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Risk of Visual Field Progression in Glaucoma Patients with Progressive Retinal Nerve Fiber Layer Thinning

A 5-Year Prospective Study

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Purpose: To investigate whether progressive retinal nerve fiber layer (RNFL) thinning is predictive of progressive visual field (VF) loss in glaucoma.

Design: Prospective study.

Participants: A total of 139 primary open-angle glaucoma patients (240 eyes) followed up for ≥5 years.

Methods: Retinal nerve fiber layer imaging and VF testing were performed at ~4-month intervals. Progressive RNFL thinning was determined by event analysis (Guided Progression Analysis [GPA]) and trend analysis (Trend-based Progression Analysis [TPA]) of serial registered RNFL thickness maps. VF progression was detected according to the Early Manifest Glaucoma Trial (EMGT) ("likely progression") and pointwise linear regression (PLR) criteria (≥3 contiguous locations with sensitivity change <0 decibels [dB]/year at $P < 0.01$). Hazard ratios (HRs) for predicting VF progression were calculated by Cox proportional hazard modeling with progressive RNFL thinning as a time-dependent covariate. The specificity of GPA/TPA for detection of RNFL changes was determined by the proportion of eyes with significant RNFL thinning/thickening in 25 normal subjects followed weekly for 8 consecutive weeks and the proportion with significant RNFL thickening in the glaucoma group.

Main Outcome Measures: The HRs of VF progression.

Results: A total of 65 (27.1%) and 117 eyes (48.8%) had progressive RNFL thinning based on GPA and TPA, respectively, and 30 (12.5%) and 39 eyes (16.3%) had VF progression per the EMGT and PLR criteria, respectively, during follow-up. Eyes with progressive RNFL thinning had lower VF survival estimates and a faster decline of visual field index than eyes without. Progressive RNFL thinning predicted the development of VF progression with HRs of 8.44 (95% confidence interval, 3.30−21.61) (EMGT criteria) and 5.11 (2.51−10.42) (PLR criteria) for TPA and 3.95 (1.74−8.93) (EMGT criteria) and 3.81 (1.83−7.92) (PLR criteria) for GPA after controlling for baseline covariates. The specificities of GPA and TPA were 100% (83.4%−100.0%) in the normal group and 81.7% (76.2%−86.4%) and 84.2% (78.9%−88.6%), respectively, in the glaucoma group.

Conclusions: Progressive RNFL thinning determined by GPA and TPA is predictive of detectable functional decline in glaucoma. This finding underscores the significance of detecting progressive RNFL thinning and its relevance to initiate or augment treatment for glaucoma patients. Regulatory authorities may consider progressive RNFL thinning as an outcome measure in clinical trials for evaluation of glaucoma treatment. *Ophthalmology 2016;■:1−10 © 2016 by the American Academy of Ophthalmology.*

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Glaucoma is the most common form of optic neuropathy with an estimated global prevalence of 64.3 million in 2013.[1] As a leading cause of irreversible blindness, early detection of optic nerve degeneration with initiation or augmentation of glaucoma treatment prevents progressive loss in vision in patients with glaucoma.[2,3] Although evaluation of progressive decline in neuronal structure and function often is difficult in neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, progressive loss of the retinal ganglion cell axons in glaucoma can be objectively and reproducibly measured as progressive thinning of the retinal nerve fiber layer (RNFL) with optical imaging technologies, including scanning laser polarimetry and optical coherence tomography (OCT).[4,5] Yet, detectable structural and functional changes of the optic nerve may not be evident simultaneously,[6,7] and the

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implication of detecting progressive RNFL thinning in the management of patients with glaucoma remains unclear. The primary outcome measure for evaluation of glaucoma progression in all landmark glaucoma treatment trials largely has been predicated on visual field (VF) assessment.[8] Regulatory authorities, such as the US Food and Drug Administration, consider structural changes of the optic nerve to be an outcome measure for the evaluation and approval of treatment to delay glaucoma progression only when there is evidence that the new outcome measure predicts functional change that is clinically relevant to a patient.[9] Identifying structural biomarkers that predict functional change of the optic nerve is an unmet need in glaucoma management.

Since its introduction in 2006, spectral-domain or Fourier-domain OCT has gained popularity over other optical imaging technologies in monitoring RNFL loss in glaucoma because of its superior resolution to discern the individual retinal layers. Spectral-domain OCT RNFL measurement has been shown to have a lower test–retest variability compared with time-domain OCT[10] and outperforms time-domain OCT and scanning laser polarimetry to detect progressive RNFL thinning.[5,11] With a high scan speed, topographic analysis of the RNFL over an optic disc region of approximately 6×6 mm^2 is possible.[12] Progressive RNFL thinning missed by the conventional circumpapillary RNFL assessment can be revealed in the RNFL thickness map.[13] Given that glaucomatous RNFL defects often can be observed before detectable VF defects, we hypothesize progressive RNFL thinning, determined by (1) Guided Progression Analysis (GPA) (Carl Zeiss Meditec, Dublin, CA) (an event-based algorithm) and (2) Trend-based Progression Analysis (TPA) (a trend-based algorithm) of the RNFL thickness maps, to be predictive of VF progression in patients with glaucoma.

