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Detection of Progressive Retinal Nerve Fiber Layer Thickness Loss with Optical Coherence Tomography Using Three Criteria for Functional Progression

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Abstract

Purpose—To compare the rates of retinal nerve fiber layer (RNFL) thickness loss using optical coherence tomography (OCT) in progressing versus non-progressing eyes using four methods to define functional progression.

Methods—Normal and glaucomatous eyes with ≥ 3 years of follow-up were prospectively enrolled. Standard automated perimetry (SAP, SITA Standard 24-2) and OCT (Stratus OCT, Carl Zeiss Meditec, Dublin, CA) imaging were performed every 6-months in glaucomatous eyes. OCT imaging was performed annually in normal eyes. Functional progression was determined using Early Manifest Glaucoma Trial (EMGT) criterion, Visual Field Index (VFI), Progressor™ software, and the 3-omitting method.

Results—76 eyes (46 glaucoma and 30 normal) of 38 patients were enrolled with a mean follow-up of 43.9 ± 5.02 months (range 36–48 months). Eleven eyes progressed using Progressor™ criterion, 5 eyes using VFI, 2 eyes using the 3-omitting method, and 2 eyes using EMGT criterion. The annual rate of average RNFL loss ($\mu\text{m}/\text{year}$) was significantly greater ($p < 0.05$) in progressing vs. non-progressing eyes using Progressor™ (-1.0 ± 1.3 vs. 0.02 ± 1.6), VFI (-2.1 ± 1.1 vs. -0.002 ± 1.4), and the 3-omitting method (-2.2 ± 0.2 vs. -0.1 ± 1.5). Mean rate ($\mu\text{m}/\text{year}$) of average

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and superior RNFL thickness change was similar ($p>0.05$) in non-progressing glaucomatous eyes compared to normal eyes. Using linear mixed-effect models, mean ($p<0.001$) and peak ($p=0.01$) IOP were significantly associated with rate of average RNFL atrophy in glaucomatous eyes.

Conclusions—Despite differences in criteria used to judge functional progression, eyes with SAP progression have significantly greater rates of RNFL loss measured using OCT compared with non-progressing eyes.

Keywords

Optical coherence tomography; glaucoma progression; standard automated perimetry; retinal nerve fiber layer thickness

Introduction

Glaucoma is a progressive optic neuropathy disease characterized by progressive loss of retinal ganglion cells and retinal nerve fiber layer (RNFL) with or without associated visual field loss.¹ Accurate methods for detecting disease progression are therefore essential to monitor patients and evaluate the efficacy of therapy. Established methods for detection of glaucoma progression include longitudinal assessment of visual function using standard automated perimetry (SAP) or optic nerve appearance using clinical examination or optic disc photography. Statistical methods for evaluating glaucomatous visual field progression have evolved considerably, yet criteria for defining progression remains inconsistent in the absence of established standards.²

Optical coherence tomography (OCT, Carl Zeiss Meditec, Dublin, CA) is a high-resolution, micron scale, cross-sectional imaging modality that is based upon interferometry.¹ OCT provides quantitative assessments of the retina and optic nerve by measuring the echo time delay and intensity of backscattered light from posterior segment structures.^{1–3} Good correlation has been reported between peripapillary retinal nerve fiber layer (RNFL) thickness measured by OCT and visual function^{2, 4, 5} as well as histological measurements of RNFL thickness.⁶ Cross-sectional studies have demonstrated that OCT can provide robust discrimination between normal and glaucomatous eyes in a manner similar to other imaging technologies.^{4, 7, 8} OCT may serve as a useful adjunct to optic disc photography to provide complementary information that may facilitate detection of glaucomatous progression^{9–12} using rate-based changes over time since the output data is quantitative and has been demonstrated to be highly reproducible at all stages of the glaucoma continuum.¹³

A recent study by Medeiros et al¹⁰ demonstrated that eyes with progressive glaucomatous optic neuropathy have greater rates of RNFL loss using OCT, compared with non-progressing eyes. We hypothesized that the rate of RNFL loss over time was significantly higher in eyes with functional progression irrespective of the criterion used to define visual field progression. This prospective analysis was designed to examine the rate of RNFL loss using OCT in progressing versus non-progressing eyes using four different criteria to define functional progression.

