Original Article

Glaucoma Progression Detection by Retinal Nerve Fiber Layer Measurement Using Scanning Laser Polarimetry: Event and Trend Analysis

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Purpose: To evaluate the use of scanning laser polarimetry (SLP, GDx VCC) to measure the retinal nerve fiber layer (RNFL) thickness in order to evaluate the progression of glaucoma.

Methods: Test-retest measurement variability was determined in 47 glaucomatous eyes. One eye each from 152 glaucomatous patients with at least 4 years of follow-up was enrolled. Visual field (VF) loss progression was determined by both event analysis (EA, Humphrey guided progression analysis) and trend analysis (TA, linear regression analysis of the visual field index). SLP progression was defined as a reduction of RNFL exceeding the predetermined repeatability coefficient in three consecutive exams, as compared to the baseline measure (EA). The slope of RNFL thickness change over time was determined by linear regression analysis (TA).

Results: Twenty-two eyes (14.5%) progressed according to the VF EA, 16 (10.5%) by VF TA, 37 (24.3%) by SLP EA and 19 (12.5%) by SLP TA. Agreement between VF and SLP progression was poor in both EA and TA (VF EA vs. SLP EA, k = 0.110; VF TA vs. SLP TA, k = 0.129). The mean (±standard deviation) progression rate of RNFL thickness as measured by SLP TA did not significantly differ between VF EA progressors and non-progressors (-0.224 ± 0.148 μm/yr vs. -0.218 ± 0.151 μm/yr, p = 0.874). SLP TA and EA showed similar levels of sensitivity when VF progression was considered as the reference standard.

Conclusions: RNFL thickness as measurement by SLP was shown to be capable of detecting glaucoma progression. Both EA and TA of SLP showed poor agreement with VF outcomes in detecting glaucoma progression.

Key Words: Event analysis, Glaucoma, Progression, Scanning laser polarimetry, Trend analysis

Glaucoma is a chronic, progressive optic neuropathy that results in functional visual field (VF) loss. To date, progression detection remains the most difficult aspect of

glaucoma management. Conventionally, standard automated perimetry (SAP) has been used as the clinical standard for determining the progression of glaucoma. SAP is used to identify the subjective light sensitivity threshold, which is used as an indicator for visual function. However, SAP has limitations. In particular, it suffers from measurement variability caused by subjective patient response, and it may not detect glaucomatous change as early as when a structural assessment is used [1-3]. Imaging devices have been suggested as possible diagnostic methods in order to overcome the variability caused by subjective responses. Such instruments offer the possibility of detecting the

progression of glaucoma earlier than can be achieved using SAP, because the techniques involve an assessment of structural loss [4-14].

Scanning laser polarimetry (SLP) is one such imaging device. SLP measures the retinal nerve fiber layer (RNFL) thickness using the birefringent property of the microtubules in the RNFL and has been used worldwide for glaucoma diagnosis. The reproducibility and glaucoma diagnostic capabilities of SLP have been verified in numerous cross-sectional studies [15-19]. A few recent reports have demonstrated the longitudinal glaucoma progression detection capabilities of SLP [9,11-14]. The present study was designed to evaluate and compare glaucoma progression detection as measured by both VF and SLP. Two analytical methods, event analysis (EA) and trend analysis (TA), have traditionally been employed for determining the progression of glaucoma. EA defines progression as a change that exceeds a predefined limit compared to the baseline value, where the limit is generally determined by measurement variability. TA explores change over a designated time period using regression analysis. In the present longitudinal study, we tested glaucoma progression detection as determined by SLP using both EA and TA and compared these findings with VF outcomes.

Materials and Methods

Subjects

We enrolled both control and study patients. Within the control group, 47 glaucoma patients were analyzed to determine the test-retest variability of RNFL thickness measurements obtained by SLP.

