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Macular Thickness Measurements in Normal Eyes with Time Domain and Fourier Domain Optical Coherence Tomography

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Abstract

Purpose—To compare macular thickness measurements using time domain optical coherence tomography (OCT) and Fourier domain OCT (FD OCT).

Methods—Thirty-two eyes from 32 normal patients underwent complete ophthalmic evaluation. Macular scanning using the StratusOCT and the RTVue-100 OCT were performed for a total of 3 times each on the same visit. The average retinal thicknesses of the 9 macular sectors as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS), along with the foveal center point and macular volume, were recorded. The standard deviation, the coefficient of variation, and the intraclass correlation coefficient were calculated for each parameter studied. Comparisons were made between the two OCTs in terms of retinal thicknesses measurements, their reproducibility, and macular regional differences. Correlations between retinal thickness and demographic variables (age and gender) were also investigated. Due to known differences in segmentation algorithms of the two OCTs, software calipers were used to measure the distance from the internal limiting membrane to the photoreceptor inner segment--outer segment junction at the foveal center point on all RTVue scans in order to allow a more fair comparison.

Results—The RTVue yielded greater retinal thickness measurements in nearly all macular subfields compared to the StratusOCT. Even after accounting for differences in segmentation algorithms, significant disparities were still evident with the RTVue measurements less than those of the StratusOCT at the foveal center. On both machines, the macula was thinnest at the fovea and thickest within the 3mm ring. There were some consistent regional variations in macular thickness evident on both OCTs. Compared to the StratusOCT, the RTVue generally had lower coefficients of variation and higher intraclass coefficients, suggesting better reproducibility. Age and gender also appeared to be important determinants in some macular thickness parameters.

Conclusion—Compared with StratusOCT, the RTVue FD OCT yields greater retinal thickness measurements with greater reproducibility, presumably due to different segmentation algorithms,

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Conflict of Interest: Dr. Sadda is a co-inventor of Doheny intellectual property related to optical coherence tomography that has been licensed by Topcon Medical Systems and is a scientific advisory board member for Heidelberg Engineering. Both companies manufacture devices that may compete directly with the devices discussed in this manuscript.

increased sampling density, and greater resolution. However, regional differences across the macula can be consistently observed with both devices.

Keywords

Fourier-domain; macular thickness; optical coherence tomography; time-domain

Over the past two decades, optical coherence tomography (OCT) has emerged as a useful instrument that produces *in vivo* cross-sectional images of tissues that resemble histological analysis.[1,2] OCT captures the interference pattern between backscattered light and a reference beam to display, with high accuracy, various ocular structures. By providing detailed morphometric and quantitative information, OCT has become an indispensable tool in the management of retinal and optic nerve diseases as well as in clinical trials.[3–7]

The evolution of OCT has been a step-wise process, starting from the prototype through the development of the first, second, and third generations of commercially available instruments. Each successor had been an improvement over the predecessor in terms of imaging speed and resolution, but the underlying concepts had largely remained the same. In these so-called time domain OCTs (TD OCT), a mechanical moving mirror is crucial for extracting depth information for light reflected from the retina. Therefore, data acquisition speed is limited by the relatively slow mechanical movement.

The latest time domain model in widespread use, the StratusOCT (Carl Zeiss Meditec, Dublin, CA), has an axial resolution of 8 to 10 μm and a maximum of 512 transverse and 1024 axial data points per image acquired over 1.25 seconds, according to the user's manual. Because eye movement may induce significant errors in measurement, the StratusOCT also allows the user to choose scanning protocols that may increase the image acquisition speed at the expense of transverse resolution. For example, the Fast Macular Thickness protocol performs six radial scans over 1.92 seconds, each consisting of 128 A-scans spread over 6mm and centered over the fixation point. This insures that all the scans are centered at the same location, usually the fovea. The radial scans are oriented 30° apart. For the retinal areas that are not imaged, the computer algorithm interpolates data from the surrounding scanned areas and then generates a circular topographical map.

