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Trend-Based Progression Analysis for Examination of the Topography of Rates of Retinal Nerve Fiber Layer Thinning in Glaucoma

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IMPORTANCE Measurement of the rates of retinal nerve fiber layer (RNFL) thinning has consisted primarily of the circumpapillary RNFL profile. This study reports the rates of RNFL thinning over the 6 × 6 mm^2 RNFL thickness map and their application for indication of visual field (VF) worsening in patients with glaucoma.

OBJECTIVE To investigate the association between the rates of RNFL thinning and the risk of VF worsening in patients with glaucoma.

DESIGN, SETTING, AND PARTICIPANTS This prospective study included 117 eyes of 89 Chinese patients with primary open-angle glaucoma followed up at approximate 4-month intervals for 5 or more years between July 1, 2007, and October 30, 2015, with progressive RNFL thinning detected by optical coherence tomography trend-based progression analysis (TPA). The mean and the peak rates of RNFL thinning and the area of progressive RNFL thinning were measured by the rates of change of RNFL thickness map. Visual field worsening was determined by the Early Manifest Glaucoma Trial and pointwise linear regression criteria.

MAIN OUTCOMES AND MEASURES Hazard ratios (HRs) for indication of VF worsening determined by time-varying Weibull survival models.

RESULTS Of 89 patients (117 eyes) included in the study, 53 (59.6%) were men; mean (SD) age was 54.0 (13.8) years. At the time that progressive RNFL thinning was confirmed by TPA, the mean and the peak rates of RNFL thinning were 9.06 (8.05) µm/y and 4.52 (3.19) µm/y, respectively, and the area of progressive RNFL thinning was 1.54 (1.83) mm^2. The inferotemporal meridians at 268° to 288° and the superotemporal meridians at 40° to 60° were the most frequent locations where progressive RNFL thinning was observed; 41.9% of the eyes had progressive RNFL thinning at these locations. After controlling for baseline covariates, the peak and the mean rates of RNFL thinning, but not the area of progressive RNFL thinning, were indicative of VF worsening. For each micrometer-per-year increase in the peak and the mean rates of RNFL thinning, the hazard ratios were 1.12 (95% CI, 1.04-1.19) for the peak rate and 1.39 (95% CI, 1.19-1.62) for the mean rate by the Early Manifest Glaucoma Trial criteria, and 1.07 (95% CI, 1.03-1.10) for the peak rate and 1.18 (95% CI, 1.09-1.28) for the mean rate by the pointwise linear regression criteria.

CONCLUSIONS AND RELEVANCE Topographic measurement of the rates of RNFL thinning by optical coherence tomography TPA is informative for risk assessment of VF loss in glaucoma. Although progressive RNFL thinning may not necessarily be associated with VF worsening, faster rates of RNFL thinning were associated with a higher risk of subsequent decline in VF.

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Supplemental content

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Progressive retinal ganglion cell loss, a hallmark of glaucomatous optic neuropathies, can be monitored by evaluating progressive thinning of the retinal nerve fiber layer (RNFL). Although optical coherence tomography (OCT) has been widely adopted in clinical practice for measurement of RNFL thickness and most clinical Fourier-domain OCT instruments image the retina and the optic nerve head with volume scans, the prevailing method for reporting the rate of change of RNFL thickness has mainly consisted of the average circumpapillary RNFL thickness profile generated from a circle scan with a diameter of approximately 3.45 mm.[1-12] Because glaucomatous RNFL defects are typically localized and wedge shaped, analysis of the topography of the rates of change of RNFL thickness is likely to be more informative to reveal the pattern and the prognosis of disease progression compared with measuring the changes of a mean value of RNFL thickness. However, the rates of change of RNFL thickness beyond the circumpapillary RNFL profile remain poorly understood in glaucoma. Although use of the Guided Progression Analysis (Carl Zeiss Meditec) 6 × 6 mm^2 RNFL thickness map provides a topographic display of longitudinal changes of RNFL thickness by comparing baseline and follow-up images,[13] it does not measure the rates of RNFL thinning.