One hundred and fifty-two glaucoma subjects evaluated between September 2003 and August 2009 at the glaucoma service of the Asan Medical Center, Seoul, Korea, and who met the inclusion criteria, were enrolled in the study group. None of the subjects enrolled in the control group were included in the study group. The first two VF results were excluded to obviate any learning effects. Baseline data on both VF and SLP testing were separated from those of the last follow-up by at least 4 years. At the initial testing, each participant received a comprehensive ophthalmologic examination, including a review of their medical history, measurement of best-corrected visual acuity (BCVA) so as to confirm that visual acuity was adequate for performance of automated perimetry, slit-lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, dilated funduscopic examination using a 90- or 78-diopter (D) lens, stereoscopic optic disc photography, central corneal thickness measurement (DGH-550; DGH Technology Inc., Exton, PA, USA), VF testing (Humphrey field analyzer [HFA], Swedish Interactive Threshold Algorithm 24-2; Carl Zeiss Meditec, Dublin, CA, USA) and SLP testing (GDx VCC,

Carl Zeiss Meditec). Simultaneous stereoscopic optic disc photographs were reviewed and glaucomatous change was agreed upon by two glaucoma specialists (KRS and MSK).

For inclusion in the study, all participants had to meet the following criteria: BCVA of 20 / 30 or better, with a spherical equivalent within ±5 D and a cylinder correction within +3 D; presence of a normal anterior chamber and open-angle on slit-lamp and gonioscopic examinations; and reliable HFA test results with a false-positive error less than 15%, a false-negative error less than 15% and a fixation loss of less than 20%. Subjects with any other ophthalmic or neurologic condition that could result in VF defects, or with a history of diabetes mellitus, were excluded.

Glaucomatous eyes were defined as those showing glaucomatous VF defects as confirmed by at least two reliable VF examinations and the presence of a glaucomatous optic disc change as agreed upon by the two glaucoma specialists. Eyes with glaucomatous VF defects were defined as those with either a cluster of three points with probabilities of less than 5% on the pattern deviation map in at least one hemifield, including at least one point with a probability of less than 1%, a cluster of two points with a probability of less than 1% and a glaucoma hemifield test result outside the normal limits, or a pattern standard deviation 95% outside of the normal limits. If surgical or laser treatment was performed during the follow-up period, only data obtained in the period before the treatment were analyzed. If both eyes were found to be eligible, one eye was randomly selected. Institutional review board approval was obtained from the Asan Medical Center and the design of this study followed the principles of the Declaration of Helsinki.

Scanning laser polarimetry

SLP images were obtained using the GDx-VCC system. The image acquisition procedure has been described in detail elsewhere [20,21]. Calibration of the system was performed on a regular basis by a technician employed by the manufacturer. All of the accepted images exhibited a centered optic disc, were well-focused with even and adequate illumination, showed no motion artifacts and did not display an atypical birefringent pattern (typical scan score >80 and had a quality score higher than 7). Among the initially analyzed 1,244 images, 97 (7.8%) were excluded because of poor quality, using the criteria described above. The temporal, superior, nasal, inferior, and temporal (TSNIT) average, the superior average and the inferior average RNFL thicknesses were included in progression analysis.

Event analysis of scanning laser polarimetry progression

To define the test-retest variability of SLP measurement, 47 glaucomatous eyes were scanned in 2 different visits

within 1 week by a single well-trained operator using the same device. Measurement reproducibility was assessed by calculating the repeatability coefficient (RC), using the TSNIT average and the superior and inferior average RNFL thicknesses. The RC was calculated as:

$$RC = 2 * \left(\sqrt{\frac{\sum (observation1 - observation2)^2}{n(observations)}} \right)$$

The RC was incorporated in the progression analysis by SLP EA [5,22]. If any change from the baseline measurement exceeded the RC in a negative direction in three consecutive follow-up SLP tests, the eye was considered to show glaucoma progression.

Trend analysis of scanning laser polarimetry progression

Linear regression analysis against participant age was performed using the TSNIT average, as well as the superior and inferior average RNFL thicknesses as measured by SLP. Progression was defined if a significantly negative slope ($p < 0.05$) was observed for each analyzed parameter.

