Evaluation of Retinal Nerve Fiber Layer Progression in Glaucoma: A Study on Optical Coherence Tomography Guided Progression Analysis

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Purpose. To evaluate optical coherence tomography (OCT) retinal nerve fiber layer thickness (RNFLT) measurement for glaucoma progression analysis.

Methods. One hundred sixteen eyes of 64 patients with glaucoma who were observed within a period of 5 years were included. All eyes had at least four serial RNFL measurements obtained with the Stratus OCT (Carl Zeiss Meditec, Dublin, CA) and with the first and last measurements separated by at least 3 years. Visual field (VF) testing was performed on the same day as RNFL imaging. Serial average RNFLTs were evaluated with guided progression analysis (GPA). VF progression was assessed with trend analysis of the visual field index (VFI). Factors associated with the rate of change in RNFLT were examined with a linear mixed model.

Results. A total of 1101 OCT scans and 1029 VFs were analyzed. Twenty-one and 22 eyes had progression according to RNFL and VF measurements, respectively, and 3 eyes had progression according to both measurements. The rate of change in VFI and RNFLT ranged between −0.5% and −7.2% per year (median loss, −3.0%/y) and between −1.2 and −15.4 μm per year (median loss, −3.3 μm/y), respectively. The sector at seven o'clock (right eye orientation) was the most frequent location that showed progression. A greater baseline RNFLT was associated with an increased rate of reduction of RNFLT ($P = 0.034$).

Conclusions. OCT GPA offers a new approach to augment glaucoma progression analysis. The rate of RNFLT thinning was variable among patients with glaucoma, with an increased rate of loss in patients with a higher baseline RNFLT. (*Invest Ophthalmol Vis Sci.* 2010;51:217–222) DOI:10.1167/iovs.09-3468

Monitoring disease progression is essential for the management of patients with glaucoma. Although progressive narrowing of the neuroretinal rim and thinning of the retinal nerve fiber layer (RNFL) are indicative of glaucoma progression, attention has been focused more on the optic disc, rather than the RNFL. The structural endpoint in major clinical trials, such as the Ocular Hypertension Treatment Study and the Early Manifest Glaucoma Trial, was based on changes in the optic disc, but not in the RNFL.[1,2] Although several algorithms have been devised to analyze temporal changes in optic disc topography, a validated method for serial analysis of RNFL thickness has not been available. There has been only one study reporting longitudinal RNFL measurement in patients with glaucoma obtained with the prototype optical coherence tomography (OCT).[3]

Approved by the U.S. Food and Drug Administration in 2002, the Stratus OCT (Carl Zeiss Meditec, Dublin, CA) is widely used for measurement of the thickness of the RNFL. A new RNFL progression analysis algorithm, guided progression analysis (GPA), has been introduced recently in the Stratus OCT software (ver. 5.0). In contrast to an event-based analysis in which progression is detected as changes fall below a preset "threshold" compared with baseline, the OCT GPA is a trend-based analysis with progression evaluated and reported as change over time in serial RNFL measurements. The association between average RNFL thickness and age is evaluated with linear regression analysis. The slope of the regression line represents the rate of change in RNFL thickness and is expressed in micrometers per year. In this longitudinal study, we evaluated the performance of OCT GPA in detecting the progressive reduction of RNFL thickness in patients with glaucoma.

Methods

Subjects

One hundred sixteen eyes of 64 patients with glaucoma who were followed up during the period from June 2003 to May 2009 were included. Each eye had at least four serial RNFL measurements, and the first and last measurements were separated by at least 3 years. At the baseline examination, all subjects underwent a full ophthalmic examination including visual acuity, refraction, intraocular pressure measurement with Goldmann tonometry, gonioscopy, and fundus examination. The inclusion criteria were best corrected visual acuity of not worse than 20/40, and spherical refractive error within the range of −10.0 to + 6.0 D with less than 5.0 D of cylinder. Individuals were excluded if they had a history of any retinal disease, surgical or laser procedures on the retina, diabetes mellitus, or neurologic diseases. Eligible subjects were then followed up and managed at the discretion of the attending ophthalmologist. All of them had narrowing of the neuroretinal rim and/or thinning of the RNFL evident in clinical examination, with corresponding visual field defects. The study was conducted in accordance with the standards of ethics stated in the Declaration of Helsinki and was approved by the local clinical research ethics committee with informed consent obtained.

