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Glaucoma Specialist Detection of Optical Coherence Tomography Suspicious Rim Tissue in Glaucoma and Glaucoma Suspect Eyes.

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Abstract

Purpose: To assess glaucoma specialists' detection of optic nerve head (ONH) rim tissue that is thin by optical coherence tomography (OCT) criteria.

Design: Reliability analysis

Methods: 5 clinicians marked the disc margin (DM) and rim margin (RM) on stereo-photos of 151 glaucoma or glaucoma suspect eyes obtained within 3 months of OCT imaging. The photo and OCT infrared image for each eye were colocalized and regionalized into twelve sectors relative to the axis between Bruch's membrane opening (BMO) centroid and the fovea. For each clinician, the distance from BMO centroid to their DM (DM radius) and RM (RM radius) was used to generate sectoral rim width (RW) (DM radius – RM radius) and cup-to-disc ratio (CDR) (RM radius / DM radius) estimates. OCT minimum rim width (MRW) was determined by sector. Among all eyes, for each OCT MRW suspicious sector (< 5% of OCT normative data base), we determined each clinician's detection (clinician CDR – 0.7).

Results: Clinicians most commonly failed to detect OCT suspicious rim tissue in the nasal sectors. Among 502 sectors with suspicious OCT MRW all 5 clinicians rated CDR – 0.7 in only 29.5% and all 5 clinicians rated CDR < 0.7 in 21%. OCT suspicious rim thickness was most

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common (32% of eyes) in the nasal and inferior sectors. MRW vs clinician RW discordance was greatest nasally, while BMO vs clinician DM discordance was greatest temporally.

Conclusions: Clinicians most commonly failed to detect OCT suspicious rim thickness nasally where suspicious rim tissues were also most common.

Introduction

Clinician variability in the clinical disc examination is well documented,¹⁻⁵ but, until recently⁶ glaucoma specialists' disc margin, rim margin and rim width variability had not been rigorously assessed. In a previous report,⁶ we asked five glaucoma specialists to independently, digitally delineate the disc margin and rim margin (Figure 1 top row), within optic disc stereo-photographs from one eye each of 214 glaucoma or glaucoma suspect eyes. Each stereo-photo was then colocalized to the infrared fundus image obtained by OCT scan, enabling ONH 30° (clock-hour) sectors to be consistently imposed upon each eye, based on the position of the fovea relative to the center of the ONH (Figure 1 bottom left).⁷ We found disc margin, rim margin, rim width and cup disc ratio (CDR), (Figure 1 bottom right), discordance among the five clinicians to be substantial and common in sectors that were suspicious for rim thinning.

In the present report, we compare each clinician's rim width estimate to colocalized OCT minimum rim width (MRW) measurements,⁸ within a subset of 151 eyes from our previous study,⁶ so as to assess their ability to detect sectors in which the rim tissue was thin by OCT MRW criteria (< 5th percentile of an OCT MRW normative data base, (NDB)).⁹ While a clinician's rim width estimate is not directly comparable to an OCT MRW measurement due to anatomic and geometric considerations,¹⁰ (Figure 2), assessing clinicians' ability to detect rim tissues that are thin by OCT MRW criteria is important because a clinician must be suspicious enough, based on their own clinical examination, to decide that subsequent OCT imaging and/or functional testing is required.

To date, no study has objectively assessed clinicians' ability to sectorally detect rim tissues that are suspicious for being thin by OCT criteria. Specifically assessing clinicians' ability to sectorally detect rim tissues that are within the thinnest 5th percentile of a robust OCT data base⁹, is additionally important because this criteria has been used to detect glaucoma^{11,12} at levels of sensitivity (at 95% specificity) that are higher than those usually achieved by individual clinicians.^{13,14}

Subjects and Methods

Background and demographics.

This study was performed on photos and OCT data sets from 151 of the 214 individuals in our previous report,⁶ that met the OCT imaging criteria outlined below. All were participants in the Portland Progression Project,¹⁵ a NIH-funded, longitudinal study of progression in high risk ocular hypertension and glaucoma, that is based at the Legacy Devers Eye Institute in Portland, OR. The protocol was approved and monitored by the Legacy Health Institutional Review Board. The study adheres to the tenets of the Declaration of Helsinki and complies with the Health Insurance Portability and Accountability Act of 1996. All

participants provided written informed consent, after having the risks and benefits of participation explained to them.

Study participants¹⁵ had best corrected vision 20/40 and one or more of the following risk factors for glaucoma progression: age>70, systemic hypertension, migraine, diet-controlled diabetes, peripheral vasospasm, African ancestry, or family history of glaucoma. Participants with ocular, neurologic or systemic diseases, medications that can affect the visual field or previous ocular trauma including ocular surgery (except for uncomplicated cataract surgery) were excluded. Each subject underwent pachymetry, stereophotography, OCT ONH and RNFL imaging and visual field testing.

Imaging.

