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Detecting Progression in Patients With Different Clinical Presentations of Primary Open-angle Glaucoma

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Précis: Glaucoma progression was more frequently identified by assessing retinal fiber layer thickness than by monitoring visual field (VF) loss for different baseline classifications in primary open-angle glaucoma.

Purpose: The aim was to compare the detection of glaucoma progression by retinal nerve fiber layer thickness (RNFLT) and VF assessments for different baseline classifications of primary open-angle glaucoma.

Methods: This study included 194 eyes from 194 patients with a minimum of 9 follow-up visits selected from the Diagnostic Innovation in Glaucoma Study (DIGS) and the African Descent and Glaucoma Evaluation Study (ADAGES). Each eye was classified according to baseline clinical signs: ocular hypertension (n=39), glaucomatous optic neuropathy only (n=60), glaucomatous visual field loss only (GVF, n=39) and definite glaucoma (concurrent optic disc and VF defect, n=56). We assessed progression by performing simple linear regression on global and sectorial mean deviations values generated for RNFLT (RNFLT-MD) and VF data (VF-MD). The proportion of eyes identified as progressing (positive rate) by RNFLT-MD and by VF-MD were compared within each classification.

Results: Whereas both parameters performed similarly among glaucomatous optic neuropathy only and definite glaucoma eyes, the positive rate obtained with global RNFLT-MD was significantly greater compared with global VF-MD by 33.3% and 30.8% among ocular hypertension eyes and GVF eyes, respectively. This finding was consistent in the inferotemporal sector; however, similar positive rates were obtained for both parameters in the superotemporal sector.

Conclusions: While both RNFLT and VF parameters showed comparable abilities to identify progression across the different classifications, RNFLT assessment may be better suited to monitor progression, particularly among patients with elevated intraocular pressure and those who present with only GVF defect at baseline.

Key Words: glaucoma, progression, RNFL thickness, visual field

Primary open-angle glaucoma (POAG) is the most common type of glaucoma[1] and its global prevalence was predicted to reach 65.5 million in 2020.[2] The diagnosis of POAG can be challenging because the degeneration of retinal ganglion cells results in both structural damage and loss of visual function and is often but not always preceded by dysregulation of intraocular pressure.[3] Landmark randomized clinical trials found that, in some patients with elevated intraocular pressure, the onset of POAG manifested first as either structural damage or abnormal visual function.[4,5] Likewise, prospective studies have shown that disease progression in some POAG patients may be detected first as either structural deterioration or worsening visual field (VF).[6–9] To date, however, no guidelines exist to determine whether structural or functional assessment is best suited to monitor glaucoma progression based on the presenting clinical signs at baseline.

The clinical presentation of disease is commonly used as a basis to classify participants at baseline in observational studies. For example, the criteria used to classify participants in the Diagnostic Innovation in Glaucoma Study (DIGS) and the African Descent and Glaucoma Evaluation Study (ADAGES) were based on clinical presentation at baseline and are detailed in Sample et al.[10] In brief, they include ocular hypertension (OHT), glaucomatous optic neuropathy only (GON), glaucomatous visual field only (GVF), and those with optic neuropathy and abnormal VF, hereinafter referred to as definite glaucoma. Similarly, in clinical practice, patients present with different signs of the disease and can be classified under one of these categories at the time of initial diagnosis. It would therefore be clinically beneficial to be able to determine whether structural or functional assessment is best suited to identify progression for each baseline presentation. This could lead to earlier detection of progression, timely evaluation of treatment efficacy and reduce the need for confirmatory tests.[4,11–14]

