Clinical Relevance of Foveal Location on Retinal Nerve Fiber Layer Thickness Using the New FoDi Software in Spectralis Optical Coherence Tomography

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Purpose. To evaluate the effect of improper foveal location on retinal nerve fiber layer (RNFL) thickness measurements by using the new FoDi software in spectral-domain optical coherence tomography (Spectralis SDOCT).

Methods. Cross-sectional study with 126 subjects: 66 healthy, 30 early, and 30 moderate glaucomatous eyes. Fast RNFL scans were performed by using the new FoDi technology. The position of the fovea was manually displaced inferiorly after acquisition (producing clockwise torsion of scan circle) and then superiorly (counterclockwise) to generate study sets of images. Differences in RNFL thickness between foveal-guided and alternative scans were analyzed and color changes in sector charts were evaluated.

Results. In healthy eyes, placing the fovea inferiorly led to significant RNFL thickness changes in all sectors. Locating the fovea superiorly seemed to have less impact. Early glaucomatous eyes were more susceptible to quantitative changes, but moderate glaucomatous eyes were more susceptible to qualitative changes.

Conclusions. Improper fovea disc alignment when using the FoDi software in Spectralis OCT significantly affected sectoral RNFL thickness measurements and color chart representation. As final report of FoDi analysis does not show the foveal position used, careful acquisition is encouraged, so that results are reliable. Otherwise, this technique can easily be misinterpreted and patients could be misdiagnosed.

Keywords: FoDi, optical coherence tomography, foveal

It has been 20 years since the first reports on optical coherence tomography (OCT) technique[1] and its use has progressively become an important tool in glaucoma diagnosis.[2–5] An increase in the sensitivity of devices that use spectral-domain technology (SDOCT) has improved the limit of resolution, and acquisition rates are faster than in time-domain OCT instruments.[6–9] New applications have helped SDOCT become a first-line imaging diagnostic tool: scan-track systems[10] and eye-tracking allow optimization of images despite eye movements, and follow-up acquisition protocols enable perfect superposition of consecutive images.

The United States Food and Drug Administration recently approved a new age-adjusted retinal nerve fiber layer (RNFL) thickness normative database and Posterior Pole Asymmetry Analysis software.[11] The RNFL thickness database was developed by using the SDOCT system's trademarked fovea-to-disc (FoDi) alignment software, which is one of the new features of Spectralis-HRA OCT 5.3 software (Heidelberg Engineering, Heidelberg, Germany), upgraded in devices in December 2011.

The FoDi software is available when the "RNFL acquisition protocol" is selected. It uses a circle scan, centered on the optic nerve head, and offers the patient a foveal fixation point. It was designed to ensure that the circle scans in the database are all properly aligned at the same start-and-stop point, virtually eliminating rotational artifacts, and making the database much more reliable. Image acquisition is then modified so that new scans can be compared with this new database. Moreover, the FoDi system enables improved comparison with consecutive examinations of the same subject. Nevertheless, these advantages require perfect fovea-to-disc alignment. While scanning with the FoDi software, an internal fixation point is provided for the subject. If the subject achieves foveal fixation, scan disc torsional status is guided by its intersection with the papillomacular bundle. This intersection is considered the middle of the temporal (T) sector. The superior (S), inferior (I), and nasal (N) sectors are then consecutively arranged. If the subject is unable to provide foveal fixation, owing to poor visual acuity, poor collaboration, or macular atrophy, the examiner must edit the original image and locate the real fovea before analysis is made to prevent incorrect arrangement of the sectors.

The aim of the present study was to investigate clinical relevance of foveal misplacement by using the new FoDi software in healthy subjects as well as in early and moderate glaucomatous eyes.

Methods

One hundred and twenty-six subjects followed up in our institution were included in the study. The tenets of the