The shortcomings of such an approach are evident. Much of the macula is unscanned, and the resolution is compromised. In order to provide a reference for these retinal thickness measurements obtained from StratusOCT, normative data has been established through a number of studies. Subsequent studies, however, have identified a systematic error in the identification of the outer retinal boundary by StratusOCT due to selection of the hyper-reflective band believed to correspond to the photoreceptor inner segment outer – segment (IS/OS) junction as the outer border of the retina.[8] Sadda *et al.* noted that the mean error in thickness measurements in normal patients due to this mis-identification was approximately 35.5 microns,[9] while Pierre-Kahn *et al.* found the error to be 46.6 microns.[10]

In Fourier domain OCT (FD OCT), the light interference pattern of an entire A-scan is detected simultaneously with spectrally separated detectors (diffraction grating) and a linear detector array (a high-speed charge coupled device, or CCD, camera). Fourier transform is used to mathematically convert the raw data into A-scan data to be displayed as a false-color map, just like previous generations of OCT. By eliminating the disadvantage of a mechanical moving part, FD OCT can generate images at far greater speed, which is only limited by the camera's frame transfer rate and computer speed. For example, the RTVue-100 FD OCT (Optovue, Fremont, CA) can perform 26,000 A-scans per second according to its user's manual, or approximately 65 times faster than StratusOCT. In addition, by increasing the bandwidth of the light source, images of higher resolution can be obtained by FD OCTs (axial resolution of 5.0 μm, or about twice as high as StratusOCT). These improvements allow more precise radial scans spaced closer together, reducing the unscanned areas and thus limiting the need for data interpolation. Therefore, the topographical maps generated would theoretically be much more accurate.

Many investigators have described the dramatic improvements in resolution and speed of OCT afforded by Fourier domain approaches.[11–15] Normative data for these new devices, however, are still being established. In addition, many of the FD OCT device manufacturers have taken the opportunity to revise the outer retinal boundary location.

For the new technology to be clinically relevant, however, it is important that the data from these devices be compared with existing, widely-accepted standards. In the present study, macular thickness measurements were performed using both time domain (StratusOCT) and Fourier domain (RTVue-100) OCTs in the same groups of normal subjects to assess the differences and correlations between these two techniques.

Methods

Patients

Consecutive patients were recruited at the Zhongshan Ophthalmic Center of Sun Yat-sen University, Guangzhou, China from February to April 2008. The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board. Informed consents were obtained from all enrolled patients.

All subjects underwent complete ophthalmic evaluation including best-refracted visual acuity, applanation tonometry, slit-lamp biomicroscopy, dilated stereoscopic examination, fundus photography, and Humphrey SITA standard 24-2 or 30-2 visual field testing.

The inclusion criteria were: 1) age 20 to 60 years old; 2) best corrected visual acuity 20/20 or better; 3) refractive error not exceeding 3 diopters spherical equivalent (hyperopia or myopia) and 1 diopter cylinder; 4) intraocular pressure <21mmHg by Goldmann applanation tonometry; 5) clear natural lens and cornea; 6) normal optic nerve appearance by dilated stereoscopic examination and fundus photography; 7) normal visual field by Humphrey perimetry; 8) no medical or family history of retinal diseases or glaucoma; 9) no medical or family history of diabetes mellitus; and 10) no prior ocular surgery.

Optical coherence tomography

For each eligible patient, one eye was randomly chosen to be scanned using the StratusOCT and the RTVue-100 following pharmaceutical pupillary dilation. Imaging was performed three times on each machine on the same visit by the same examiners (JH or HX). Individual measurements from the three scans for each parameter were averaged for each machine and used for comparisons. The standard deviation, the coefficient of variation (CV=standard deviation divided by mean), and intraclass correlation coefficient (ICC) for each parameter were also calculated.

For the StratusOCT, the Fast Macular Thickness Map protocol was used. The retinal map thickness analysis protocol reconstructed a false-color topographic image displayed with numeric averages of the thickness measurements for each of the 9 map sectors as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS) (Figure 1).[16] The inner and outer rings, with diameters of 3mm and 6 mm, respectively, were each segmented into 4 quadrants (superior, inferior, nasal, temporal). For ease of discussion, the superior subfield in the 3mm ring was labeled S3, while the nasal subfield in the 6mm ring was labeled N6, etc. (Figure 1).

Foveal central subfield (FCS) thickness was defined as the average thickness in the central 1mm diameter circle (C1) of the ETDRS grid. Foveal center point (FCP) thickness was defined as the mean thickness at the point of intersection of the 6 radial scans. The software (Version 4.0) also calculates the total macular volume within the 6mm-diameter scanned area.

The mm6 scan protocol of the RTVue-100, which performs 12 radial line scans of 6 mm each over a total of 0.27 seconds, was used to obtain data in the same macular region in each patient. The topographic map also displays retinal thicknesses in each of the 9 ETDRS map sectors, the FCP thickness, and the macular volume within the 6mm-, 3mm-, and 1mm-diameter scanned areas.