A previous study following 240 eyes of 139 patients with primary open-angle glaucoma (POAG) at approximately 4-month intervals for 5 or more years[14] investigated the performance of trend-based progression analysis (TPA), an algorithm for measurement of the rates of change of RNFL thickness for detection of progressive RNFL thinning at individual superpixels of the RNFL thickness map (50 × 50 superpixels) controlled with a false discovery rate of 5% or less (**Figure 1**). With the use of the TPA RNFL thickness change map (Figure 1B), the study showed that TPA detected 117 eyes with progressive RNFL thinning at specificities of 84.2% to 100.0% and that the detection of progressive RNFL thinning was associated with an 8.44-fold increase in the risk of visual field (VF) worsening.[14] Only 23.1% to 23.9% of eyes with progressive RNFL thinning developed VF worsening during the study follow-up; 97.6% of eyes without progressive RNFL thinning did not develop VF worsening. Based on these results, we hypothesized that eyes with faster rates of RNFL thinning measured using the rates of change of RNFL thickness map (Figure 1C) are at a higher risk of developing VF worsening in patients with glaucoma. In this companion study, we examined the topography of the rates of RNFL thinning in 117 eyes of 89 patients with POAG detected with progressive RNFL thinning by TPA, measured the mean and the peak rates of RNFL thinning from the rates of change of RNFL thickness map generated at the time when progressive RNFL thinning was confirmed, and calculated the hazard ratios (HRs) for subsequent development of VF loss.

Key Points

Question Can topographic measurements of the rates of retinal nerve fiber layer thinning be used to indicate the risk of visual field loss in patients with glaucoma?

Findings In this 5-year prospective cohort study of 89 patients (117 eyes), the peak and the mean rates of retinal nerve fiber layer thinning were associated with an increased risk of subsequent development of visual field worsening as measured by criteria of both the Early Manifest Glaucoma Trial and pointwise linear regression.

Meaning Topographic measurements of the rates of retinal nerve fiber layer thinning are informative for risk assessment of visual field decline in patients with glaucoma.