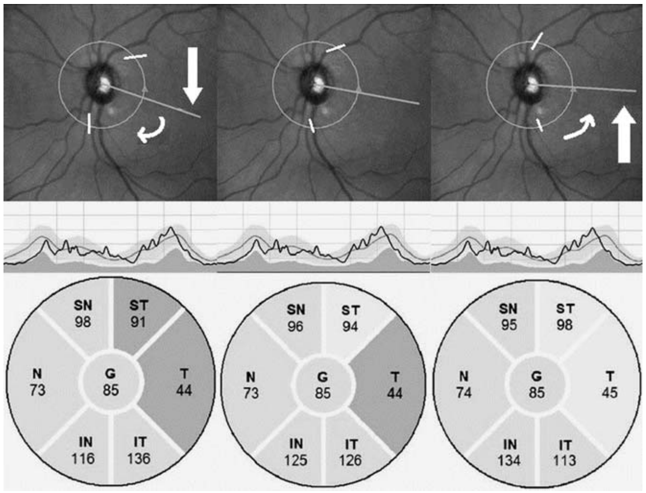

Figure 1. Example of how torsions were induced. In the *center*, the baseline image as obtained with the routine foveal fixation FoDi protocol. By manually editing a new position of the fovea in the same acquired image, a patient incapable of foveal fixation is recreated. Changes in the color charts are displayed below. Color sector is represented as different intensities of *gray*: *dark* corresponds to red color, *medium* to green color, and *clear* to yellow color. G, average.

Declaration of Helsinki and Spanish legislation were adhered to and the Institutional Review Board approved the study protocol. Each patient signed an informed consent after receiving a detailed explanation of the nature of the study procedures. Only one eye from each patient was included (better eye). The subjects underwent complete ophthalmic examination, including a review of the medical history, slit-lamp biomicroscopy, intraocular pressure (IOP) measurement, extraocular motility examination, fundus examination, and standard automated perimetry. Humphrey Automated Field Analyzer II (Carl Zeiss Meditec, Dublin, CA) with SITA STANDARD 24-2 protocol was used. Only visual fields with fewer than 33% false-negative errors, fewer than 33% false-positive errors, and fewer than 20% fixation losses were considered. A normal visual field was required for the healthy group. Glaucomatous eyes had an IOP greater than 21 mm Hg and reliable pathologic visual fields. All eyes included in the study had a best-corrected visual acuity of 20/40 or better, sphere within ±5.0 diopters (D), cylinder within ±3.0 D, and absence of peripapillary atrophy, disc tilt, or papillary abnormalities (other than glaucomatous abnormalities in the glaucoma group). Subjects who had undergone intraocular surgery (other than trabeculectomy) or who were currently using medication that could affect visual field sensitivity were excluded from the study. Laser trabeculoplasty (selective or argon) or the use of hypotensive drops was not considered exclusion criteria for this study.

To stage glaucomatous visual field loss severity, we used the method proposed by Hodapp et al.[12] based on the overall extent of the damage, the number of defective points in the deviation probability map, and the proximity of the defect to fixation point. Early glaucomatous visual fields had mean deviation between −2 and −6 dB, fewer than 25% of the points were depressed below the 5% level and fewer than 10 points were depressed below 1% on the pattern deviation plot, and all points in the central 5° had a sensitivity of at least 15 dB. Moderate glaucomatous visual fields had mean deviation less than −12 dB; fewer than 50% of the points were depressed below the 5% level and fewer than 20 points were depressed below 1% on the pattern deviation plot; and no points in the central 5° had a sensitivity of 0 dB, and no more than one hemifield had a sensitivity of less than 15 dB within 5° of fixation. Sixty-six eyes were categorized as healthy, 30 were classified as early glaucomatous, and 30 as moderate glaucomatous.

The Spectralis SDOCT (software version 5.3, including the FoDi software) fast RNFL examination protocol was used. All pupils were first dilated with 1% tropicamide (Colircusi Tropicamida 1%; Alcon Cusi, SA, Barcelona, Spain). A minimum image quality score of 35 was required. Image acquisition was repeated if the quality was insufficient. The fundus image allowed for surveillance of the fovea and disc during imaging acquisition. Internal fixation was encouraged. The same investigator performed all scans and adequately relocated the fovea of the intermediate image when internal fixation failed owing to poor patient cooperation. This final image was considered as the baseline for each patient. Relocation of the fovea was allowed even on a day different from the acquisition day in the new FoDi software when "RNFL acquisition protocol with FoDi enhancement" was being used. This option would have not been available if the "circle scan" protocol had been used because in this regimen, the reference point is the center of the circle and not the fovea.

By manually lowering the position of the fovea, the baseline image was modified without requiring the presence of the patient (the position of the fovea was edited after the initial image acquisition): clockwise torsion of the scan disc of 5°, 10°, and 15° from the original fovea–disc alignment. By raising the position of the fovea, counterclockwise torsion of 5° and 10° was created (Fig. 1). Further counterclockwise torsion was not induced, because it resulted in foveal simulated positions that were superior to that of the optic nerve head in all subjects. As this foveal location is extremely rare according to the results of population studies,[13] we considered only those situations that might lead to errors in actual clinical practice. Thus, the five created images for each patient were the result of postacquisition manipulation of baseline images and did not include successive imaging.

