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Article

Central Glaucomatous Damage of the Macula Can Be Overlooked by Conventional OCT Retinal Nerve Fiber Layer Thickness Analyses

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Purpose: To assess the extent to which glaucomatous damage of the macula can be detected using the summary statistics of a commercial report based upon the circumpapillary retinal nerve fiber layer (cpRNFL) thickness obtained with frequency domain optical coherence tomography (fdOCT).

Methods: One hundred forty-three eyes of 143 open-angle glaucoma patients and suspects (56.4 ± 13.8 years) had 10-2 visual fields (VFs) and fdOCT macular and disc cube scans. RNFL and retinal ganglion cell plus inner plexiform layer thickness and probability maps were generated and combined with 10-2 VF information in a single-page, custom report previously described. Three graders evaluated these reports and classified each eye as "abnormal macula" or "normal macula." Commercially available fdOCT reports for cpRNFL thickness were generated using the automatic segmentation algorithm and norms from the machine. The ability of the reports to detect macular damage was analyzed in three ways: temporal quadrant (TQ) < 5%; TQ < 5% or clock hour 7 < 1% (TQ + CH7); and clock hours 7 through 10 with two sectors < 5% or one sector < 1% (CH7−10).

Results: Sixty-one (43%) eyes were classified "abnormal macula" and 41 (29%) as "normal macula"; the 10-2 VFs and OCT probability maps did not agree in the remaining eyes. Of the 61 abnormal eyes, the TQ criterion missed 47 (77%); TQ + CH7 missed 24 (39%); and CH7−10 missed 22 (36%).

Conclusions: Conventional cpRNFL analyses on commercial OCT reports can miss macular (central field) damage.

Translational Relevance: To detect glaucomatous damage of the macula, additional tests, such as macular cube scans and/or 10-2 VFs, should be performed.

Glaucomatous damage to the macula occurs early in the disease process and is more common than generally thought.[1–9] This early damage can take the form of local, arcuate defects; widespread, diffuse damage; or a combination of both.[8] A growing body of evidence suggests that macular damage is overlooked or underestimated when using the most common clinical test, the 24-2 (6°grid) visual field (VF) obtained with automated perimetry.[4–9]

Although the use of optical coherence tomography (OCT) has grown in recent years, it is not clear how best to detect macular damage using OCT. Some have argued for using retinal ganglion cell plus inner plexiform layer (RGC+),[7,8,10] or macular retinal nerve fiber layer (RNFL)[11] measurements from macular cube scans. However, for diagnosing and following glaucomatous damage, macular scans are not routinely obtained in many clinics. Often, only the circumpapillary circle or optic disc cube scans are acquired. From these scans, the circumpapillary

RNFL (cpRNFL) thickness around a circle 3.4 mm in diameter is determined, either directly from the circle scan of the disc or extracted from the disc cube scan. This cpRNFL thickness map is typically used for clinical analysis of glaucoma.[12]

For detecting glaucomatous damage, a number of studies have found that measures based upon macular scans do not perform better than cpRNFL thickness measured from disc scans.[13–16] However, these findings do not preclude the possibility that macular damage is better detected with macular scans. It is possible that macular damage is missed with cpRNFL thickness measures, just as typical arcuate damage may be missed with macular RGC+ measures. Moreover, in most of the studies that favor the cpRNFL, the inclusion criteria for glaucoma was based on the 24-2 or 30-2 VFs, both of which have test points on a 6° grid. These tests can miss macular damage detected with the 10-2 VF test pattern, which is performed with a 2° grid within the central ±10° of vision.[4–7,9,17]

Here we test the hypothesis that cpRNFL thickness analyses of OCT cube scans of the disc, as typically done with summary statistics, will miss glaucomatous damage of the macula. In particular, commercial cpRNFL thickness reports were evaluated for a group of patients with macular damage, which was confirmed with both 10-2 VFs and OCT macular RGC+ analysis.