Methods

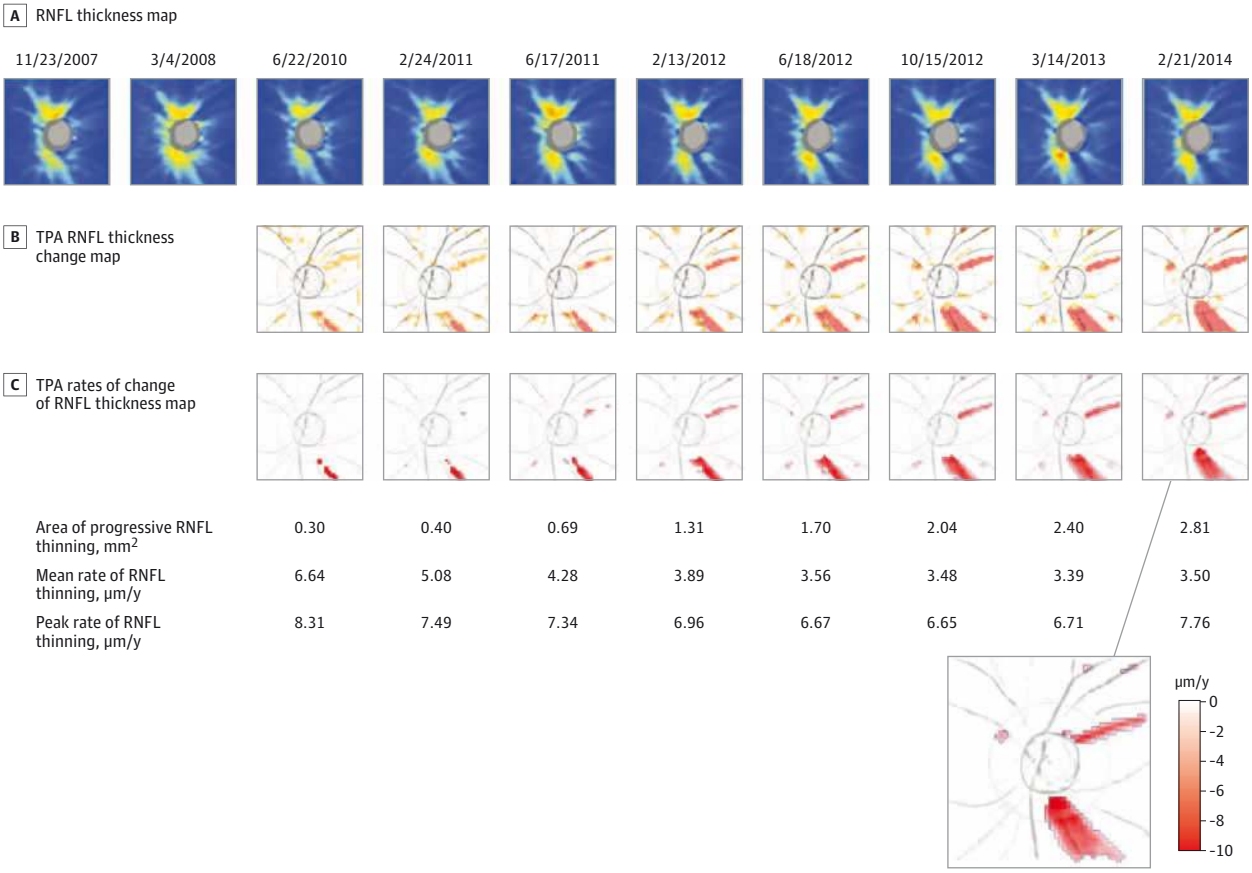
Participants

A total of 117 eyes of 89 patients with POAG and progressive RNFL thinning detected by TPA in a previous study[14] were included for generation and analysis of the rates of change of RNFL thickness map. The inclusion and exclusion criteria and the methodology of RNFL imaging and perimetry have been described.[14] In brief, 240 eyes of 139 patients with POAG were consecutively recruited and followed up at approximately 4-month intervals for 5 or more years between July 1, 2007, and October 30, 2015. At the baseline examination, all patients had glaucomatous optic nerve head changes (narrowed neuroretinal rim and optic nerve head deformation) with corresponding VF defects in standard automated white-on-white perimetry (ie, ≥3 significant [$P < .05$] nonedge contiguous locations and ≥1 location with $P < .01$ on the same side of the horizontal meridian in the pattern deviation plot) independent of the levels of intraocular pressure (IOP) in at least 1 eye. Intraocular pressure was measured with Goldmann applanation tonometry, central corneal thickness (CCT) was measured with ultrasonography pachymetry, and axial length was measured with partial coherence laser interferometry. Participants were followed up at approximate 4-month intervals for RNFL imaging (Cirrus HD-OCT optic disc cube scan; Carl Zeiss Meditec) and VF testing (Humphrey Field Analyzer II-i SITA standard 24-2 protocol; Carl Zeiss Meditec). Patients were treated with reference to the target IOP determined by the attending ophthalmologists without considering progressive RNFL thinning. At the most recent follow-up visit, TPA detected 117 eyes of 89 patients with POAG with progressive RNFL thinning in which 27 eyes (25 patients) and 28 eyes (24 patients) also developed VF worsening demonstrated by the Early Manifest Glaucoma Trial (EMGT) and pointwise linear regression (PLR) criteria, respectively, described below. The study was conducted in accordance with the ethical standards stated in the Declaration of Helsinki[15] and approved by the Kowloon Central/East Research ethics committee with written informed consent obtained; there was no financial compensation.

Trend-Based Progression Analysis of Progressive RNFL Thinning

The RNFL was imaged at the 6 × 6 mm^2 optic disc region, and the RNFL thicknesses was reported in the RNFL thickness map (50 × 50 superpixels). Superpixel RNFL thickness values of the RNFL thickness maps (Figure 1A) (all included RNFL thickness maps had a signal strength ≥6 without motion artifact) were exported to a computer for TPA (MATLAB; MathWorks Inc). Trend-based progression analysis determines the rates of change of RNFL thickness by performing linear regression analysis between RNFL thickness and follow-up time at individual superpixels after aligning and registering the longitudinal RNFL thickness map series of an eye. A minimum of 4 follow-up visits for each eye was required for TPA. The level of significance required in the linear regression analysis was determined after controlling the false discovery

Figure 1. Trend-Based Progression Analysis (TPA) for Detection of Progressive Retinal Nerve Fiber Layer (RNFL) Thinning and Analysis of the Topography of the Rates of RNFL Thinning



A, The RNFL thickness maps of an eye with primary open-angle glaucoma were exported for TPA. B, The RNFL thickness change map (50 × 50 superpixels) encodes superpixels with a significant negative trend (ie, RNFL thinning) in yellow before and in red after controlling the false discovery rates at 5% or lower. C, The rates of change of RNFL thickness map (50 × 50 superpixels) report the rates of change of RNFL thickness with reference to a color-coded scale with increasing intensities of red representing increasing rates of RNFL thinning at superpixel locations encoded in red in the RNFL thickness change map. Progressive RNFL thinning was first confirmed by TPA on June 22, 2010. Images from selected follow-up visits are displayed.