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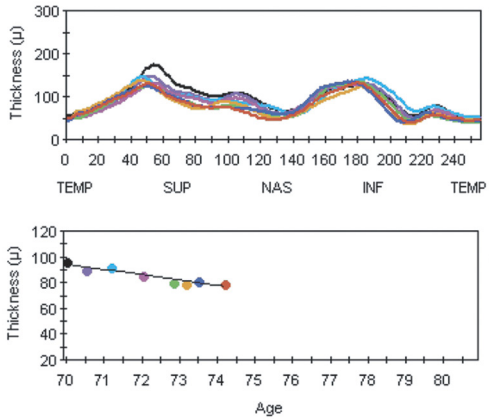
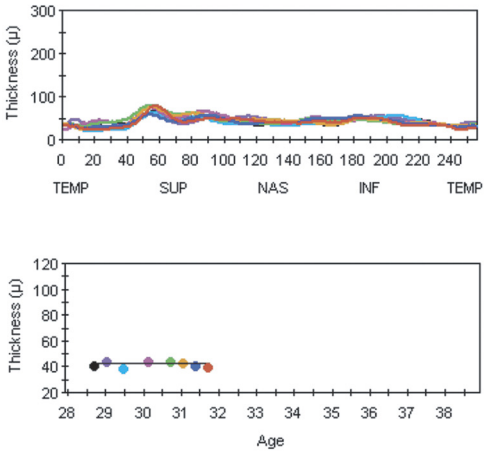
(a)



OD	SS,Q	AVG	SUP	INF
2/3/2004 3:34:03 PM (N=3)	9	95.86	130.00	99.00
8/13/2004 4:41:57 PM (N=3)	7	90.43	114.00	101.00
4/25/2005 2:20:19 PM (N=3)	8	92.18	112.00	111.00
2/16/2006 10:09:23 AM (N=3)	7	85.47	105.00	95.00
12/1/2006 10:34:41 AM (N=3)	7	80.57	99.00	96.00
4/2/2007 10:49:41 AM (N=3)	8	79.54	100.00	84.00
8/2/2007 11:21:04 AM (N=3)	8	81.60	99.00	90.00
4/7/2008 11:50:54 AM (N=3)	7	78.61	98.00	89.00

Rate of change: -4.171 +/- 1.267 µ/year*
Statistically significant P < 0.1%, seek clinical correlates

(b)



OS	SS,Q	AVG	SUP	INF
9/30/2005 11:33:33 AM (N=3)	9	41.12	50.00	42.00
1/27/2006 11:59:17 AM (N=3)	9	44.28	45.00	49.00
6/2/2006 2:12:05 PM (N=3)	10	39.57	47.00	48.00
2/9/2007 10:11:25 AM (N=3)	9	44.84	57.00	43.00
9/25/2007 9:48:42 AM (N=3)	10	44.45	60.00	41.00
1/21/2008 12:57:19 PM (N=3)	9	43.22	56.00	41.00
5/20/2008 12:45:33 PM (N=3)	10	41.76	48.00	46.00
9/26/2008 1:27:13 PM (N=3)	10	40.64	50.00	42.00

Rate of change: -0.009 +/- 1.775 µ/year*
Statistically not significant P > 5%

FIGURE 1. Optical coherence tomography GPA printouts (ver. 5.0) showing the overlay of serial RNFL thickness profiles and the linear regression analysis of average RNFL thickness against time (age) in two patients with glaucoma, one with (**a**) and another without (**b**) a significant trend of progression. The date and time, signal strength, and average, superior, and inferior RNFL thicknesses are shown in the table (*right*). The rate of change was calculated and expressed in micrometers change per year with a probability.

Visual Field Testing

Standard visual field testing was performed with static automated white-on-white threshold perimetry (SITA Standard 24-2, Humphrey Field Analyzer II; Carl Zeiss Meditec) during the same visit when the RNFL thickness was measured. A visual field test result was defined as reliable when fixation losses were less than 33%, and false-positive and -negative rates were less than 25%. Only reliable tests were included in the analysis. A visual field defect was defined as having three or more significant ($P < 0.05$) nonedge contiguous points with at least one at the $P < 0.01$ level on the same side of the horizontal meridian in the pattern deviation plot, classified as outside normal limits in the glaucoma hemifield test and confirmed in at least two consecutive visual field tests.