Methods

Subjects

In this prospective study, 143 eyes of 143 open-angle glaucoma patients and suspects were included (56.4 ± 13.8 years). All eyes had an abnormal or suspicious appearing optic disc upon evaluation of stereophotographs by a glaucoma specialist and a mean deviation (MD) of better than −6 dB on the 24-2 VF (Humphrey Field Analyzer; Carl Zeiss Meditec, Inc., Dublin, CA). Additionally, all eyes had a refractive error between ±6 diopters (D), were free of other disease processes that could affect the VF, and had a cataract score of N02, NC02, C2, P2.24, or better as defined by the Lens Opacities Classification System (III).[18] The study was approved by the Columbia University and New York Eye and Ear Infirmary of Mount Sinai Institutional Review Board and adheres to the tenets set forth in the Declaration of Helsinki and the Health Insurance Portability and Accountability Act. Written informed consent was obtained from all subjects.

All eyes had 10-2 VFs and frequency domain OCT (fdOCT) cube scans of the macula and the disc (3D-OCT 2000; Topcon, Inc., Oakland, NJ). The average maximum time between 10-2 and OCT tests was 38.7 ± 71.0 days (range 0–341 days); only 4 of the 143 eyes had more than 9 months between tests. More important for the criteria we use to judge macular damage (see next section), the 10-2 VF was either performed on the same day as, or before the day of, the OCT test in all but 1 of the 22 eyes missed by the disc cube scan using any of the criteria described below. In any case, the OCT commercial report and the OCT data for the inner retinal report described below were collected at the same time.

The healthy control group consisted of 54 eyes (53.2 ± 8.0 years) of 54 individuals (data supplied by Topcon, Inc.). These eyes were selected from a larger group ($n = 128$) of controls based upon being older than 40 years.[6] All eyes included had a refractive error between +3.0D and −6.0D, intraocular pressure (IOP) ≤ 21 mmHg; axial length between 22 and 26 mm; a normal clinical examination; and normal 24-2 VFs with false negative (FN) responses and fixation losses ≤ 33% and false positives (FPs) ≤ 15%. Those with a history of ocular disease or a family history of glaucoma were excluded.

Commercial Report Analysis

Commercial reports for the fdOCT disc cube scans were generated by the machine using a built-in automatic segmentation algorithm and a set of normative data (3D OCT 2000; Topcon, Inc.). A Food and Drug Administration-approved normative database was not available, so the normative database associated with the international version of the fdOCT machine was utilized as an institutional review board-approved configuration. Figures 1A and 1B show the RNFL quadrant and clock hour results used. All clock hours here and in Figures 2 to 5 are labeled in the right eye orientation, where the temporal quadrant (TQ) corresponds to clock hours 8, 9, and 10.

The ability of the reports to detect macular damage was analyzed in three ways.

Temporal Quadrant

If the average cpRNFL thickness of the TQ fell at or under the fifth percentile of norms (i.e., it appeared as yellow or red in Figs. 1A, 1B, left panel), then the macula was classified as abnormal.

