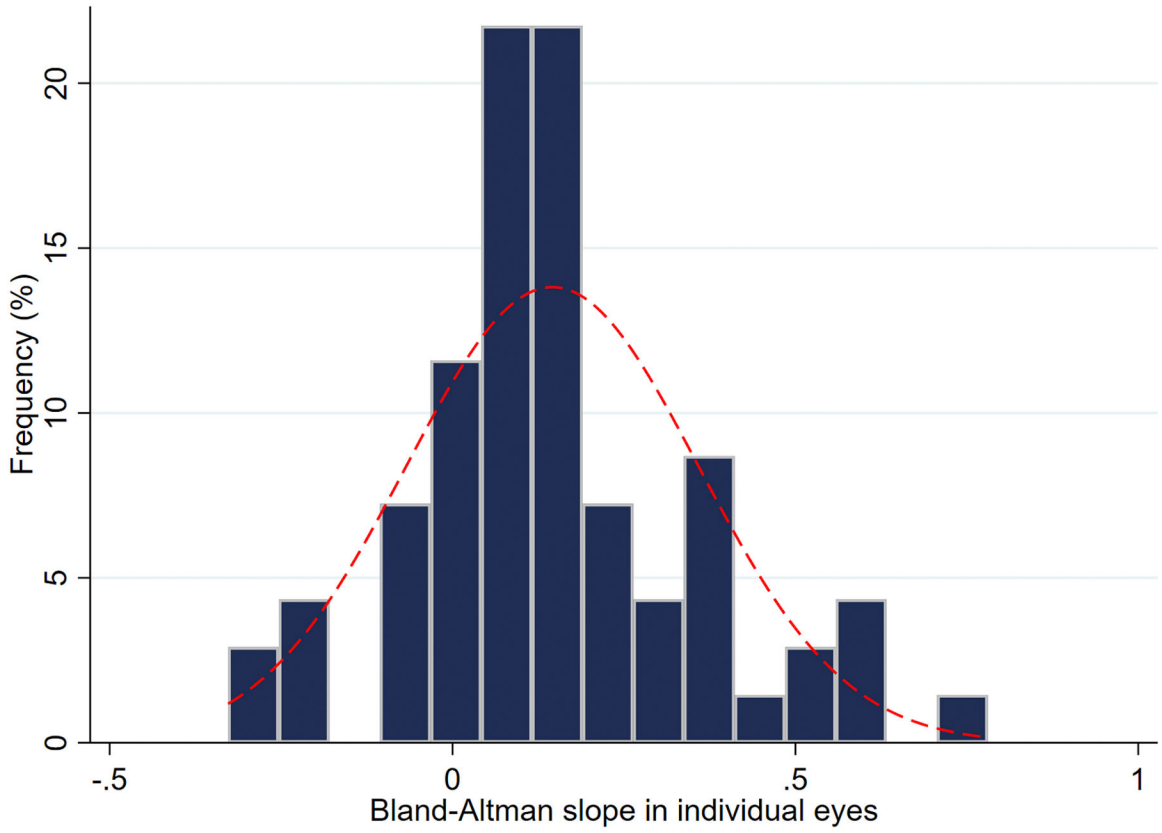

Figure 7.
Histogram demonstrates the distribution of the slopes of the fitted regression lines for Bland-Altman plots in individual eyes.

Table 1.

Demographic and clinical characteristics of the study sample.

Number of eyes (patients)	69 (63)
Gender: female/male, n (%)	43/26 (62.3%/37.7%)
Eye: right/left, n (%)	37/32, (53.6%/46.4%)
Age, mean ± SD	66.7 ± 11.9
Race n (%)	
White	39 (56.5%)
African-American	8 (11.6%)
Asian	16 (23.2%)
Hispanic	6 (8.7%)
Type of glaucoma	
Primary open-angle glaucoma	48 (69.6%)
Chronic angle-closure glaucoma	5 (7.3%)
Normal-tension glaucoma	13 (18.8%)
Pigmentary glaucoma	2 (2.9%)
Pseudoexfoliation glaucoma	1 (1.5%)
Axial length (mm, mean ± SD)	24.7 ± 1.49
MD 10–2 (dB, median (IQL))	−8.3 (−4.6, −11.9)
MD 24–2 (dB, median (IQL))	− 6.8 (−4.9, −12.3)
PSD 10–2 (dB, median (IQL))	10.1 (5.7, 12.5)

SD, Standard Deviation; IOP, Intraocular Pressure; MD, Mean Deviation; PSD, Pattern Standard Deviation.