Only subjects with ONH photography and OCT imaging performed within 3 months of each other were included in this study. ONH stereophotographs were obtained using a simultaneous stereoscopic camera (3-Dx; Nidek Co Ltd, Gamagori, Japan) after maximum pupil dilation. The images were acquired on 35-mm slide film, developed and processed into color slides. The slides were digitized with a slide scanner (Nikon LS-5000 ED, Nikon Corporation, Tokyo, Japan) at a resolution of 4800 dpi. OCT imaging, (Spectralis, Heidelberg Engineering GmbH, Heidelberg, Germany), included a 30-degree infrared fundus image of the posterior pole including the ONH and fovea (using the integrated confocal scanning laser ophthalmoscope), and a 24 radial B-scan data set (each B-scan was 15-degrees wide, contained 768 A-scans and was the average of 9 repetitions).

One eye of each subject was randomly selected for analysis. For each study eye, the illumination and focus of the left and right images of the stereoscopic image-pair were qualitatively compared and the best was chosen for simultaneous digital delineation of the disc and rim margins, as outlined below, (Figure 1).

Clinician disc margin and rim margin assessment within each stereophotograph.

Five glaucoma specialists independently viewed the stereophoto-pairs of each study eye using a stereoscopic viewer (Screen Vu™, PS Manufacturing, Portland, OR) on a computer monitor without instructions as to how to mark the disc margin and rim margin points or awareness of the other clinicians' marks (Figure 1 top left). The clinical training and years of experience as a glaucoma specialist for the 5 clinicians ranged from 0 to 19 years. The disc margin and rim margin points of each examiner were digitally "burned" onto a separate copy of the better-focused image of the stereophoto pair, using a second adjacent monitor and custom software (Figure 1 top right). The purpose of this exercise was to document clinician variability in disc and rim margin assignment. Clinicians were not asked to assess if the rim tissue was abnormally thin nor were they told their derived rim widths would be compared to OCT MRW measurements.

Clinician-specific disc margin, rim margin, rim width and CDR measurements within the stereophoto of each study eye.

For each study eye, the delineated BMO points and the BMO centroid from its ONH OCT data set, (Figures 1 bottom left and Figure 2 top, and further explained in OCT methods

below), were projected onto the OCT infrared fundus image, wherein the axis between the BMO centroid and the fovea, (the FoBMO axis), was established. The boundaries of each FoBMO 30-degree (“clock-hour”) sector were then defined relative to this axis (Figure 1 bottom left). Thus, a common set of retinal and ONH anatomical landmarks were employed to consistently define the position of the 30° FoBMO ONH sectors in each study eye, rather than using the orientation of the fundus relative to the horizontal axis of the acquired image frame, which can vary from eye to eye.⁷ The disc margin and rim margin points for each clinician, (Figure 1 bottom left), were colocalized to the OCT IR fundus image, (Figure 1 bottom left), using a previously described technique¹⁶ performed within Image J (version 1.43u, TurboReg plug-in, National Institutes of Health, Bethesda, MD).

Within each photo, each clinician’s disc margin and rim margin points were connected and a single sectoral measurement of disc margin radius, rim margin radius and rim width (disc margin radius – rim margin radius), were made from the BMO centroid along the centerline of each 30° sector (Figure 1 bottom right). Sectoral CDR equivalents for each clinician were then calculated as: sectoral rim margin radius/disc margin radius (rounded to a single decimal place to mimic clinical practice). All left eye data were converted into right eye orientation.¹⁷

OCT MRW measurements by FoBMO 30° sectors.

BMO was manually segmented within each of the 24 ONH radial B-scans for each eye, and OCT MRW was calculated as the minimum distance between BMO and the ILM, (Figure 2), as previously described.⁸ Sectoral values for MRW were derived from 48 equally spaced angular positions around the BMO centroid, with the 12 sectoral mean MRW measurements being the average of 4 MRW measurements per sector.

Data Analysis.

The experiment-wide (n=151 eyes), mean disc margin radius, rim margin radius, and rim width were calculated for each clinician by sector. For each eye, the root-mean-square difference (RMSD) between the BMO radius and the disc margin radii of the 5 clinicians as well as the RMSD between OCT MRW and the rim widths of the 5 clinicians was calculated for each sector. The statistical significance of inter-sectoral differences in the RMSDs across all 151 study eyes were assessed for each comparison by Wilcoxon test.

To assess the clinicians’ ability to detect ONH sectors that were thin by OCT criteria, we first identified all sectors in which the sectoral MRW value, (after being corrected for age and BMO area),⁹ was < the 5th percentile of the OCT Caucasian NDB.⁹ We then assessed clinician “detection” of these sectors using two definitions of detection: a sectoral CDR equivalent 0.6, and a sectoral CDR equivalent 0.7, based on previous studies that have used these definitions.¹⁷⁻²² Finally, to estimate the rate of false positive clinician determination of suspicious rim thinning using each detection definition, we assessed their performance within “normal” sectors, using two OCT MRW definitions of “normal”, (the 5th percentile and the 10th percentile of the NDB, respectively).