Methods

Subjects

Between July 2007 and October 2015, 139 patients with primary open-angle glaucoma were consecutively recruited from the Caritas Medical Center, Hong Kong Eye Hospital, and the University Eye Center of the Chinese University of Hong Kong. They were followed up every 4 months for at least 5 years at the University Eye Center for RNFL imaging and perimetry. All subjects had a complete ophthalmic examination, including measurement of best-corrected visual acuity, axial length (partial coherence laser interferometry; Carl Zeiss Meditec), central corneal thickness (CCT) (ultrasound pachymetry), intraocular pressure (IOP) (Goldmann applanation tonometry), gonioscopy, and biomicroscopy examination of the optic disc and retina. Inclusion criteria included best-corrected visual acuity ≥20/40 and having ≥5 years of longitudinal follow-up. Subjects with non-glaucomatous VF loss were excluded from the study at baseline, and it was checked during the study follow-up. No causes other than glaucoma could be identified that were accountable for the RNFL or VF loss observed in the study. Glaucoma was diagnosed by the presence of optic disc excavation and narrowed neuroretinal rim as determined by the ISNT rule[14] with slit-lamp biomicroscopy and corresponding VF defects in standard automated perimetry (described later) in at least 1 eye independent of the levels of IOP. All patients with glaucoma had RNFL imaging and VF testing for both eyes at ~4-month intervals. They were treated during the study follow-up with reference to the target IOP determined by the attending ophthalmologists without considering the analysis of progressive RNFL thinning. Twenty-five healthy subjects also were consecutively enrolled during the study period and followed up weekly for 8 consecutive weeks for RNFL imaging and VF testing in 1 randomly selected eye to determine the specificity of GPA and TPA detection of progressive RNFL thinning. These subjects had no optic disc abnormalities in clinical examination, no RNFL abnormalities on spectral-domain OCT, no VF abnormalities on VF testing, and no history of ocular disease (except for early cataract), neurologic disease, or major systemic illness. The study was conducted in accordance with the ethical standards stated in the 1964 Declaration of Helsinki and was approved by the local research ethics committee, with informed consent obtained.

Optical Coherence Tomography Retinal Nerve Fiber Layer Imaging

The Cirrus HD-OCT (Carl Zeiss Meditec; software version 6.5) imaged the RNFL with the "optic disc cube" scan, generating an RNFL thickness map (200×200 pixels) in an optic disc region of approximately 6×6 mm^2. Only images with a signal strength ≥6 were included. Images with motion artifact, poor centration, or missing data (e.g., blinking) were checked by the operator and discarded, with re-scanning performed in the same visit. After excluding 11 images with signal strength consistently <6 and 10 eyes with registration failure with the baseline images for progression analysis, 4072 RNFL thickness maps from 4072 follow-up visits among 139 patients (240 eyes) with glaucoma were available for RNFL change analysis. The RNFL measurements obtained with the Cirrus HD-OCT have been shown to have low test–retest variability.[10,15,16]

Guided Progression Analysis

The Cirrus HD-OCT GPA (Carl Zeiss Meditec) evaluated progressive RNFL thinning of the RNFL thickness map in 50×50 superpixels (1 superpixel = 4×4 pixels) using an event-based analysis. The GPA aligned, registered, and compared the baseline and follow-up RNFL thickness maps in individual superpixel locations. A superpixel would be encoded in yellow in the RNFL thickness change map when the differences in RNFL thickness between the follow-up and the first and second baseline images were greater than the test–retest variability of a superpixel location, and in red if the differences were evident in a consecutive follow-up image. In this study, progressive RNFL thinning was defined when at least 20 contiguous superpixels (factory default) encoded in red in the RNFL thickness change map were detected during the study follow-up and the same changes were observed in the latest follow-up visit (Fig 1A).

Trend-based Progression Analysis

The same 4072 RNFL thickness maps analyzed by GPA were exported to a computer for TPA, which is a trend-based algorithm custom-designed in MATLAB (The MathWorks, Inc., Natick, MA), to determine the rate of change of RNFL thickness in individual superpixels of the RNFL thickness map.[17] After aligning and registering the longitudinal image series (similar to GPA), linear regression analysis between RNFL thickness and follow-up time was performed at individual superpixels of the