rate[16-19] at 5% or lower to minimize the probability of false-positive detection consequential to multiple testing. A false discovery rate of 5% indicates that 5% of the superpixels detected with a significant negative trend (<0 µm/y) in the RNFL thickness change map would be expected to be false-positive. Superpixels with a significant negative trend were encoded in yellow before and in red after controlling the false discovery rate at 5% or lower in the TPA RNFL thickness change map (Figure 1B). An eye with confirmed progressive RNFL thinning was defined when 20 or more contiguous superpixels (an arbitrary cutoff adopted in the Guided Progression Analysis) were encoded in red in the TPA RNFL thickness change map during the study follow-up, and the same changes were also evident at the most recent follow-up visit. The specificity of TPA for detection of progressive RNFL thinning has been estimated to range from 84.2% to 100%.[14]

The Rates of Change of RNFL Thickness Map

In contrast to the RNFL thickness change map in which only the locations of progressive RNFL thinning are revealed, the rates of changes of RNFL thickness map (Figure 1C) also report the rates of change of RNFL thickness at the corresponding superpixel locations with reference to a color-coded scale with increasing intensities of red representing increasing rates of RNFL thinning. In this study, 3 factors were measured from the rates of change of RNFL thickness map generated at the time when progressive RNFL thinning was confirmed by TPA for indication of VF worsening: (1) the area of progressive RNFL thinning (in millimeters squared), (2) the mean rate of RNFL thinning (in micrometers per year), and (3) the peak rate of RNFL thinning (in micrometers per year). The area of progressive RNFL thinning represented the total area encoded in red in the rates of change of RNFL thickness map or the RNFL thickness change map. The mean rate of RNFL thinning was calculated by determining the mean rates of change of RNFL thickness at superpixel locations encoded in red in the rates of change of RNFL thickness map. The peak rate of RNFL thinning was identified from a superpixel location with the greatest rate of RNFL thickness reduction within a cluster (≥20 superpixels) of progressive RNFL thinning detected in the rates of change of RNFL thickness map.

Analysis of VF Worsening With EMGT and PLR Criteria

Visual field worsening was determined by the EMGT criteria[20] (event analysis) and the PLR criteria (trend analysis).[21] For the EMGT criteria, worsening was confirmed when 3 or more test locations showed a significant reduction in visual sensitivity compared with 2 baseline examinations for 3 or more consecutive visits (ie, likely progression as indicated in the VF report) during the study follow-up and the changes were also observed at the most recent follow-up visit. For the PLR criteria, linear regression analysis between VF sensitivity threshold values (in decibels) and follow-up time was performed in each of the 52 VF locations. Progression was confirmed when 3 or more contiguous locations showed a significant negative trend (ie, <0 dB/y) at $P < .01$ during the study follow-up and the changes were also detected in the most recent follow-up visit. Among the 117 eyes included in the study, 45 VF tests from 32 eyes were excluded because of fixation losses and false-positive or false-negative errors greater than 20%. None of the excluded tests were baseline VF.

Table. Biometric Measurements of 117 Eyes of 89 Patients With POAG and Progressive RNFL Thinning

Characteristic	Mean (SD) [Range]
Sex, No. (%)	
Male	53 (59.6)
Female	36 (40.4)
Age, y	54.0 (13.8) [24 to 84]
Axial length, mm	25.25 (1.97) [20.5 to 30.1]
CCT, µm	540.7 (38.8) [408 to 610]
Baseline levels	
Intraocular pressure, mm Hg	18.2 (4.0) [8 to 36]
RNFL thickness, µm	73.6 (12.5) [50 to 109]
Visual field MD, dB	−6.95 (6.67) [−30.36 to 0.95]
Eyes with visual field progression, No. (%)	
EMGT criteria	27 (23.1)
PLR criteria	28 (23.9)

Abbreviations: CCT, central cornea thickness; EMGT, Early Manifest Glaucoma Trial; MD, mean deviation; PLR, pointwise linear regression; POAG, primary open-angle glaucoma; RNFL, retina nerve fiber layer.