A Chi-square test was used to assess the statistical significance of sectoral differences in the frequency of clinician detection of rim tissue that was suspicious by OCT MRW criteria, as

well as differences in the frequency of false positive detection of suspicious rim thickness in sectors that were “normal” by OCT criteria.

Results

This study included 151 eyes of 151 subjects ranging in age from 33 to 89 years old (mean $\pm$ standard deviation 64 ± 11 years). Eighty-four, (56.6%) were right eyes and the mean visual field mean deviation was -0.61 ± 2.86 decibels (range -14.97 to 2.74). Most of the participants were Caucasian (143, 94.7%) and approximately half (84, 56.6%) were female. Stereophoto and OCT imaging were acquired on the same day in 84% of study eyes.

Each clinician's mean disc margin radius versus the mean OCT BMO radius by sector across all 151 eyes are reported in Figure 3 (left). On average, BMO radius was smaller than the disc margin radii of all 5 clinicians within the temporal and superior sectors, and smaller than the disc margin radii of most clinicians, within the nasal and inferior sectors. Among the 151 study eyes, the sectoral frequency of BMO radius being smaller than all 5 clinicians' disc margin radii ranged from 21.2% to 68.2% being most frequent within the *inferior-temporal* (51.7%), *temporal-inferior* (64.2%), *temporal* (65.6%), *temporal-superior* (68.2%) and *superior-temporal* (66.9%) sectors. The frequency of BMO radius being larger than all 5 clinicians' disc margin radii ranged from 7.9% to 26.5% being most frequent within the *nasal* (26.5%), *nasal-inferior* (23.2%), *inferior-temporal* (19.2%), *temporal-inferior* (18.5%), *temporal* (18.5%), and *temporal-superior* (14.6%) sectors. The sectoral magnitude of OCT BMO versus clinicians' disc margin radii discordance, across all 151 eyes, (Figure 3 right), was highest in the *temporal* and *temporal-inferior* sectors compared to all other sectors ($p < 0.001$, Wilcoxon test).

Each clinician's mean rim width versus the mean OCT MRW by sector across all 151 eyes are reported in Figure 3 (center). The mean rim width for 4 clinicians, (Clinicians 2-5), was greater than the mean OCT MRW in all sectors, (Figure 3 center). Among the 1812 study eye sectors, the frequency of each clinicians' sectoral rim width being greater than OCT MRW was 44% for Clinician 1 and 83%, 81%, 72% and 91% for Clinicians 2-5, respectively. The sectoral magnitude of OCT MRW versus clinician rim width discordance, (Figure 3 right), was highest in the *nasal-superior* and *nasal* sectors compared to all other sectors ($p = 0.003$).

The sectoral distribution (mean, 5th and 95th percentiles) of the study eye OCT MRWs are reported relative to the distribution of the Caucasian NDB in Supplemental Figure 1. Among the 1812 study eye sectors, (151 eyes $\times$ 12 sectors/eye), 502 (28.7%) were suspicious, by OCT MRW criteria, (Figure 4). Among the 502 suspicious sectors, all 5 clinicians' CDR equivalent was ≥ 0.7 in only 148 sectors (29.5%), (Figure 4), and ≥ 0.6 in only 290 sectors (57.8%), (Supplemental Figure 2).

Suspicious OCT MRW rim thickness occurred most commonly in the nasal sectors, and inferior sectors and least commonly in the temporal sectors, (Figure 5). The sectoral frequency of all 5 clinicians' detecting OCT MRW suspicious rim thickness using a CDR criteria of ≥ 0.7 ranged from 10% to 61%, (Figure 5). Whereas the sectoral frequency of

fewer than 3 clinicians detecting OCT MRW suspicious rim thickness using CDR 0.7 ranged from 9.0% to 60%. The frequency of detection for CDR 0.7 was greatest within the temporal sectors and least within the nasal sectors, ($p<0.001$, chi-square). The sectoral frequency of all 5 clinicians' detection of OCT MRW suspicious rim thickness using a CDR criteria of 0.6 ranged from 33% to 91%, (Supplemental Figure 3), whereas the sectoral frequency of fewer than 3 clinicians detecting OCT MRW suspicious rim thickness using CDR 0.6 ranged from 3% to 56%. The frequency of detection for CDR 0.6 was also greatest within the temporal sectors and least within the nasal sectors, ($p<0.001$, chi-square).

A representative study eye in which clinicians variably failed to detect rim tissue that was suspicious in 10 of the 12 sectors, (CDR 0.7 criteria), is shown in Figure 6. A broad region in which the clinical disc margins of all 5 clinicians fell outside of BMO may have contributed to the under-diagnosis of suspicious rim tissue in the temporal sectors. Yet all 5 clinicians also failed to detect suspicious rim tissues within the *inferior-nasal*, and *nasal-inferior* sectors, where disc margin versus BMO discordance was minimal.