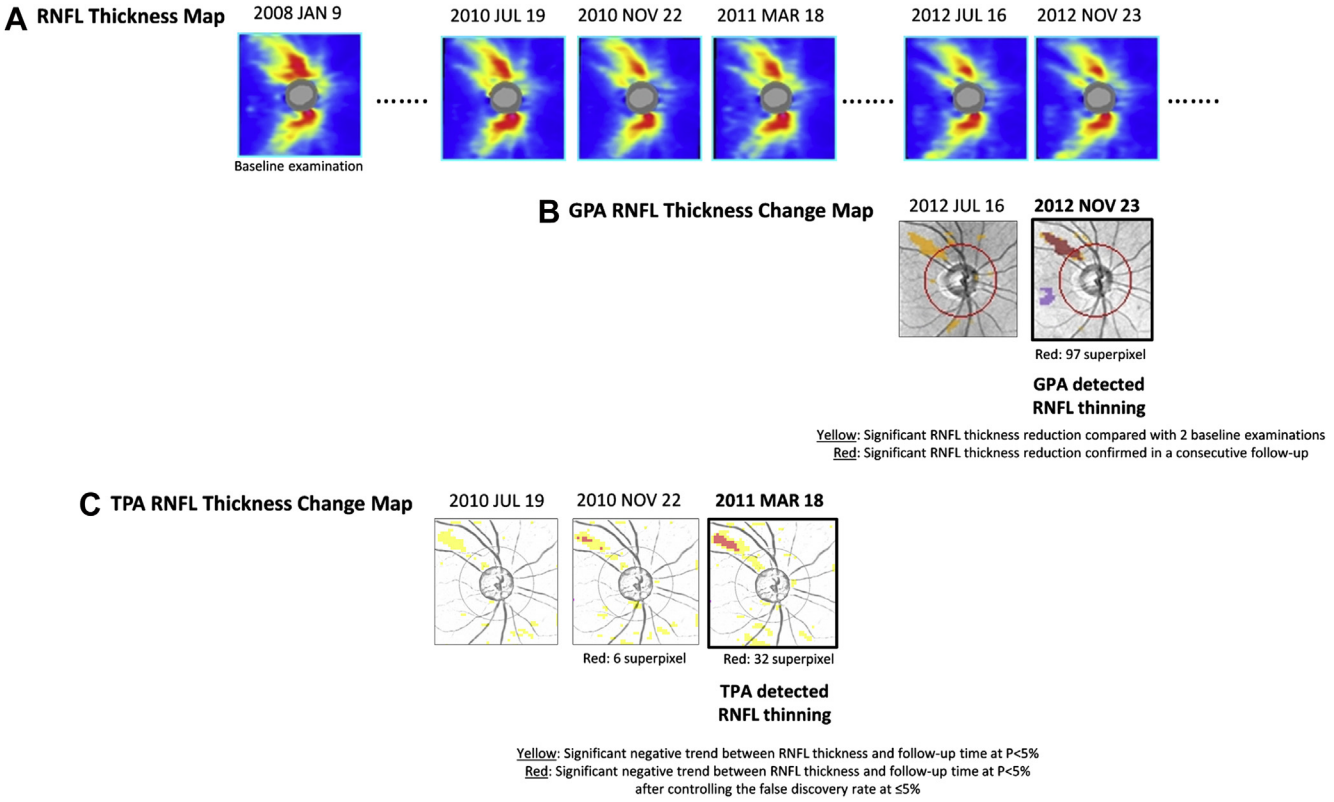

Figure 1. An example illustrating the application of Guided Progression Analysis (GPA) and Trend-based Progression Analysis (TPA) for detection of progressive retinal nerve fiber layer (RNFL) thinning. Serial RNFL thickness maps (**A**) collected at approximately 4-month intervals from a glaucomatous eye were analyzed by (**B**) GPA and (**C**) TPA. In this example, progressive RNFL thinning was first detected by TPA on March 18, 2011 (i.e., >20 superpixels encoded in red in the TPA RNFL thickness change map) and then by GPA on November 23, 2012 (i.e., >20 superpixels encoded in red in the GPA RNFL thickness change map).

RNFL thickness maps. A TPA-derived RNFL thickness change map was then generated. To reduce the probability of type I error (incorrect rejection of a true null hypothesis, which in this case was that the rate of change of RNFL thickness at an individual superpixel location was 0 μm/year) as a consequence of multiple tests performed in the RNFL thickness maps, the significance level of hypothesis testing at individual superpixels was determined after controlling the false discovery rate (FDR) at ≤5% (the details of the procedure are described in the Appendix, available at www.aaojournal.org).[18–21] We adopted the FDR controlling procedures to estimate the number of false positives without compromising the sensitivity to detect change that would otherwise be inevitable with familywise error rate controlling procedures, such as the Bonferroni adjustment. An FDR of 5% indicates that 5% of the superpixels detected with a significant change in the RNFL thickness change map would be considered as false positives. In the TPA RNFL thickness map, progressive RNFL thinning in a superpixel location would be encoded in yellow if a significant negative trend was found with a $P \leq 5\%$ in an individual regression analysis of a superpixel, and in red if the significant negative slope was detected after controlling the FDR at 5% (Fig 1C). Similar to the GPA, progressive RNFL thinning was defined when at least 20 contiguous superpixels were encoded in red in the TPA RNFL thickness change map during the study follow-up and the same changes were observed at the latest follow-up visit.

Specificities of Guided Progression Analysis and Trend-based Progression Analysis for Detection of Progressive Retinal Nerve Fiber Layer Thinning

The specificity of GPA and TPA for detection of RNFL changes was determined using 2 proxy measures: (1) the proportion of eyes with significant RNFL thinning/thickening in the normal group and (2) the proportion of eyes with significant RNFL thickening in the glaucoma group. For GPA, significant RNFL thinning and thickening were defined when 20 contagious superpixels showed decreases and increases in RNFL thickness greater than the test–retest variability in the GPA RNFL thickness change maps for 2 consecutive visits, respectively. For TPA, significant RNFL thinning/thickening was defined when 20 contiguous superpixels had a significant negative/positive trend in the linear regression between RNFL thickness and follow-up time in the TPA RNFL thickness change map.

Visual Field Testing

Visual field testing was conducted with standard automated white-on-white perimetry (Swedish Interactive Threshold Algorithm standard, 24-2, Humphrey field analyzer II-i; Carl Zeiss Meditec). A VF test was considered as reliable when fixation losses and false-positive and false-negative errors were ≤20%. Only reliable VF

tests were included in the analysis. A VF defect was defined when there were ≥3 significant ($P < 0.05$) nonedge contiguous points with at least 1 at the $P < 0.01$ level on the same side of the horizontal meridian in the pattern deviation plot. A total of 84 VF tests from 47 eyes had fixation losses, false-positive errors, or false-negative errors >20%. These VF tests were excluded from the analysis. None of the excluded VF tests were of baseline VF.

Visual Field Progression Analysis

Visual field progression was evaluated with reference to (1) the Early Manifest Glaucoma Trial (EMGT) criteria,[22] an event-based analysis, and (2) the pointwise linear regression (PLR) criteria, a trend-based analysis.[23] For event analysis, VF progression was defined when there were ≥3 locations that showed a significant change (i.e., change greater than the test−retest variabilities) compared with 2 baseline examinations (separated by ~4 months in this study) for at least 3 consecutive tests (i.e., "likely progression" reported in the GPA) during the study follow-up and when the changes also were observed at the latest follow-up visit. For trend analysis, linear regression analysis between VF threshold values (decibels [dB]) and follow-up time was performed at each of the 52 VF locations. Visual field progression was defined when there were ≥3 contiguous locations that showed a significant negative trend (i.e., a sensitivity change <0 dB/year) in the linear regression analysis at $P < 0.01$ (1-tailed) during the study follow-up and when the changes also were observed at the latest follow-up visit.

Statistics

Statistics were performed using Stata (version 14.0; StataCorp LP, College Station, TX). The hazard ratios (HRs) of progressive RNFL thinning for development of VF progression were evaluated using univariable and multivariable Cox proportional hazard models with "progressive RNFL thinning" as a time-dependent covariate (the time points when progressive RNFL thinning and VF progression were recorded). Baseline covariates adjusted in the multivariable model included age, IOP, CCT, axial length, circumpapillary average RNFL thickness, and VF mean deviation (MD). A shared frailty model following a gamma distribution was used to adjust for correlation between fellow eyes. The statistical power of progressive RNFL thinning for prediction of VF progression was calculated post hoc using the method described by Schoenfeld.[24] The VF survival estimates (i.e., "likely" progression by the EMGT criteria) between the groups with and without progressive RNFL thinning were evaluated by the Kaplan−Meier estimator and compared with the log−rank test. The rates of change of the visual field index (VFI) (which was used to measure VF progression because it has been shown to be less affected by cataract and cataract surgery compared with MD)[25,26] and circumpapillary average RNFL thickness between eyes with and without progressive RNFL thinning detected by TPA/GPA were computed and compared with linear mixed modeling with adjustment of correlation between fellow eyes. The agreement of progression detection between GPA and TPA was calculated with kappa statistics.[27] $P < 0.05$ was considered statistically significant.