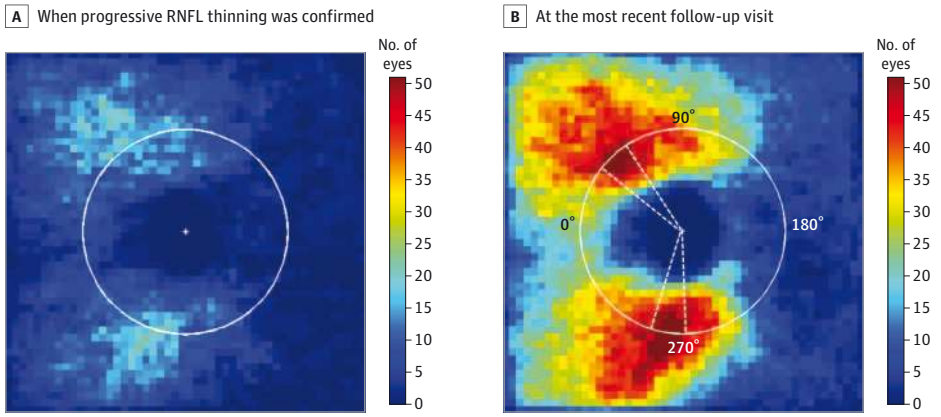
Statistical Analysis

Hazard ratios of the area of progressive RNFL thinning and the mean and peak rates of RNFL thinning for development of VF worsening were computed using univariable and multivariable time-varying Weibull survival models. The area of progressive RNFL thinning and the mean and peak rates of RNFL thinning were considered time-dependent covariates. Baseline covariates adjusted in the multivariable models included age, IOP, CCT, axial length, and circumpapillary average RNFL thickness. A shared frailty model following a γ distribution was used to adjust for correlation between fellow eyes. A 2-tailed value of $P < .05$ was considered statistically significant. Statistical analysis was performed with Stata, version 14.0 (StataCorp).

Results

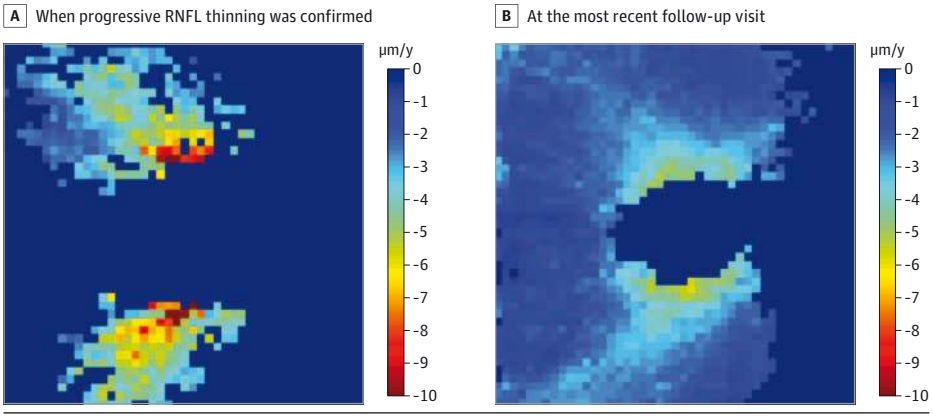
A total of 2041 OCT images from 117 eyes of 89 patients with POAG followed-up for between 4.9 and 7.2 years were included in the analysis. Among the patients, 53 (59.6%) were men and the mean (SD) age was 54.0 (13.8) years. Each eye had a median of 18 visits. All eyes developed progressive RNFL thinning determined by TPA during the study follow-up. When progressive RNFL thinning was confirmed by TPA, the follow-up time was between 1.7 and 6.5 years. At the baseline visit, 70 eyes (59.8%) had VF mean deviation (MD) of −6 dB or better, 25 eyes (21.4%) had VF MD between −6 and −12 dB, and 22 eyes (18.8%) had VF MD of −12 dB or worse. Visual field worsening was detected in 27 (23.1%) and 28 (23.9%) eyes by the EMGT and PLR criteria, respectively. The **Table** reports the demographic data and biometric measurements.

Figure 2. Frequency Distribution of Progressive Retinal Nerve Fiber Layer (RNFL) Thinning



Frequency distribution plots generated by overlapping 117 trend-based progression analysis RNFL thickness change maps from 117 eyes with reference to the follow-up visit when progressive RNFL thinning was confirmed by trend-based progression analysis (A) or the most recent follow-up visit (B). The inferotemporal (268°-288°) and the superotemporal (40°-60°) meridians (dotted lines) were the most frequent locations where progressive RNFL thinning was observed. The white circles represent the conventional scan circle (diameter 3.46 mm) for measurement of circumpapillary RNFL thickness. All the RNFL thickness change maps were overlapped with right eye orientation.