The overall frequency of false positive determination of suspicious rim thickness is reported for CDR criteria 0.7 in Figure 7 and CDR criteria 0.6 in Supplemental Figure 4. Among the 1298 sectors with OCT MRW above the 5th percentile of the NDB, all 5 clinicians CDR equivalent was 0.7 in 4% and all 5 clinicians CDR equivalent was 0.6 in 18%. Among the 1065 sectors with MRW above the 10th percentile of the NDB, all five clinicians CDR equivalent was 0.7 in 3%, and all 5 clinicians CDR equivalent was 0.6 in 15%.

The sectoral frequency of clinician "false-positive" determination of suspicious rim thickness is reported for a CDR criteria of ★ 0.7 in Figure 8 and for CDR criteria 0.6 in Supplemental Figure 5. In sectors with OCT MRW the 5th percentile of the NDB distribution, the sectoral frequency of all five clinicians CDR being 0.7 ranged from 0% to 15% and the sectoral frequency of all five clinicians CDR being 0.6 ranged from 0 to 41%. In sectors with OCT MRW the 10th percentile of the NDB distribution, the sectoral frequency of all five clinicians CDR being 0.7 ranged from 0% to 13% and the sectoral frequency of all five clinicians CDR being 0.6 ranged from 0 to 36%. For both definitions of normal, and for both detection criteria, false positive determinations occurred most frequently within the temporal sectors ($p<0.001$). A representative study eye demonstrating the false positive determination of rim thinning temporally and inferiorly is shown in Figure 9.

Supplemental Table 1 reports the overall mean sensitivity and specificity of the five clinicians' using CDR equivalents of 0.6, 0.7, 0.8 and 0.9 as detection criteria for all suspicious sectors. These data demonstrate that for these 5 clinicians, specificities of 90% in all sectors were only achieved using a CDR equivalent 0.9, but at unacceptably low levels of sensitivity. Sensitivities of 90% were only achieved using a CDR equivalent 0.6 within the temporal sectors but at unacceptably low levels of specificity. These data led us to emphasize our findings using the CDR 0.7 detection criteria, rather than the CDR 0.6 criteria throughout this report.

Discussion

In our cohort of glaucoma and glaucoma suspect eyes, clinicians most commonly failed to detect OCT suspicious rim thickness nasally, where suspicious rim tissues were common and clinician versus OCT rim width discordance was greatest. To the best of our knowledge, no other study has compared glaucoma specialists' sectoral rim width assessments to colocalized OCT MRW measurements or directly assessed clinicians' ability to detect rim tissues that were thin or normal by OCT criteria. Doing so also allowed us to detect that clinicians false-positively determined rim tissue to be thin most commonly in the temporal sectors and to provide OCT anatomic insight into the causes of clinician versus OCT rim width discordance. To this point specifically, most eyes demonstrated regions of BMO that were either outside or inside of all 5 clinicians' disc margins, (suggesting BMO was clinically invisible to the clinicians) and the frequency of this discordance was greatest for BMO being inside of the clinician disc margins within the temporal sectors. Finally, the specificity of clinician detection of OCT rim thinning only achieved levels ~90% when a CDR ~0.8 or 0.9 was utilized which resulted in unacceptably low sensitivity.

Our finding that OCT suspicious rim tissue occurred as commonly within the nasal sectors as the inferior temporal sectors, and less commonly within the superior temporal sectors, challenges the commonly held notion that the inferior temporal and superior temporal regions of the ONH are most susceptible to glaucomatous damage and are also therefore the first to show damage early in the disease.²³⁻²⁶ The frequency of nasal rim loss is important because current automated visual field testing does not meaningfully test the retinal areas that correspond to the nasal rim and RNFL and is therefore insensitive to the loss of retinal ganglion cells that correspond to damage within these areas. In a study of 40 healthy, 41 ocular hypertensive, 50 preperimetric and 50 perimetric glaucoma eyes, Gmeiner, et al, reported frequent nasal rim thinning using OCT MRW criteria within all three study groups.¹² Leung, et al, reported longitudinal RNFL progression to be most common within the inferior temporal clock hours in 116 eyes from 64 glaucoma subjects; however, they also found that progression within the nasal clock hours was only slightly less common in the same eyes.²⁷

Reis and co-authors first described the phenomena of clinically invisible BMO being "inside" or "outside" of the clinically visible disc margin in 30 glaucoma and 10 healthy control subjects.²⁸ In the current study, BMO was most commonly (27% of eyes) "outside" all 5 clinicians' disc margins in the *nasal* sector, and it was most commonly (68% of eyes) "inside" all 5 clinicians' disc margins within the *superior-temporal* sector (Figures 6, 9 and 10). We propose that in this study BMO is suspicious for being "clinically invisible" within regions of a given eye when all 5 clinicians marked the disc margin "inside" or "outside" of BMO. However, because identifying regions of clinically invisible BMO was not a primary goal of this study, and because we did not specifically ask the clinicians to identify the innermost hyper-reflective boundary of the rim tissues as their disc margin, (Figure 10), our results only indirectly address this issue. With these limitations, our data confirm the findings of the Reis et al., study,¹⁰ and expand them to 5 clinicians and 151 study eyes.