Results

A total of 240 eyes of 139 patients with glaucoma (85 male and 54 female) followed up for a mean of 5.8 years (range, 4.9−7.2 years) were included. Each eye had an average of 17.0 follow-up measurements for analysis. The mean age, axial length, IOP, and CCT were 55.3±13.7 years, 25.0±1.9 mm, 17.8±4.4 mmHg, and 542.3±38.6 μm, respectively, at the baseline visit. The baseline average circumpapillary RNFL thickness was 70.2±13.0 μm, and the baseline MD was −9.5±9.1 dB. Some 52.5% (126 eyes) had mild VF loss (MD ≥−6 dB), 16.7% (40 eyes) had moderate VF loss (−6>MD>−12 dB), and 30.8% (74 eyes) had advanced VF loss (MD ≤−12 dB).

Performance of Guided Progression Analysis and Trend-based Progression Analysis for Detection of Progressive Retinal Nerve Fiber Layer Thinning

Guided Progression Analysis detected 65 eyes (27.1%) and TPA detected 117 eyes (48.8%) with progressive RNFL thinning during the study follow-up. A total of 30 eyes (12.5%) showed "likely" VF progression by the EMGT criteria, and 39 eyes (16.3%) showed VF progression by the PLR criteria. Eyes with progressive RNFL thinning had lower VF survival estimates compared with eyes without progressive RNFL thinning for both GPA and TPA ($P \leq 0.002$) (Fig 2). The rates of VFI decline were significantly faster in eyes with progressive RNFL thinning detected by GPA/TPA than in eyes without ($P \leq 0.020$) (Table 1). Likewise, the rates of average RNFL thickness reduction were significantly faster for eyes with progressive RNFL thinning detected by GPA/TPA than eyes without ($P < 0.001$) (Table 1). The agreement between TPA and GPA for the detection of progressive RNFL thinning was fair (Cohen's kappa: 0.309; 95% confidence interval [CI], 0.200−0.418) (Fig 3A).

Specificity of Guided Progression Analysis and Trend-based Progression Analysis for Detection of Retinal Nerve Fiber Layer Changes

A total of 200 follow-up visits of RNFL measurements (weekly for 8 consecutive weeks) from 25 eyes of 25 healthy controls (11 male and 14 female) were analyzed to measure the specificity of GPA and TPA in the detection of RNFL changes. The age, axial length, average RNFL thickness, and VF MD at baseline were 45.1±12.9 years, 24.0±1.1 mm, 100.5±10.2 μm, and −0.76±0.89 dB, respectively. There were no significant changes in the VFI (2.0×10^{-5} %/year; 95% CI, −0.20−0.20; $P = 1.000$) and average circumpapillary RNFL thickness (−0.35 μm/year; 95% CI, −6.94−6.23; $P = 0.916$) during the 8-week follow-up. No eyes in the normal group showed progressive RNFL thinning/thickening by GPA or TPA. Therefore, the specificity for detection of RNFL changes was 100% (95% CI, 83.4−100.0) by either algorithm. Among the 240 eyes of 139 patients with glaucoma, 44 eyes (18.3%) and 38 eyes (15.8%) showed significant increases in RNFL thickness by GPA and TPA, respectively, during the study follow-up (Fig 3B). The estimated specificity was 81.7% (95% CI, 76.2−86.4) for GPA and 84.2% (95% CI, 78.9−88.6) for TPA in the glaucoma group. There were no significant differences in the specificities between GPA and TPA ($P \geq 0.440$, McNemar's test).

Risk of Visual Field Progression in Eyes with Progressive Retinal Nerve Fiber Layer Thinning

Eyes with progressive RNFL thinning detected by TPA had an HR of 9.01 (95% CI, 3.67−22.15) ($P < 0.001$) for the development of "likely" VF progression by the EMGT criteria in the univariable Cox proportional hazards model and 8.44 (95% CI, 3.30−21.61) in the multivariable analysis ($P < 0.001$) after adjusting for the baseline