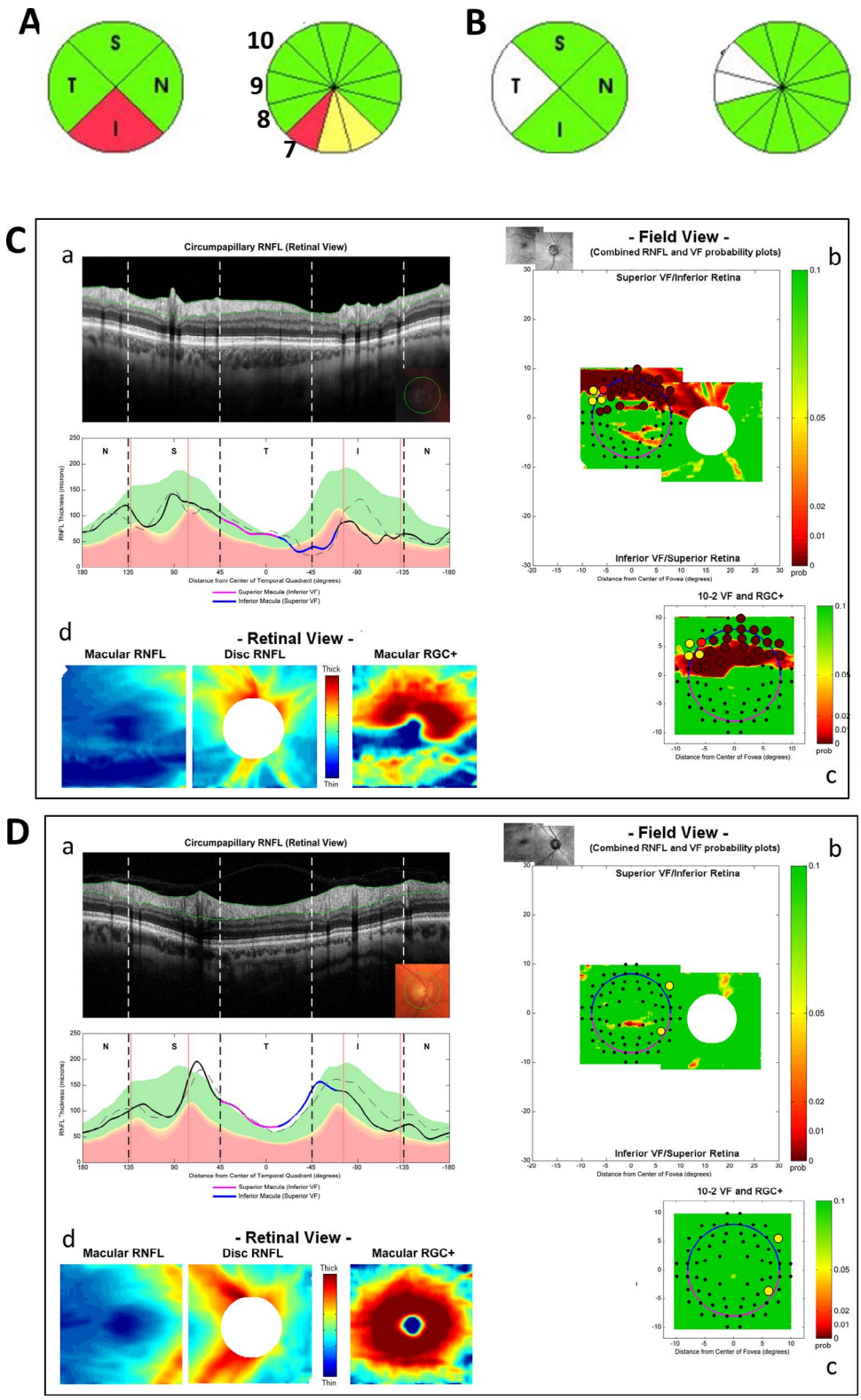

Figure 1. (A, B) The quadrant and clock hour summaries from the commercial reports for the eyes in panels C and D, respectively. (C, D) The custom inner retinal reports used to judge macular damage. These reports include the circumpapillary scan with the RNFL thickness profile presented as an NSTIN plot (a); the RNFL disc and macular probability maps in field view (b); RGC+ macular probability map in field view with 10-2 VF points superimposed (c); and RNFL and RGC+ disc and macular thickness maps in retinal view (d).