Visual field progression was evaluated with linear regression analysis between visual field index (VFI) and age. VFI is an age-corrected index with a range from 0 to 100 calculated based on the pattern deviation probability map and the total deviation plot.[4]

OCT RNFL Imaging

The pupils were not routinely dilated during RNFL imaging. However, dilation with tropicamide and phenylephrine (0.5% each) was performed when the pupil size was too small to obtain images with the required quality. All the scans were checked for proper centration and RNFL segmentation. Images with poor centration, incorrect segmentation, poor focus, or missing data were detected by the operator at the time of imaging, with rescanning performed in the same session.

Optical Coherence Tomography

Optical coherence tomography was performed with the Stratus OCT (Carl Zeiss Meditec Inc.) and analyzed with software version 5.0. The calibration of our OCT is checked regularly by the manufacturer's technicians, as recommended. Each subject underwent RNFL scanning with the fast RNFL (3.4; 256 A-scans) protocol. The RNFL with its high reflectivity signal can be visualized as the first layer in red on the scan. Its thickness is determined by the difference in distance between the vitreoretinal interface and a posterior border based on a predefined reflectivity signal level. The RNFL thickness was reported in the analysis printout after averaging the results of three sequential circular scans. All the images obtained had a signal strength of at least 6. Six RNFL scans from six visits were excluded because of suboptimal signal strength.

At least four visits are necessary to generate the GPA report. The GPA overlays serial RNFL thickness profiles and performs linear regression analysis of average RNFL thickness against the duration of follow-up (Fig. 1). The current version of the software does not provide progression analysis on clock hour RNFL measurements. Clock hour RNFL changes over the follow-up period were evaluated by exporting individual clock hour sector RNFL thicknesses from each visit for each eye to a computer for linear regression analysis against age.

Three RNFL trend analysis strategies were evaluated: GPA (average RNFL thickness), GPA (two adjacent clock hours), and GPA (any clock hour). For GPA (average RNFL thickness), progression was defined when a significant negative slope ($P < 0.05$) was found in the linear regression analysis between average RNFL thickness and age. GPA (two adjacent clock hours) and GPA (any clock hour) were designed to

detect localized RNFL loss. For GPA (two adjacent clock hours), progression was defined when significant negative slopes were observed in the linear regression analysis between two adjacent clock hour RNFL thicknesses and age. GPA (any clock hour) has less stringent criteria. Progression was defined when there was a significant negative slope in the linear regression analysis between RNFL thickness at any clock hour and age. Right eye orientation was used for documentation of clock hour measurements with 12 o'clock corresponding to the superior region, 3 o'clock corresponding to the nasal region, 6 o'clock corresponding to the inferior region, and 9 o'clock corresponding to the temporal region in both eyes.

Statistical Analysis

Statistical analyses were performed with commercial software (SPSS ver. 15.0; SPSS Inc, Chicago, IL and Stata ver. 10.0; StataCorp., College Station, TX). Linear regression analyses were performed between RNFL measurements and age. The slope of the regression equation represents the rate of change in RNFL thickness. The coefficients of determinations (R^2) were computed. A linear mixed model of average RNFL thickness was fitted with fixed coefficients (fixed effects) on baseline RNFL thickness, duration at follow-up, spherical error, age, signal strength, and the interaction between baseline RNFL thickness/age/spherical error and follow-up duration and with random intercepts and coefficients (random effects) at both the subject and eye levels (each eye nested within subject) for the effect of time (i.e., follow-up duration). A total of 1101 OCT measurements were included in the model.

Lacking a reference standard, the specificities of the GPA strategies and trend analysis of visual field mean deviation (MD) were determined by a proxy measure of specificity.[5] Assuming that a significant increase in VFI/RNFL thickness does not occur over time in healthy or glaucomatous eyes, a significant positive trend in the linear regression analysis between VFI/RNFL thickness and age would indicate the presence of a false-positive result. The specificity was then estimated by the proportion of eyes demonstrating no significant improvement. The Wilson score method of asymptotic variance was used to calculate the 95% confidence interval (CI) of the estimated specificity.[6] $P < 0.05$ was considered statistically significant in all the analyses.