OCT scans were repeated if any were found to be de-centered or were determined to have segmentation errors, and such suboptimal scans were excluded from analysis. Additionally, due to the known differences in segmentation algorithms between the two devices, software calipers available on the RTVue device were used to manually measure the distance from the internal limiting membrane to the IS/OS junction at the foveal center point on all RTVue scans and then compared to analogous measurements from the StratusOCT.

Statistical analysis

SAS version 9.1 (SAS Institute, Cary, NC, USA) programming language was used for all analyses. For each of the 11 parameters investigated (the 9 ETDRS subfields, the FCP, and the macular volume within the 6mm circle), the retinal thicknesses and the CVs on the StratusOCT were compared with those on the RTVue using paired *t*-tests. For the FCP, automated and manually-segmented RTVue values were compared with the StratusOCT.

Pairwise comparisons were performed on the central foveal subfield, the inner ring, and outer ring average thicknesses. Similarly the thicknesses of the four quadrants were compared pairwise with each other within the inner and outer rings. The relationship between retinal thickness and age was investigated using Pearson correlation coefficients, while the relationship between retinal thickness and gender was studied using Spearman correlation coefficients.

Results

Thirty-two eyes (16 left eyes, 16 right eyes) from 32 normal subjects (all Chinese) were examined clinically and by the Stratus and RTVue-100 OCTs. The average age was 42.66±9.39 years (range 21 to 55 years old). The average refractive error was −0.13±0.78D (range −3D to +1.5D). There were 19 men and 13 women.

For nearly all of the 11 parameters (FCP, the 9 ETDRS map sectors, and macular volume), the RTVue measurements were statistically significantly greater than the corresponding measurements performed by the StratusOCT (Table 1, Figure 2, Figure 3). The one exception was the nasal subfield in the 6mm ring (N6).

The average thickness from the internal limiting membrane to the IS/OS junction, as determined using software calipers manually, was found to be 141.02±12.59 μm at the foveal center point on the RTVue, which was significantly different from the analogous StratusOCT measurement of 164.69±25.92 μm (p<0.001).

With both the StratusOCT and the RTVue, the macula was thinnest in the foveal central subfield (C1), thickest in the inner ring, then gradually thinned toward the outer ring (Table 1). In the inner 3mm ring, the order of macular thickness was temporal<nasal<inferior<superior on the

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StratusOCT and temporal<inferior<nasal<superior on the RTVue. In the outer 6mm ring, the order was temporal<inferior<superior<nasal on both devices.

The coefficients of variation (CV) are lower for the RTVue than the StratusOCT in all 11 parameters investigated (Table 2), although the difference was statistically significant in only three of them (C1, N3, S6). The intraclass correlation coefficients (ICC) are generally higher in the RTVue (Table 2). Both suggest that RTVue is superior to the StratusOCT in terms of reproducibility of these measurements.

Age was positively correlated to retinal thickness on some but not all subfields (correlation coefficient *r* ranged from 0.05 in the N6 subfield to 0.46 in the C1 subfield on the Stratus, and from 0.19 in the N6 subfield to 0.54 in the T6 subfield on the RTVue). Men appeared to have greater retinal thicknesses in almost all subfields than women (*r* ranged from 0.32 in the N6 subfield to 0.61 in the I3 subfield on the Stratus and from 0.28 in the N6 subfield to 0.67 in the I3 subfield on the RTVue) on both OCT devices.

Discussion

In this study comparing two generations of OCT, we found that FD OCT, as represented by the RTVue, yielded data that were more reproducible than the third generation of TD OCT, represented by the StratusOCT. StratusOCT yielded lower retinal thickness measurements in nearly all of the ETDRS macular subfields. Both machines revealed similar patterns in terms of regional differences in the fovea and parafovea. Gender, and perhaps age, appeared to be determining factors in some macular thickness measurements in this Chinese population.

The StratusOCT defined the outer boundary of the retina to be the hyperreflective band which corresponds to the junction between the inner and outer segment of the photoreceptors. The newer FD OCTs purportedly measure the distance from the internal limiting membrane to the retinal pigment epithelium (RPE).[14,15] Comparisons of ultra-high resolution OCT with pig and monkey retinal histology have been performed to investigate the validity of this approach.[17,18] The change in segmentation algorithm likely explains some of the differences in retinal thickness measurements. It is unclear why the nasal outer subfield was the only exception in our study. Other investigators have not found this difference with the Cirrus HD OCT (Carl Zeiss Meditec, Dublin, CA) or the 3D OCT 1000 (Topcon Inc., Paramus, NJ).[19,20] However, it is clear from our manual measurement sub-analysis using RTVue software calipers that difference in segmentation algorithm alone cannot entirely explain the discrepancies in thickness measurements. The distance between the IS/OS junction and the RPE was about 34.7 μm at the foveal center in our study, very similar to what other investigators have found.[9]