Figure 3. Topography of the Rates of Change of Retinal Nerve Fiber Layer (RNFL) Thickness



The median rates of change of RNFL thickness were indicated with reference to a color-coded scale at the individual superpixel locations with reference to the follow-up visit when progressive RNFL thinning was confirmed by trend-based progression analysis (A) and the most recent follow-up visit (B). The median rates of change of RNFL thickness were reported only when the superpixel locations had at least 10 measurements. All rates of change of RNFL thickness change maps were analyzed with right eye orientation.

Topography of Rates of Change of RNFL Thickness

Figure 2 displays the overlays of the RNFL thickness change maps of the 117 eyes with progressive RNFL thinning detected by TPA. The mean (SD) area of progressive RNFL thinning was 1.54 (1.83) mm^2 (range, 0.27-13.59 mm^2) at the time when progressive RNFL thinning was confirmed and 5.24 (4.37) mm^2 (range, 0.39-20.55 mm^2) at the most recent follow-up visit. At the most recent follow-up visit, the inferotemporal meridians at 268° to 288° and the superotemporal meridians at 40° to 60° were the most frequent locations where progressive RNFL thinning was detected; 41.9% of the eyes had progressive RNFL thinning at these locations (Figure 2B). At the time when progressive RNFL thinning was confirmed, the peak rate of RNFL thinning ranged between 41.91 and 0.66 μm/y (mean, 9.06 [8.05] μm/y) and the mean rate of RNFL thinning ranged between 18.21 and 0.80 μm/y (mean, 4.52 [3.19] μm/y). **Figure 3** shows the median rates of change of RNFL thickness at the individual superpixel locations at the time when progressive RNFL thinning was confirmed (Figure 3A) and at the most recent follow-up visit (Figure 3B). The rates of RNFL thinning were generally faster at the inferotemporal and superotemporal sectors near the optic disc margin than other locations in the rates of change of RNFL thickness map. Eyes with VF worsening had significantly greater mean and peak rates of RNFL thinning (6.69 μm/y for the mean rate and 13.87 μm/y for the peak rate) compared with eyes without VF worsening (3.87 μm/y for the mean rate and 7.61 μm/y for the peak rate) when evaluated using the EMGT criteria ($P \leq .001$) as well as the PLR criteria (6.17 μm/y for the mean rate and 13.23 μm/y for the peak rate vs 4.00 μm/y for the mean rate and 7.74 μm/y for the peak rate) ($P \leq .006$) (eTables 1 and 2 in the Supplement).

Application of the Rates of Change of RNFL Thickness Map for Indication of VF Worsening