The fact that the mean rim width for 4 out of the 5 clinicians was greater than the mean OCT MRW in all sectors (Figure 3), confirms the predictions of a second study by Reis and colleagues¹⁰ which suggested that clinicians' rim width measurements would most commonly be larger than OCT-based minimum rim width estimates made from BMO, due to anatomic and geometric differences that were inherent to each form of rim measurement (Figure 10). The geometric difference between the "plane" of clinical estimation, (roughly parallel to the retina), and the "plane" of the OCT MRW measurement, (perpendicular to the ILM), predispose the clinical estimate to be greater than the OCT MRW measurement in most circumstances (Figure 10). However, the anatomic components of clinical rim width estimation, (disc margin versus BMO discordance and rim margin variability),⁶ lead clinicians to overestimate or underestimate the width of the rim tissues within the "clinical" (i.e retinal) plane of estimation, independent of these geometric concerns. To our surprise, we found instances in which all 5 clinicians assigned a rim margin that did not have a clear OCT anatomic foundation and was profoundly different from the ILM, (Figure 10), a finding that was not modeled in the Reis, et al,¹⁰ study.

The fact that Clinician 1's rim width determinations demonstrate a different relationship to OCT MRW compared to the other 4 clinicians, may be related to Clinician 1 having had the greatest exposure to histologic and OCT studies of ONH anatomy prior to the performance of this study. Clinician 1's rim width was greater than OCT MRW in only 44% of sectors compared to 72% to 91% for the other 4 clinicians. However, while this translated to a higher sensitivity to OCT MRW suspicious rim tissue detection using CDR 0.7 criteria, (72% of all suspicious sectors compared to a range of 40% to 56% for the other 4 clinicians), it also yielded a higher rate of false-positive rim thinning detection using an MRW 10% of the NDB criteria (41%, compared to 8 to 20% for the others).

While there are no other studies that have directly compared clinicians' sectoral rim width assessments to colocalized OCT MRW measurements, there are many studies comparing clinicians' CDRs to OCT derived CDRs.²⁹⁻³³ In the most recent of these, Mwanza et al,³³ compared vertical and horizontal CDR measurements of 2 glaucoma specialists in 195 glaucoma and glaucoma suspect eyes and reported poor agreement between the clinician and OCT values, with OCT CDRs being greater than the clinicians' CDRs. This CDR result is compatible with the finding that clinician rim width estimates were on average larger than OCT MRW measurements in our study eyes.

In the present study, in addition to the fact that OCT MRW suspicious rim tissues most commonly occurred in the nasal sectors, clinicians most commonly failed to detect them there. This finding, combined with those of others,^{12,27} strongly suggests that there is a need to improve the clinical examination of the nasal ONH for both the detection of glaucoma and its progression. We believe that the goal of these efforts should be to improve the sensitivity and specificity of their ability to detect OCT suspicious rim tissue rather than to make clinicians rim width estimation equal to OCT MRW. However, to do so, we propose that characterizing the anatomic causes of disc margin and rim margin discordance will be necessary (Figure 10) and that integrating what is learned into clinical disc examination instruction will eventually improve clinician performance. Studies to test these hypotheses are necessary.

Our study is limited by the small number of clinician examiners. However, five clinicians is equal to or exceeds the number of examiners in most previous studies²⁹⁻³³ and their range of training and experience is likely similar to most tertiary care glaucoma services. Our study is also limited by the fact that it only assessed the ability of a clinical rim width estimate to detect rim tissues that were suspicious for being thin by OCT criteria. We focused on disc margin and rim width estimation because these components of the clinical examination could be quantified and compared to OCT rim anatomy. We did not directly compare clinician rim margin to OCT MRW rim margin assessment because of the geometric differences that are inherent to the two measurement strategies. Whether the OCT MRW rim margin can be or should be a target for clinician rim margin assignment, is of interest, but beyond the scope of this report. We also did not ask the clinicians if each disc sector was suspicious for glaucoma and did not allow them to include other aspects of the clinical examination such as pallor, nerve fiber layer thinning and nerve fiber layer hemorrhages. We only assessed glaucoma specialists. How their performance compares to general ophthalmologists and optometrists and whether the clinical examination of all clinicians can be improved through OCT-based instruction, deserve further study.

Finally, it is also worth noting that while one clinician was in glaucoma fellowship training during the study and a second was an early-career visiting clinician-scientist from China, neither of these clinicians, (clinicians 2 and 4, respectively) were outliers when compared to clinicians 1 and 5. Our study was not designed to demonstrate the effect of practice duration on clinician performance. Such a study would require multiple clinicians at each level of experience over the full duration of an average career and include a non-linear assessment of the post-fellowship learning curve. These kinds of analyses are beyond the scope of the present report.

