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Rates of Retinal Nerve Fiber Layer Loss in Contralateral Eyes of Glaucoma Patients with Unilateral Progression by Conventional Methods

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Purpose: To determine whether progressive retinal nerve fiber layer (RNFL) loss occurs in the contralateral eye of patients with glaucoma showing unilateral progression according to conventional diagnostic methods.

Design: Prospective, longitudinal, observational cohort study.

Participants: Three hundred forty-six eyes of 173 patients (118 eyes with glaucoma and 228 eyes with suspect glaucoma at baseline) followed up for an average of 3.5 ± 0.7 years.

Methods: All subjects underwent standard automated perimetry (SAP; Humphrey Field Analyzer; Carl Zeiss Meditec, Dublin, CA) and spectral-domain (SD) optical coherence tomography (OCT; Spectralis; Heidelberg Engineering, Inc., Carlsbad, CA) in both eyes at 6-month intervals. Eyes were determined as progressing by conventional methods if there was progression on masked grading of optic disc stereophotographs or SAP Guided Progression Analysis (GPA; Carl Zeiss Meditec; “likely progression”). Rates of change in SD OCT average RNFL thickness were obtained using a linear mixed effects model. Rate of global loss was calculated using a random coefficient model and compared for nonprogressing patients, progressing eyes, and fellow eyes of unilateral progressing patients.

Main Outcomes Measures: Rate of change in global RNFL thickness.

Results: Thirty-nine subjects showed evidence of unilateral progression by GPA, disc photographs, or both during follow-up. Mean $\pm$ standard error rate of RNFL loss in eyes progressing by conventional methods was -0.89 ± 0.22 $\mu\text{m}/\text{year}$ ($P < 0.001$). The contralateral eyes of these subjects also showed significant loss of RNFL over time (-1.00 ± 0.20 $\mu\text{m}/\text{year}$; $P < 0.001$). One hundred thirty-four subjects did not show progression by conventional methods in either eye. These eyes also showed a significant decline over time in average RNFL thickness (-0.71 ± 0.09 $\mu\text{m}/\text{year}$; $P < 0.001$); however, the rate of change in these eyes was slower than that of the contralateral eye of patients showing unilateral progression ($P < 0.001$).

Conclusions: Loss of RNFL thickness was seen in a substantial number of contralateral eyes of glaucoma patients showing unilateral progression by conventional methods. These findings indicate that assessment of RNFL thickness by SD OCT may show progressive glaucomatous damage that is not detected by visual fields or optic disc stereophotography. *Ophthalmology* 2015;122:2243-2251 © 2015 by the American Academy of Ophthalmology.

Detection of progression is the cornerstone of management of patients with glaucoma. Assessment of progression relies on establishing accurate baseline measurements and monitoring for change over time.¹ In clinical practice, progressive visual field loss generally has been evaluated using standard automated perimetry (SAP). Although there is currently no consensus regarding the best method for detecting progressive field loss on SAP, tools such as Guided Progression Analysis (GPA; Carl Zeiss Meditec, Dublin, CA) have been used widely in clinical practice to assist in management and treatment decisions.²⁻⁴

Despite SAP being the most commonly used method to assess progression, the results of several longitudinal investigations have provided evidence that many patients may

show progressive structural damage in the absence of detectable visual field losses on SAP. Clinical trials such as the Ocular Hypertension Treatment Study have used serial assessment of optic disc stereophotographs to detect progressive damage from glaucoma.⁵ However, interpretation of optic disc stereophotographs is subjective, and this method may be relatively insensitive to detecting certain patterns of progression, such as diffuse retinal nerve fiber layer (RNFL) loss.⁶ Therefore, it is conceivable that progression may occur in some patients, despite going largely undetected by conventional tests such as SAP GPA and optic disc stereophotography.

Over the past decade, several longitudinal investigations have validated the use of imaging technologies for detection

of progressive structural damage in glaucoma.^{7–10} Assessment of RNFL using spectral-domain (SD) optical coherence tomography (OCT) can provide objective and reproducible measurements of RNFL thickness and quantify rates of structural deterioration in glaucoma. Rates of RNFL thinning as measured by OCT have been shown to be predictive of future functional losses in the disease and to be related to measures of quality of life.^{11–14}

Although glaucoma typically is a bilateral disease, unilateral progression may be seen often in clinical practice. However, it is conceivable that assessment of progression with more sensitive methods actually may reveal deterioration to occur in those eyes that do not show progression when measured by conventional methods. Despite the increasing use of OCT in clinical practice, to the best of our knowledge, there have been no reports evaluating the ability of this technology to detect progression in the fellow eyes of patients who show only unilateral progression by conventional assessment with SAP or optic disc photographs. This is an important topic because, arguably, undetected progression in the better eye may be of greater significance for a patient's quality of life than progression in the worse eye.^{14,15} The purpose of this study was to determine whether progressive RNFL loss occurs in the contralateral eye of patients with glaucoma showing unilateral progression according to conventional diagnostic methods and to compare rates of change in these eyes.