Results

A total of 116 eyes of 64 patients with glaucoma with 1101 OCT scans and 1029 visual field test results were analyzed. The average number of OCT scans and visual field tests for each eye was 9.5 and 8.9, respectively, with a median follow-up interval of approximately 4 months. The follow-up duration ranged between 3.0 and 5.2 years. Table 1 presents the demographic, visual field, and RNFL measurements. The mean age (SD) was 53.6 (15.4) years. The respective baseline visual field MD and average RNFL thickness were −8.17 ± 7.83 dB (range, 2.02 to −30.62dB) and 77.66 ± 19.58 μm (range, 34.3 to 124.0 μm). There were significant differences between baseline and final MD and average RNFL thickness measurements ($P < 0.001$). The frequency distributions of the baseline visual field MD and average RNFL measurements are shown in Figure 2.

Trend Analysis of VFI

Twenty-two eyes (17 patients) showed progression by trend analysis of VFI. The rate of change in VFI ranged between −0.5% and −7.2% per year (median loss of −3.0% per year). Three of the 22 eyes had concurrent progression by GPA (average RNFL thickness; Fig. 3).

Trend Analysis of Average RNFL Thickness

The GPA (average RNFL thickness) detected 21 (18.1%) eyes of 19 subjects with progression. The rate of change in average RNFL thickness ranged between −1.2 and −15.4 μm per year (median loss, −3.3 μm/y). When the baseline RNFL thickness was used as a reference (100%), the proportional loss of RNFL thickness ranged between 1.8% and 12.4% per year (median loss, 3.8% per year). The median coefficient of determination was 0.582, with a range between 0.393 and 0.829.

Table 1. Demographics, Visual Field, and OCT RNFL Measurements

Demographics	
Subjects, *N*	64
Eyes, *N*	116
Sex (female/male)	27/37
Age, y	53.6 ± 15.4
Spherical error, D	−1.4 ± 3.7
Visual field measurement	
Visual field tests, *N*	1029
Average visual field tests per eye, *n*	8.9 ± 2.6
Median visual field test duration, m	4.07
Baseline MD, dB	−8.17 ± 7.83
Baseline PSD, dB	6.53 ± 4.70
MD at final visit, dB	−9.18 ± 8.16*
PSD at final visit, dB	6.79 ± 4.56†
OCT-RNFL measurements	
OCT tests, *N*	1101
Average OCT tests per eye, *n*	9.5 ± 1.6
Median OCT test duration, m	4.17
Baseline average RNFL thickness, μm	77.66 ± 19.58
Average RNFL thickness at final visit, μm	73.75 ± 19.37*

* $P < 0.001$, linear mixed model with adjustment of fellow eyes for the same subject.

† $P = 0.060$, linear mixed model with adjustment of fellow eyes for the same subject.

Trend Analysis of Clock Hour RNFL Thicknesses

GPA (two adjacent clock hours) detected 22 (19.0%) eyes (20 patients) with progression and 14 of them (12 patients) were also identified by GPA (average RNFL thickness; Fig. 4). A total of 56 eyes (48.3%; 42 patients), including the 20 eyes identified by GPA (average RNFL thickness), had progression by GPA (any clock hour; Fig. 4). Figure 5 shows the frequency distribution of clock hour RNFL measurements that had a significant negative trend (progression) and a positive trend (improvement). Seven o'clock was the most frequent location that showed progression (18 eyes; 15.5%). One eye showed improvement at this clock hour. Eleven of the 18 eyes at 7 o'clock also showed progression by GPA (average RNFL thickness). Among the 56 eyes that showed progression in at least one clock hour, 45 of them had fewer than four clock hours that showed progression (localized loss) whereas only 5 eyes showed progression in more than six clock hours (diffuse loss).

Estimation of Specificity of OCT GPA

Table 2 shows the estimated specificity for average and clock hour RNFL trend analysis. The specificity of GPA (average RNFL thickness) was 97.4% (95% CI, 92.7%–99.3%). GPA (two adjacent clock hours) and GPA (any clock hour) had specificities of 94.8% (95% CI, 89.2%–97.6%) and 78.4% (95% CI, 70.1%–85.0%), respectively.