Patients and Methods

Participants consisted of patients with perimetric glaucoma and normal subjects who were prospectively enrolled in the Advanced Imaging in Glaucoma Study (AIGS). Informed consent was obtained from all subjects using a consent form approved by the Institutional Review Board for Human Research of the University of Miami Miller School of Medicine, which was in agreement with the provisions of the Declaration of Helsinki. Subjects meeting inclusion criteria with a minimum of 36 months of follow-up were selected for review from

one clinical site (Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Palm Beach Gardens, Florida). Both eyes were enrolled if they satisfied the inclusion criteria. Inclusion criteria common to both groups consisted of spherical equivalent refractive error between -7.00 diopters (D) and $+3.00$ D, best corrected visual acuity equal to or better than 20/40, age range between 40 and 85 years, reliable SAP ($<33\%$ rate of fixation losses, false positives, and false negatives) and no prior history of intraocular surgery except for uncomplicated cataract extraction. Subjects with ocular disease other than glaucoma or cataract, best-corrected visual acuity below 20/40, parapapillary atrophy extending to 1.7 mm from the center of the optic disc, unreliable SAP, or those who had poor quality OCT images were excluded.

Glaucoma patients had glaucomatous optic nerve damage and corresponding abnormal SAP defined as abnormal glaucoma hemifield test and pattern standard deviation (PSD) outside 95% normal limits. Glaucomatous optic neuropathy was defined as neuroretinal rim narrowing to the optic disc margin, notching, excavation, or RNFL defect. Patients with SAP abnormalities had at least one confirmatory visual field examination. Normal subjects had no history of ocular disease except cataract, $IOP \leq 21$ mmHg, had a normal optic disc appearance based upon clinical stereoscopic examination and review of stereo disc photography, and normal SAP.

All patients underwent a baseline examination consisting of a complete ophthalmic examination including slit lamp biomicroscopy, gonioscopy, Goldmann applanation tonometry, ultrasound pachymetry, dilated stereoscopic examination, and photography of the optic disc, SAP, and OCT imaging. Follow-up SAP and OCT imaging were performed at 6 month intervals in glaucoma and glaucoma suspects. OCT imaging was performed at annual intervals in the normal subjects. All patients underwent a dilated eye exam with optic disc stereophotography at annual visits.

OCT Imaging and Analysis

A commercially available Stratus OCT (Carl Zeiss Meditec, Dublin, CA, software version 5.0) was used for imaging the RNFL. Poor quality scans were excluded including images that were unfocused, poorly centered, obtained during eye movement, had a scan score <6 , or those with failure to correctly segment the borders of the RNFL. The OCT calibration was checked annually by authorized technicians in accordance with the manufacturer's guidelines. The fast RNFL algorithm was used to obtain RNFL thickness measurements. The OCT software determined the RNFL thickness as the difference in distance between the vitreoretinal interface and a posterior border based on a predefined reflectivity signal level. At each visit, two images were acquired from each subject, with each image consisting of three sets of 256 A-scans along a 3.4-mm-diameter circular ring around the optic disc. Peripapillary RNFL thickness parameters evaluated in this study were average thickness (360°), superior quadrant thickness (46° – 135°), and inferior quadrant thickness (226° – 315°). These values were provided in the printout after averaging the results of three sequential circular scans captured during acquisition.

Assessment of Progression Using Standard Automated Perimetry

SAP was performed using the Swedish Interactive Threshold Algorithm strategy (Humphrey Field Analyzer 750 II-i, SITA Standard 24-2; Carl Zeiss Meditec, Dublin, CA, USA). Only reliable test results ($\leq 33\%$ fixation losses, false-negative results and false-positive results) were included. All the patients were experienced with automated perimetry and had undergone a minimum of 2 visual field tests prior to study enrolment.

SAP progression was defined using four analysis methods. The first method employed Guided Progression Analysis (GPA; Humphrey Field Analyzer; Software version 4.2, Carl Zeiss Meditec Inc, Dublin, CA). GPA uses statistical criteria designed for the EMGT¹⁴ and compares the sensitivity values of individual points on follow-up visual fields to the sensitivity values of the same locations on an average of 2 baseline exams. An automated analysis identifies points that show change greater than the expected variability (at the 95% significance level). Progression was defined as a significant change detected in ≥ 3 points, and repeated in the same points in 3 consecutive follow-up tests, categorized by the GPA software as *Likely Progression*. (Figure 1, left)

The second method employed automated pointwise linear regression (PLR) analysis of SAP sensitivity values using ProgressorTM software (version 3.3; Medisoftware Inc, London, England) which generates slopes to analyze the rate of global and local sensitivity change and the associated level of statistical significance (p-values).¹⁵ (Figure 1, center) Progression was defined as the presence of a test point with a slope of sensitivity across time > 1 dB loss per year, with $p < 0.01$. For edge points, a stricter slope criterion of > 2 dB loss per year (also with $p < 0.01$) was used.^{16–21}

The 3-Omitting method²² uses automated PLR analysis of SAP sensitivity values using ProgressorTM software, but increases specificity by requiring that progression must be confirmed at two further visits when omitting from the series the visual field that caused progression to be suspected. With the 3-Omitting method, a test point is identified as progressing if it satisfies confirmatory progression criteria in each of three slopes. The first slope is constructed using all time points up to time point n , the second slope is constructed omitting point n and including the next time point in the series ($n + 1$), and the final slope is constructed by omitting points n and ($n + 1$) and including the subsequent point in the series ($n + 2$).