Methods

Patients

This was a longitudinal observational cohort study involving 346 eyes of 173 participants from the Diagnostic Innovations in Glaucoma Study, a prospective longitudinal study designed to evaluate optic nerve structure and visual function in glaucoma. The study was conducted at the Hamilton Glaucoma Center at the Department of Ophthalmology, University of California, San Diego. Methodologic details have been described previously.¹⁶ Written informed consent was obtained from all participants, and the institutional review board and human subjects committee at University of California, San Diego, prospectively approved all protocols and methods, which adhered to the Declaration of Helsinki. The study was also conducted in accordance with the regulations of the Health Insurance Portability and Accountability Act.

At each visit during follow-up, patients underwent a comprehensive ophthalmologic examination, including review of medical history, best-corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure (IOP) measurement with Goldmann applanation tonometry, gonioscopy, dilated funduscopic examination with 78-diopter (D) lens, stereoscopic optic disc photography (Kowa WX3D; Kowa OptiMed, Torrance, CA), Spectralis SD OCT (software version 5.4.7.0; Heidelberg Engineering, Inc., Carlsbad, CA), and SAP (Humphrey Field Analyzer; Carl Zeiss Meditec, Dublin, CA) using the Swedish interactive threshold algorithm standard 24-2. Only patients with open angles on gonioscopy were included. Subjects were excluded if they had visual acuity less than 20/40, spherical refraction outside ± 5.0 D, cylinder correction outside ± 3.0 D, a combination thereof, or any other ocular or systemic disease that could affect the optic nerve or the visual field.

The study included patients diagnosed with glaucoma, as well as those suspected of having the disease, both of whom were

determined at baseline visit. Patients were diagnosed with glaucoma if either eye had repeatable (≥ 3 consecutive) abnormal SAP results, defined as pattern standard deviation outside 95% normal confidence limits, or glaucoma hemifield test results outside normal limits. Glaucoma suspects were diagnosed if they had a history of elevated IOP (> 21 mmHg), suspicious or glaucomatous appearance of the optic nerve, or both, but normal and reliable visual field results.

For the purposes of the analysis, subjects with both eyes eligible from the Diagnostic Innovations in Glaucoma Study were included and those with only 1 eye eligible were excluded. To be included in the analysis, each patient was required to have undergone at least 5 SAP tests and 5 SD OCT tests over a duration of at least 1 year of follow-up. The images of RNFL with Spectralis and visual field tests with SAP using the Swedish interactive threshold algorithm standard 24-2 were obtained at 6-month intervals during follow-up. The study included a total of 2646 Spectralis visits, with an average of 752 visits per year.

Stereophotographs

All patients underwent stereoscopic optic disc photography repeated at least every 12 months during follow-up. The images were reviewed with a stereoscopic viewer (Screen-VU stereoscope; PS Manufacturing, Portland, OR) by 2 or more experienced graders masked to the subjects' identity and any other test results. Details of the methodology used to grade the optic disc photographs at University of California, San Diego, Optic Disc Reading Center have been described elsewhere.^{16,17} Discrepancies between the 2 graders were resolved by consensus or adjudication by a third experienced grader. Only photographs with adequate quality were used.

Progression assessment was based on focal or diffuse thinning of the neuroretinal rim, or both; increased excavation; and appearance or enlargement of RNFL defects. Change in rim color, presence of disc hemorrhage, or progressive parapapillary atrophy was not sufficient for characterization of progression.

Optical Coherence Tomography

Spectralis SD OCT was used to measure global RNFL in this study. Details of the operation have been described previously.^{18,19} All images were reviewed by experienced technicians at the Imaging Data Evaluation and Assessment Center. To be included, images had to be centered, with accurate segmentation, and to have a signal strength of more than 15 dB. For this study, we used the global RNFL thickness, which corresponds to the average RNFL thickness in the 3.4-mm-diameter peripapillary circle around the optic nerve head. This parameter has been shown to perform well in the assessment of rates of change in previous studies.^{17,20}

Standard Automated Perimetry

All visual field results were reviewed by University of California, San Diego, Visual Field Assessment Center.¹⁶ Visual fields with more than 33% fixation losses or false-negative errors, or more than 15% false-positive errors, were excluded. Glaucomatous visual field progression was evaluated by Humphrey Field Analyzer GPA software. For each individual point on the visual field, GPA compares the sensitivity of a follow-up test with the one from averaging 2 baseline visits at the same location. It flags points whose changes demonstrate more than expected variability (at 95% significance level). If significant change is detected in more than 3 points and is repeated at the same location in 2 consecutive follow-up tests, GPA flags the last test as "possible progression." If more than 3 points have significant changes detected and repeated in 3 consecutive follow-ups at the same location, GPA flags the last

one as “likely progression.” For the purpose of the study, only the classification of likely progression was considered as visual field progression. In this study, the baseline was chosen as the test closest to SD OCT date and the last visual field test was also the one closest to the last available SD OCT date.