Optical coherence tomography (OCT)[13,15] and static automated perimetry (SAP)[14,16] are the most commonly used tests for monitoring glaucoma progression. It has been reported that baseline disease characteristics impact the detection of progression by OCT and SAP differently.[17–22] Previous studies, involving patients classified at baseline into preperimetric (or glaucoma suspects) and perimetric glaucoma, found that OCT assessment identified progression more frequently than SAP evaluation.[19,23,24] However, in 2 of these studies, the level of specificity was not adjusted for using multiple parameters from

each test to assess progression[19] and for defining progression as a significant negative change observed with either event-based or trend-based analysis.[23] In addition to using a relatively small sample size, Wollstein et al[24] grouped OHT and GON patients together as glaucoma suspects instead of handling them as separate classifications. Because the relationship between baseline disease classification and the detection of progression by OCT and SAP has not been well established and quantified, clinicians use both tests simultaneously to monitor progression or choose one test depending on the availability of resources. The aim of the current study was to compare the ability of OCT and SAP to detect progression in different baseline classifications of the disease. In contrast to the previous studies, we performed a trend-based analysis with one parameter from each test to detect progression among eyes classified into OHT, GON, GVF, and definite glaucoma at study baseline.

METHODS

Participants

This study is a secondary analysis of OCT and SAP data selected from the DIGS and ADAGES datasets. DIGS was conducted at the Hamilton Glaucoma Center at the University of California, San Diego (UCSD), whereas ADAGES, being a multicenter study, was conducted at UCSD, the University of Alabama at Birmingham, and the New York Eye and Ear Infirmary. These observational studies were designed to prospectively evaluate retinal structure and visual function.[10,25] Both studies were approved by Institutional Review Board at UCSD and by all study centers. The DIGS and ADAGES adhered to the tenets of the Declaration of Helsinki and all participants gave written informed consent. Method of recruitment and eligibility criteria have been explained in detail elsewhere.[10] Briefly, participants of the DIGS and ADAGES studies had open anterior chamber angles, a corrected visual acuity not worse than 20/40, refractive error < 5.0 diopters sphere and/or 3.0 diopters cylinder, and no history of intraocular surgery (except for uncomplicated cataract removal or glaucoma surgery). Participants were excluded if they had other ocular or systemic or ocular diseases which affect the VF or were incapacitated to perform VF tests. At baseline, one good-quality stereophotograph of the optic disc and one reliable VF test were obtained for every enrolled participant.

Inclusion Criteria and Baseline Classification of Eyes for the Current Study

For the current study, we required participants to have a minimum 9 pairs of OCT and SAP tests, with each pair constituting a visit. Of the 2103 OCT-SAP pairs available, 72% had both tests taken on the same day, whereas for the remaining pairs, OCT and SAP were performed no more 30 days apart. Only successive visits separated by at least 2 months and by no more than 36 months were included in this study. We also excluded participants with baseline VF mean deviation worse than −15 dB and baseline retinal nerve fiber layer thickness (RNFLT) below 50 μm.

One hundred and ninety-four participants, with a mean (SD) age of 64.7 (10.1) years, met our inclusion criteria. Only 1 eye per patient was selected for this study (the eye with less advanced disease was selected when 2 eyes were eligible). The 194 eyes were further classified into the 4 groups based on the presenting clinical signs at baseline as described in Sample et al.[10] Sterophotographs of the optic disc were reviewed for the presence of glaucomatous abnormalities such as cupping, neuroretinal rim thinning, retinal nerve fiber layer defect and a vertical cup-disc ratio asymmetry > 0.2. When an optic disc abnormality was detected, it had to be confirmed with a second stereophotograph before the disc was considered to be abnormal. Baseline VF tests were also reviewed and considered to be abnormal if the pattern SD was triggered at 5% or worse, and/or the Glaucoma Hemifield Test had an "outside normal limits" outcome. Two additional abnormal VF tests were needed to confirm a VF abnormality. The baseline classifications in the current study reflect one or a combination of the following: an elevated intraocular pressure (> 22 mm Hg), an abnormal optic disc appearance, and an abnormal VF. The 4 baseline classifications are described as follows:

(1) OHT (n = 39 eyes): elevated intraocular pressure but a healthy optic disc appearance and a normal VF.
(2) GON (n = 60 eyes): a confirmed abnormal optic disc appearance but a normal VF.
(3) GVF (n = 39 eyes): healthy optic disc appearance but a confirmed abnormal VF.