Visual field assessment

VF progression was also determined by 2 methods: EA and TA. For EA, commercial software (HFA guided progression analysis [GPA], Carl Zeiss Meditec) was employed. VF EA progression was defined as a significant deterioration from the baseline pattern deviation at three or more of the same test points on three consecutive examinations [23]. Specifically, we identified VF EA progression if the deterioration of three or more points occurred in the same hemifield. Additionally, the location of VF progression (superior vs. inferior) was determined so as to determine if there was a spatial correlation with SLP sectors that showed progression. The other VF progression criterion was determined with trend-based linear regression analysis using a newly introduced global index, the visual field index. As with SLP TA, a significantly negative slope ($p < 0.05$) indicated VF TA progression.

Statistical analysis

Correlations of progression detection among the different methods used to analyze SLP and VF examination data was tested using Kappa statistics. The sensitivities and specificities of SLP progression were calculated and compared between EA and TA using McNemar's test with reference to progression by VF EA or TA as the standards. The progression rates of the average RNFL thickness, in other words, the slope of RNFL change as assessed by SLP TA with respect to patient age, were compared between VF progressors and non-progressors using an unpaired t-test. The progression rates of the average RNFL thickness assessed by SLP TA were also compared between SLP progressors and non-progressors. All statistical analyses were performed using SAS ver. 9.1 (SAS Inc., Cary, NC, USA) and SPSS ver. 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Table 1 lists the test-retest variability as determined by the RC in average, superior and inferior RNFL thickness measurements of the control group. This group displayed a glaucoma severity level similar to that of the study group (average ± standard deviation [SD] VF mean deviation [MD] of the control group: -4.27 ± 4.4 dB, study group: -4.14 ± 5.4 dB, $p = 0.72$). These RCs for the three parameters were used to define progression in subsequent SLP EA.

The final analysis included 152 eyes of 152 glaucoma patients in the study group. Among these 152 subjects, 72 were men, 80 were women and all were ethnically Korean. The baseline average ± SD age of the study participants was 52.0 ± 16.2 years; VF MD was -4.14 ± 5.4 dB at baseline, compared to -4.61 ± 6.3 dB at the last follow-up visit. The mean follow-up period was 4.99 ± 0.6 years. The number of perimetric examinations analyzed ranged from 5 to 11 (mean, 6.8 ± 1.9). The characteristics of the study participants are described in Table 2.

Twenty-two eyes (14.5%) showed progression when using VF EA, whereas 16 (10.5%) showed progression by VF TA. As measured by SLP EA, 19 eyes progressed in the average RNFL thickness assessment (12.5%), 29 progressed in superior sector thickness (19.1%) and 28 in inferior sector thickness (18.4%). Overall, 37 eyes (24.3%) showed progression in the SLP EA used in the evaluation of average superior, or inferior RNFL thickness. In the SLP TA, 7 eyes progressed in average RNFL thickness (4.6%), 11 in superior sector thickness (7.2%) and 12 in inferior sector thickness (7.9%). Overall, 19 eyes (12.5%) exhibited progression as calculated using SLP TA in average, superior or inferior RNFL thickness. The number of eyes showing progression as determined by SLP and VF are summarized in Table 3.

Among the 37 SLP EA progressors, 8 eyes also progressed according to VF EA, whereas, among the 19 SLP

Table 1. Test-retest measurement variability of scanning laser polarimetry to measure RNFL thickness was determined by a repeatability coefficient in the control group (n = 47)

	Repeatability coefficient (μm)
Average RNFL thickness	5.23
Superior RNFL thickness	6.07
Inferior RNFL thickness	6.78

RNFL = retinal nerve fiber layer.

TA progressors, 3 eyes also progressed as determined by VF EA. Among the 37 SLP EA progressors, 6 eyes also progressed in the VF TA, whereas among the 19 SLP TA progressors, 4 eyes also progressed in the VF TA. Among the 22 progressors by VF EA, 12 eyes did not show progression in either the SLP EA or the SLP TA. Among the 16 progressors using VF TA, 7 eyes did not show progression in either the EA or the TA of SLP. Overall, the agreement between VF and SLP progression was poor in both EA and TA (VF EA vs. SLP EA, k = 0.110, p = 0.155; VF TA vs. SLP TA, k = 0.129, p = 0.110). A Venn diagram il-

lustrating the level of agreement among the four methods (VF EA, VF TA, SLP EA, and SLP TA) is presented in Fig. 1.