By comparing the StratusOCT and the Cirrus HD OCT (software version 2.0), the differences in retinal thickness measurements in the 9 macular subfields were found to be between 43.7 to 61.1 μm, which appeared to be much higher than the differences found in the current study.[19] The Topcon 3D OCT-1000 also overestimated the foveal central subfield by 33.9 μm and the average macular thickness by 21.3 μm compared to the StratusOCT.[20] The discrepancy may be due to differences among the three commercially available FD OCTs, which suggests that even different FD OCTs have slightly different segmentation capabilities and definitions. Therefore, macular thickness measurements are not interchangeable among different machines.

Another reason for the differences in measurements between the FD OCT and StratusOCT may be that greater resolution images could be obtained in the former. Different generations of OCTs are known to give variable measurements. For example, the StratusOCT overestimates retinal thickness measurements by an average of 25 μm compared to OCT1.[10] The average central foveal subfield thickness was 183.5 μm among 166 healthy eyes on the OCT1.[21]

However, the corresponding measurement was 205.9 μm using the StratusOCT's Fast Macular protocol after pupillary dilation.[22] The higher axial resolution of StratusOCT allows display of two different outer hyper-reflective lines, versus only one for the OCT1. The RTVue defines the outer boundary even more precisely, and more hyper-reflective bands may be evident.

Given the greater image resolution and data acquisition speed, it is not unexpected to see more reproducible results from the RTVue compared to the StratusOCT. The more than six-fold decrease in scan time (0.27 seconds vs. 1.92 seconds) reduces motion artifacts and increases the signal-to-noise ratio. The foveal center point, the thinnest point in the retina, would likely be the parameter most affected by eye movements because even slightly decentered fixation would lead to significantly higher measurements. This was evidenced by the higher CV and lower ICC of the FCP thickness measurement compared to those of the other parameters, even with the RTVue. Similarly, the foveal central subfield had the next highest CV on both machines. These results were consistent with previous findings.[23]

A second reason for the higher reproducibility of RTVue is the greater scanned area (12 vs. 6 radial lines). With the StratusOCT, segmentation errors in any of the six radial scan lines would be propagated to adjacent interpolated areas. In contrast, the zones of interpolation in RTVue scans are significantly smaller, minimizing the effect that a segmentation error has on the overall measurements.

Regional differences in macular thickness measurements of the ETDRS subfields in normal subjects have been well-documented previously by various generations of OCT. The fact that the fovea is the thinnest point, while the 3mm inner ring has the highest retinal thickness, is well-known histologically and tomographically. Due to the arcuate nerve fiber bundles, the superior and inferior retina is thought to be the thickest.[24] However, the superior and nasal parafoveal regions were thicker than the inferior and temporal regions of myopic eyes, as measured by the OCT1 (which uses a scan length of 4.5mm).[25] With the StratusOCT (scan length of 6mm), the order of retinal thickness in the inner ring was nasal<superior<inferior<temporal, but in the outer ring, the order was nasal<inferior<superior< temporal.[22] In another study using StratusOCT, the order in the inner ring was temporal<superior<inferior<nasal, while the order in the outer ring was temporal=inferior<superior<nasal.[26] On the Cirrus HD OCT, both the inner and outer rings were ordered temporal<inferior<superior<nasal.[19] Among 6-year old children, the temporal quadrant was thinner in both the inner and outer regions of the macula.[27] In the current study in which pairwise comparisons were performed to analyze subfield differences (data not shown), there was good agreement between the StratusOCT and the RTVue in terms of regional differences. However, only some pairwise comparisons were statistically significant. Therefore, these highly divergent results may be due to random errors or other confounding factors. Our study is likely to be underpowered to make truly meaningful comparisons. Nevertheless, it is reassuring that the RTVue and Cirrus results are nearly identical.