New analyses of these images were performed. Total mean and quadrant (I, S, N, T, and superior temporal [ST], superior nasal [SN], inferior temporal [IT], and inferior nasal [IN] subdivisions of T and N in the second pie chart) thickness measurements were recorded for the analysis.

Normality of quantitative data was analyzed with Shapiro-Wilk test. Quantitative variables were expressed as their corresponding means and standard deviations. Differences in total mean and sector thickness between baseline images and modified images were assessed by using ANOVA test. Least significant difference Fisher test was conducted post hoc if ANOVA showed statistical significance. Percentage of eyes with color change in each sector was calculated for all groups. All analyses were performed by using SPSS software version 18.0 (SPSS, Inc., Chicago, IL). A *P* value of less than 0.05 was considered statistically significant.

Results

One hundred and twenty-six eyes were evaluated, with acquisition of the baseline image and generation of the five altered images for each patient. Image acquisition was repeated in 22 patients (17.5%) owing to poor quality. A third acquisition was not needed in any patient. Location of the fovea was not achieved in 25 patients (19.8%), so new baseline images were created. The characteristics of the patients and baseline mean and quadrant RNFL thickness measurements are shown in Table 1.

TABLE 1. Baseline Characteristics of the Participants in the Study

	Total No., $n = 126$	Controls, $n = 66$	Early Glaucoma, $n = 30$	Moderate Glaucoma, $n = 30$
Mean age, y (SD)	69.2 (11.4)	67.6 (11.2)	74.9 (8.5)	69.8 (13.5)
Sex, % females	70.3	73.1	78.9	52.4
Ocular torsion measurement (SD)	7.2 (3.7)	7.3 (3.6)	6.7 (3.8)	7.2 (4.1)
Mean RNFL thickness (SD)				
Total mean	86.7 (17.6)	98.5 (10.9)	76.0 (10.6)	62.4 (12.5)
Superior	104.3 (25.9)	120.6 (15.4)	91.1 (18.4)	69.7 (21.3)
Temporal	63.4 (12.9)	66.0 (8.9)	61.8 (11.1)	54.0 (20.4)
Nasal	68.7 (16.9)	76.1 (12.6)	58.7 (15.5)	55.4 (11.2)
Inferior	111 (31.1)	131.1 (18.6)	92.3 (20.5)	70.3 (23.1)
Superior temporal	114.8 (30.3)	133.6 (17.6)	101.4 (24.1)	73.7 (23.0)
Superior nasal	93.8 (25.7)	107.8 (19.3)	80.7 (17.3)	65.9 (25.1)
Inferior temporal	117.8 (38.7)	143.6 (20.5)	94.3 (29.6)	69.6 (29.6)
Inferior nasal	103.4 (30.6)	119 (25.0)	90.3 (23.4)	70.7 (25.8)

Values are expressed as mean (±SD) in micrometers.

The quality score did not differ for each patient because the same image, with different positions of the papillomacular bundle, was used. Total mean thickness also did not differ because the scan disc was not vertically or horizontally shifted, only rotated.

Differences were detected between each baseline sector and their corresponding sectors after rotating the scan disc. When the whole sample was included, any inferior displacement of the foveal location studied (rotations of 5°, 10°, and 15°) significantly affected all combined sectors (ST, SN, IT and

TABLE 2. Quantitative (Left Side of the Table) and Qualitative (Right Side) Differences Between Basal and Modified Scan Disc in Each Combined Sector for the Study Groups