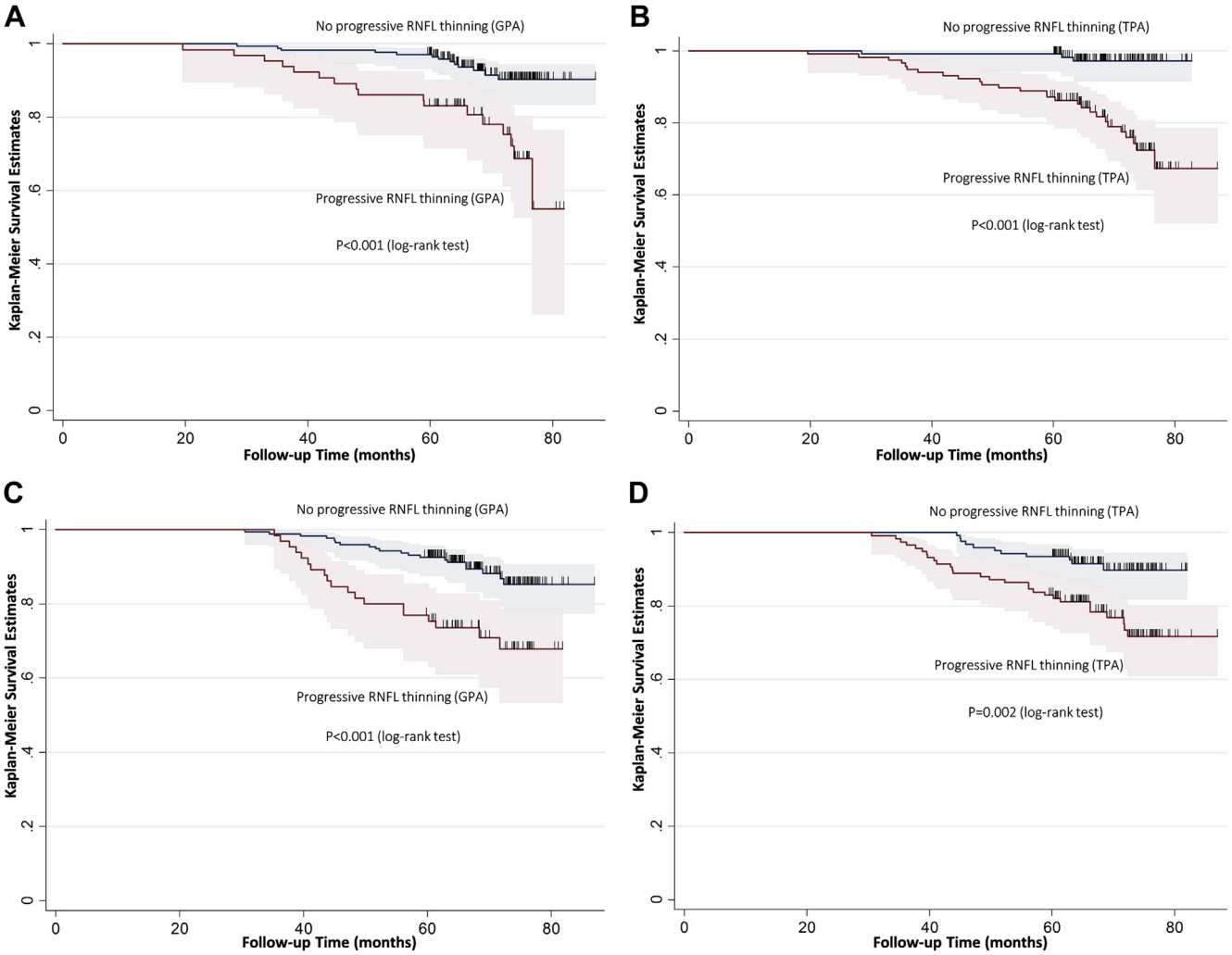

Figure 2. Comparison of Kaplan–Meier visual field (VF) survival estimates with VF progression determined by the Early Manifest Glaucoma Trial (EMGT) criteria (**A** and **B**) and the pointwise linear regression (PLR) criteria (**C** and **D**) between eyes with and without progressive retinal nerve fiber layer (RNFL) thinning evaluated with Guided Progression Analysis (GPA) (**A** and **C**) and Trend-based Progression Analysis (TPA) (**B** and **D**). *Hash marks* represent censoring time, and *shaded areas* represent the regions of 95% confidence intervals.

measures (age, axial length, CCT, IOP, average RNFL thickness, and VF MD) (Table 2). Likewise, progressive RNFL thinning detected by GPA was predictive of "likely" VF progression, and the HR was 3.83 (95% CI, 1.76–8.33) (P = 0.001) in the univariable analysis and 3.95 (95% CI, 1.74–8.93) in the multivariable analysis (P = 0.001) (Table 3). Similar findings were observed when VF progression was analyzed using the PLR criteria. Progressive RNFL thinning detected by TPA and GPA was

Table 1. Comparisons of Rates of Change of Visual Field Index and Average Retinal Nerve Fiber Layer Thickness in Eyes with and without Progressive Retinal Nerve Fiber Layer Thinning Detected by Guided Progression Analysis and Trend-based Progression Analysis

	GPA			TPA		
	Eyes with RNFL Thinning (95% CI)	*Eyes without RNFL Thinning (95% CI)*	*P*	*Eyes with RNFL Thinning (95% CI)*	*Eyes without RNFL Thinning (95% CI)*	*P*
Rate of change of VFI	−0.76 %/yr (−1.07 to −0.46 %/yr)	−0.26 %/yr (−0.46 to −0.07 %/yr)	0.019	−0.59 %/yr (−0.87 to −0.32 dB/yr)	−0.19 %/yr (−0.39 to 0.02 %/yr)	0.020
Rate of change of average RNFL thickness	−0.90 μm/yr (−1.25 to −0.56 μm/yr)	−0.21 μm/yr (−0.29 to −0.14 μm/yr)	<0.001	−0.72 μm/yr (−0.92 to −0.51 μm/yr)	−0.07 μm/yr (−0.14 to 0.01 μm/yr)	<0.001

CI = confidence interval; dB = decibels; GPA = Guided Progression Analysis; RNFL = retinal nerve fiber layer; TPA = Trend-based Progression Analysis; VFI = visual field index.

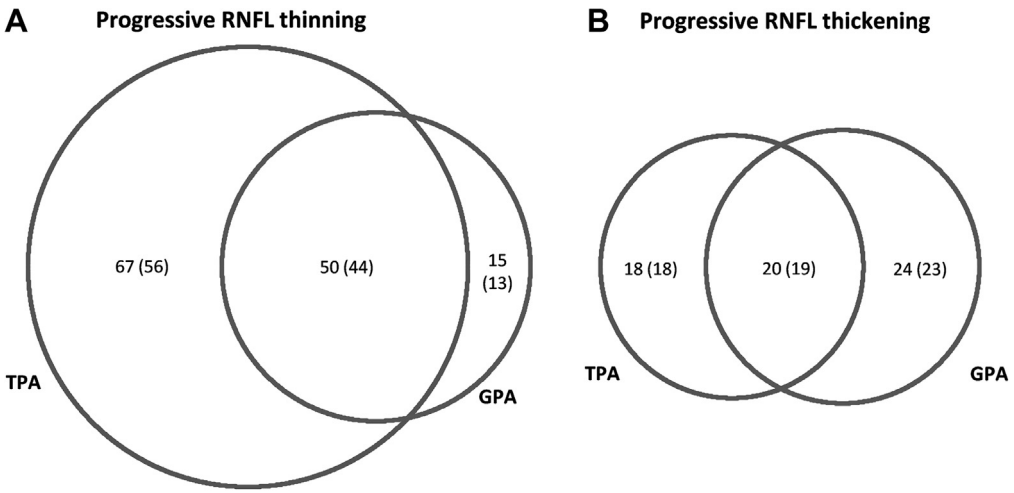

Figure 3. Proportional Venn diagram showing the number of eyes (patients) detected with progressive retinal nerve fiber layer (RNFL) thinning (**A**) and progressive RNFL thickening (**B**) by Guided Progression Analysis (GPA) and Trend-based Progression Analysis (TPA).

associated with an HR of 4.33 (95% CI, 2.21−8.50) and 3.24 (95% CI, 1.59−6.60), respectively, in the univariable analysis and 5.11 (95% CI, 2.51−10.42) and 3.81 (95% CI, 1.83−7.92), respectively, in the multivariable analysis (Tables 2 and 3). Post hoc power analysis revealed that the current sample size had a power of ≥99.7% for both GPA and TPA in the univariable Cox proportional hazards models for progressive RNFL thinning to predict VF progression at an HR of ≥3.24 after adjusting for censoring.