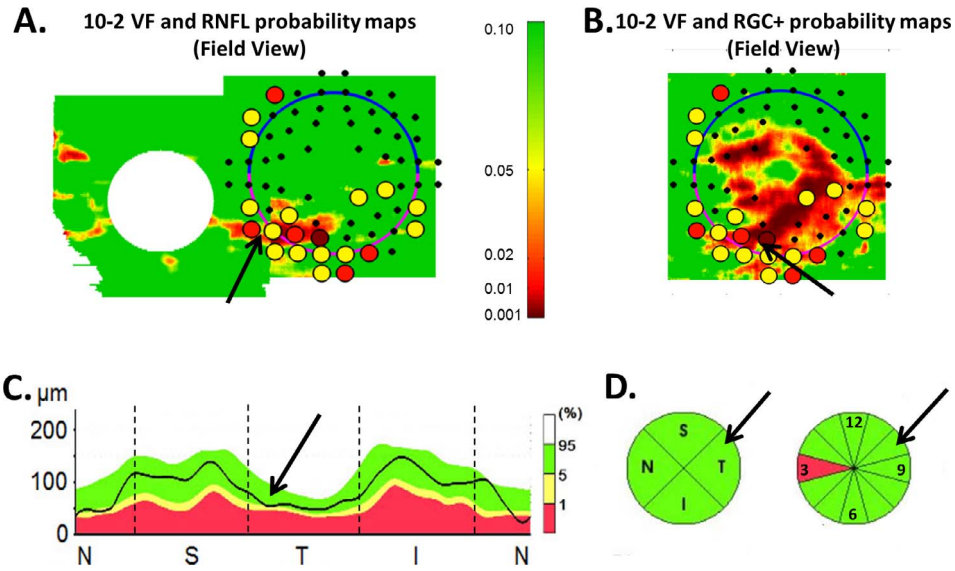

Figure 2. Subtle arcuate defects missed by all criteria. A and B are from our custom report (panels b and c in Figs. 1C, 1D) used to classify the macula as abnormal. C and D are from the commercial circumpapillary report. (A) RNFL thickness probability map for the disc and the macula with 10-2 VF points overlaid. (B) RGC+ thickness probability map for the macula with 10-2 VF points overlaid. The scale between panels A and B shows the significance level that refers to both panels and both VF and OCT data. The *black circle* has a radius of 8°. (C) The cpRNFL thickness profile (*black line*) against norms (*colored background*) and presented as an NSTIN plot. (D) Quadrant and clock hour report based on cpRNFL thickness in C.

TQ + Clock Hour 7 (TQ + CH7)

On average, the RGCs of the macula project to the most temporal portion of the inferior quadrant of the disc, as well as the inferior portion of the TQ.[6,7] In fact, the region of the disc between −38° and −65° is particularly susceptible to damage,[6,7] where 0° corresponds to the center of the TQ, and the TQ to ±45°. This region between −38° and −65° has been called the macular vulnerability zone (MVZ).[6,7,19] Defects in this region are relatively common[5–7,20] and produce superior VF arcuate defects in the macula close to fixation. To incorporate this region, CH7 (−45° to −60°) was included in the second criterion. (Note: The clock hour orientation is based upon a right eye.) In particular, for the TQ + CH7 criterion, if either the cpRNFL thickness of the TQ or the cpRNFL

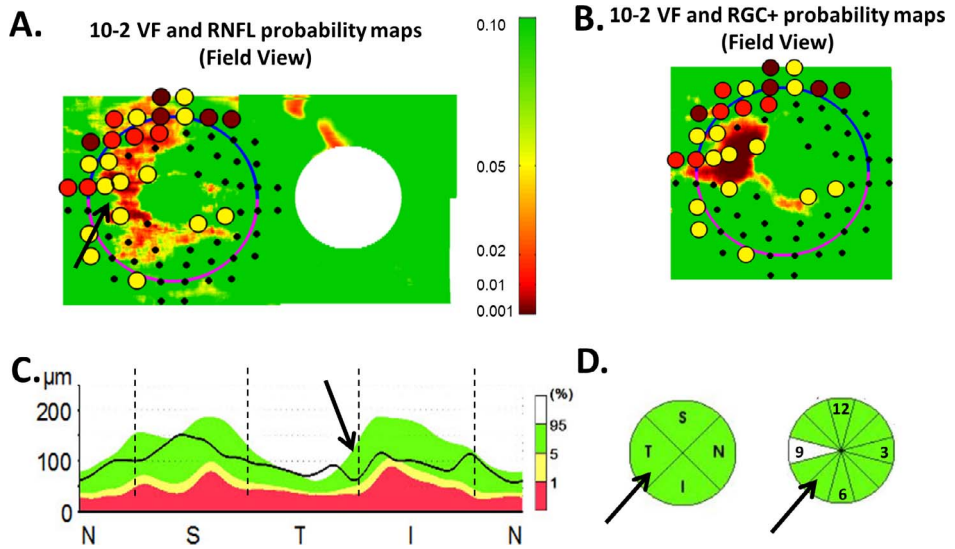

Figure 3. Same as Figure 2 for an eye with a defect in the inferior macula/superior VF.