TABLE 1. Participants' Baseline Information

Baseline Characteristic	OHT (n = 39)	GON (n = 60)	GVF (n = 39)	Definite Glaucoma (n = 56)
Parameter mean (SD)				
Age, years	64.0 (10.6)	64.7 (9.2)	60.9 (10.9)	67.9 (9.1)
Follow-up, years	5.7 (1.3)	5.5 (1.1)	5.4 (1.2)	5.4 (1.1)
RNFLT, μm	88.8 (9.8)	87.2 (12.5)	88.4 (14.1)	74.3 (14.6)
RNFLT-MD, μm	−11.3 (19.0)	−16.1 (16.1)	−12.0 (15.4)	−14.5 (18.5)
VF-MD, dB	−0.4 (1.2)	−0.6 (1.6)	−3.3 (3.1)	−4.3 (3.9)
VF-STATPAC MD, dB	−0.2 (1.2)	−0.5 (1.6)	−2.9 (2.8)	−4.0 (3.8)
Visual field severity, n (%)				
Early	39 (100)	60 (100)	34 (87.2)	42 (75.0)
Moderate	0	0	5 (12.8)	11 (19.6)
Advanced	0	0	0	3 (5.4)
RNFLT classification, n (%)				
Within normal limits	28 (71.8)	43 (71.7)	28 (71.8)	17 (30.4)
Borderline	7 (17.9)	9 (15.0)	5 (12.8)	8 (14.4)
Outside normal limits	4 (10.3)	8 (13.3)	6 (15.4)	31(55.4)

GON indicates glaucomatous optic neuropathy only; GVF, glaucomatous visual field; OHT, ocular hypertension; RNFLT-MD, mean deviations values for retinal nerve fiber layer thickness; VF-MD, mean deviations values for visual field; VF-STATPAC MD, mean deviation value generated by the STATPAC software.
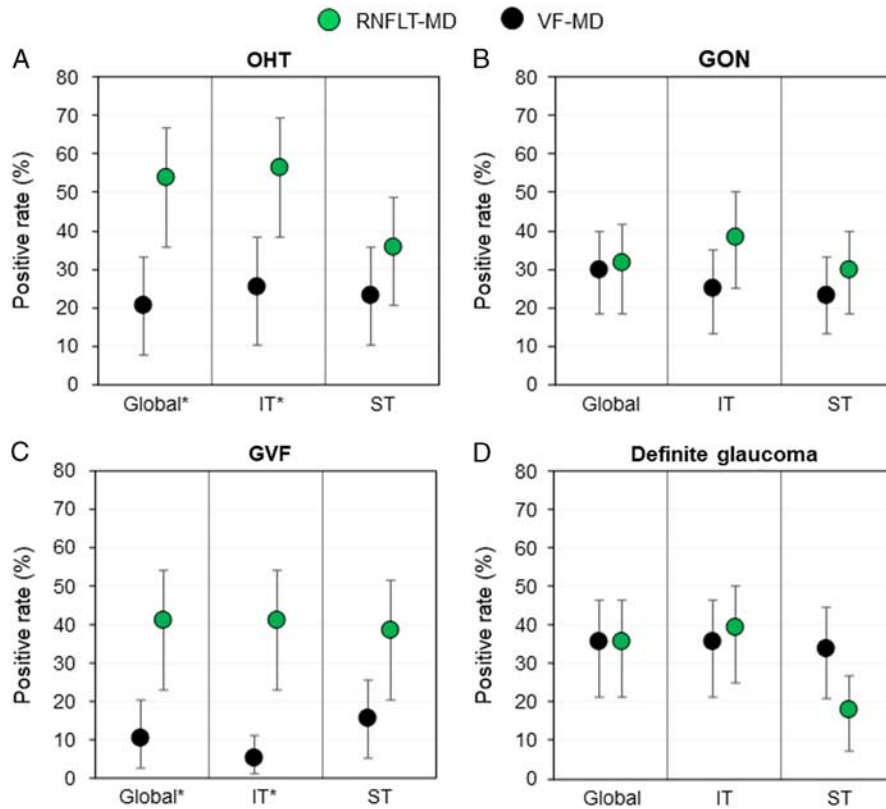
FIGURE 1. Comparison of positive rates (and 95% confidence interval) obtained for RNFLT-MD (green circle) and VF-MD (black circle). Comparisons are shown for OHT eyes (A), GON eyes (B), GVF eyes (C), and definite glaucoma eyes (D). Asterisk indicates a significant difference after Bonferroni correction. GON indicates glaucomatous optic neuropathy only; GVF, glaucomatous visual field; IT, inferotemporal; OHT, ocular hypertension; RNFLT-MD, mean deviation values for retinal nerve fiber layer thickness; ST, superotemporal; VF-MD, mean deviation values for visual field.