A Case Example

Figure 4 illustrates that progressive RNFL thinning was evident before VF progression in a 73-year-old man with primary open-angle glaucoma. Progressive RNFL thinning at the inferotemporal sector was first detected by TPA on February 26, 2010, which was approximately 24 months earlier than that detected by GPA (February 13, 2012). "Likely" VF progression (June 18, 2012) was observed approximately 28 months after TPA detection and approximately 4 months after GPA detection of RNFL thinning. Superotemporal RNFL thinning detected by TPA (June 17, 2011) also occurred before the GPA detection (March 4, 2013). The rate of change of the RNFL thickness map (calculated using all follow-up visits) reveals that the inferotemporal RNFL thickness decreased at a faster rate compared with the superotemporal RNFL thickness.

Discussion

In 240 eyes of 139 patients with glaucoma who were followed for at least 5 years, progressive RNFL thinning analyzed by TPA and GPA was strongly predictive of subsequent development of VF progression. Specifically, eyes with progressive RNFL thinning had a more than 8-fold (HR, 8.44; 95% CI, 3.30−21.61) and 3-fold (HR, 3.95; 95% CI, 1.74−8.93) increase in risk, respectively, in developing "likely" VF progression based on the EMGT criteria compared with eyes without progressive RNFL thinning after controlling for the baseline measures (Tables 2 and 3). To our knowledge, these data represent an initial account demonstrating that progressive RNFL thinning analyzed topographically in the 6×6-mm^2 optic disc region is informative to predict VF progression. That progressive RNFL thinning confers an increased risk of

Table 2. Multivariable Cox Proportional Hazards Modeling Evaluating Hazard Ratios of Progressive Retinal Nerve Fiber Layer Thinning Detected by Trend-based Progression Analysis and Other Baseline Covariates for Prediction of Visual Field Progression Determined by the Early Manifest Glaucoma Trial Criteria and Pointwise Linear Regression Criteria

	EMGT Criteria		PLR Criteria	
	Hazard Ratio (95% CI)	*P*	*Hazard Ratio (95% CI)*	*P*
Progressive RNFL thinning	8.44 (3.30−21.61)	<0.001	5.11 (2.51−10.42)	<0.001
Age (yrs)	0.98 (0.96−1.01)	0.262	1.01 (0.98−1.03)	0.649
Baseline IOP (mmHg)	1.06 (0.96−1.15)	0.247	1.03 (0.96−1.11)	0.358
Baseline average RNFL thickness (μm)	0.98 (0.95−1.02)	0.344	0.97 (0.94−1.00)	0.076
Baseline VF MD (dB)	1.05 (0.98−1.12)	0.171	1.02 (0.97−1.07)	0.517
CCT (μm)	1.00 (0.99−1.02)	0.419	1.00 (1.00−1.01)	0.305
Axial length (mm)	1.04 (0.84−1.28)	0.732	1.01 (0.84−1.22)	0.924

CCT = central corneal thickness; CI = confidence interval; dB = decibels; EMGT = Early Manifest Glaucoma Trial; IOP = intraocular pressure; MD = mean deviation; PLR = Pointwise Linear Regression; RNFL = retinal nerve fiber layer; VF = visual field.

Table 3. Multivariable Cox Proportional Hazards Modeling Evaluating Hazard Ratios of Progressive Retinal Nerve Fiber Layer Thinning Detected by Guided Progression Analysis and Other Baseline Covariates for Prediction of Visual Field Progression Determined by the Early Manifest Glaucoma Trial Criteria and Pointwise Linear Regression Criteria

	EMGT Criteria		PLR Criteria	
	Hazard Ratio (95% CI)	*P*	*Hazard Ratio (95% CI)*	*P*
Progressive RNFL thinning	3.95 (1.74–8.93)	0.001	3.81 (1.83–7.92)	<0.001
Age (yrs)	0.98 (0.95–1.01)	0.215	1.00 (0.97–1.03)	0.938
Baseline IOP (mmHg)	1.03 (0.94–1.13)	0.519	1.01 (0.94–1.09)	0.736
Baseline average RNFL thickness (μm)	0.99 (0.95–1.02)	0.468	0.97 (0.94–1.00)	0.071
Baseline VF MD (dB)	1.06 (1.00–1.13)	0.057	1.04 (0.99–1.08)	0.129
CCT (μm)	1.00 (0.99–1.02)	0.372	1.00 (1.00–1.01)	0.369
Axial length (mm)	1.10 (0.88–1.37)	0.411	1.02 (0.85–1.22)	0.862

CCT = central corneal thickness; CI = confidence interval; dB = decibels; EMGT = Early Manifest Glaucoma Trial; IOP = intraocular pressure; MD = mean deviation; PLR = Pointwise Linear Regression; RNFL = retinal nerve fiber layer; VF = visual field.

subsequent VF loss is directly relevant to the treatment plan of patients with glaucoma. In this regard, patients with progressive RNFL thinning may require augmentation of IOP-lowering therapy to decrease the risk of VF progression. Therefore, progressive RNFL thinning can serve as a biomarker to reflect disease deterioration behavior and guide glaucoma management.