The relationship between age and macular thickness in our study was complex, as the StratusOCT and the RTVue gave inconsistent results in many of the subfields. Because of the small sample size, it is difficult to draw conclusions with confidence. It is well-known that the retinal nerve fiber layer thickness decreases with age,[21,28] but most previous studies have revealed no significant correlation between age and macular thickness.[3,26,28–31] Guedes *et al* showed a consistent decrease of perifoveal thickness with age,[21] but in our study, the foveal central subfield (C1) thickness increased significantly with age on the StratusOCT and showed a similar trend on the RTVue. The macular volume may offer a broader view of the variation in retinal thickness, and in our study, increased with age on both the StratusOCT and the RTVue. Our result was consistent with a study of 170 normal subjects in India, which found age to be positively correlated with macular thickness and volume parameters (r=0.23, $P<0.01$).

[32] These seemingly contradictory results may be due to the relatively small sample size of these studies. Additionally, because the oldest subject in our study was only 55 years old, it would be inappropriate to extrapolate these findings into an older population.

Some previous studies found no difference in macular thickness between men and women,[21,26] but in our study men had greater retinal thicknesses in 8 out of 11 macular subfield parameters studied (data not shown). Wong *et al*[33] and Massin *et al*[34] showed that men have significantly greater central (3mm diameter) retinal thickness than women, but age was not a determining factor. Chamberlain *et al* also demonstrated that men have greater foveal thickness.[35] The FCP, FCS, and the inner 3mm diameter ring were thicker in 6-year old boys than girls.[27] Unfortunately, these studies used different instruments to measure retinal thickness, making cross-comparisons problematic. To our knowledge, this is the first study that uses the FD OCT to analyze gender and age correlations to macular thickness. The reasons for these differences are unknown, but clearly these findings require replication in larger studies.

Ethnic differences may be an important confounding factor. Asians and African-Americans have thinner maculas compared to Caucasians.[21,36] Our study focused exclusively on the population in southern China. In one study, Chinese subjects had slightly, but not statistically significantly, lower macular thickness than Westerners.[31] Thus, the normative values described in this study may not be relevant to non-Chinese populations.

In summary, retinal thickness values determined by a time domain OCT and a Fourier domain OCT were found to be highly correlated in this normal Chinese population. Although the segmentation algorithms for the two devices are different and partially account for the greater retinal thicknesses seen in FD OCT, regional variations in thickness across the macula are still observed with Fourier domain instruments. The data obtained in this study may be useful in future investigations of retinal disease and for comparison with other OCT devices and future imaging technologies.

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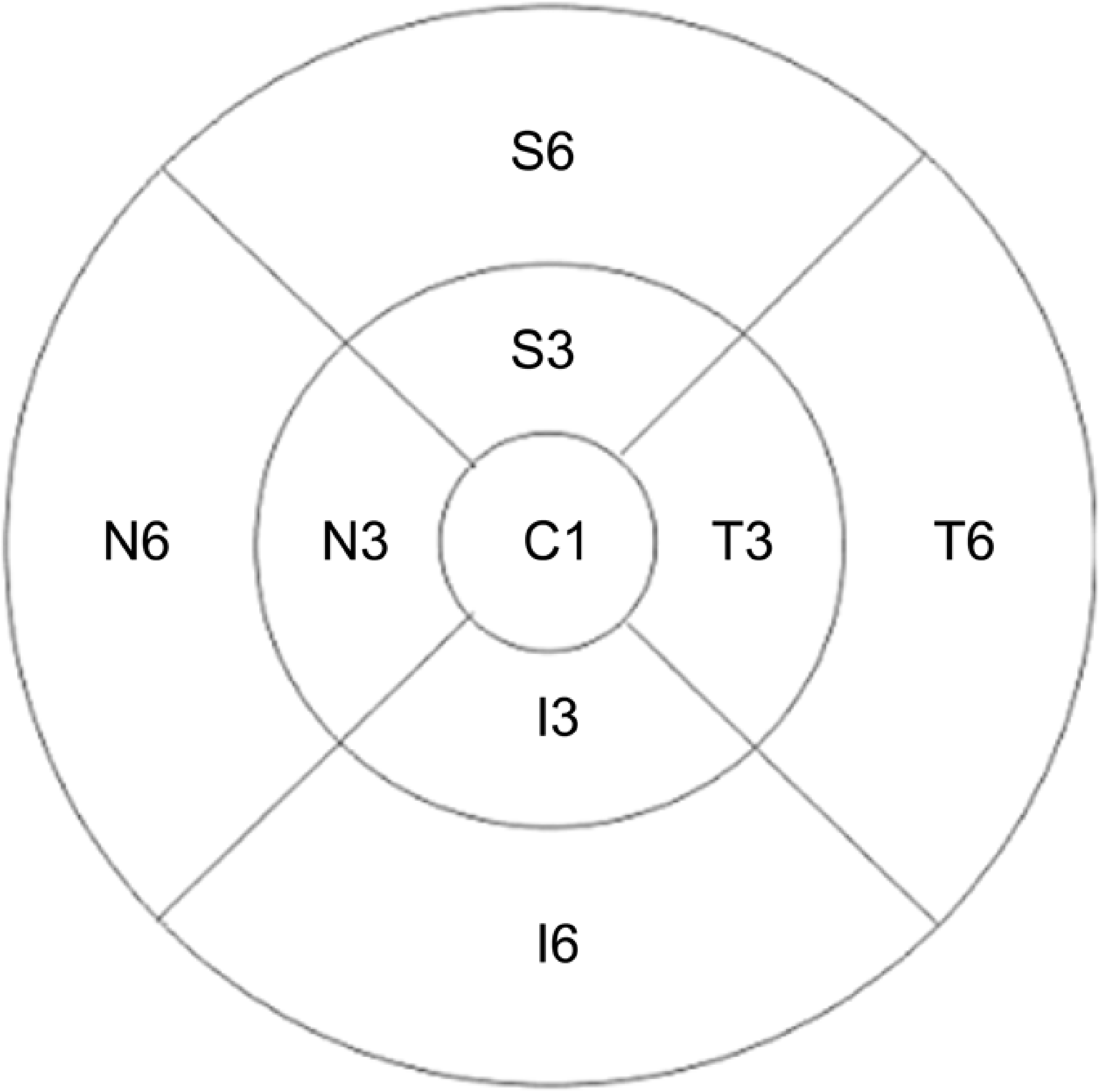