(4) Definite Glaucoma (n = 56 eyes): presence of both abnormal optic disc appearance and abnormal VF.

Structural and Functional Measurements

The Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) was used to measure RNFLT. The UCSD Imaging Data Analysis and Evaluation Reading Center reviewed all scanned images to ensure that they were well centered, had a signal strength was > 15 dB and had no artifacts.[10] The segmentation algorithm for nerve fiber layer was manually adjusted to correct for segmentation errors.[26] Only OCT scans determined as usable by the reading center were included in the current study.

To account for the impact of aging on progression,[27] age-corrected (mean deviation) values were generated for RNFLT using a reference data set with 232 healthy eyes enrolled in the DIG/ADAGES. RNFLT mean deviation (RNFLT-MD) values were generated by first by transforming the 768 thickness values into 360 sectors, with each accounting for 1 degree of the OCT circular scan of the optic disc. Age-corrected thickness deviation for each sector was then obtained in a similar manner as perimetric total deviation values.[28] Thus, thickness deviations were obtained by subtracting the mean normal thickness for an age-matched healthy subject from the measured thickness. Finally, the average of the 360 thickness deviations was computed as the global RNFLT-MD. Thickness deviations from 45 to 90 degrees and between 270 and 315 degrees were averaged as RNFLT-MD values for the superotemporal (ST) sector and inferotemporal (IT) sector, respectively.

Using the Humphrey Field Analyzer II (Carl Zeiss Meditec Inc., Dublin, CA), VF sensitivities were measured with the 24-2 SITA standard strategy. The UCSD Visual Field Assessment Center processed and reviewed all VF tests to ensure that they had no artifacts and were reliable, with less than 33% false positives, false negatives, and fixation losses.[25] For the current study, we included only SAP tests determined as usable.

For methodological consistency, we did not use MD values generated by the STATPAC software[28] as the functional parameter. Instead, we used visual field mean deviation (VF-MD) values derived in the same manner as RNFLT-MD. For each eye, the global VF-MD values were computed as the average of 52 total deviation values generated in reference to mean normal threshold sensitivities for an age-matched healthy subject from the reference data set with 232 healthy eyes. Unlike STATPAC MD, VF-MD was not centrally weighted. With reference to the Garway-Heath et al[29] map, the total deviation values corresponding to the IT and ST sectors of the optic disc were averaged to obtain sectorial VF-MD values.

Data Analysis

Structural progression was assessed with RNFLT-MD, whereas VF-MD was used to assess functional progression. Progression was evaluated with global and sectorial (IT and ST) measures for each parameter. We performed simple linear regression on the measurements from the first 6 visits and when a statistically significant negative slope ($P < 0.05$) was obtained, progression was deemed to have occurred.
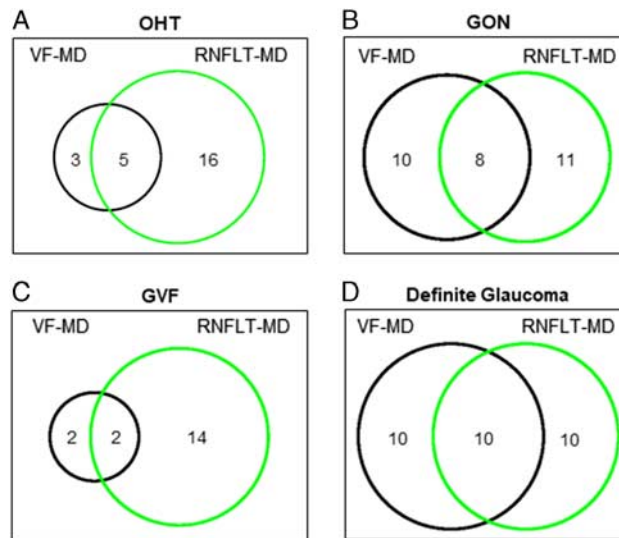
FIGURE 2. Venn diagrams showing the agreement between eyes identified to have progressed by RNFLT-MD and by VF-MD for global assessment of progression. Panels A, B, C, and D show agreement among OHT eyes, GON, GVF, and definite glaucoma eyes, respectively. GON indicates glaucomatous optic neuropathy only; GVF, glaucomatous visual field; OHT, ocular hypertension; RNFLT-MD, mean deviation values for retinal nerve fiber layer thickness; VF-MD, mean deviation values for visual field.