In summary, in glaucoma and glaucoma suspect eyes, clinicians commonly failed to detect OCT suspicious rim thickness in all ONH sectors, but most frequently nasally, where suspicious rim tissues were also most common and clinician versus OCT rim width discordance was greatest. Clinicians falsely determined the rim to be thin most frequently in the temporal sectors, where regions that were suspicious for demonstrating clinically invisible BMO were also most common. Clinician rim width estimates were consistently larger than OCT MRW measurements for 4 of the 5 clinicians, and the difference between the two was greatest in the nasal sectors. We propose that the incorporation of sectoral OCT rim anatomy and its quantification into the clinical disc examination, and its instruction, may be necessary to improve clinician rim width estimation, especially within the nasal sectors of the ONH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Clinician disc margin (DM) radius, rim margin (RM) radius and rim width (RW) measurements in each study eye.⁶

A stereo-photo of each ONH (**Top left**) was individually viewed by each clinician while simultaneously marking the DM (green dots) and RM, (black dots), within the best focused image of the stereo-pair, (**Top right**), viewed within custom marking software on an adjacent monitor. (**Bottom left**) After colocalization of each disc photograph to the infrared fundus reflectance image of the paired OCT data set, a line connecting the Bruch's membrane opening (BMO) centroid (red dot) and the foveal center (blue dot) was drawn to establish the Foveal-BMO axis (red line), which was then used as the horizontal axis for twelve 30°, (clock hour), sectors, (black borders). (**Bottom right**) After connecting the DM and RM points of each clinician by straight lines (DM, green; RM, black), a single measurement of DM radius, RM radius and RW (DM radius – RM radius) was made along the midline of the sector, relative to the BMO centroid. Cup disc ratio (CDR) was calculated as RM radius/ DM radius, and CDR equivalent was defined to be the CDR rounded to the nearest single decimal place). All CDR data in this report are CDR equivalents to most closely mimic clinical practice. Throughout the text the 12 FoBMO sectors shown in the bottom left Panel are italicized when referred to individually (*S*) *superior*, (*SN*) *superior-nasal*, (*NS*) *nasal-superior*, (*N*) *nasal*, (*NI*) *nasal-inferior*, (*IN*) *inferior-nasal*, (*I*) *inferior*, (*IT*) *inferior-temporal*, (*TI*) *temporal-inferior*, (*T*) *temporal*, (*TS*) *temporal-superior*, (*ST*) *superior-temporal*. Note that while it is most common for the fovea to be “below” the acquired image frame (AIF) horizontal axis⁷, in this eye, likely due to cyclotorsion and/or head tilt during imaging, the fovea is above the AIF horizontal axis of the disc. Linking ONH sectoral regionalization to retinal anatomy, (the FoBMO axis), instead of the AIF horizontal axis, ensures that ONH regionalization is not affected by cyclotorsion and/or head tilt.⁷

Figure 2. OCT Bruch's membrane opening minimum rim width (BMO-MRW). (Top) OCT BMO points (red dots) and the location of the FoBMO axis B-scan (red line) has been projected onto the infrared reflectance image of the OCT data set. (Center) The portion of the FoBMO axis B-scan shown in white in the top panel. (Bottom) Bruch's membrane, (BM, orange dots), BMO, (red dot) and BMO-MRW (yellow arrow) are shown. BMO-MRW is defined to be the shortest distance between BMO and the internal limiting membrane (ILM). Because OCT MRW measurements are a three dimensional "minimum thickness" measurement and the clinician rim width estimate, of necessity is made within the plane of the retina, OCT MRW is not directly comparable to clinician rim width, (see Figure 10 for more details).

Figure 3. Polar plots of the sectoral mean values for each clinician's disc margin (DM) radius versus OCT BMO radius (solid red) (Left) and clinician's rim width (RW) versus the mean OCT minimum rim width (MRW, solid grey) (Center) across all 151 study eyes and the sectoral discordance (root-mean-square differences (RMSDs) between OCT Bruch's membrane opening (BMO) and clinicians' disc margin (DM) radius (red) as well as OCT MRW and clinicians' rim width (RW) (blue) (Right).

Data are in microns. **(Left)** Note that the mean OCT BMO radius is less than, the mean DM radius of most clinicians within most sectors, suggesting that OCT BMO lies inside of the clinically visible disc margin in most sectors of most eyes relative to the center of BMO. **(Center)** The mean rim width for 4 of the 5 clinicians falls inside of, (i.e. is greater than), the mean OCT MRW in all sectors ($p < 0.001$ by Wilcoxon test). Clinician 1's mean rim width overlies the mean OCT MRW in all sectors except in the superior and superior temporal sectors where it is smaller than OCT MRW ($p < 0.001$ by Wilcoxon test). **(Right)** Discordance between BMO and the clinicians' DM was greatest in the temporal sectors (red stars, T and TI, $p < 0.001$ by Wilcoxon test), whereas, discordance between OCT MRW and clinicians' RW was greatest in the nasal sectors (blue stars, NS and N, $P = 0.003$ by Wilcoxon test). See Figure 1 for sectoral nomenclature.