Figure 1.
The Early Treatment of Diabetic Retinopathy Study (ETDRS) macular map sectors. The four quadrants of the outer, 6mm diameter ring around the fovea are labeled S6, T6, I6, and N6 to represent the superior, temporal, inferior, and nasal regions, respectively. The inner, 3mm diameter ring is labeled analogously. C1 represents the innermost 1mm diameter ring around the fovea.

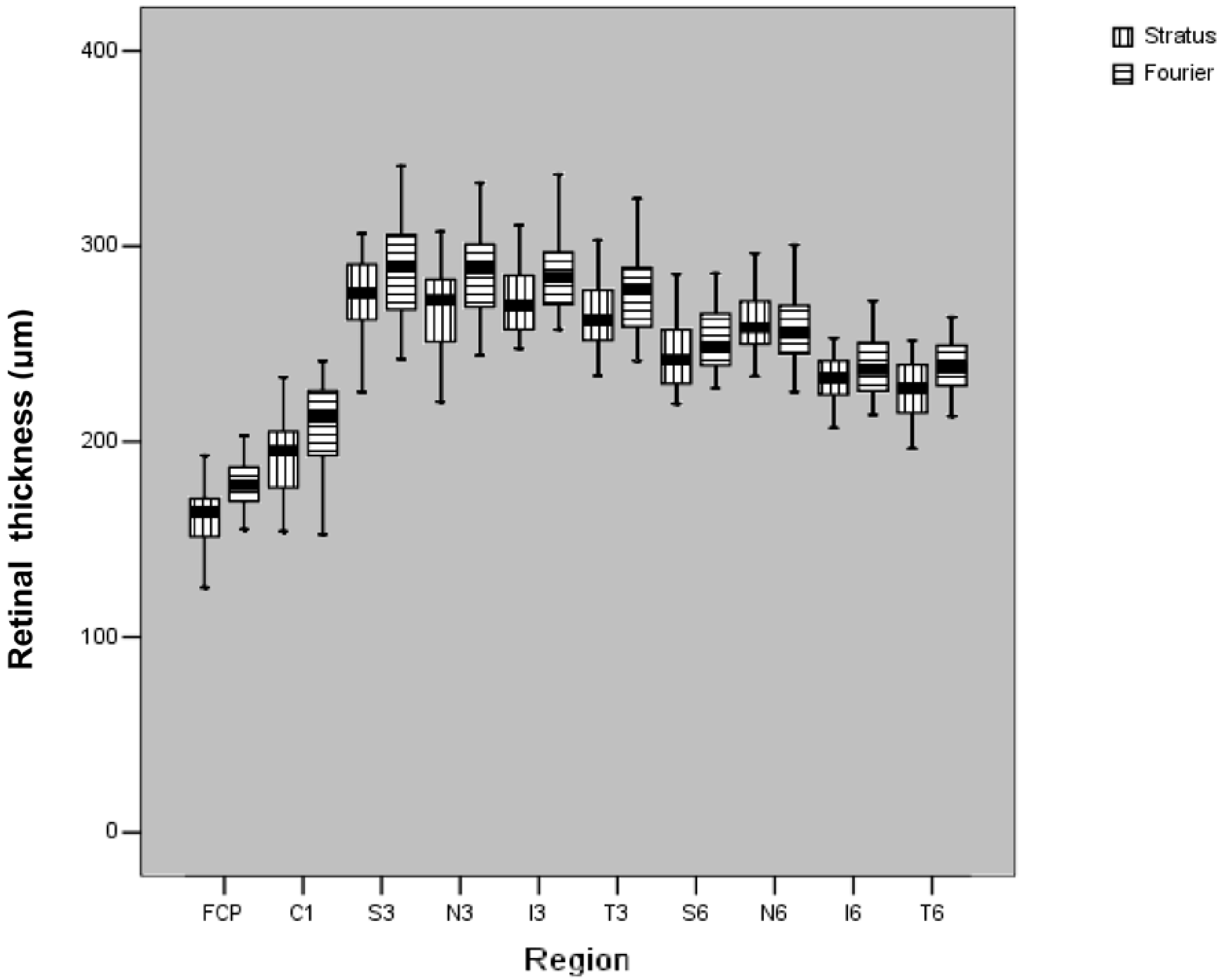

Figure 2.
Boxplot of macular thickness (ETDRS map sectors, see Figure 1). The retinal thicknesses ± standard deviation, as measured by the StratusOCT and the Fourier-domain OCT for a particular region, are plotted next to each other for comparison.