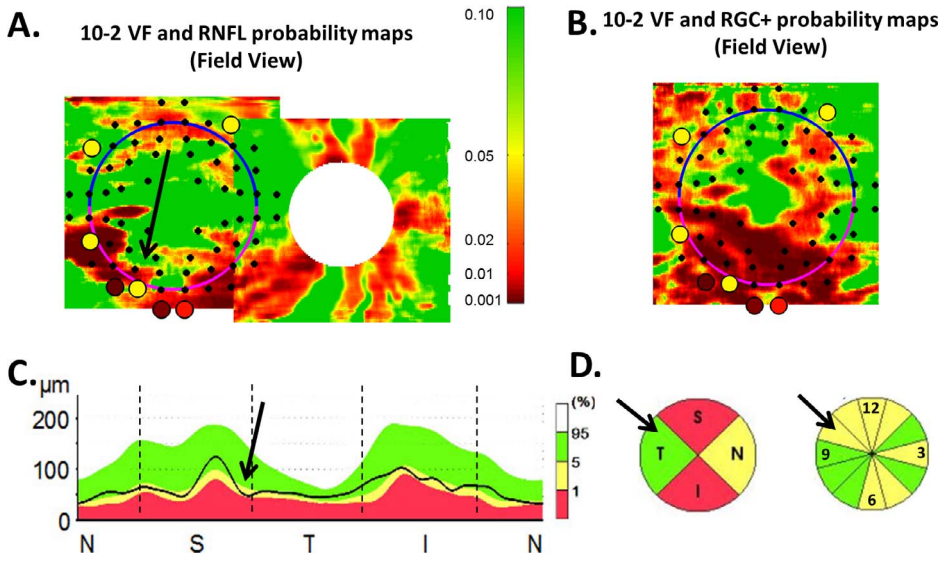

Figure 4. Same as Figure 2 for an eye with superior arcuate damage impinging on the macula.

thickness of CH7 fell at or under the first percentile of norms (red region), then the eye was classified as having macular damage.

Clock Hours 7 Through 10 (CH7–10)

Finally, a criterion of one red (1%) or two yellow (5%) clock hours within a four-clock hour region from 7 to 10 o'clock was used to assess whether an eye was abnormal in the macula.[21]

Custom Inner Retina Reports and Ratings

Before analysis, the macular cube scans were centered based on the location of the foveal center. The thickness of the RNFL and RGC+ layers was measured using an automated segmentation algorithm, which was corrected manually.[22–24] The same procedure was performed for the RNFL on the disc cube scan, after centering these scans based upon the center of the optic disc.

To be reasonably confident that an eye had macular damage, we required an abnormality on both the 10-2 VF and OCT probability maps. Further, these abnormalities had to appear in approximately the same location. To make this judgment, the RGC+ and RNFL probability maps, with 10-2 VF total deviation probability information

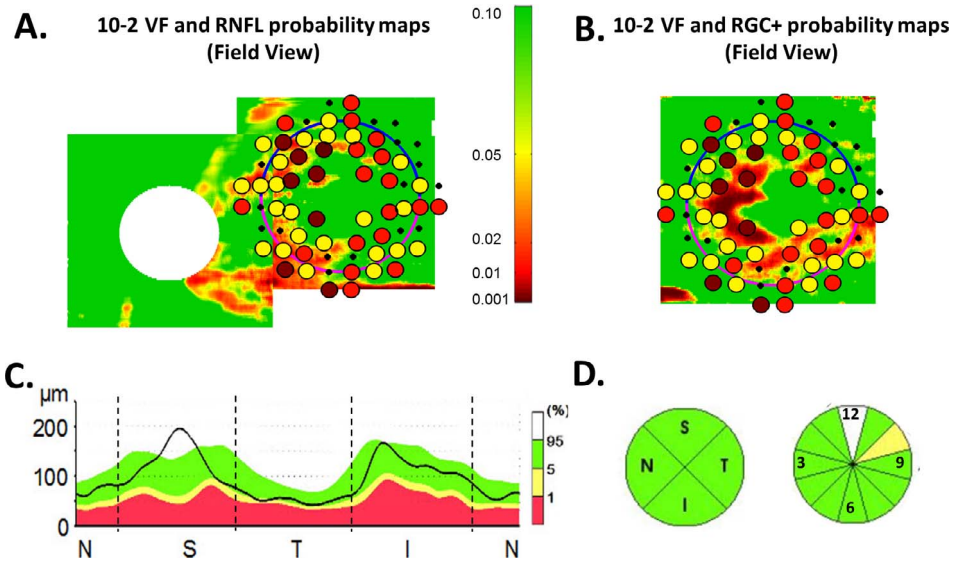

Figure 5. Same as Figure 2 for an eye with diffuse macula damage.