OCT Parameters	RNFL Thickness Difference				Color Change			
Eyes	Superior Temporal	Superior Nasal	Inferior Temporal	Inferior Nasal	Superior Temporal, %	Superior Nasal, %	Inferior Temporal, %	Inferior Nasal, %
Control								
CW								
15°	17.9 (11.1)*	7.7 (8.2)*	13.5 (5.3)*	18.6 (11.1)*	0	0	9	4.5
10°	10.2 (8.4)†	4.4 (4.3)	6.5 (4.5)	12.6 (6.8)†	0	0	3	2
5°	4.1 (4.5)	1.7 (4.0)	4.1 (5.0)	5.8 (3.1)†	0	0	0	0
CCW								
10°	6.3 (4.3)*	9.5 (4.3)*	16.5 (9.6)*	11.1 (6.0)*	3	0	5	0
5°	1.5 (4.4)	3.4 (3.6)	7.4 (5.7)†	5.8 (3.5)†	0	0	0	0
Early glaucomatous								
CW								
15°	9.3 (11.4)*	8.1 (10)*	6.3 (4.0)*	13.4 (11.0)*	33	22	26	30
10°	5.4 (7.5)	4.7 (3.4)†	6.3 (3.2)*	8.6 (9.1)	14	4	22	22
5°	2.0 (3.6)	1.9 (2.4)	3.9 (5.3)	3.9 (5.0)	7	4	11	4
CCW								
10°	5.0 (3.7)*	2.0 (3.0)*	3.7 (4.7)*	6.0 (9.4)*	15	19	26	19
5°	3.1 (2.7)	3.7 (5.2)	8.7 (5.4)†	3.4 (4.4)	7	11	15	7
Moderate glaucomatous								
CW								
15°	6.5 (14.8)*	4.6 (11.6)	8.5 (14.7)†	10.2 (11.1)*	28	28	28	48
10°	3.1 (11.1)	1.3 (9.1)	6.3 (9.5)	5.3 (6.7)	16	20	16	32
5°	2.9 (5.2)	1.4 (5.2)	3.3 (4.7)	1.8 (3.7)	16	8	8	16
CCW								
10°	2.5 (6.5)*	1.1 (8.9)	5.9 (12.0)†	4.6 (10.4)*	28	32	20	28
5°	1.9 (9.5)	0.7 (7.3)	3.2 (6.9)	2.1 (8.9)	20	16	16	16

Data are expressed in micrometers and correspond to means of differences (±SD) in RNFL thickness between baseline images and modified images. Right side: Percentage of eyes with color chart change in each sector. CCW, counterclockwise; CW, clockwise.

* Significant difference: $P < 0.001$.

† Significant difference: $P < 0.05$.

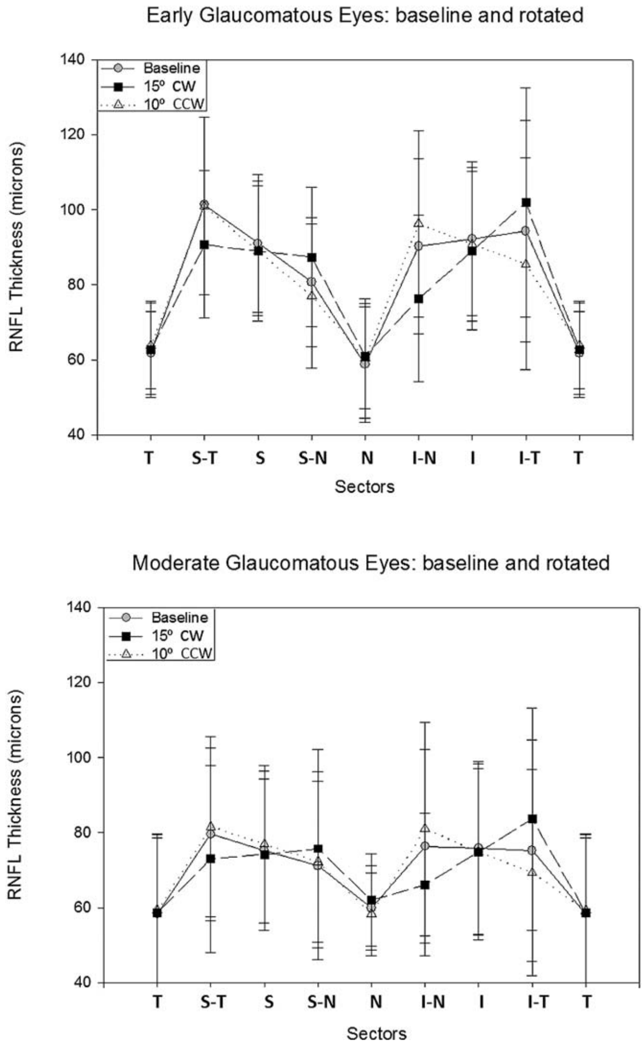

Figure 2. Mean and standard deviation for thickness in all sectors in basal acquisition and after editing in early and moderate glaucomatous eyes. Symbols: *gray circle*, baseline; *black square*, 15° clockwise torsion; *triangle*, 10° counterclockwise torsion. Note that range of variation is wider in early glaucomatous eyes.