Definitions of Groups

Figure 1 shows a flowchart depicting the selection of eyes and subjects for the study. Because the purpose of this study was to evaluate the global RNFL thickness changes in the contralateral eye of subjects with unilateral progression, those subjects with both eyes progressing by conventional methods were excluded from further analyses. Therefore, we denominated progressing patients as those patients who had only 1 eye progressing by SAP, stereophotographs, or both, whereas their contralateral eye did not show progression by these methods. In contrast, we denominated nonprogressing patients as those who did not have progression by conventional methods in either eye. The eyes of these nonprogressing patients were labeled as control eyes.

Statistical Analysis

Linear mixed effects models were used to evaluate the relationship between change in global RNFL thickness over time and progression by conventional parameters. Details of the use of these models for evaluation of rate of change in glaucoma have been reported previously.^{8,21}

We considered measurements of global RNFL thickness as the dependent variable. The variable time (time from baseline in years) was included as a continuous predictor. Significance of the coefficient associated with the variable time indicated whether there was a significant trend in RNFL thickness measurements over time, that is, whether RNFL thickness measurements tend to decrease or increase significantly over time. Progression as defined by stereophotographs, SAP GPA, or both was depicted as the fixed-effect covariate (the variable progression) with the value of 1 if the eye progressed by stereophotographs, SAP GPA, or both, and the value of 0 if the eye did not show progression by either of the methods.

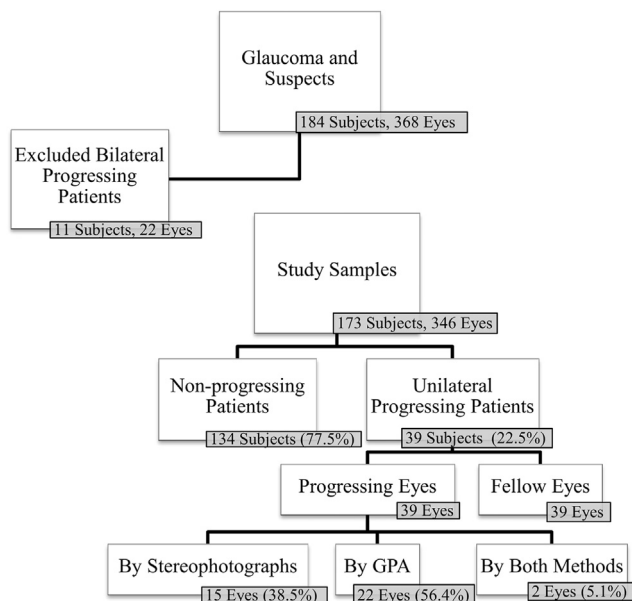


Figure 1. Flowchart showing the number of patients enrolled and analyzed. GPA = Guided Progression Analysis.

The 2-way interaction between time and progression (progression $\times$ time) also was included in the model to evaluate whether there is significant difference in the longitudinal RNFL thickness measurements over time between progressing eyes and control eyes. The following random components for both the intercept and slope were added to the model: random patient-specific effects and random eye-specific effects (i.e., progressing in one eye but not progressing in the fellow eye) for each eye of each patient. The inclusion of random intercepts allows for the variation in baseline global RNFL measurements, whereas the random slopes allow for the variation in the rate of progressive RNFL loss among eyes and patients.

Subsequent models were built taking into account other possible predictors such as ancestry, gender, baseline age, baseline SAP 24-2 mean deviation (MD), central corneal thickness, mean IOP during follow-up, as well as their interactions with the variable time. Initially, univariate models were constructed, containing only 1 putative predictor along with its time-interaction term. Subsequently, more complex models comprising multiple predictors and interaction terms were created. Significance of the predictors was assessed using Wald tests and deviance statistics to reach the most parsimonious final model. When the final model was built, estimates of rate of RNFL loss for individual eyes were obtained by best linear unbiased prediction.^{3,22}

All statistical analyses were performed with STATA software version 13.1 (StataCorp LP, College Station, TX). The α level (type I error) was set at 0.05.

Results

Study Sample

Overall, there was an average of 8.3 OCT examinations (range, 5–16 examinations) per eye during an average follow-up of 3.5 ± 0.7 years. Table 1 shows the demographic and clinical characteristics of all subjects at baseline. Progressing eyes of progressing patients had worse MD and thinner global RNFL thickness at baseline compared with control eyes ($P < 0.001$ for both comparisons). Global RNFL thickness also was thinner in the progressing eyes of unilateral progressing patients compared with their fellow eyes ($P = 0.004$). Figure 2 shows the distribution of baseline global RNFL thickness in progressing eyes, fellow eyes of progressing patients, and control eyes at baseline.