superimposed,[23] were displayed in a single-page report.[25,26] The reports, illustrated in Figures 1C and 1D were evaluated by three experienced graders in order to determine the eyes that were abnormal in the macula. Figure 1 shows examples of reports for an eye with an abnormal (C) and a normal (D) macula; the corresponding quadrant and clock hour summaries are shown in panels A and B, respectively. Going clockwise from the upper left hand image in Figures 1C and 1D, each report shows the circumpapillary image with the RNFL thickness profile (a); the RNFL disc and macular probability maps in field view with 10-2 VF points superimposed (b); RGC+ macular probability map in field view with 10-2 VF points superimposed (c); and RNFL and RGC+ disc and macular thickness maps in retinal view (d). (Note: The RNFL thickness profile [panel a in Figs. 1C, 1D and panel C in Figs. 2–5] is presented as a nasal-superior-temporal-inferior-nasal [NSTIN] plot, rather than the usual STIN plot. The NSTIN plot allows for easier comparison to the VF, RGC, and RNFL probability maps.[25])

Based on this report, the graders categorized each eye by hemifield as normal, abnormal, or mismatch (i.e., the 10-2 VF and OCT probability maps did not agree). In the relatively rare (less than 5% of the eyes) cases where there was disagreement among at least two of the graders, other information such as repeat VFs were used to reach a consensus. Eyes with at least one hemifield abnormal on both OCT and VF were called "abnormal," and eyes normal in both hemifields on both OCT and VF were called "normal"; the others were classified as mismatches and not analyzed further in this study.

Results

Of the 143 total eyes, 61 (43%) were categorized as abnormal and 41 (29%) as normal; for the remaining 41 eyes, the OCT and 10-2 VF did not agree. Figure 1C is an example of an abnormal macula that was missed by the TQ criterion (panel A, left), but correctly identified by the TQ + CH7 and CH7–10 criteria (panel A, right).

Of the 61 eyes with an abnormal macula, 47 eyes (77%) were missed with the TQ criterion. As expected, the TQ + CH7 criterion did markedly better than the TQ alone. However, it still missed 24 eyes (39%) with macular damage. The CH7–10 criteria did only slightly better than the TQ + CH7 criteria; it missed 22 eyes (36%).

For all three criteria, there were no FPs for both the healthy controls and the "normal" group. This was expected as neither the 10-2 VF nor the RGC+ probability maps were abnormal. Figure 1D is an example of an eye with a normal macula. In this case, the TQ (panel B, left), TQ + CH7, and CH7–10 criteria (panel B, right) all correctly identified this eye.

FNs on the Commercial Report (CH7–10)

To better understand why the commercial report missed macular damage with the CH7–10 criterion, the commercial and custom reports were examined and the 22 FN eyes placed into the following categories.

Subtle Damage Within the Macula

Ten eyes showed a subtle arcuate defect in the macula that was missed even by the CH7–10 criteria. In eight of these eyes, the subtle defect was in superior macula (lower VF). Figure 2 provides an example. Both the RNFL (A) and the RGC+ (B) probability maps showed a significant thinning in the superior macula (lower VF), as indicated by the black arrows, which corresponded to the location of abnormal points on the 10-2 VF, as shown by the large yellow and red circles. However, the corresponding affected regions on the commercial report appeared normal, as indicated by the black arrows in the temporal portion of the cpRNFL profile (C), the temporal portion of the quadrant plot (D, left), and CH7–10 (D, right). Figure 3 shows the results for an eye with a defect in the inferior macula (upper VF). There is a local dip in the cpRNFL profile at the corresponding location (black arrow in C), but the RNFL was not thin enough to be classified as abnormal and thus the TQ and CH7–10 (panel D) were in the normal range, although there is clearly a macular defect as seen in panels A and B.

Typical Arcuate Impinging on the Macula

In seven of the FN eyes, the macular damage appeared to be a part of a large arcuate defect that was mainly affecting regions outside the macula. Three of these eyes had damage in the inferior retina (upper VF) and four had damage in the superior retina (lower VF). For example, Figure 4 shows an eye with arcuate damage in the superior retina (lower VF), which is evident on the probability maps in panels A and B. While the cpRNFL thickness (C) showed thinning in the supero-temporal region of the disc (black arrow), the CH7–10 criterion did not capture this damage. Because only the edge of the macula was affected, it was missed on the commercial

report. The damage does, however, involve the RGCs of the macula as is evident in Figure 4B.