Among the 16 superior and inferior hemifields of 8 eyes showing progression by both SLP EA and VF EA, 64 hemifields showed both SLP and VF EA progression in the corresponding sectors. In other words, 10 hemifields showed only VF or SLP progression. Among the 8 superior and inferior hemifields of 4 eyes showing progression by both SLP TA and VF EA, 4 hemifields showed both SLP TA and VF EA progression in the corresponding sectors,

Table 2. Characteristics of the 152 glaucoma subjects in the study group

Variable	Value
Age (yr)	52.0 ± 16.2
Male / female	72 / 80
Mean follow-up period (yr)	4.99 ± 0.6
Baseline visual field data (dB)	
Mean deviation	-4.14 ± 5.4
Pattern standard deviation	4.27 ± 3.8
Baseline retinal nerve fiber layer thickness (μm)	
Average	48.9 ± 9.4
Superior	58.1 ± 13.1
Inferior	55.2 ± 12.6

Values are presented as mean ± SD or number.

Table 3. The number of eyes (%) showing progression by event analysis and trend analysis using scanning laser polarimetry data and visual field assessment

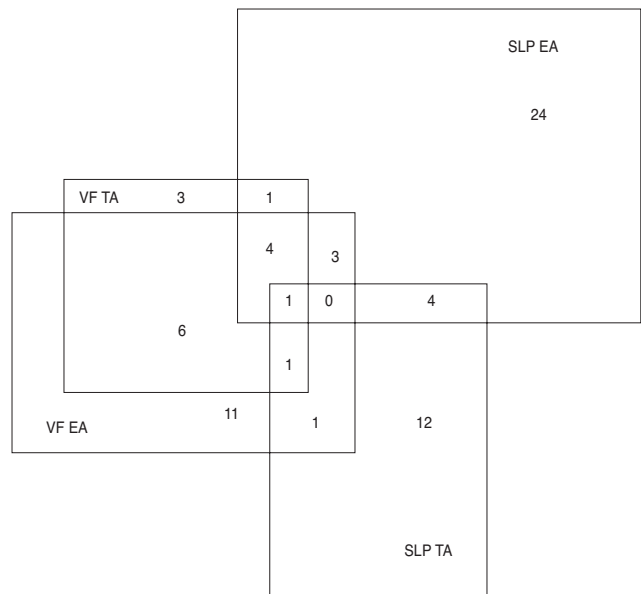|	Event analysis	Trend analysis
Visual field	22 (14.5)	16 (10.5)
Scanning laser polarimetry	37 (24.3)	19 (12.5)

Fig. 1. Venn diagram showing agreement of glaucoma progression detection among the four tested methods (visual field [VF] event analysis [EA], VF trend analysis [TA], scanning laser polarimetry [SLP] EA, and SLP TA).

Table 4. Retinal nerve fiber layer thickness progression rate (μm/yr) of non-progressors and progressors as determined by each of the four different methods

		Non-progressors	Progressors	p-value
VF EA	Average	-0.218 ± 0.151	-0.224 ± 0.148	0.874
	Superior	-0.276 ± 0.183	-0.355 ± 0.177	0.535
	Inferior	-0.315 ± 0.176	-0.326 ± 0.188	0.889
VF TA	Average	-0.209 ± 0.154	-0.300 ± 0.163	0.447
	Superior	-0.266 ± 0.182	-0.474 ± 0.168	0.245
	Inferior	-0.308 ± 0.183	-0.449 ± 0.174	0.545
SLP EA	Average	-0.178 ± 0.135	-0.399 ± 0.142	0.030
	Superior	-0.277 ± 0.174	-0.552 ± 0.156	0.011
	Inferior	-0.256 ± 0.166	-0.554 ± 0.175	0.003
SLP TA	Average	-0.155 ± 0.145	-0.759 ± 0.121	<0.001
	Superior	-0.145 ± 0.172	-1.13 ± 0.133	<0.001
	Inferior	-0.199 ± 0.158	-1.029 ± 0.146	<0.001

VF = visual field; EA = event analysis; TA = trend analysis; SLP = scanning laser polarimetry.

that is, 4 showed only VF or SLP progression.