When progression was not identified, we repeated linear regression with data from the first 7 visits and then with data from first 8 visits until available data from all visits have been used to assess progression.

For each baseline classification, the proportions of eyes identified as progressing by RNFLT-MD and by VF-MD were determined and reported as their respective positive rates. We used positive rate to quantify the proportion of eyes with progression instead of sensitivity. This is because it is impossible to determine the true positive rate needed to compute the sensitivity of each parameter[30,31] considering that there is currently no ground truth for structural and functional glaucoma progression. McNemar's test was used to assess whether there were significant differences between positive rates for RNFLT-MD and VF-MD. We applied Bonferroni correction for the three comparisons performed within each classification by adjusting significance level to 0.017 (obtained by dividing the significance level of 0.05 by 3). The agreement between eyes identified as progressing by RNFLT-MD and by VF-MD was also determined for each classification. Time-to-progression for RNFLT-MD and VF-MD were evaluated with Kaplan-Meier survival curves. The log-rank test was used to determine whether there was a significant difference between time-to-progression for the two parameters. Data analyses were performed with R[32] and the Statistical Package for the Social Sciences (SPSS Version 27.0; IBM Corp., Armonk, NY).

RESULTS

The 194 participants were followed for an average of 5.5 (1.2) years and had a median (interquartile range) of 10 (9 to 12) visits. On the basis of Hodapp-Parrish-Anderson VF severity criteria,[33] the majority of eyes (90.2%) had early VF loss. Detailed participants' baseline information is presented in Table 1.

Figure 1 presents the global and sectorial positive rates obtained for RNFLT-MD and VF-MD for each baseline classification. The positive rate obtained with global VF-MD was 20.5% for OHT eyes, 30.0% for GON eyes, 10.3% for

GVF eyes, and 35.7% for definite glaucoma eyes. Except for definite glaucoma eyes, the positive rate obtained with global RNFLT-MD was greater compared with VF-MD by 33.3% for OHT eyes, 1.7% for GON eyes, and 30.8% for GVF eyes. These differences were statistically significant ($P < 0.01$) among only OHT eyes (Fig. 1A) and for GVF eyes (Fig. 1C). Similarly, progression assessment in the IT sector showed that RNFLT-MD had significantly greater positive rate than VF-MD among only OHT and GVF eyes. Across all classifications, similar positive rates were obtained for both parameters when progression was assessed in the ST sector.

Figure 2 presents the agreement between eyes identified as progressing by global RNFLT-MD and by global VF-MD for each baseline classification. Altogether, 25 eyes were identified as progressing by both parameters: 5 OHT eyes, 8 GON eyes, 2 GVF eyes, and 10 definite glaucoma eyes.

Figure 3 shows survival curves comparing time-to-progression between RNFLT-MD and VF-MD for each baseline classification. Across all classifications, RNFLT-MD appeared to identify progression earlier than VF-MD, however, the log-rank test revealed that time-to-progression was significantly shorter ($P < 0.001$) for RNFLT-MD compared with VF-MD among only OHT eyes (Fig. 3A) and GVF eyes (Fig. 3C).