Although the association between a thinner RNFL and VF loss, both globally and locally, has been demonstrated,[28–30] the temporal relationship between progressive RNFL thinning and progressive VF decline is poorly understood and the clinical significance of detecting progressive RNFL thinning in glaucoma management remains obscured. Longitudinal studies investigating the association between optic disc and RNFL changes and VF progression are sparse, and all evaluated the optic disc/RNFL using subjective examination of the optic disc or imaging instruments of the prior generation.[31–34] Using the time-domain OCT (Stratus OCT; Carl Zeiss Meditec), Sehi et al[32] measured the circumpapillary RNFL thickness obtained from a circle scan with a diameter of approximately 3.45 mm in 115 patients with perimetric glaucoma and 181 preperimetric glaucoma/glaucoma suspects and showed that for each 10-μm reduction in the average circumpapillary RNFL thicknesses, the risk of VF

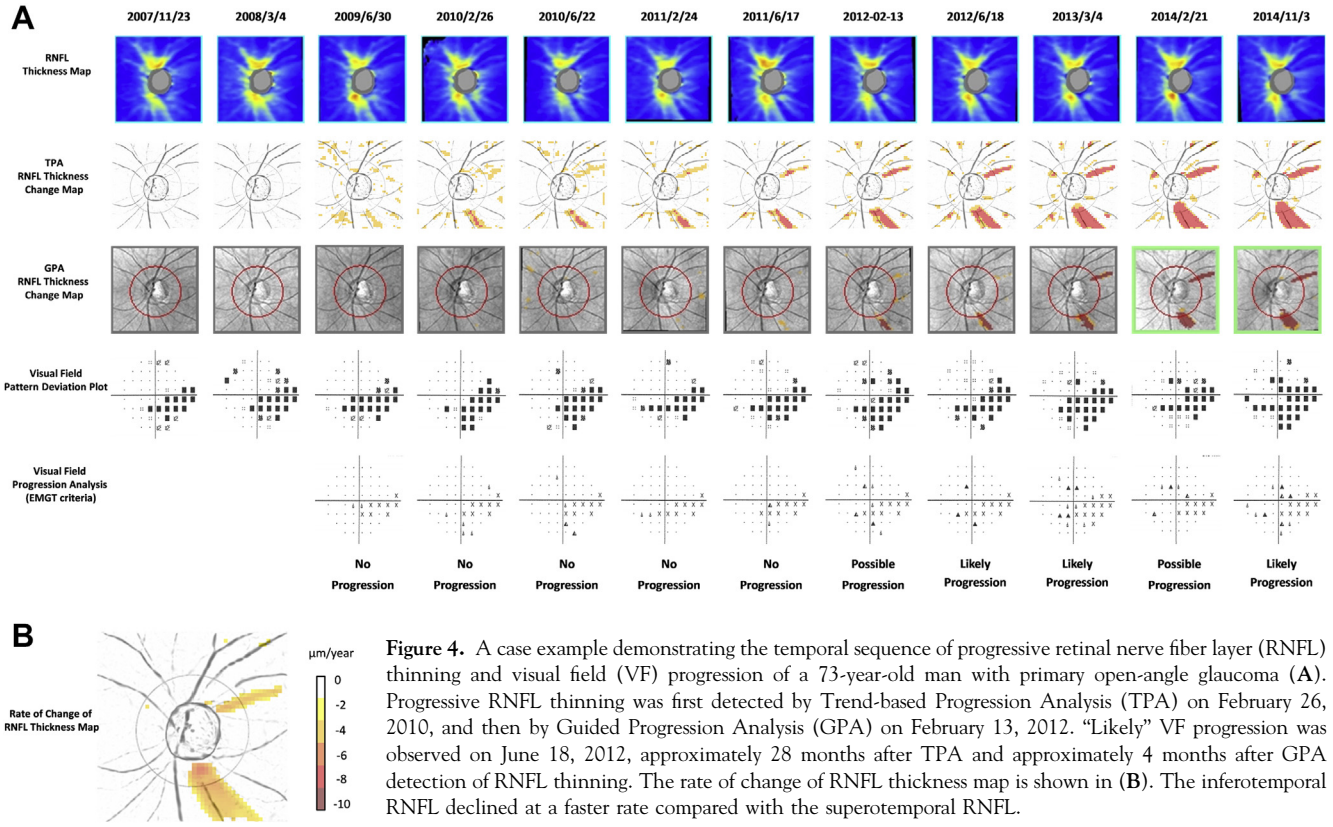

Figure 4. A case example demonstrating the temporal sequence of progressive retinal nerve fiber layer (RNFL) thinning and visual field (VF) progression of a 73-year-old man with primary open-angle glaucoma (**A**). Progressive RNFL thinning was first detected by Trend-based Progression Analysis (TPA) on February 26, 2010, and then by Guided Progression Analysis (GPA) on February 13, 2012. "Likely" VF progression was observed on June 18, 2012, approximately 28 months after TPA and approximately 4 months after GPA detection of RNFL thinning. The rate of change of RNFL thickness map is shown in (**B**). The inferotemporal RNFL declined at a faster rate compared with the superotemporal RNFL.

progression increased by 18%. A significant negative slope of average circumpapillary RNFL thickness over time was associated with an 85% increase in the risk of VF progression. Had confounding effects such as baseline disease severity been adjusted in the survival analysis, it is uncertain whether progressive RNFL thinning would have remained predictive of VF progression. In comparison with the study by Sehi et al,[32] in the current study a higher risk of VF progression was observed in eyes detected with progressive RNFL thinning (5.11- to 8.44-fold and 3.81- to 3.95-fold increases in risk for TPA and GPA, respectively), after adjusting for baseline measures (age, axial length, CCT, IOP, average RNFL thickness, and VF MD) (Tables 2 and 3). The differences between the studies could be in part due to the advancement in OCT technology and the progression analysis algorithm. Topographic analysis of the RNFL with spectral-domain OCT has substantively improved the detection of RNFL thinning compared with time-domain OCT. In fact, progressive RNFL thinning can be missed if progression analysis is limited to the circumpapillary RNFL measurement.[13] Spectral-domain OCT is an essential tool for change analysis of the RNFL for prediction of VF progression.