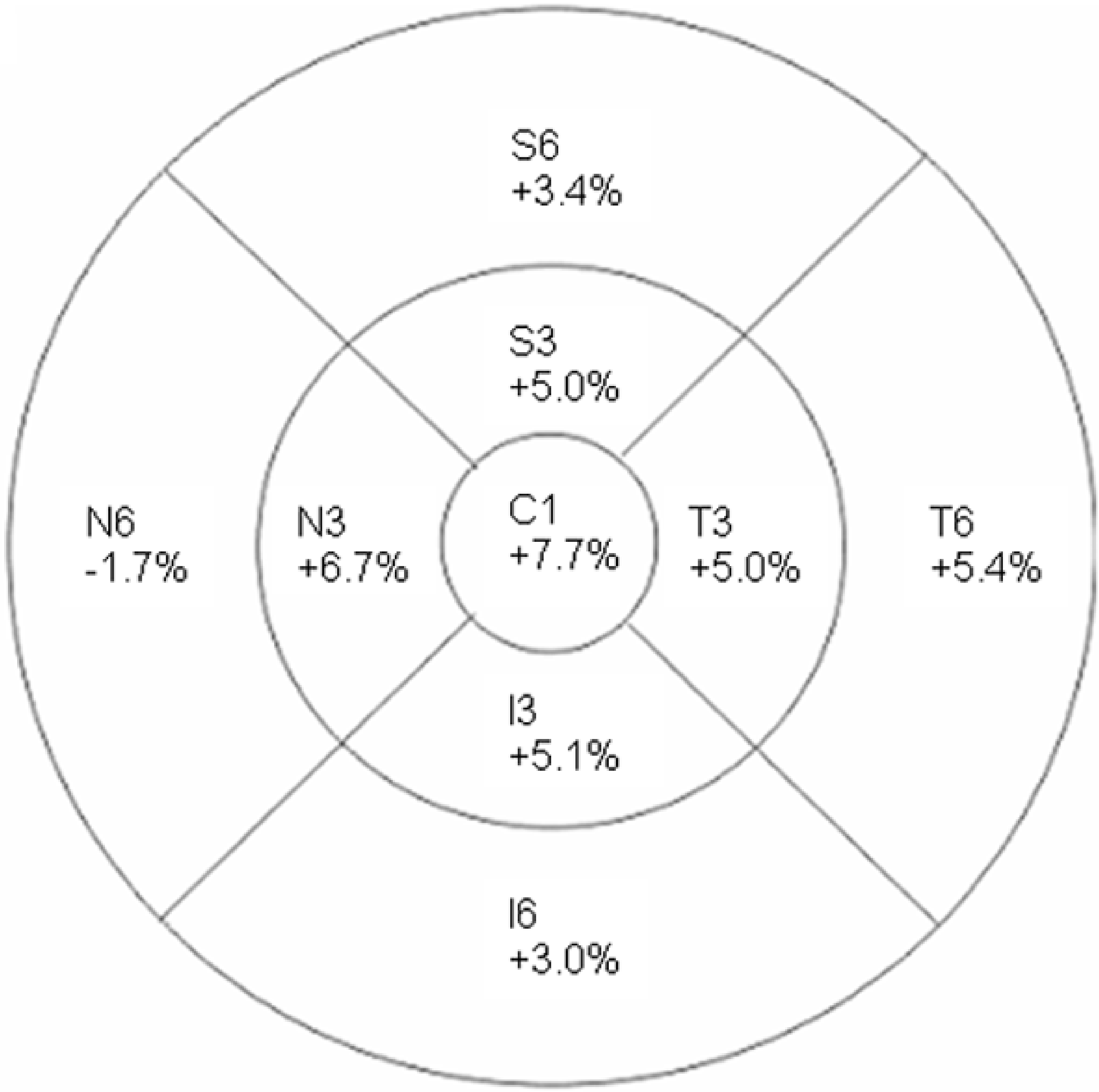

Figure 3.
The Early Treatment of Diabetic Retinopathy Study (ETDRS) macular grid is shown depicting regional differences in retinal thickness between the RTVue-100 and the StratusOCT. The RTVue-100 generally yielded thicker (positive percentage) measurements.

Table 1

Macular thickness measurements using StratusOCT and RTVue-100 in μm (statistically significant correlations are in bold)

Region		Stratus OCT	RTVue -100	Difference	Percentage difference (%)	p*
Foveal Center Point (FCP) Thickness		164.69±25.92	175.71±16.81	11.02±24.64	6.69	**0.0167**
Fovea Central Subfield Thickness (1mm diameter, C1)		193.73±22.23	208.62±21.71	14.89±13.17	7.69	**<.0001**
Medial ring thicknesses (3mm diameter)	Superior (S3)	274.57±19.25	288.42±22.63	13.85±15.62	5.04	**<.0001**
	Nasal (N3)	269.06±21.62	287.22±22.28	18.16±11.37	6.75	**<.0001**
	Inferior (I3)	271.54±17.26	285.26±19.55	13.72±8.22	5.05	**<.0001**
	Temporal (T3)	263.80±17.19	276.89±19.79	13.09±7.60	4.96	**<.0001**
Outer ring thicknesses (6mm diameter)	Superior (S6)	244.33±17.64	252.61±16.00	8.28±8.03	3.39	**<.0001**
	Nasal (N6)	261.79±15.53	257.39±17.58	−4.41±8.97	−1.68	**0.0092**
	Inferior (I6)	232.67±13.31	239.63±15.86	6.96±14.07	2.99	**0.0087**