Predictors of Rate of Change in RNFL Thickness

In the linear mixed model, the coefficient of the interaction term between baseline average RNFL thickness and duration at follow-up was negative (−0.026, $P = 0.034$; Table 3), indicating that the baseline average RNFL thickness was negatively associated with the rate of reduction of RNFL thickness. For example, a baseline RNFL measurement of 100 μm would have an RNFL thickness reduction of approximately 100 × 0.026 × 1 = 2.6 μm per year. No association was found between the rate of change in RNFL thickness and refraction ($P = 0.651$) and age ($P = 0.751$) in the linear mixed model.

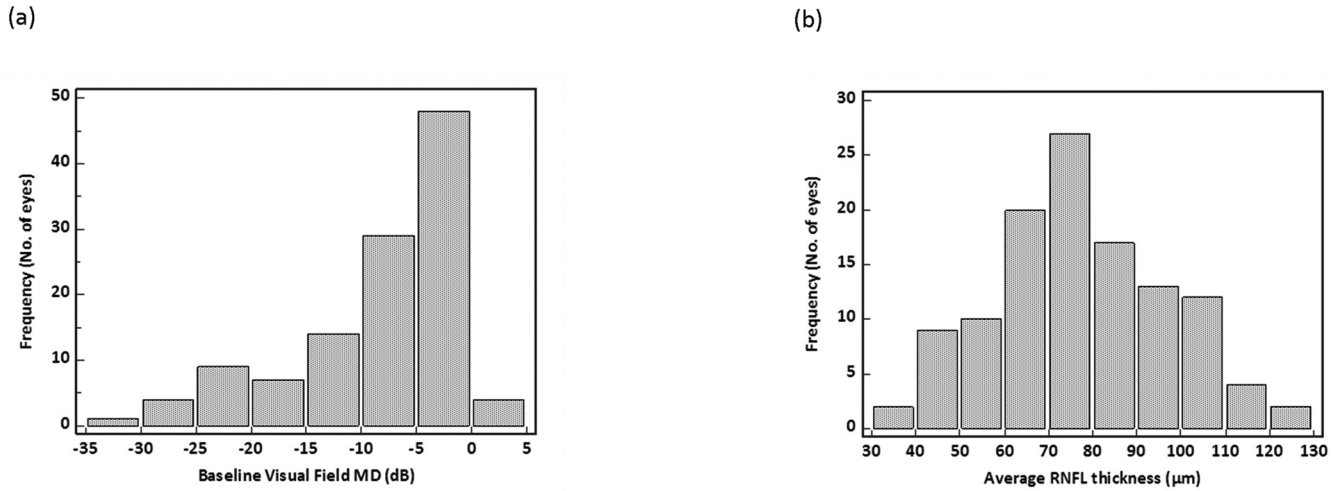


FIGURE 2. Frequency distribution profile of baseline visual field MD (**a**) and baseline average RNFL thickness (**b**).

DISCUSSION

In this longitudinal study, we demonstrate the use of trend analysis of serial global and clock hour RNFL measurements obtained with Stratus OCT (GPA) for evaluation of glaucoma progression. At a comparable level of specificity, GPA (average RNFL thickness) and trend analysis of VFI had a poor agreement for detection of progression. Localized reduction of RNFL thickness was common, and 7 o'clock, which corresponds to the inferotemporal sector, was the most frequent location that showed progression. Measuring the rate of change in RNFL thickness would serve as a new paradigm for observing and managing patients with glaucoma.

There has been only one study reporting the use of serial OCT measurement of RNFL thickness for evaluation of glaucoma progression,[3] although longitudinal studies on GDx measurement were recently available.[7,8] Using a prototype optical coherence tomograph with a scanning speed of 40 A-scan per second, Wollstein et al.[3] studied RNFL progression with an event-based approach. They defined progression as thinning of average RNFL thickness of at least 20 μm, which was calculated based on doubling the reproducibility error of the prototype OCT (10 μm). In that study, 37 patients with glaucoma and or suspected glaucoma (64 eyes) were followed up for a median of 4.7 years. Of those eyes, 22% were found to have progression by OCT compared with only 9% by visual field MD. In a recent study, we reported that the longitudinal variability (reproducibility coefficient) of Stratus OCT average RNFL thickness was 11.7 μm.[9] Although a reduction of average RNFL thickness more than the instrument measurement variability could be considered as progression (an event-based approach), the trend-based analysis is the only method that can quantify the rate of change.