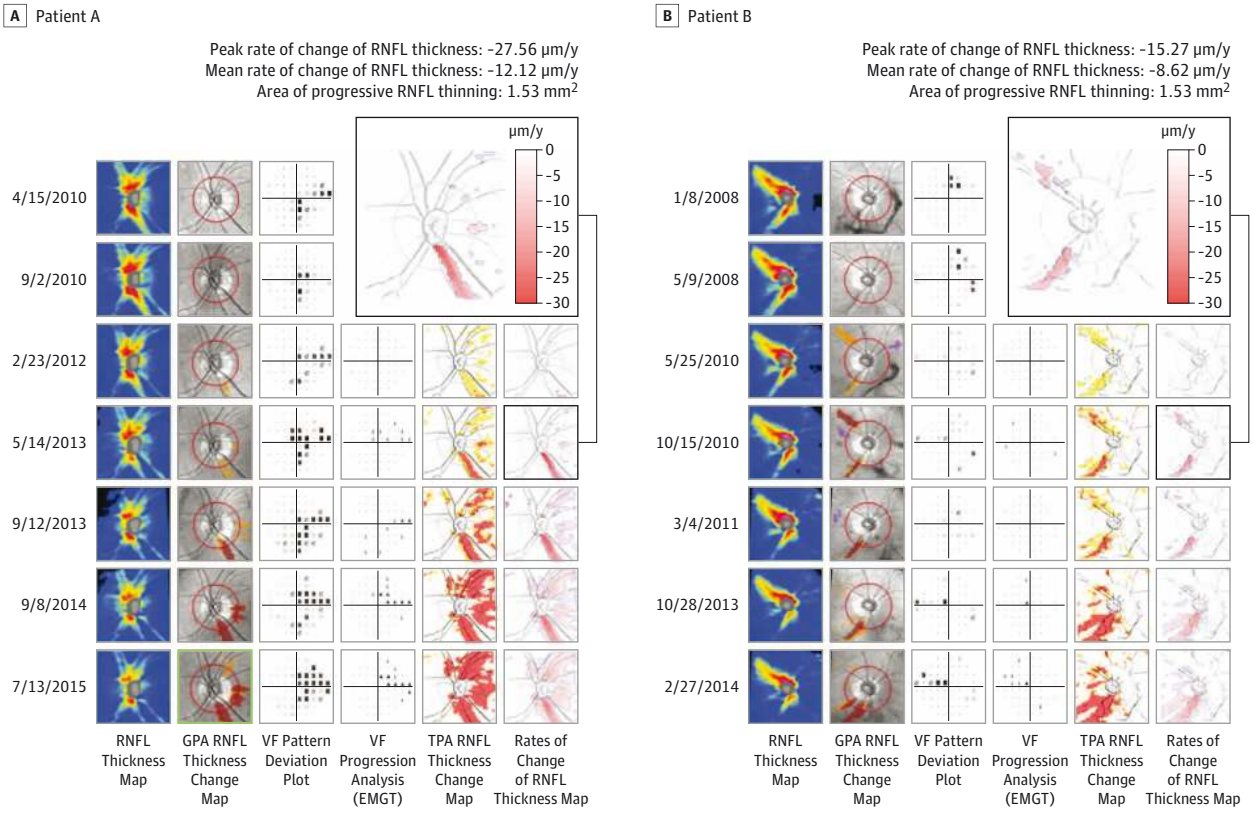
In the univariable time-varying Weibull survival models, the peak and mean rates of RNFL thinning (measured at the time when progressive RNFL thinning was confirmed), but not the area of progressive RNFL thinning, were indicative of VF worsening by the EMGT and PLR criteria (eTable 3 in the Supplement). After controlling for age, IOP, CCT, axial length, and mean circumpapillary RNFL thickness at baseline, the mean and peak rates of RNFL thinning remained indicative of VF worsening (eTables 4-6 in the Supplement). For each micrometer-per-year increase in the mean rate of RNFL thinning, the risk of VF worsening increased by 39% (HR, 1.39; 95% CI, 1.19-1.62) by the EMGT criteria and by 18% (HR, 1.18; 95% CI, 1.09-1.28) by the PLR criteria. For each micrometer-per-year increase in the peak rate of RNFL thinning, the risk of VF worsening increased by 12% (HR, 1.12; 95% CI, 1.04-1.19) by the EMGT criteria and 7% (HR, 1.07; 95% CI, 1.03-1.10) by the PLR criteria. **Figure 4** illustrates the application of the rates of change of RNFL thickness map for risk assessment of VF worsening in 2 patients with POAG who had progressive RNFL thinning detected by TPA during the study follow-up.

Discussion

To our knowledge, this study is the first to apply the topography of the rates of RNFL thinning for risk assessment of VF worsening in glaucoma. We showed that the peak and mean rates of change of RNFL thickness, but not the area of progressive RNFL thinning, measured from the rates of change of RNFL thickness map, were indicative of VF worsening. Examination of the topography of the rates of change of RNFL thickness would be relevant to guide treatment decisions in the management of patients with glaucoma.

Measurement of the rate of change of RNFL thickness with OCT has been based solely on the circumpapillary RNFL thickness profile in clinical practice and in clinical studies (eTable 7 in the Supplement). With the use of the rates of change of RNFL thickness map, it is feasible to visualize not only the locations, but also the corresponding rates of RNFL thinning. We showed that the rates of RNFL thinning varied considerably between as well as within individual eyes. Among the 117 eyes of 89 patients with POAG, the peak rate of RNFL thinning ranged from 41.91 to 0.66 μm/y and the mean rate of RNFL thinning ranged from 18.21 to 0.80 μm/y. Each micrometer-per-year increase in the peak and mean rates of reduction of RNFL thickness was connected to a higher risk of subsequent development of VF worsening defined by both event-based (EMGT criteria) and trend-based (PLR criteria) criteria after controlling for age, IOP, CCT, axial length, and average circumpapillary RNFL thickness at baseline (eTables 5 and 6 in the Supplement). The area of progressive RNFL thinning was not indicative of VF worsening (eTable 4 in the Supplement).