The progression rates of the average RNFL thickness (i.e., the slope of RNFL change with respect to patient age) as assessed by SLP TA did not differ between VF EA progressors and non-progressors (progressors, -0.224 ± 0.148 μm/yr; non-progressors, -0.218 ± 0.151 μm/yr; $p = 0.874$). The progression rates of superior and inferior RNFL thickness showed similar results. However, as expected, RNFL progression rates were significantly higher in SLP progres-

sors than in non-progressors when assessed by either SLP EA or TA. Comparative results on RNFL progression rates are listed in Table 4.

When VF EA was defined as the reference standard for glaucoma progression detection, the sensitivity of the change in average RNFL thickness as assessed by SLP EA was 36.4%, and specificity was 77.7%. Sensitivity of SLP TA and SLP EA for glaucoma progression detection when both VF EA and VF TA were considered as refer-
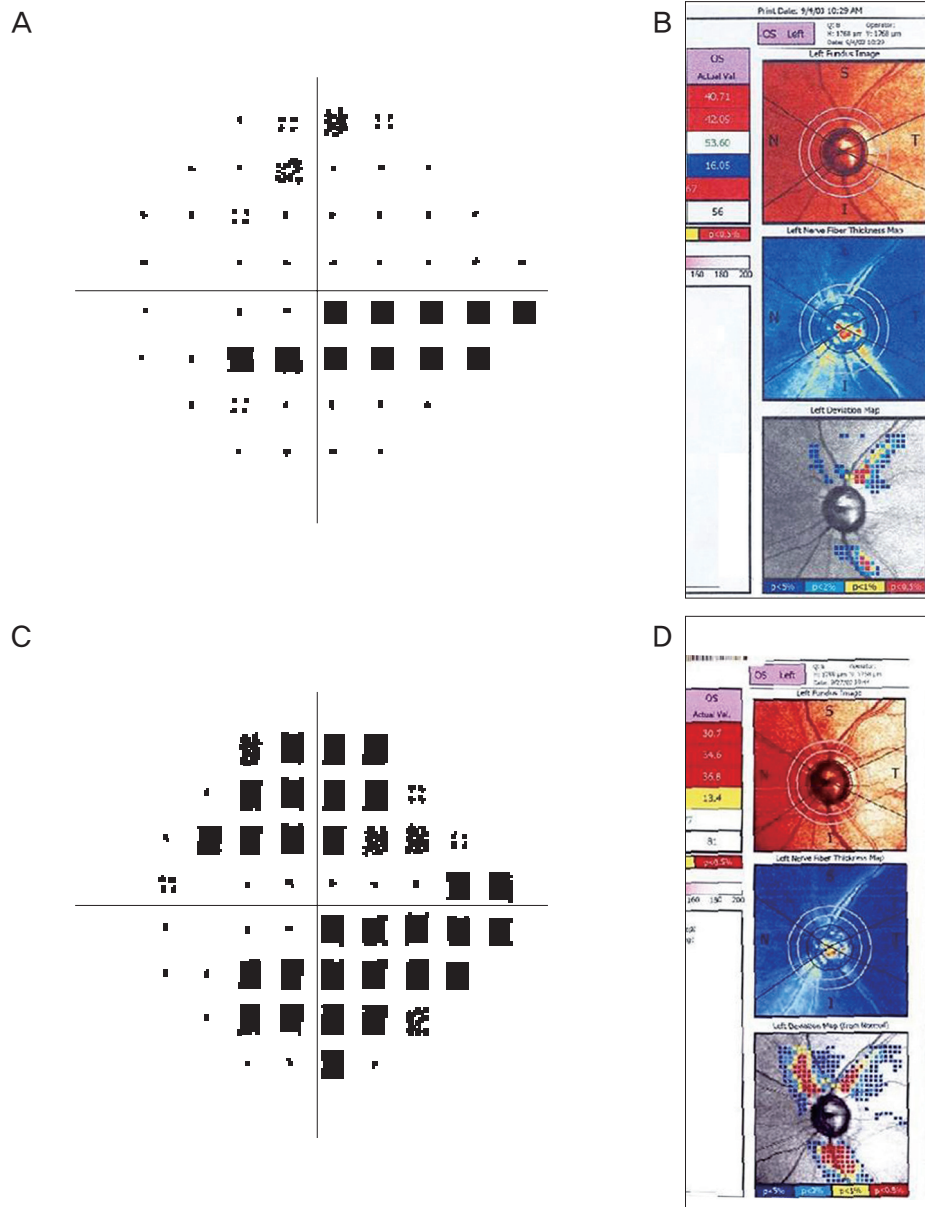