In this study, 18.1% (21 eyes of 19 patients) and 19.0% (22 eyes of 20 patients) of glaucomatous eyes were detected as showing progression by GPA (average RNFL thickness) and GPA (two adjacent clock hours), respectively. GPA (two adjacent clock hours) detected eight additional eyes with progression not detected by GPA (average RNFL thickness; Fig. 4), at a comparable level of specificities [94.8%; 95% CI, 89.2%–97.6% and 97.4%; 95% CI, 92.7%–99.3%, respectively]. This result indicates that localized loss of RNFL may not always be reflected by a detectable change in the average RNFL thickness. Analyzing both average and clock hour RNFL thicknesses is important in maximizing the detection of progression. Although GPA (any clock hour) detected even more progression events (56 eyes, 48.3%), it is difficult to compare the relative performance of GPA (average RNFL thickness), GPA (two adjacent clock hours), and GPA (any clock hour) without a reference standard. Functional progression with visual field test cannot be used as a reference standard for structural progression with RNFL measurement, because it has been well recognized that the agreement between progression by visual field and progression by optic disc is poor,[3,5] which in part could be related to the fact that the time frame for structural

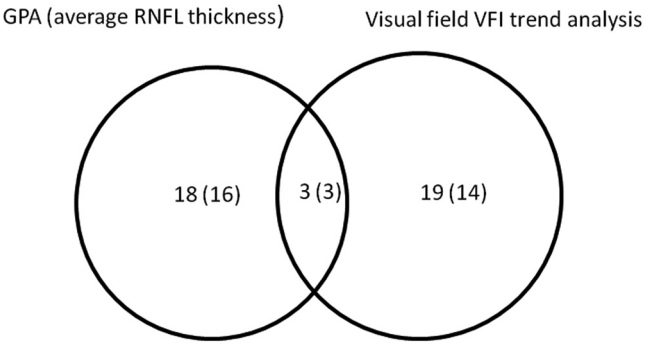


FIGURE 3. A Venn diagram comparing the number of eyes with progression by GPA of the average RNFL thickness and trend analysis of VFI. The number of subjects is shown in brackets.

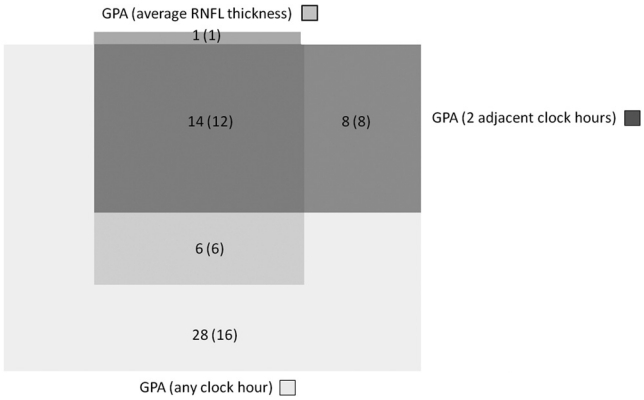


FIGURE 4. A proportional rectangular diagram comparing the number of eyes with progression by GPA (average RNFL), GPA (two adjacent clock hours), and GPA (any clock hour). The number of subjects is shown in brackets.