Trend-based Progression Analysis outperformed GPA in detecting more eyes with progressive RNFL thinning at a similar level of specificity (Fig 3) and providing visualization of the distribution of the rates of RNFL thinning (Fig 4B). That TPA detected more eyes with progressive RNFL thinning than GPA is in line with our previous study using computer simulation models to evaluate the performance of trend versus event progression analysis.[35] By modeling with reference to the individual's test−retest variability, the pattern of progression (linear and nonlinear losses), and the rate of change of average circumpapillary RNFL thickness, trend analysis attained a sensitivity and accuracy ≥80% earlier than event analysis for detection of progressive RNFL thinning. The visualization of the distribution of the rates of change of RNFL thickness in the RNFL thickness change map can help predict the locations of VF progression and assist clinicians to determine the intensity of treatment. Eyes that progress at a faster rate may require a more aggressive treatment regimen. However, TPA is not without limitation. The performance of TPA could be undermined if the number of follow-up examinations is limited. Event analysis may be more useful for change analysis when the reduction in RNFL thickness is abrupt or in eyes with a large test−retest variability.[35] Trend-based Progression Analysis may not replace but enhance GPA for topographic analysis of RNFL thinning.

The methods used for change analysis in this study, GPA for RNFL progression analysis and EMGT criteria for VF progression analysis, largely reflect the current standard and are thus directly relevant to clinical practice and to clinical trials. However, GPA and TPA did not differentiate disease-related from age-related RNFL thinning.[36,37] The lack of adjustment of age-related RNFL thinning might confound the interpretation of the risk of VF progression determined by the EMGT criteria because age-corrected normal threshold values were used to generate pointwise pattern deviations for VF progression analysis.[22] Therefore, we also included the PLR criteria, with a sensitivity change <0 dB/year at $P < 0.01$ for ≥3 contiguous test locations, to measure VF progression. Although a common PLR standard to define VF progression is based on any 3 locations with a sensitivity change <−1 dB/year at $P < 0.01$,[23,38,39] the PLR criteria adopted in this study can provide a non−age-corrected measure (a sensitivity change <0 dB/year instead of <−1 dB/year) with an increased specificity of the location requirement (3 contiguous locations instead of any 3 locations) to minimize a potential age-confounding effect in the analysis of the association between progressive RNFL thinning and VF progression. Of note, progressive RNFL thinning remained predictive of VF progression analyzed by the PLR criteria for both TPA (HR, 5.11; 95% CI, 2.51−10.42) and GPA (HR, 3.81; 95% CI, 1.83−7.92), and there were significant differences in the VF survival estimates, determined by both the PLR criteria and the EMGT criteria, between eyes with and without progressive RNFL thinning (Fig 2).

For VF progression analysis using the EMGT criteria, "likely" instead of "possible" progression was selected as the survival end point in the calculation of HRs because the former is more widely adopted in clinical studies evaluating glaucoma progression and has been shown to have a higher specificity for change detection.[40] Artes et al[40] reported the specificity of "likely" and "possible" progression after 10 follow-up VF tests to be 97.4% and 81.5%, respectively. In the present study, the specificity for detection of progressive RNFL thinning was estimated at worst at 81.7% for GPA and 84.2% for TPA. The relatively high specificity of "likely" VF progression might account for the temporal lag between progressive RNFL thinning and VF progression, contributing to the finding of progressive RNFL thinning being predictive of VF progression. Nevertheless, it is worth noting that TPA and GPA of progressive RNFL thinning remained predictive of "possible" VF progression, and the HRs were 9.28 (95% CI, 4.20−20.51) and 3.29 (95% CI, 1.59−6.81), respectively, after adjustment of the same baseline covariates (data not shown in "Results").

Treatment decisions in glaucoma management have been predicated largely on the level of IOP because a higher IOP confers a higher risk of VF progression. For example, in the EMGT, each millimeter of mercury increase in baseline IOP translates to a 13% (HR, 1.13, 95% CI, 1.07−1.16) increase in risk of VF progression[41] (the nonsignificant association between baseline IOP and VF progression in our multivariable models could be due to the fact that the patients were already receiving treatment at the time of recruitment). Of note, the risk of VF progression incurred by an eye detected with progressive RNFL thinning determined by TPA (8.44-fold increase in risk) would approximate that incurred by an eye with 17.5-mmHg elevation of baseline IOP [$\ln(8.44)/\ln(1.13) = 17.5$ mmHg]. This finding underscores the significance of detecting progressive RNFL thinning and its relevance to initiate or augment treatment for patients with glaucoma. Prospective studies are needed to determine whether glaucoma treatment prescribed upon detection of progressive RNFL thinning would be effective to prevent or slow VF progression.

Study Limitations

A major limitation is the generalizability of the finding. The study contains relatively high-quality RNFL and VF data collected from a close follow-up schedule in a tertiary center. Yet, OCT and perimetry may be performed less frequently in daily practice. The impact of RNFL imaging frequency on prediction of VF progression remains to be determined. Although only 11 OCT images were excluded for poor signal strength, 84 VF tests were excluded for high fixation losses and false-positive and false-negative rates. The missing VF data at some time points may delay the detection of VF progression. Another limitation is the lack of a normal group followed for a sufficiently long period of time for estimation of the specificity of GPA and TPA for detection of progressive RNFL thinning. Specificities estimated from the normal group contained only 8 weekly measurements and therefore did not capture age-related RNFL changes. Specificities estimated from the glaucoma group were based on the proportion of eyes with increasing RNFL thickness over 5 years. An FDR of at least 15.8% and 18.3% would be expected from the TPA and GPA detected RNFL thinning, respectively.

To summarize, progressive RNFL thinning evaluated with topographic analysis of the RNFL is an informative biomarker indicative of disease deterioration behavior, which is strongly predictive of VF progression. This finding is of direct relevance to clinicians in glaucoma management and to regulatory authorities in considering progressive RNFL thinning as a surrogate outcome measure in clinical trials for glaucoma treatment.

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Abbreviations and Acronyms:
CCT = central corneal thickness; **CI** = confidence interval; **dB** = decibel; **EMGT** = Early Manifest Glaucoma Trial; **FDR** = false discovery rate; **GPA** = Guided Progression Analysis; **HR** = hazard ratio; **IOP** = intraocular pressure; **MD** = mean deviation; **OCT** = optical coherence tomography; **PLR** = pointwise linear regression; **RNFL** = retinal nerve fiber layer; **TPA** = Trend-based Progression Analysis; **VF** = visual field; **VFI** = visual field index.

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