IN) as well as the superior quadrant. Superior displacements of foveal position induced significant changes only in the I, IT, and IN sectors. Table 2 shows results for combined sectors in maximum rotations induced for the three groups studied. Assessment of the control group alone indicated significant changes for the S, N, I, and all combined sectors for any degree of inferior tilting of the fovea–disc line. Maximum differences could reach 46 μm in this group. Patients with early glaucoma were also affected by induced rotation of the scan disc, although differences tended to be less marked and reached statistical significance in fewer sectors. In patients with moderate glaucoma, statistical differences decrease in significance and number of sectors. When the scan disc was clockwise rotated (foveal position misplaced inferiorly to the actual position), RNFL changes were observed in the superior sectors, whereas the contrary resulted in modification of the inferior sectors (Fig. 2).

The extent of the change for every specific sector was proportional to the degree of rotation induced, as illustrated in Figure 3.

How does the FoDi software interpret these quantitative modifications? Changes in sector color codifications (comparison versus normative database) were minimal in healthy eyes, but common in early and moderate glaucoma (Table 2). In these groups, both positive and negative color modifications were observed, and cannot be predicted for one specific sector in a particular patient. To set an example, clockwise rotation of 15° produced color change in the inferior nasal sector in 48% of moderate glaucomatous eyes studied, improving one-third and worsening the rest. Figure 1 shows one of these patients.

Discussion

The FoDi software in SDOCT provides an automatic value for ocular torsion angle and prints a reference line for the papillomacular bundle in an intermediate image in which the foveal position can be manipulated. When this image is analyzed, the results sheet does not show the torsion used. If the subject fails to fixate, the fovea will be placed at random, and what appears to be the temporal sector will not correspond to the real temporal sector because the scan disc will be rotated clockwise or counterclockwise. The other sectors are consequently also affected and will be compared to a reference database that is no longer suitable. These errors cannot be detected in the results sheet. Failure of the patient to cooperate and poor visual acuity are typical reasons leading to poor internal fixation.

Because OCT is used as a complementary examination tool in glaucoma, several studies have investigated the factors that interfere with measurement reproducibility. Vizzeri et al.[14] have analyzed the effect of signal strength and horizontal alignment on RNFL thickness in 94 healthy subjects, using the Stratus OCT (Carl Zeiss Meditec), and report a positive linear relationship between signal strength and mean RNFL thickness. They also state that horizontal, but not vertical, shifts are significantly associated with the variability in mean RNFL thickness when image acquisition is repeated. Hwang et al.[15] have used the HD-Cirrus OCT (Carl Zeiss Meditec) to analyze the effect of head tilt in 30 healthy subjects and have found that a right head tilt causes superior temporal RNFL thickening and inferior temporal RNFL thinning; but, for each subject, the achieved head tilt varies, and a mean value for the group is given. In our study, 126 eyes were evaluated, including healthy and glaucomatous eyes. Manual alteration of the fovea-to-disc alignment allowed us to assess a dose–effect relationship in a reproducible way. An additional advantage is that the rotation was the only factor altered in our study, because the scan was not repeated; only image processing of the original scan was performed. Therefore, scan quality, which is an established independent factor, could not interfere with the analysis.[14]

The Stratus or the HD-Cirrus allows for the relocation of the fovea during the examination, but not after the acquired image is saved. When the image is already saved, the HD-Cirrus permits horizontal and vertical shifts of the scan disc, but not torsional shifts, because foveal position is only considered while scanning the patient and does not appear in the resultant image used for analysis. The FoDi-enhanced Spectralis OCT is the only system that has the ability to induce a postacquisition torsional shift in the scan disc.

Fovea-to-disc misalignment cannot affect average RNFL thickness measures, but the thickness in each sector can vary as much as 46 μm, 10 times higher than the previously reported values of test–retest variability in RNFL thickness measurements, using the Spectralis OCT (up to 4.95 μm).[16]