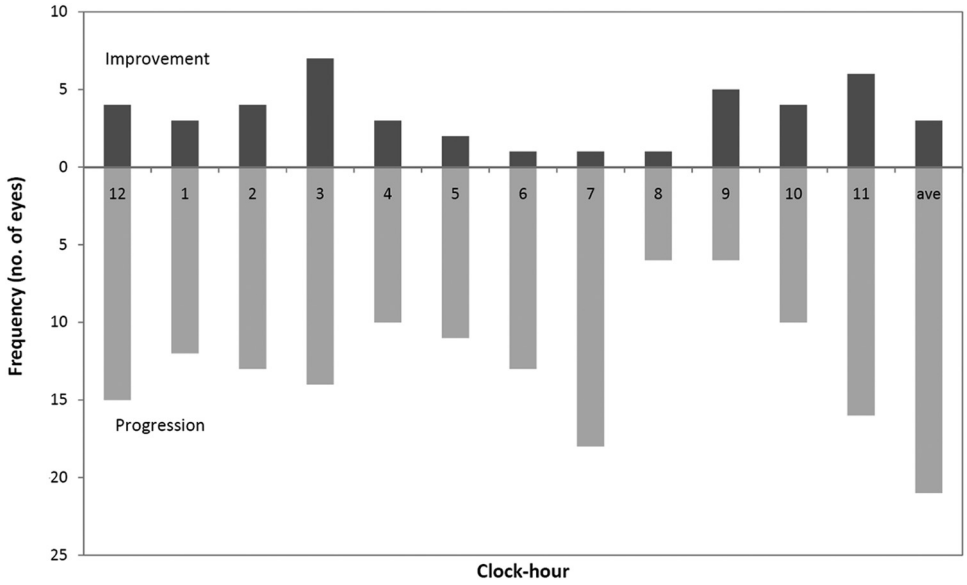


FIGURE 5. Frequency distribution of clock hour retinal nerve fiber layer measurements that showed significant negative trend (progression) and positive trend (improvement).

and functional progression may not be synchronized. Serial optic disc stereophotograph assessment is also a poor reference standard. In a recent study by Jampel et al.,[10] the interobserver agreement in assessing progressive optic disc changes from photographs was shown to be only slight to fair. In addition, 40% of those determined to be progressing were in fact false positives. In the absence of a reference standard, a proxy measure of specificity was estimated in this study to compare the relative performance of GPA (described in the Methods section). The estimated specificity of GPA (any clock hour; 78.4%; 95% CI, 70.1%–85.0%) was significantly lower than those of GPA (average RNFL thickness; 97.4%; 95% CI, 92.7%–99.3%) and GPA (two adjacent clock hour; 94.8%; 95% CI, 89.2%–97.6%). The higher detection rate of GPA (any clock hour) was traded off by a lower specificity.

GPA on individual clock hour revealed that 7 o'clock (inferotemporal sector) was the most frequent location that showed significant progression and the least to show improvement. Although previous studies have already demonstrated high diagnostic sensitivity and specificity for discrimination of glaucomatous from normal eyes using the inferotemporal RNFL measurement,[11,12] it is evident in this study that this location is also important in detecting progressive loss of RNFL thickness over time. It is worth noting that the frequency of progression was lowest in the temporal clock hour sectors (8 and 9 o'clock; Fig. 5). The temporal RNFL, corresponding to the papillomacular bundle, is relatively well preserved along the course of glaucoma progression. This result is in agreement with the observation that patients with glaucoma retain their central vision until the late stage of the disease.

TABLE 2. Estimated Specificity of GPA and Trend Analysis of VFI

	Eyes with Progression (*n*)	Eyes with no Significant Improvement (*n*)	Specificity (%) (95% CI)
GPA (average RNFL thickness)	21	113	97.4 (92.7–99.3)
GPA (two adjacent clock hours)	22	110	94.8 (89.2–97.6)
GPA (any clock hour)	56	91	78.4 (70.1–85.0)
VFI trend analysis	22	115	99.1 (95.3–99.9)

In eyes with progression by GPA (average RNFL thickness), the average RNFL thickness changed at a rate of −1.2 to −15.4 μm/year. These changes were remarkable compared with the estimated age-related decline of RNFL thickness. Budenz et al.[13] showed that for every year's increase in age, the average RNFL thickness measured by Stratus OCT was thinner by 0.21 μm. This value closely matched the estimation by Parikh et al.,[14] (0.16 μm/y) although it is notable that both studies were cross-sectional in study design. The minimum significant change in average RNFL thickness detectable in this longitudinal study was −1.2 μm/y, which exceeds the expected age-related decline and thus probably represents genuine glaucoma progression. Measurement variability of the Stratus OCT could limit its ability to detect minute change. Age-related RNFL reduction within 3 to 5 years (0.5–0.8 μm) is almost negligible. Since most eyes (81.9%, 95/116) did not show progression by GPA (average RNFL thickness), it is unlikely that normal aging effect could be detected with analysis of average RNFL thickness over 3 to 5 years. Further studies are