Rates of Global Retinal Nerve Fiber Layer Loss

Eyes progressing according to GPA or changes on optic disc stereophotographs had statistically significant rates of global RNFL thickness loss during follow-up, with an average loss of -0.89 ± 0.22 $\mu\text{m}/\text{year}$ ($\pm$ standard error of the coefficient; $P < 0.001$; Table 2). The fellow eyes of progressing patients also showed significantly reduced global RNFL thickness over time, with an average loss of -1.00 ± 0.20 $\mu\text{m}/\text{year}$ ($P < 0.001$). In 18 of these eyes (46%), the slopes were statistically significant, and the mean rate of change in these eyes with statistically significant slopes was -1.81 ± 0.43 $\mu\text{m}/\text{year}$. There was also a decrease in global RNFL thickness in eyes of patients without progression by conventional methods in either eye, with an average decrease in global RNFL thickness of -0.71 ± 0.09 $\mu\text{m}/\text{year}$ ($P < 0.001$). The average rate of RNFL progression of the progressing eyes of progressing patients was significantly faster than that of control eyes (-0.89 $\mu\text{m}/\text{year}$ [95% confidence interval (CI), -1.33 to -0.45 $\mu\text{m}/\text{year}$] vs. -0.71 $\mu\text{m}/\text{year}$ [95% CI, -0.86 to -0.56 $\mu\text{m}/\text{year}$]; $P < 0.001$). In addition, the

Table 1. Demographic and Clinical Characteristics at Baseline for All Subjects

Characteristic	Nonprogressing Patients (n = 134)	Unilaterally Progressing Patients (n = 39)		P Value
	Control Eyes (n = 268)	Progressing Eyes (n = 39)	Fellow Eyes (n = 39)	
Mean baseline age $\pm$ standard deviation (yrs)	65.7 $\pm$ 10.4		70.6 $\pm$ 9.7	0.003 ^{*,†}
Female sex, no. (%)	84 (63)	14 (36)		<0.001 ^{†,‡}
Ancestry, no. (%)				0.978 ^{†,‡}
European	88 (66)	26 (67)		
African	46 (34)	13 (33)		
Baseline MD (dB)				
Mean	−1.80	−5.13	−3.26	<0.001 ^{*,†,§}
Range	−2.30 to 0.27	−7.99 to −1.40	−3.47 to −0.54	0.169 ^{*,§,}
Baseline gRNFL thickness (μ m)				
Mean	85	70	79	<0.001 ^{*,†,§}
Range	75–95	63–79	70–90	0.004 ^{*,§,}
IOP during follow-up (mmHg)				
Mean	18	16	17	0.296 ^{*,†,§}
Range	14–21	12–20	14–19	0.623 ^{*,§,}
CCT (μ m)				
Mean	555	548	543	0.099 ^{*,†,§}
Range	526–581	518–579	513–579	0.723 ^{*,§,}
Mean follow-up $\pm$ standard deviation (yrs)	3.5 $\pm$ 0.7		3.5 $\pm$ 0.7	0.825 ^{†,¶}

CCT = central cornea thickness; dB = decibels; gRNFL = global retinal nerve fiber layer; IOP = intraocular pressure; MD = mean deviation.

*Wilcoxon rank-sum test.

[†]Progressing eyes vs. control eyes.

[‡]Fisher exact test.

[§]Median (interquartile range).

^{||}Progressing eyes vs. fellow eyes.

[¶]t Test.