Figure 4. Frequency of clinician rim thinning detection using cup disc ratio (CDR) criteria ≥ 0.7 within OCT suspicious sectors.

The number at the top of the column is the number of sectors, among all 1812 (151×12) study eye sectors, in which OCT MRW was suspicious (< the 5th percentile of the OCT MRW normative data base (NDB)). White or black numbers at the top of each shade of grey are the number of suspicious sectors, (expressed in percent), in which the given number of clinicians' CDR was ≥ 0.7 . The white number at the top of the black portion of the column is the number of suspicious sectors, (expressed in percent) in which all 5 clinicians CDR was ≥ 0.7 , (29.5%).

Figure 5. Frequency of OCT MRW “suspicious” rim tissue among the 151 study eyes by FoBMO sector and the frequency and agreement of its detection by clinicians using a cup disc ratio (CDR) criteria of ≥ 0.7 . (Left)

The outer-most area (yellow) represents the number of study eyes in which OCT MRW is *suspicious* ($< 5^{\text{th}}$ percentile of the normal data base (NDB)) for each sector. Each shade of gray represents the number of suspicious eyes in which the corresponding number of clinicians’ CDR was ≥ 0.7 (i.e. their agreement). **(Right)** The outermost yellow area denotes 100% of the suspicious eyes in each sector. Each shade of gray represents the percent of suspicious eyes in which the corresponding number of clinicians’ CDR was ≥ 0.7 (i.e. their agreement). Taken together, these data suggest that while the frequency of OCT MRW suspicious rim tissue was greatest within the nasal and inferior sectors, clinician detection of OCT MRW suspicious rim tissue was lowest in the nasal sectors and greatest within the superior temporal sectors at all levels of clinician agreement.

Figure 6. Clinician failure to detect nasal and temporal OCT MRW suspicious rim thickness in a representative study eye using a CDR = 0.7 detection criterion.

(**Top left**) Fundus photograph from study subject DIS132. (**Top middle**) Bruch's membrane opening (BMO), the centroid of BMO, the Fovea- BMO axis (FoBMO axis, red line) and the 12 FoBMO 30° (clock-hour) sectors, (black lines) (**Top right**). BMO relative to the disc margin points of all five clinicians. Note that BMO is well inside the clinical disc margin points of all 5 clinicians temporally, (black arrows), suggesting that BMO was clinically invisible to these clinicians in this region.^{10,24} (**Center panels**). BMO and each clinician's disc margin and rim margin points have been superimposed on the fundus photo in the center, and OCT rim anatomy along with its quantification relative to a Caucasian Normative Data Base (NDB), are shown for each FoBMO sector. Note that the OCT anatomy boxes have been outlined in yellow and red when the OCT MRW anatomy (yellow or red arrow) is < the 5th percentile or < the 1st percentile, of the NDB. While our study treats all sectors <

the 5th percentile of the NDB as suspicious, we include the red distinction to be consistent with several clinical imaging devices. In a white circle at the top of each OCT anatomy box, the number of clinicians that were suspicious for rim thinning by CDR ≥ 0.7 criteria are noted. **(Bottom row)** Each clinician's rim width, (purple) and their CDR equivalent for the OCT MRW *suspicious* sectors of interest are shown. Note that while the clinicians rim width and CDRs are relatively concordant, within the inferior, nasal sectors, none of the 5 clinicians were suspicious for rim thinning by CDR ≥ 0.7 criteria. See Figure 10 for a more detailed discussion of the *temporal-inferior (IT)* and *inferior-nasal (IN)* sectoral anatomy.

Figure 7. Frequency of false-positive rim thinning determination by clinicians using CDR criteria 0.7 within OCT MRW "normal" sectors defined using two definitions of normal.

(left column) OCT MRW the lowest 5th percentile of the OCT MRW normative data base, (NDB) and (right column) OCT MRW the lowest 10th percentile of the NDB. Black numbers at the top of each column are the number of sectors, (among all 1812 (151 $\times$ 12) study eye sectors) in which OCT MRW was "normal" by the specific MRW criteria. Within each column, white or black numbers at the top of each shade of grey are the number of normal sectors, (expressed in percent), in which the given number of clinicians' CDR was 0.7. White numbers at the top of the black portion of the columns are the number of normal sectors, (expressed in percent) in which all 5 clinicians CDR was 0.7.

Figure 8. Frequency of OCT MRW “normal” rim tissue among the 151 study eyes by FoBMO sector and the frequency and agreement of false-positive determination of rim thinning by clinicians using a cup disc ratio (CDR) criteria of 0.7.