Figure 4. Case Examples Illustrating the Application of the Rates of Change of Retinal Nerve Fiber Layer (RNFL) Thickness Map for Risk Assessment of Visual Field Loss



Patient A (age, 40s) and patient B (age, 70s) had primary open-angle glaucoma with inferotemporal RNFL defects evident in the optical coherence tomography RNFL thickness map (left eye for patient A; right eye for patient B) at the baseline visit (April 15, 2010, for patient A; January 8, 2008, for patient B). Progressive RNFL thinning was subsequently confirmed in both patients by Guided Progression Analysis (GPA) (September 12, 2013, for patient A; October 15, 2010, for patient B) and trend-based progression analysis (May 14, 2013, for patient A; October 15, 2010, for patient B). At the time when progressive RNFL thinning was confirmed by trend-based progression analysis, the peak and the mean rates of RNFL thinning were greater for patient A (27.56 and 12.12 µm/y, respectively) than patient B (15.27 and 8.62 µm/y, respectively). Patient A subsequently developed visual field (VF) worsening by the Early Manifest Glaucoma Trial (EMGT) criteria (likely progression) on September 8, 2014, whereas patient B did not develop VF worsening during the study follow-up. The total follow-up duration was 5.2 years and 6.1 years for patients A and B, respectively.

The area of progressive RNFL thinning was indicative of VF worsening only when all eyes in the original study[14] (ie, 240 eyes of 139 patients with POAG) were included in the analysis (eTable 8 in the Supplement). This finding is simply in line with the fact that the detection of progressive RNFL thinning by TPA per se (ie, presence or absence of progressive RNFL thinning) is linked to an increased risk of VF worsening.[14] Measurement of the area of progressive RNFL thinning did not provide additional information to refine the risk for development of VF worsening in eyes that had already developed progressive RNFL thinning. Our finding underscores the relevance of analyzing the topography of the rates of RNFL thinning for risk assessment of VF loss in patients with glaucoma (Figure 4).

The rates of RNFL thinning varied from location to location in the rates of change of RNFL thickness map in an individual eye (Figure 1 and Figure 4). The distribution of the rates of change of RNFL thickness generally followed the distribution of the RNFL thickness, with the inferotemporal and superotemporal meridians near the optic disc margin showing faster rates of RNFL thinning compared with other locations (Figure 3). Although a greater baseline RNFL thickness is generally associated with a faster rate of RNFL thinning,[22-25] such an association did not appear to hamper TPA to detect progressive RNFL thinning of VF worsening in eyes with moderate to advanced glaucoma. This finding is supported by the fact that 40.2% of eyes included in this study had moderate to advanced glaucoma with VF MD worse than −6 dB at baseline and the mean and peak rates of change of RNFL thickness remained indicative of VF worsening after controlling for baseline RNFL thickness.

Limitations

Analysis of progressive RNFL thinning is currently limited by the lack of adjustment for age-related RNFL thinning.[23,24] While age-related RNFL thinning in healthy eyes is unlikely to have a significant effect on the VF, any form of further RNFL loss in glaucomatous eyes may contribute to deterioration of visual function. It remains to be investigated whether adjustment of age-related RNFL thinning in TPA would improve its performance to indicate VF worsening. Another limitation of the study is the lack of a sufficiently long follow-up time to detect VF worsening. Although

77% to 78% of the eyes did not develop VF worsening during the study follow-up despite demonstrating progressive RNFL thinning, it is important to note that when progressive RNFL thinning was confirmed by TPA, it was already 1.7 to 6.5 years from the baseline visit. Patients with slow RNFL progression have a lower risk of VF worsening and may need a longer follow-up time to detect VF decline.

Conclusions

The rates of RNFL thinning are highly variable among patients with glaucoma, and the analysis of the topography of the rates of change of RNFL thickness with TPA can provide an effective approach to reveal the locations and the corresponding rates of RNFL thinning. Although progressive RNFL thinning may not be associated with VF worsening, individuals with more rapid rates of RNFL thinning may require a more frequent follow-up schedule and a lower target IOP since they are more likely to develop VF loss. It remains to be investigated whether there are cutoff levels in the rates of RNFL thinning that would be useful to discriminate patients with VF progression from those without VF progression. A prospective study investigating the performance of these cutoffs for risk assessment of VF loss in patients with glaucoma would be relevant.

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Study concept and design: Leung.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Leung.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Lin, Yu, Leung.
Obtained funding: Leung.
Administrative, technical, or material support: Leung.
Study supervision: Leung.

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