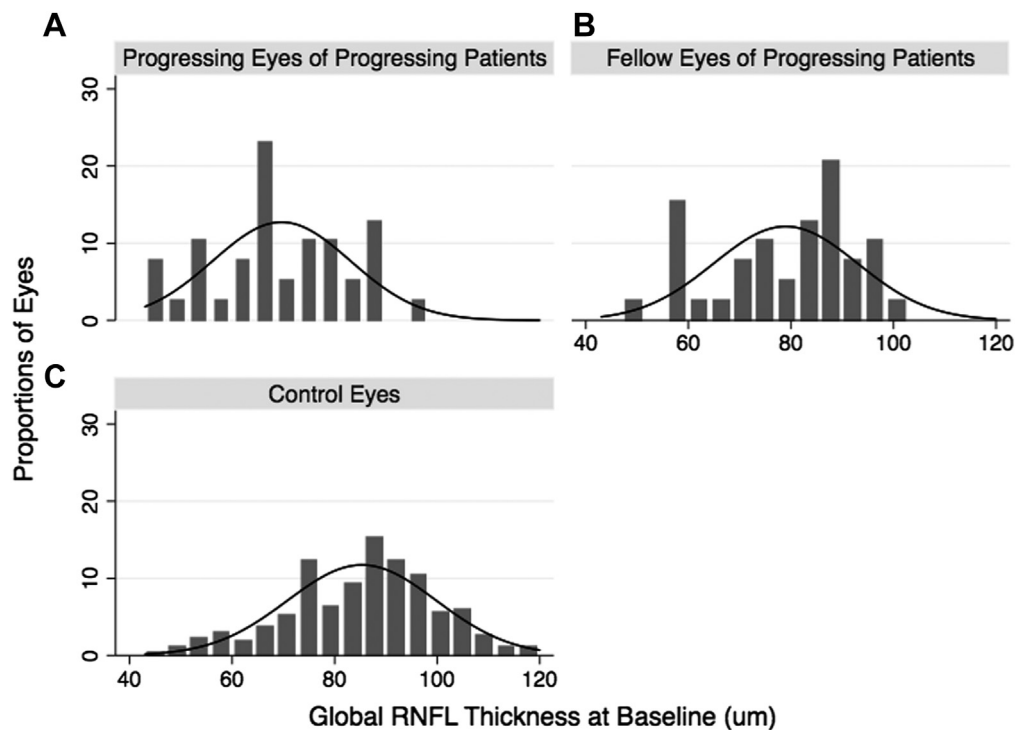


Figure 2. Histograms showing the distribution of global retinal nerve fiber layer (RNFL) thickness in (A) progressing eyes, (B) fellow eyes of unilateral progressing patients, and (C) control eyes at baseline.

Table 2. Results of the Mixed Effects Model Investigating Longitudinal Changes in Global Retinal Nerve Fiber Layer Thickness in Progressing and Fellow Eyes of Patients with Progression by Guided Progression Analysis or Disc Stereophotographs (Unilateral Progressors) Compared with Rates in Nonprogressing Patients

Parameters	Control Eyes (n = 268)		Unilaterally Progressing Patients (n = 39)				P Value
			Progressing Eyes (n = 39)		Fellow Eyes (n = 39)		
	Mean	Standard Error	Mean	Standard Error	Mean	Standard Error	
Intercept	84.71	1.16	69.37	2.11	78.62	2.23	<0.001 ^{*,†} <0.001 ^{†,‡} 0.003 ^{§,}
Change of gRNFL thickness (μm/year)	−0.71	0.09	−0.89	0.22	−1.00	0.20	<0.001 ^{*,†} <0.001 ^{†,‡} 1.000 ^{§,}

gRNFL = global retinal nerve fiber layer.

*Progressing eyes of unilateral progressing patients vs. control eyes.

†Linear mixed model.

‡Fellow eyes of unilateral progressing patients vs. control eyes.

§Progressing eyes vs. fellow eyes.

||Sign test.

average rate of RNFL progression in the fellow eye of progressing patients also was faster than that of control eyes (−1.00 μm/year [95% CI, −1.39 to −0.61 μm/year] vs. −0.71 μm/year [95% CI, −0.86 to −0.56 μm/year]; $P < 0.001$). A significant correlation in rates of change was observed between the 2 eyes of patients with unilateral progression ($r = 0.41$; $P = 0.009$, Pearson's correlation).

It was also important to consider the effect of possible confounding variables on differences in the rate of global RNFL loss between fellow eyes of progressing patients versus control eyes. This was evaluated using a multivariate random coefficient model including progression, baseline age, baseline MD, gender, race, central corneal thickness, mean IOP during follow-up, and their interactions with time (Table 3). The model showed that there was a significant difference in rates of RNFL loss over time between fellow eyes of unilateral progressing patients and control eyes, even after accounting for the effects of potentially confounding variables. The adjusted rates of progression for these 2 groups were −1.21 μm/year (range, −1.82 to −0.58 μm/year) versus −0.73 μm/year (range, −0.97 to −0.48 μm/year), respectively ($P = 0.013$). Both better baseline MD and higher mean IOP also were associated significantly with faster RNFL thickness loss over time.

Figure 3 shows the distribution of rates of RNFL loss of progressing eyes and fellow eyes of progressing patients as well as of the control eyes during follow-up. Figure 4 shows an example of a patient included in the study whose right eye showed progression on GPA and had a rate of RNFL thickness change of −2.25 μm/year. The left eye did not show progression on GPA or optic disc stereophotographs; however, this eye had a rate of RNFL loss of −2.75 μm/year, which was even faster than that of the right eye.