(Upper Left) The outer-most area (green) represents the number of study eyes in which OCT MRW is normal (the 5th percentile of the normal data base (NDB)) for each sector. Each shade of gray represents the number of normal eyes in which the corresponding number of clinicians’ CDR was 0.7 (i.e. their agreement). **(Upper Right)** The outermost green area denotes 100% of the normal eyes in each sector. Each shade of gray represents the percent of normal eyes in which the corresponding number of clinicians’ CDR was 0.7 (i.e. their agreement). **(Lower Left and Right)** The same as above except the criteria for “normal” is the 10th percentile of the NDB for each sector. Taken together, these data suggest that the frequency of OCT MRW normal rim tissue was greatest within the superior-temporal sectors, which is also where the clinicians’ false-positive determination of OCT MRW normal rim tissue was highest at all levels of clinician agreement.

Figure 9. Clinician false-positive determination of rim thinning temporally and inferiorly in a representative study eye using a CDR 0.7 criterion.

(**Top left**) Fundus photograph from study subject DIS413. (**Top center**) Bruch's membrane opening (BMO), the centroid of BMO, the Fovea - BMO axis (FoBMO axis, red line) and the 12 FoBMO 30° (clock-hour) sectors, (black lines). (**Top right**). BMO relative to the disc margin points of all five clinicians. Note that BMO is well inside the clinical disc margin points of all 5 clinicians superiorly and superior temporally, (black arrows), suggesting that BMO is clinically invisible to these clinicians in this region.^{10,24} (**Center panels**). BMO and each clinician's disc margin and rim margin points have been superimposed on the fundus photo in the center, and OCT rim anatomy along with its quantification relative to a Caucasian Normative Data Base, (NDB), are shown for each FoBMO sector. Note that in the *inferior (I)*, *inferior-temporal (IT)*, *temporal- inferior (TI)*, *temporal (T)*, and *temporal-superior (TS)* sectors, all 5 clinicians are suspicious for rim thinning by CDR criteria 0.7

in sectors in which the OCT MRW values are the 20th percentile of the NDB. Note also the variable levels of clinician detection of OCT MRW suspicious rim thickness within the nasal-superior, *nasal- inferior* and *inferior-nasal* sectors. In a white circle at the top of each OCT anatomy box, the number of clinicians that were suspicious for rim thinning by CDR 0.7 criteria are noted. **(Bottom row)** Each clinician's rim width, (purple) and their CDR equivalent for the OCT MRW *suspicious* sectors are shown. See Figure 10 for a more detailed discussion of the *inferior-temporal* sector anatomy.

Figure 10. While clinician rim width is predisposed to be larger than OCT MRW by geometry alone, the anatomic components of clinician rim width estimation produce rim width overestimation or rim width underestimation within the clinician's plane of reference, that are separate from the geometric effects.

(**Top left**) Color photo of study eye DIS132, (from Figure 6) showing Clinician 3's disc margin (DM - green) and rim margin (RM - blue) points relative to OCT Bruch's membrane opening (BMO - red) and the *inferior-temporal* location of the cropped OCT B-scan shown in the top right panel. (**Top right**) OCT BMO and the projection of clinicians DM and RM points are displayed. The "geometric" difference between the clinical use of a "retinal" plane for rim estimation, (Clinician 3's rim width estimate, (blue line)), and an OCT MRW

measurement (yellow) predispose the clinical rim width estimate to be larger than the OCT MRW measurement. However, at least two additional anatomic influences can lead to clinician overestimation (top right and center right panels) or underestimation (bottom right panel) of rim width within the “horizontal” clinical plane of estimation. The first is OCT BMO versus clinical DM discordance, (**A**), which at this location further increases the clinical rim width measurement. The second is clinical RM versus ILM discordance which is illustrated in center and bottom panels. (**Center left**) Similar to the top left panel, but shows the *inferior-nasal* location of the cropped OCT b-scan in (**Center right**) in which there is DM versus OCT BMO discordance, (smaller than *inferior-temporally*, above) but also RM versus ILM discordance, (**B**), likely due to the presence of a vessel (**v**) that obscures the clinician’s view of the ILM. In both of these locations, top right and center right panels, overestimation of the rim width within the retinal plane underlies the low number of clinicians (circled number in upper right corner of each panel) that detected rim tissues that were thin by OCT. (**Bottom left**) Similar to top panels, but showing study eye DIS413, (from Figure 9) and the *inferior-temporal* location of b-scan shown in the bottom right panel. (**Bottom right**) In this sector, there is DM versus BMO discordance that is likely related to the externally oblique border tissues,^{10, 24} and profound RM versus ILM discordance, (**C**), the underlying reasons for which are not clear. Why none of the 5 clinicians were able to discern the ILM (?) in this location, (clinical RMs are similar here in Figure 9), warrants further study. Underestimation of rim tissue thickness within the retinal estimating plane in this location underlies the fact that all 5 clinicians determined rim tissues to be suspicious, which were normal by OCT.