The final analysis method was based upon linear regression analysis of sequential fields to measure the slope of the Visual Field Index (VFI; Humphrey Field Analyzer; software version 4.2 Carl Zeiss Meditec Inc, Dublin, CA). Progression was defined as a significant ($p < 0.05$) decline in the slope of the VFI (Figure 1, right), an age-corrected index with a range from 0 to 100 calculated based on the pattern deviation probability map and the total deviation plot.²³

All patients had visual fields and OCT imaging performed on the same day. A minimum of 7 visual fields and imaging examinations were included for each patient in the progression analyses. The mean number of visual fields and OCT images available for progression assessment were 8.5 ± 0.9 (range 7 – 11). During the follow-up period, twenty-eight eyes had 7 OCT images and visual fields available, forty-two eyes had 8 available, sixty-one eyes had 9 available, two eyes had 10 available, and two eyes had 11 examinations available.

Statistical Analysis

Statistical analysis was performed using JMP software version 8.0 (SAS Inc., Cary, NC) and SPSS 17 (SPSS, Chicago, IL). The rate of RNFL thickness loss over time was calculated for each eye using linear regression analysis. Clinical characteristics of the study population were compared using independent samples T-test, paired T-test and chi-square test. Linear mixed-effect models were constructed with both fixed and random effects included. These models facilitated the analysis of all available data considering the group effects, and random patient effects. Categorical and continuous clinical predictor variables were simultaneously tested for their association with the rate of RNFL loss over time in non-progressing and progressing eyes assessed by VFI and ProgressorTM. All tests were two-sided and p-value of < 0.05 was considered significant.

Results

Seventy-six eyes (46 glaucoma eyes and 30 normal eyes) of 38 patients (mean age 68.9 ± 8.8 at baseline, range 46–82 years) were enrolled. The mean length of follow-up was 44.2 ± 4.4 months (range 36–48 months). A total of 814 OCT measurements were acquired during the follow-up period. Twenty-nine scans (2.6%) did not meet the quality criteria and were excluded and 785 OCT measurements were included in the analysis. Table 1 describes the clinical characteristics of the study population.

Eleven glaucomatous eyes (24%) demonstrated SAP progression using Progressor™ criterion, 5 eyes (11%) using VFI criterion, 2 eyes (4%) using the 3-Omitting method, and 2 eyes (4%) using EMGT criterion. Four eyes (8.7%) progressed using both Progressor™ and VFI criteria ($\kappa = 0.41$, $p = 0.009$), 2 eyes (4.4%) progressed using both Progressor™ and EMGT criteria ($\kappa = 0.25$, $p = 0.05$), 2 eyes (4.4%) progressed using both Progressor™ and 3-Omitting method ($\kappa = 0.25$, $p = 0.05$), 1 eye (2.2%) progressed using both VFI and EMGT criteria ($\kappa = 0.24$, $p = 0.21$), 1 eye (2.2%) progressed using 3-Omitting and EMGT criteria ($\kappa = 0.48$, $p = 0.09$), and 2 eyes (4.4%) progressed using both 3-Omitting and VFI criteria ($\kappa = 0.54$, $p = 0.01$).

Table 2 illustrates the baseline RNFL thickness values in progressing and non-progressing eyes of glaucoma patients. No difference in baseline TSNIT average, superior average, or inferior average RNFL thickness was observed in eyes judged to have visual field progression judged using each of 4 criteria compared to non-progressing eyes. As demonstrated in Table 3, the annual rate of average RNFL loss ($\mu\text{m}/\text{year}$) was significantly greater ($p < 0.05$) in progressing vs. non-progressing eyes using Progressor™ (-1.0 ± 1.3 vs. 0.02 ± 1.6), VFI (-2.1 ± 1.1 vs. -0.002 ± 1.4), and the 3-omitting method (-2.2 ± 0.2 vs. -0.1 ± 1.5). The mean rate ($\mu\text{m}/\text{year}$) of superior RNFL thickness decline was significantly greater ($p < 0.05$) in progressing eyes judged using VFI, Progressor™ and the 3-omitting method compared to non-progressing eyes. Using the baseline RNFLT as a reference (100%), the proportional loss of average RNFL thickness was -2.2 ± 1.8 %/year for eyes progressing using Progressor™, -2.6 ± 1.0 %/year using VFI, -2.5 ± 1.6 %/year for eyes progressing using the 3-omitting method, and -4.9 ± 1.8 %/year using EMGT criteria.