Discussion

This study found that a substantial proportion of the fellow eyes of patients showing unilateral progression by conventional methods had significant decline of RNFL thickness over time. When adjusted for confounding factors, the mean rate of global RNFL loss in the fellow eyes of patients showing unilateral progression was −1.21 μm/year

compared with −0.73 μm/year for the eyes of patients who did not show progression by conventional methods in either eye. Almost half of the fellow eyes of patients with unilateral progression by conventional methods showed statistically significant progression by SD OCT. This finding may have significant implications for clinical practice because it suggests that the contralateral eye of some patients with apparent unilateral progression also may have progressive

Table 3. Results of the Random Coefficient Model Investigating Rates of Change in Global Retinal Nerve Fiber Layer Thickness in Control Eyes Compared with the Fellow Eyes of Patients Progressing in 1 Eye

Parameters	Coefficient	95% Confidence Interval	P Value
Time (yrs)	−0.73	−0.97 to −0.48	<0.001
Progression (yes)	−4.78	−9.24 to −0.32	0.036
Progression × time	−0.48	−0.85 to −0.10	0.013
Age at baseline (yrs)	−0.09	−0.10 to 0.02	0.344
Age × time	0.01	0.00–0.04	0.258
MD at baseline (dB)	1.56	1.25–1.87	<0.001
MD × time	−0.09	−0.12 to −0.05	<0.001
IOP (mmHg)	−0.13	−0.41 to 0.15	0.358
IOP × time	−0.03	−0.06 to 0.00	0.034
CCT (per 100 μm thicker)	0.04	0.00–0.07	0.038
CCT × time	0.00	0.00–0.00	0.423
Race (African descent)	3.88	0.03–7.72	0.048
Race × time	−0.20	−0.53 to 0.12	0.219
Gender (male)	−5.62	−9.28 to −1.97	0.003
Gender × time	−0.10	−0.41 to 0.20	0.509
Intercept	93.80	81.72–105.88	<0.001

dB = decibels; CCT = central corneal thickness; IOP = intraocular pressure; MD = mean deviation.

The model adjusted for potential confounding factors and their interactions with time. Progression was assigned the value of 1 if the patient demonstrated progression using Guided Progression Analysis or optic disc stereophotographs in either eye, or a value of 0 if neither eye demonstrated progression using these conventional parameters.

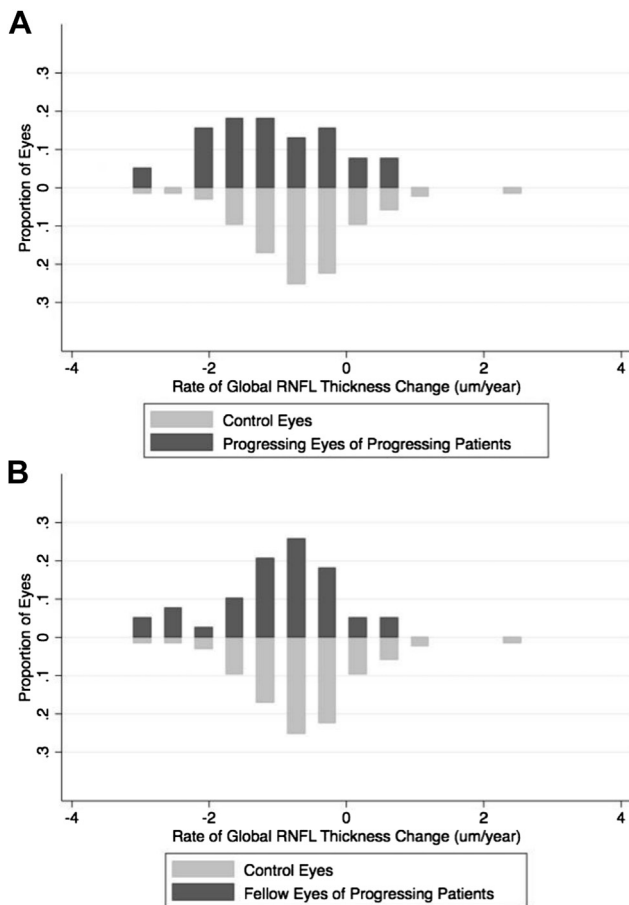


Figure 3. Histograms showing the distribution of rates of change in global retinal nerve fiber layer (RNFL) thickness during follow-up (A) in control eyes compared with progressing eyes of progressing patient and (B) in control eyes compared with fellow eyes of progressing patients.

glaucomatous damage, even in the absence of progression using conventional measures.

Although, after adjustment for confounding variables, we found that contralateral eyes of patients with unilateral progression by conventional tests had an average rate of RNFL loss of $-1.21 \mu\text{m}/\text{year}$ (Table 3), there was a wide range in rates of RNFL loss in these eyes, varying from $-3.20 \mu\text{m}/\text{year}$ to $0.52 \mu\text{m}/\text{year}$. Therefore, some fellow eyes actually were progressing very quickly, despite absence of progression on conventional tests. Conversely, some contralateral eyes of patients with unilateral progression had slow rates of change in RNFL thickness, with rates similar to that of control eyes (Fig 3B). It is important to differentiate eyes experiencing fast and slow rates of RNFL loss because previous studies have shown that faster rates of RNFL thinning are associated with an increased risk of future visual field progression.^{11,12} Evaluation of rate of RNFL loss therefore may be a useful parameter for discriminating eyes at higher risk of progression to functional impairment or blindness that may benefit from more aggressive and earlier treatment escalation.