DISCUSSION

The present study compared the detection of structural and functional assessment of glaucoma progression in patients with different baseline classifications of POAG. Using age-corrected OCT and SAP measurements, we found that, across all classifications, a greater proportion of eyes were identified as progressing by RNFLT-MD than by VF-MD. For each classification, progression was identified earlier in more eyes by RNFLT-MD compared with VF-MD. However, we observed significantly greater positive rate and shorter time-to-progression for RNFLT-MD among only OHT and GVF eyes. While some eyes were identified as progressing by VF assessment, the results of this study demonstrate that OCT assessment of RNFLT may be better suited for monitoring
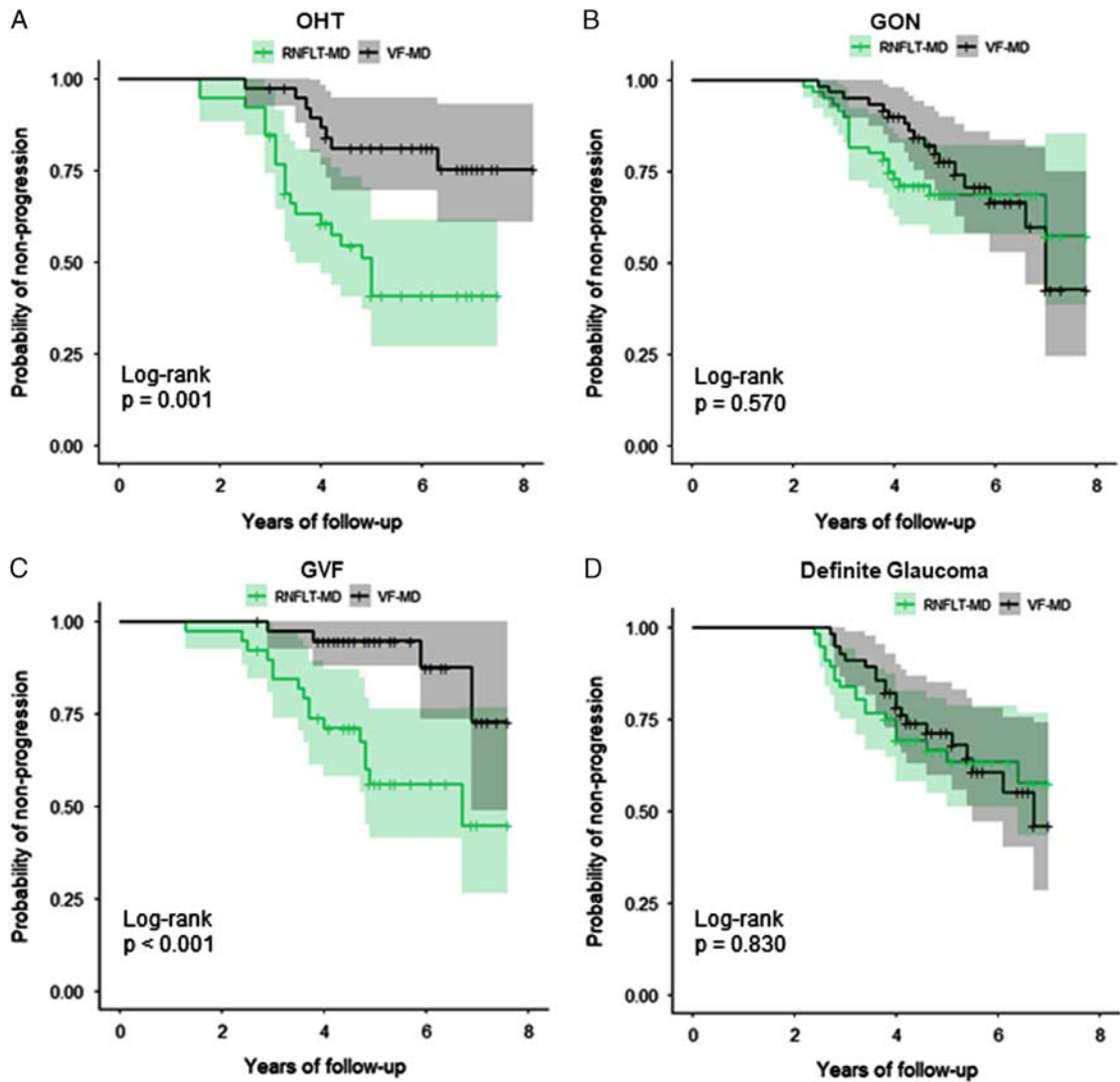
FIGURE 3. Kaplan-Meier curves illustrating the time-to-progression for RNFLT-MD (green line) and VF-MD (black line) for OHT eyes (A), GON eyes (B), GVF eyes (C) and definite glaucoma eyes (D). GON indicates glaucomatous optic neuropathy only; GVF, glaucomatous visual field; OHT, ocular hypertension; RNFLT-MD, mean deviations values for retinal nerve fiber layer thickness; VF-MD, mean deviations values for visual field.