Diffuse Damage

For three eyes, the macular damage was shallow and widespread, and not deep enough to fall into the abnormal region on the summary statistics of the commercial report. One example is shown in Figure 5. Although the cpRNFL thickness (C) of this eye dips into the yellow region in a very small portion of the TQ, it is well within the 95% limits in the remaining regions of the disc. The RGC+ probability map (B) shows a diffuse abnormality, as do the 10-2 VF probability points. Other examples of mild widespread damage of the macula can be seen in Reference 8.[8]

Other Reasons

Two eyes were misses on the commercial report for reasons other than those listed above. In both cases, an examination of the OCT scans identified possible reasons. In one of these eyes, although the RNFL had normal thickness, there were abnormal, hypodense regions ("holes") in the temporal region of the disc. The appearance of holes has previously been associated with glaucomatous damage.[27] The other eye was missed due to clear errors in the identification of the RNFL borders by the segmentation algorithm.

Discussion

To test the hypothesis that cpRNFL thickness analyses of OCT cube scans of the disc, as typically done, will miss glaucomatous damage of the macula, we selected a group of patients we were reasonably confident had macular damage. In particular, we required clear abnormalities on both the 10-2 VF and RGC+ probability maps. Further, these abnormal regions had to topographically agree. Unlike repeat VF or OCT tests, VF and OCT results should have largely independent sources of error. Thus, while a FP is possible, it should be rare.

The results argue that the summary measures of circumpapillary RNFL thickness, as seen on commercial reports, will often miss macula damage. First, the quadrant analysis of cpRNFL thickness is commonly used to diagnose glaucoma.[21,28] However, 47 of the 61 eyes with macular damage had a TQ thickness in the normal range. Thus, if detection of macular damage were dependent upon the TQ, many eyes with macular damage would be missed.

The addition of CH7 reduced the number of eyes missed by 23, from 47 to 24. Based upon our previous work, this was not surprising, as adding CH7 included more of the MVZ. Based upon our model, the axons of the RGCs that correspond to most of the inferior portion of the macular project to a location inferior to the TQ.[6,7,19] That is, CH7 receives input from the RGCs in the macula and is particularly vulnerable to glaucomatous damage.

Finally, when the CH7–10 criteria were used, sensitivity improved further because damage that was more local in nature was detected. However, there were still 22 eyes (36%) that were missed using the CH7–10 analysis.

Lessons from the Eyes Missed with cpRNFL Analysis

The most common pattern of damage seen in the eyes that were missed was subtle damage within in the macula (10 eyes), followed by a typical arcuate impinging on the macula (seven eyes). Whereas the impinging arcuate category describes macular defects that are part of larger arcuates outside the central ±10°, the subtle damage is primarily confined to the macula. While typical arcuates are more easily detected on 24-2 VFs and OCT, subtle damage is easily overlooked. This subtle damage is clearly seen with RGC+ thickness analysis.[7,8]

Early macular damage can be shallow and widespread, as well as local and deep.[8,29] Only three of the missed eyes had widespread macular damage. All three had cpRNFL thicknesses that were borderline but not significant, although widespread damage was seen on the RGC+ probability maps as well as on the 10-2 VF, as previously reported.[8]

Finally, we have also argued that it is important to carefully scrutinize a high resolution circumpapillary image.[25,26] The two eyes in the "other reasons" category illustrate why. First, one can recognize segmentation errors that may give a false impression of the thickness of the RNFL. Second, local defects, such as hypodense regions/holes, can be identified.

Conclusions and Clinical Implications

Typical analyses of the disc cube OCT scan using the cpRNFL thickness maps can miss glaucomatous macular damage, especially if only the global and/or TQ thickness measures are employed. While detection of macular damage can be substantially improved by including the clock hour (7 o'clock) associated with macular damage, macular damage confirmed on fdOCT cube scans and 10-2 VFs will still be missed.