	Temporal (T6)	226.56±15.17	238.72±13.27	12.15±7.17	5.36	**<.0001**
Volume (6mm diameter, in mm^3)		6.98±0.37	7.19±0.41	0.21±0.17	3.01	**<.0001**

* Paired *t*-test *p* value. Significance level: $p<0.05$.

Table 2

The reproducibility of macular thickness measurements using StratusOCT and RTVue-100 (statistically significant correlations are in bold)

		Coefficients of Variation (%)			Intraclass Correlation Coefficients (%)	
Region		**StratusOCT**	**RTVue-100**	***p*** *	**StratusOCT**	**RTVue-100**
Foveal Center Point Thickness		5.37±5.24	3.57±3.59	0.123	81.6	80.0
Foveal Central Subfield Thickness (1mm diameter)		2.65±2.83	1.36±1.14	**0.016**	90.6	97.5
Medial ring thicknesses (3mm diameter)	Superior (S3)	1.09±0.69	1.03±1.02	0.766	96.9	97.1
	Nasal (N3)	1.45±0.97	1.02±0.72	**0.037**	95.6	97.4
	Inferior (I3)	1.36±1.21	0.91±0.62	0.058	92.7	97.4
	Temporal (T3)	1.06±0.77	0.94±0.75	0.456	96.2	97.3
Outer ring thicknesses (6mm diameter)	Superior (S6)	1.43±1.02	0.98±0.67	**0.048**	94.4	96.7
	Nasal (N6)	0.89±0.53	0.71±0.43	0.134	97.0	98.7
	Inferior (I6)	1.20±0.78	0.94±0.59	0.095	93.8	97.4
	Temporal (T6)	1.51±1.06	1.13±0.83	0.138	92.6	95.2
Volume (6mm diameter)		0.72±0.71	0.53±0.51	0.256	96.7	98.4

* Paired *t*-test *p* value. Significance level: $p<0.05$.