Fig. 2. Clinical example showing visual field (VF) data and scanning laser polarimetry (SLP) retinal nerve fiber layer (RNFL) information in a 54-year old woman with glaucomatous eyes. This patient was a 54-year old woman with open- angle glaucoma and had an inferior VF defect in the left eye at baseline (A). The SLP image showed a thinning of the RNFL where the average RNFL thickness was 40.71 μm (B). After 2 years of follow-up, the average RNFL thickness was significantly reduced to 30.7 μm, D), which corresponded with VF progression (C).

Table 5. Sensitivity and specificity (%) with 95% CI based on SLP EA and SLP TA for glaucoma progression detection determined by VF EA and VF TA

		SLP EA		SLP TA		*p*-value
		Estimate	95% CI	Estimate	95% CI	
VF EA	Sensitivity	36.4	16.3 - 56.5	13.6	0 - 28.0	0.18
	Specificity	77.7	70.5 - 84.9	87.7	82.0 - 93.3	0.047
VF TA	Sensitivity	37.5	13.8 - 61.2	25.0	3.8 - 46.2	0.727
	Specificity	77.2	70.2 - 84.3	89.0	83.7 - 94.2	0.014

CI = confidence intervals; SLP = scanning laser polarimetry; EA = event analysis; TA = trend analysis; VF = visual field.

ence standards was not significantly different. However, the specificity of the SLP TA was significantly higher than that of the SLP EA when both VF EA and VF TA were considered as reference standards (Table 5).

Fig. 2 is a clinical example of VF data and SLP RNFL information. This patient was a 54-year old woman with open- angle glaucoma and an inferior VF defect in the left eye at baseline (A). The SLP image showed a thinning of the RNFL; the average RNFL thickness was 40.71 μm (B). After two years of follow-up, the average RNFL thickness was significantly reduced to 30.7 μm, which corresponded with VF progression (C).

Discussion

Our results indicate that SLP RNFL thickness measurements are capable of revealing glaucoma progression using both EA and TA. The sensitivity of the SLP EA and SLP TA for glaucoma progression detection was not significantly different when VF progression was considered as the reference standard. At the same time, the specificity of the SLP TA for detecting progression was significantly higher than that of the SLP EA in our current analysis. Test-retest measurement variability is frequently used to determine the cut-off value in EA. Thus, the prevalence of progression as assessed by EA is dependent on this value. Using the RC of in-house data as the cut-off value, we demonstrated the capability of SLP RNFL thickness measurement to detect glaucoma progression. It would be ideal if each glaucomatous subject had determined measurement reproducibility at baseline, given that the reproducibility error is potentially different in each individual. Therefore, one potential limitation of the current study is that we used measurement reproducibility derived from a reference data set.

In general, EA requires fewer examinations for detecting progression than TA. EA aims to detect 'change from baseline'. Thus, if only two test results, a baseline test and a follow-up test, are available, EA becomes theoretically possible. However, to confirm that any observed change is real, and not observed by chance because of measurement variability, 2 or 3 follow-up tests are usually employed in clinical practice. We defined progression if 'change from baseline' exceeded the RC in three consecutive follow-up tests. We used three consecutive follow-up tests for confirmation because VF EA is typically confirmed by three consecutive worsening measurements, however, no generally accepted guidelines or consensus on the number of follow-up tests appropriate for confirmation are available. The prevalence of detected progression can of course be affected by the number of follow-up tests applied.