TABLE 3. Coefficient Estimate of the Linear Mixed Model for Average RNFL Thickness

	Coefficient Estimate	*P*	95% CI
Baseline RNFL thickness, μm	0.950	<0.001	0.911 to 0.989
Duration at follow-up, y	0.350	0.824	−2.733 to 3.433
Spherical error, D	0.111	0.426	−0.162 to 0.384
Signal strength	1.388	<0.001	1.063 to 1.712
Baseline age, y	0.036	0.303	−0.032 to 0.103
Duration at follow-up × baseline age	0.007	0.751	−0.034 to 0.048
Duration at follow-up × baseline RNFL thickness	−0.026	0.034	−0.051 to −0.002
Duration at follow-up × spherical error	−0.039	0.651	−0.208 to 0.130

The average RNFL thickness was fitted with fixed coefficients (fixed effects) for baseline RNFL thickness, duration at follow-up, spherical error, age, signal strength and the interaction between baseline RNFL thickness/age/spherical error and duration at follow-up, and with random intercepts and coefficients (random effects) at both the subject and eye level (each eye nested within subject) for the effect of time (i.e. duration at follow-up).

needed to determine the number of scans required and the minimum rate of change that can be reliably detected by Stratus OCT.

An important finding in this study is that the rate of change in RNFL thickness was related to the baseline RNFL thickness. A greater baseline RNFL measurement was associated with an increased rate of RNFL reduction. This result signifies that progression may be more rapid in early than in advanced disease, in contrast to several studies showing that advanced glaucoma is associated with a higher risk of progression with visual field assessment.[15–17] The apparent discrepancy, in fact, is in agreement with the curvilinear structure–function relationship observed in previous cross-sectional studies, suggesting that progression by RNFL thickness is more noticeable than progression by visual field in early glaucoma whereas progression by visual field is more noticeable than progression by RNFL thickness in advanced glaucoma when visual field measurement is expressed on a decibel scale.[18–20] It is notable that the ability to detect progression may vary considerably between functional and structural tests depending on the stage of disease and the measurement variability of the instruments. The superiority of OCT RNFL measurement in detection of early glaucoma could be related to the relative difference in standard deviations of OCT and visual field measurements.[21] In the early stage of disease, more patients show significant RNFL loss and normal visual field results than those with significant visual field loss and normal RNFL measurement.[21] For this reason, it is not surprising to observe a poor agreement between functional and structural tests in the evaluation of glaucoma progression.

In this study, a trend-based approach was selected for analysis of both functional and structural progression. It has been shown that glaucoma progression analysis with VFI is less affected by cataract and cataract surgery than is trend analysis with visual field MD.[4] Trend analysis of RNFL measurements with GPA is a simple and practical method for detection of localized and diffuse loss of RNFL. It is based on the assumption that progressive loss of RNFL thickness in glaucoma is related linearly with time. Although analysis with a longer follow-up duration is necessary to validate this assumption, the relatively high values of coefficient of determination observed in the trend analyses support that the loss of RNFL thickness was largely linearly progressive during the several years of study.

The study is limited by the lack of a control group that was observed for a duration comparable to the follow-up of the glaucoma group. This lack of a control group would be important in the measurement of the true specificity of OCT GPA. The performance of OCT GPA is influenced by intervisit measurement variability, which is directly related to the consistencies in scan position and signal strength of the image series. In an ideal situation, the same operator should perform all the scans, and the scan position and the signal strength should be kept constant. These conditions, however, are difficult to achieve in a practical setting in a long-term study. In the present study, images with unacceptable signal strength (<6) were excluded. In addition, potential confounding factors including signal strength, spherical error and age were adjusted in the linear mixed model for longitudinal analysis of RNFL thickness. With the availability of spectral domain OCT, RNFL measurement variability could be reduced and the performance for detection of progression would be improved.

In summary, OCT GPA allows detection of localized and diffuse loss of RNFL and measurement of rate of change in RNFL thickness in patients with glaucoma. Measuring the rate of RNFL loss would be important in discerning the course of glaucoma progression, prediction of disease prognosis, and evaluation of treatment response.

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