glaucoma progression, particularly among OHT patients and those who initially present with only GVF defects.

Our results are comparable to the findings of previous studies in which OCT assessment of RNFLT identified progression in 3% to 33% more eyes than SAP parameters.[19,23,24] These previous studies involved preperimetric glaucoma, glaucoma suspects, and perimetric glaucoma eyes which, by their definitions, are comparable to the GON, OHT, and definite glaucoma classifications used in the current study. Whereas the assessment of progression included event-based analysis in Zhang et al,[19] Wollstein et al,[24] and Banegas et al,[23] we used trend analysis which enabled direct comparison of positive rates for RNFLT-MD and VF-MD at a fixed level of specificity. The identification of a greater proportion of eyes as progressing by RNFLT-MD across all classification re-emphasizes that disease progression may be detected more frequently by RNFLT assessment.

Contrary to our expectation that VF evaluation would be more likely to identify progression among GVF eyes,

RNFLT-MD identified 14 more of those eyes as progressing compared with VF-MD (Fig. 2C). Similarly, among OHT eyes, RNFLT-MD identified 16 more eyes than VF-MD (Fig. 2A). These observations may be explained by the notion that OCT is better suited to detect progression in the early stages of glaucoma, whereas SAP may become more useful in the later stages of the disease. This notion, strongly pivoted on the presence of "floor effect" in RNFLT measurement,[34,35] has been strengthened by recent studies[18,19] in which OCT outperformed SAP in detecting progression among early glaucoma eyes. In the current study, 175 of the 194 eyes (90%) were classified within the early stages of glaucoma, with baseline mean STATPAC MD better than –6.0 dB (Table 1). For these 175 eyes, the positive rate for RNFLT-MD was 13% greater compared with VF-MD. These findings suggest that RNFLT assessment may be more sensitive for detecting early disease progression, particularly in patients who present initially with only elevated intraocular pressure and in those with only GVF damage at baseline.
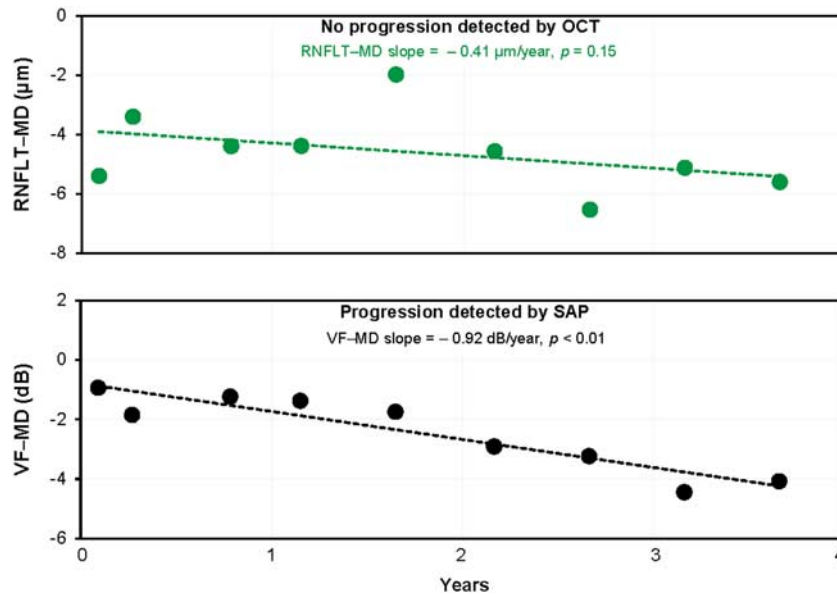
FIGURE 4. A GON eye, with baseline MD of –0.53 dB and 3.6 years of follow-up, identified to have progressed by VF-MD alone. GON indicates glaucomatous optic neuropathy only; GVF, glaucomatous visual field; OCT, optical coherence tomography; OHT, ocular hypertension; RNFLT-MD, mean deviation values for retinal nerve fiber layer thickness; SAP, static automated perimetry; VF-MD, mean deviation values for visual field.