The use of TA generally requires more examinations to obtain a reliable regression slope reflecting significant change (or not), as such slopes can be substantially affected by outliers. However, compared to EA, TA has the advantage of providing progression rates which permit an estimation of how fast glaucoma progression is occurring in a particular patient. Interestingly, RNFL thickness progression rates obtained using SLP TA did not differ significantly between VF non-progressors and progressors. Similar findings were obtained using both VF TA and VF EA data. In the mean time, as expected, the progression rate of RNFL thickness differed significantly between SLP non-progressors and progressors. The finding that the rate of RNFL progression (structural progression) does not significantly differ between VF progressors and non-progressors (functional progression) may suggest a dissociation of glaucoma structural progression from functional progression within the same timeframe. This observation was confirmed by the data in Fig. 1, detailing the poor agreement among the four different progression detection strategies (VF EA, VF TA, SLP EA, and SLP TA). When we searched for regional correspondence of structural and functional progression, fewer than half of the hemifields (in those eyes showing progression by both structural and functional assessment) demonstrated a correspondence between SLP and VF progression data. Such poor agreement between structural and functional progression analyses has also been noted with other imaging devices [4,7,10]. As seen in previous reports using other imaging modalities, including confocal scanning laser ophthalmoscopy and optical coherence tomography [4,7,10], our current work employing SLP also demonstrated poor agreement between SLP- and VF-defined progression assessed during the same follow-up period. As suggested by others, one possible explanation for such poor agreement may be that structural

and functional losses do not occur simultaneously. According to Sommer et al. [2], detectable glaucomatous RNFL loss may occur up to six years before the development of any apparent VF defect. Another possible reason for the disagreement between structural and functional assessment may be the lack of any gold standard defining glaucoma progression in both structural and functional aspects. For example, although VF assessment has long been used as a clinical standard for glaucoma diagnosis, no single method is used to define progression. Therefore, various criteria have been used in the many relevant reports, and consequently, the detection of progression varies greatly according to the criteria employed. Similarly, no gold standard defining structural progression is available. The lack of such standards for each of the two relevant measurements means that patients vary in progression levels from report to report, depending on the criteria employed, thus contributing to difficulties in comparison. Inevitable measurement variability of each modality (structure and function) may also contribute to the poor agreement between structural and functional progression.

Alencar et al. [13] reported that SLP progression detection was of higher sensitivity (50%) than noted in the present report (13.6% to 37.5%). As the cited study used the commercially available GPA software for SLP progression detection and the present study employed in-house reproducibility criteria, direct comparison of the study outcomes may be difficult. However, both analyses found relatively high levels of specificity for SLP in detecting glaucoma progression. Medeiros and associates reported that the rate of decline in RNFL thickness was significantly higher in the progressing group (-0.70 μm/yr), compared to the non-progressing group (-0.14 μm/yr, $p = 0.001$) [12]. The cited authors used VF assessment or optic disc stereophotography as reference standards for progression. The progression rate of the non-progressing group in the cited study was similar to that seen in our SLP non-progressors (-0.155 μm/yr). However, as mentioned earlier, it is difficult to compare studies that vary in design.

Progression detection remains the most difficult aspect of glaucoma diagnosis and it is not easy to find relevant research outcomes. Such problems may have two distinct causes, of which one is the innate nature of the disease. As glaucoma progresses slowly, and the extent of progressive change is hence small, making the detection of minute changes is essential in identifying progression. A device with test-retest reproducibility smaller than these tiny changes is therefore needed. Furthermore, glaucomatous individuals may show progression rates that may not be clearly discriminated from the normal physiological changes, especially considering that a substantial proportion of glaucoma patients are elderly. The other problem is a lack of technology that can detect small glaucomatous changes both reliably and accurately. Several imaging modalities have been suggested as tools for detecting the structural progression of glaucoma [4-13]. However, more advanced and imaginative work may be required prior to the clinical application of such imaging devices.

In conclusion, we explored the progression detection capability of SLP, using in-house measurement variability data in EA. SLP to measure RNFL thickness can be used for glaucoma progression detection. In our analysis, both EA and TA showed similar abilities to detect the progression of glaucoma. As in previous reports using other imaging devices, SLP progression data were in poor agreement with VF progression results.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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