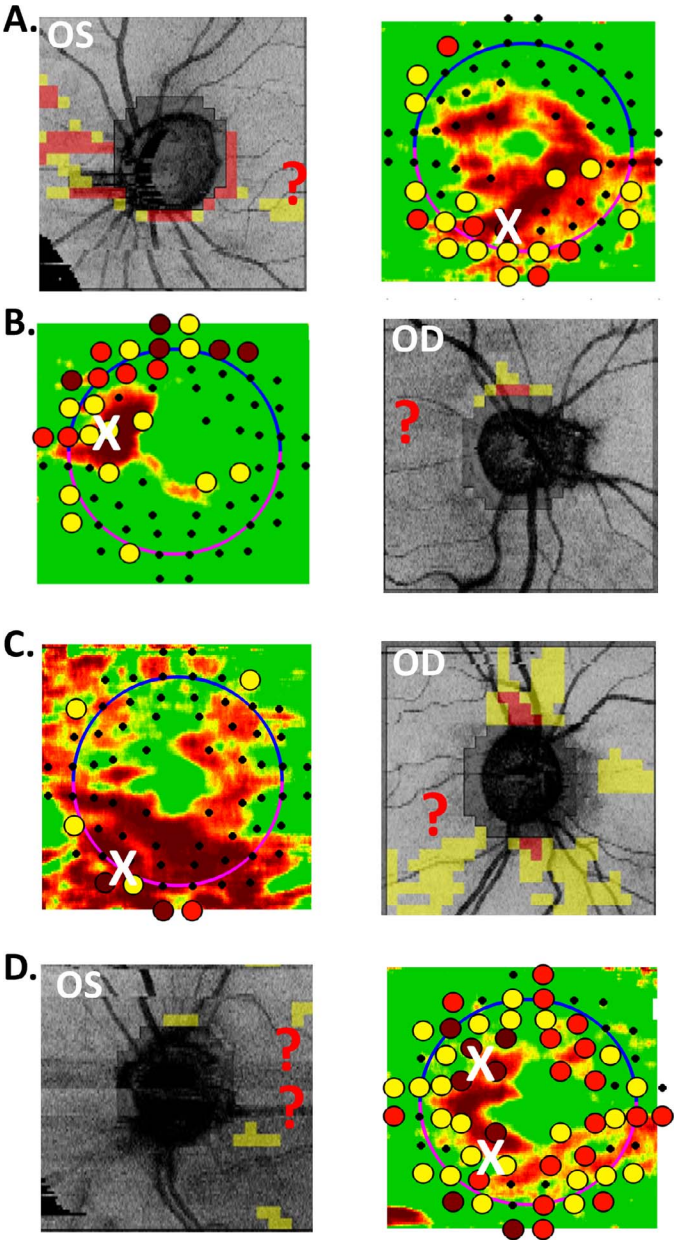

Figure 6. (A) Commercial RNFL probability map (*left panel*) and the 10-2 and RGC+ probability maps (*right panel*) for eye in Figure 2. (B) Commercial RNFL probability map (*right panel*) and the 10-2 and RGC+ probability maps (*left panel*) for eye in Figure 3. (C) Same as B for eye in Figure 4. (D) Same as A for eye in Figure 5. All panels are shown in field view. The *white X* indicates the region with confirmed macular damage based upon the 10-2 and macular RGC+ probability plots, and the red question mark indicates an approximate region within which one should see RNFL thinning associated with confirmed macular damage.

It could be argued that a RNFL probability map of the disc scan would reveal macular damage without the need for a macular scan. In fact, many commercial reports, including the one we used for this study, show a RNFL probability map. Figure 6 shows these maps from the commercial report for the same eyes as in Figures 2 to 5, along with the combined 10-2 and RGC+ maps from those figures. All panels are shown in field view. The white X indicates the region with confirmed macular damage based upon the 10-2 and macular RGC+ probability plots, and the red question mark indicates an approximate region within which one should see RNFL thinning associated with confirmed macular damage. Notice that the RNFL probability map will not replace the RGC+ probability map. First, damage can be missed by the RNFL map as indicated in panels B and D. Second, even if the RNFL probability map shows an abnormal region, it is hard to know if the macula is involved. (Note: The relative placement of the disc and macular results for each eye is arbitrary in Fig. 6.) For example, consider panels A and C. Although both of these eyes have a clear arcuate defect, it is difficult, if not impossible, to know if the damaged area includes the macula. Finally, many clinicians do not have the time or the training needed to integrate these probability plots in their decision making about macular damage. On the other hand, the RGC+ probability plots of the macular scans are relatively straightforward to interpret.

Thus, in addition to the disc cube scan, macula scans should be incorporated into clinical protocols for detecting glaucomatous damage. The RGC+ analysis of the macular cube scan can be used to detect macular damage missed, or difficult to identify, with cpRNFL analysis. In the case of the cpRNFL analysis, one should not solely rely on summary statistics, such as those based on the cpRNFL quadrant or clock hour thickness values. Finally, the circumpapillary images should be viewed directly to identify other factors that may lead to inaccurate cpRNFL thickness measures, such as errors in segmentation algorithms, the presence of epiretinal membranes (ERMs), or schisis.[30]

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