When measuring rates of change in either structural or functional indices it is important to consider the stage of

disease. In more advanced glaucoma, a floor may be reached in structural or functional measurements, and as this floor is approached, the rate of change is likely to decrease. In this study, fellow eyes had thicker RNFL at baseline than eyes progressing on GPA or stereophotographs (79 vs. $70 \mu\text{m}$; $P = 0.004$). Moreover, the coefficient for $\text{MD} \times \text{time}$ in Table 3 also denoted that for every 1-decibel better MD, the rate of RNFL thickness change was $0.09 \mu\text{m}/\text{year}$ faster. Therefore, we infer that the so-called room for fellow eyes to decrease in RNFL thickness is larger than that of eyes already showing progression on GPA or stereophotographs. This may explain why the average rate of change in RNFL thickness in the fellow eyes actually was somewhat faster than in eyes progressing by conventional methods.

Previous studies also have examined rates of change in RNFL thickness in glaucoma,^{10,11,21} and the slope for the progressing eyes in the current study ($-0.89 \mu\text{m}/\text{year}$) was similar. Studies using time-domain OCT¹⁰ in a mixed population of glaucoma patients and glaucoma suspects have reported RNFL losses of $-0.72 \mu\text{m}/\text{year}$. Using SD OCT, Miki et al¹² found a faster rate of RNFL loss in patients showing progression on SAP, with losses of $-2.02 \mu\text{m}/\text{year}$, which was a faster rate than that of progressing patients in the current study. This is not surprising because their study included only glaucoma suspects, which may imply more room for RNFL thickness to decrease.

Retinal nerve fiber layer thickness is known to decrease with age, with a recent longitudinal study of healthy subjects reporting a $-0.52 \mu\text{m}/\text{year}$ decrease in RNFL thickness using Cirrus SD OCT.²³ The control eyes in our cohort had faster rates of RNFL loss than would be expected with normal aging, losing on average $0.71 \mu\text{m}/\text{year}$, which may support the hypothesis that some of these control eyes actually had glaucomatous progression that had not yet resulted in detectable changes by conventional methods. Future longitudinal follow-up in a cohort of these eyes is needed to clarify the hypothesis. This rate was similar to that reported by Miki et al¹² ($-0.82 \mu\text{m}/\text{year}$) and Sung et al²⁴ ($-0.90 \mu\text{m}/\text{year}$) for control eyes in glaucoma suspects and patients with advanced glaucoma, respectively.

It is important to consider the influence of possible confounding factors on rates of RNFL loss. Better baseline SAP MD was associated significantly with faster rates of RNFL thinning ($P < 0.001$). This observation may have been the result of eyes with more advanced disease receiving more aggressive treatment or of having RNFL thicknesses closer to the floor of OCT measurements, as previously discussed. Higher mean IOP during follow-up also was associated significantly with faster rates of RNFL loss ($P = 0.034$). In contrast, age, race, gender, and central corneal thickness were not associated with the rate of RNFL losses.

These results should be interpreted in the context of some limitations. First, because SD OCT is a relatively new technology, the study had a relatively short follow-up period. With longer follow-up, additional patients may have shown progression on conventional parameters, which may have influenced average rates of change between groups. However, a potential advantage of SD OCT is that it