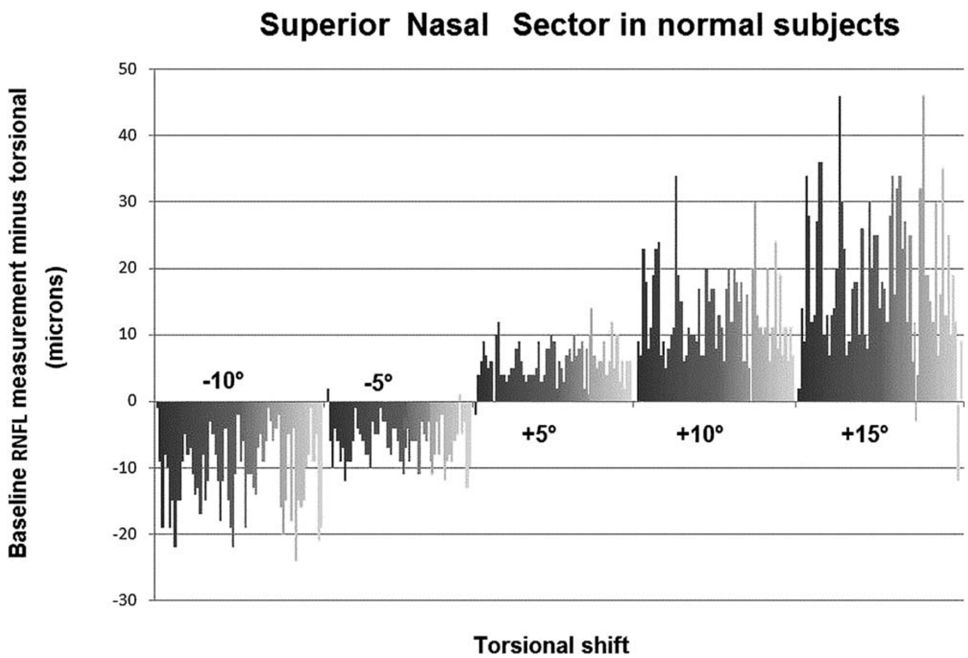

FIGURE 3. For each sector, thickness differences between baseline and each rotated image are proportional to the amount of rotation. Differences for superior nasal sector in normal subjects are displayed as an example.

Quantitative impact of induced torsion is greater in healthier patients. In these patients, the optic disc clearly alternates between peaks (superior and inferior) and valleys (nasal, and more importantly, temporal). As little as 5° of torsion will displace the peaks and valleys through the sectors. In general, the software does not consider additional fibers as edema in the receiving sectors. But "moved" fibers are detected as a loss from donor sector. As glaucoma progresses, the peaks are reduced and mean thickness in retinal layer is affected (i.e., the RNFL profile is flattened). As a result, torsions of the disc in these patients lead to more comparable profiles and baseline thickness is less disturbed. However, smaller changes in a previously reduced RNFL lead to greater changes in color assessment in the probability charts.

The length of the papillomacular bundle fibers is approximately 3500 to 4000 μm. When acquiring the images, undetected misalignment of fovea–disc line of 5° alters the distance between the real fovea and false fovea by only 300 to 350 μm. Up to 20% of the examinations in this study had an initially wrongly located fovea. Thus, foveal location must be carefully checked before analysis is performed.

An important issue must be addressed. Horizontal and vertical shifts of the scan disc are often detected in the image shown in the results sheet, but errors in torsion assessment are masked because the fovea–disc line is not shown or printed. In a follow-up examination, changes in the position of superior and inferior RNFL peaks, compared to previous examinations, can help the ophthalmologist to suspect incorrect rotation of the previous images. Changes in color charts, with a similar value of mean RNFL might make the specialist suspect that the measurement is the result of an artifact. Thus, a first-visit examination, especially in the absence of a healthy RNFL profile, can easily be mistaken. If tomography has been performed in an external diagnostic center, access to the original image is limited, and edition of the original image, less feasible.

If a subject fails to achieve foveal fixation to correctly orient the scan disc in a first visit, and tomography is selected as a reference for the follow-up scans, the subsequent images will also be rotated. Exquisite orientation of the scan disc on the first visit is extremely important to successful follow-up examinations.

In conclusion, our results showed that the new FoDi software improves OCT performance when used correctly, but can significantly affect RNFL measurement if the foveal location is not confirmed. Lowering the position of the fovea induces changes in the superior sectors, and raising it affects the inferior sectors. The greater the torsion induced in the scan disc, the greater the effect on sectoral RNFL thickness. When referring to glaucoma, as the disease progresses, the RNFL thickness profile becomes flatter, and alternations between peaks and valleys become more subtle. Therefore, rotation of the scan disc has less impact on quantitative thickness, but qualitative interpretation has shown to be more affected in moderate than in early glaucomatous eyes. Larger studies would be interesting to confirm these findings and improve glaucoma structural imaging.

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