Although RNFLT-MD appeared to identify progression more frequently, the proportion of GON and definite glaucoma eyes identified as progressing by RNFLT-MD were not significantly greater than the proportion of eyes flagged by VF-MD (Figs 1B, D). This finding suggests that RNFLT and VF assessment have comparable capabilities to identify progression in patients presenting with only structural defect or with concurrent functional and structural defects at baseline. Consistent with previous studies in which only functional assessment identified progression in some eyes,[4–6] a fair proportion of eyes were identified as progressing by VF-MD alone in the current study. Approximately 34% of progressing GON eyes (Fig. 2B) and 33% of progressing definite glaucoma eyes (Fig. 2D) were identified by VF assessment alone. This underscores the need for functional assessment, particularly when there is absence of noticeable structural changes. Figure 4 presents a case example of a GON eye that was identified to have progressed by VF assessment alone.

Compared with SAP, OCT measurements have relatively lower test-retest variability which may translate to earlier detection of progression. Zhang et al[19] reported that RNFLT assessment detected progression in 20% of preperimetric and perimetric glaucoma eyes 1 to 2 years earlier than SAP evaluation. We observed that, across all classifications, RNFLT-MD identified progression earlier in more eyes compared with VF-MD, however, the difference in time-to-progression was significant among only OHT and GVF eyes (Figs. 3A, B). Whereas this observation suggests that RNFLT assessment may be ideal for earlier detection of glaucomatous changes, VF evaluation may perform just as well in patients with only structural damage or with corresponding VF defect at baseline.

The current study has limitations. First, the approach we used to generate age-corrected OCT and SAP parameters is not available to clinicians. This, however, does not limit the clinical applicability of our findings as not applying this correction would have resulted in an even greater sensitivity of RNFLT to identify progression. We corrected for age because it is critical to minimize the likelihood of detecting eyes with changes not because of glaucoma.[27,36,37] In this study, we have developed a simple age-linear model to generate age-corrected RNFLT values. This approach can be adopted and improved upon by researchers and device manufacturers to produce clinically useful age-corrected RNFLT measurements. The age-corrected VF parameter (VF-MD) was generated in a similar manner as RNFLT-MD to ensure methodological consistency and fairer comparison of positive rates. As a result, VF-MD was not computed as a weighted average to account for the greater variability in threshold sensitivity with eccentricity as is the case for VF-STATPAC MD.[28] However, the mean difference (0.24 dB, 95% confidence interval: 0.18-0.30) between VF-STATPAC MD and VF-MD was marginal. This indicates that using VF-MD, instead of STATPAC MD, to assess progression did not significantly impact the performance of SAP in this current study. Another limitation is the lack of standardized treatment across the different baseline classification as participants continued to receive glaucoma treatment at the discretion of their doctors. Whereas different treatment decisions may have been made within each of the baseline classifications used in this study, our interest was to assess the ability of RNFLT and VF assessments to identify progression as they are used in the clinics.

In conclusion, we found that both RNFLT and VF assessments can identify progression in patients with different baseline classification of POAG. RNFLT assessment, however, tended to identify more eyes as progressing compared with VF assessment in all baseline classifications. Our results suggest that although both assessments are capable of detecting progression in patients with different baseline clinical signs, preference may be given to RNFLT assessment when prevailing circumstances permit for only a single test.

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