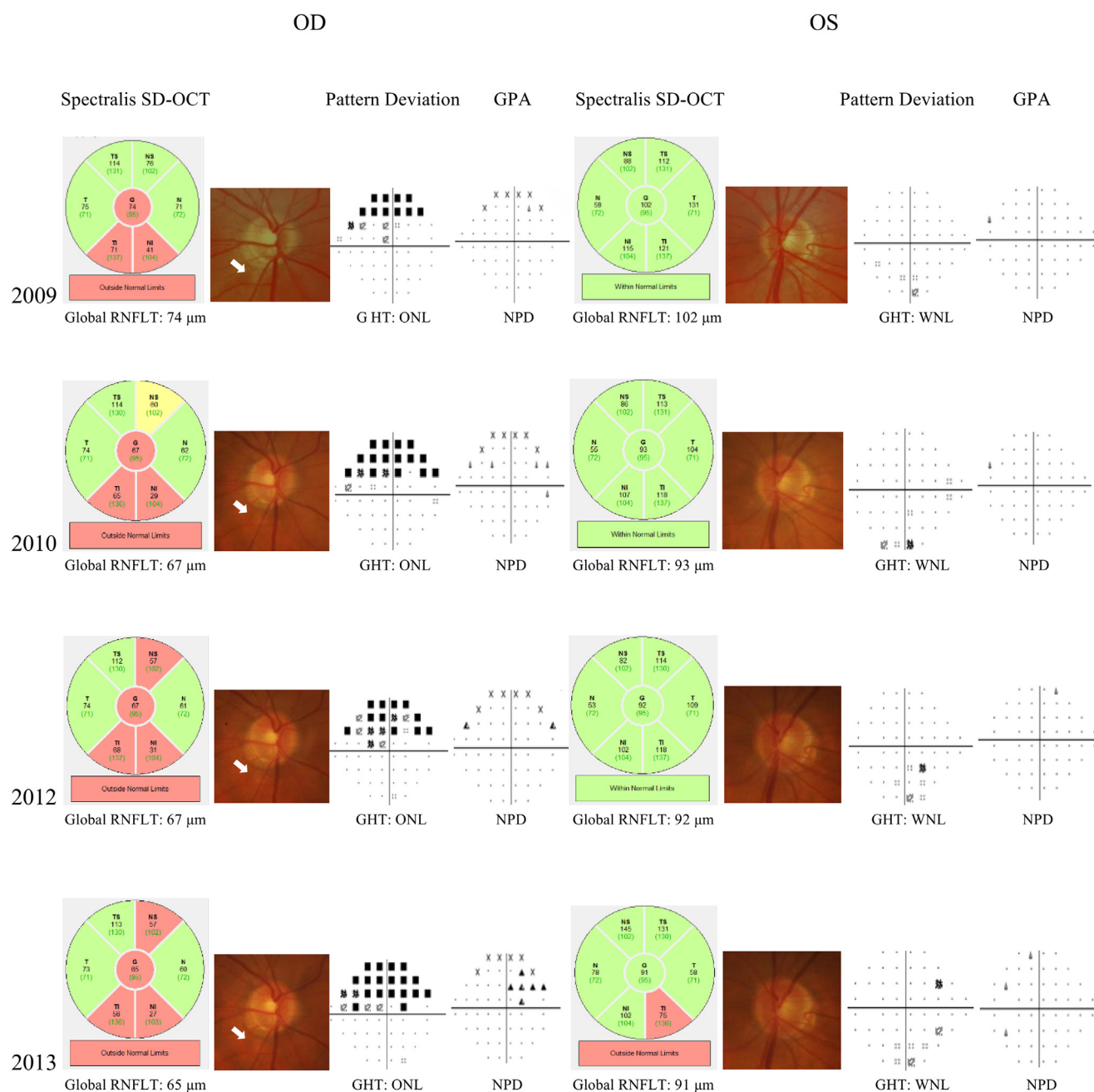


Figure 4. Example of a patient included in the study with progression by Guided Progression Analysis (GPA) in the right eye (OD). The fellow eye (left eye [OS]) showed no progression by conventional parameters; however, spectral-domain optical coherence tomography (SD OCT) showed a significant slope of change in global retinal nerve fiber layer thickness (RNFLT) during follow-up in the fellow eye (OS). GHT = glaucoma hemifield test; NPd = no progression detected; ONL = outside normal limits; WNL = within normal limits.

may allow earlier detection of change and hence shorten the duration of follow-up needed to determine whether an eye is progressing. Despite this, it would be interesting to see whether the fellow eyes with fast rates of change in global RNFLT thickness did indeed demonstrate visual field end points with further follow-up. Another limitation of this study was the relatively small sample size, which limited the power to evaluate the effect of some possible confounding

variables on the rate of global RNFLT thinning. Furthermore, the relationship between measurements from structural and functional tests in glaucoma is complex and not fully understood. It is possible that some eyes show progression on visual field indices such as GPA without evidence of progressive RNFLT loss, and for this reason, a combination of structural and functional assessments is likely to be needed to provide optimal detection of progression.^{24–27}

In conclusion, this study showed that RNFL thickness loss occurs in a substantial number of the contralateral eyes of patients with glaucoma showing unilateral progression by conventional methods. These findings indicate that assessment of RNFL thickness by SD OCT may detect progressive glaucomatous damage that is not detected by visual fields or optic disc stereophotography. Because damage from glaucoma is irreversible, prevention of visual impairment depends on identification of progression at an early stage. When one eye is noted to have progressive optic disc or visual field changes, our results suggest that the other eye also may be progressing.

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Abbreviations and Acronyms:

CI = confidence interval; **D** = diopter; **GPA** = Guided Progression Analysis; **IOP** = intraocular pressure; **MD** = mean deviation; **OCT** = optical coherence tomography; **RNFL** = retinal nerve fiber layer; **SAP** = standard automated perimetry; **SD** = spectral-domain.

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