Thirty eyes of 15 age-matched normal patients (mean age 64.3 ± 9.2 years) were longitudinally examined (mean follow-up 44 months, range 36 to 47 months) to serve as a control population in order to quantify the normal age-related decline in RNFL thickness. Table 4 compares the mean rate of average, superior, and inferior RNFL thickness loss ($\mu\text{m}/\text{year}$) among normal eyes and non-progressing glaucomatous eyes. Mean rate ($\mu\text{m}/\text{year}$) of average and superior RNFL thickness change was similar ($p > 0.05$) in non-progressing glaucomatous eyes compared to normal eyes.

Using linear mixed-effects models we examined the associations between the rate of average RNFL thickness loss ($\mu\text{m}/\text{year}$) and race, central corneal thickness (CCT), age, exfoliation, disc hemorrhage, phakic status, SAP MD and PSD, peak IOP, mean IOP, long-term IOP fluctuation (defined as peak IOP – trough IOP during the follow-up period), and baseline IOP. The following clinical parameters were significantly ($p < 0.05$) associated with the rate of RNFL thickness atrophy: Mean IOP (average RNFL thickness loss), peak IOP (average RNFL thickness loss), age (average RNFL thickness loss), baseline CCT (average, superior and inferior RNFL thickness loss); disc hemorrhage (average and inferior RNFL thickness loss), exfoliation (superior and inferior RNFL thickness loss) and baseline SAP MD and PSD (superior and inferior RNFL thickness loss). There was also a significant relationship ($r = 0.34$, $p = 0.02$) between the mean rate of average RNFL thickness loss ($\mu\text{m}/\text{year}$) and the

slope of the overall visual field sensitivity (dB/year) using Progressor™ among glaucomatous eyes (Figure 2).

Discussion

Although controlled prospective studies are limited, there is preliminary evidence suggesting that OCT is capable of detecting progressive glaucomatous and non-glaucomatous RNFL atrophy.^{9–1224–27} Medeiros and colleagues²⁴ reported a patient in whom progressive RNFL atrophy was detected using OCT seventy days following traumatic optic neuropathy. Wollstein and colleagues¹¹ demonstrated that OCT was at least as sensitive as standard automated perimetry in detection of glaucomatous progression among 64 eyes with POAG followed for a mean of 4.7 years. Recently, Leung et al²⁷ reported that Stratus OCT detected variable rates of RNFL thickness loss (median loss $-3.3 \mu\text{m}/\text{year}$) among a cohort of 64 patients followed for 5 years.

No consensus exists regarding the ideal method for detection of visual field progression and there continues to be a complete absence of agreement amongst studies in the literature. In the present study, we used four analysis methods to judge progression. Most clinical trials in glaucoma have employed event-based methods that define progression based upon localized confirmatory change in SAP sensitivity (for example using EMGT criteria). Trend-based methods define progression using linear regression analysis of all available fields to quantify the global rate (VFI) or localized rate (Progressor™) of SAP sensitivity loss. It has been shown by several authors^{28,29} that event analyses detect glaucoma progression earlier than trend analyses if visual field testing frequency is reasonably high. It should be noted however, that the primary purpose of the VFI regression is not detection of progression but quantification of rate of progression.

Several recent studies^{18–21} have used Progressor™ software to judge visual field progression in a similar manner as we employ in the present study. Although using a single-point to define progression using Progressor™ is a highly sensitive method for identifying progression, this strategy may have limited specificity. Simulated analyses performed using a Humphrey 30-2 full threshold strategy have reported a specificity of approximately 20–40%.^{30,22} The 3-omitting method²² uses PLR analysis of SAP sensitivity values using Progressor™, but increases specificity by requiring that progression must be confirmed at two further visits when omitting from the series the visual field that caused progression to be suspected.

We conducted the present study in order to examine the hypothesis that the rate of RNFL loss over time measured using OCT was significantly higher in eyes with functional progression irrespective of the criterion used to define visual field progression. There is currently no consensus among clinicians or investigators as to the best method for defining glaucomatous visual field progression.^{9, 18,32–36} Regardless of the criteria used to detect SAP progression, which in our study varied from 4% to 24%, those eyes demonstrating glaucomatous progression by visual fields had significantly higher rates of RNFL loss over time than did non-progressive eyes. These data provide support to clinicians and investigators who seek adjunctive methods to perimetry for identifying glaucoma progression in clinical practice and research studies. In our study, we found the mean rate of average RNFLT loss in progressing eyes ranged from -0.67 to $-3.72 \mu\text{m}/\text{year}$ depending on the method used to define visual field progression. These results are consistent with recent data published by Medeiros and associates using GDx^{33,37} and OCT.¹⁰ We observed that non-progressing eyes had a similar rate of RNFL loss as normal controls of similar age consistent with age-dependent RNFL attrition.

In the present study, progressive RNFL loss was associated with several IOP parameters including mean and peak IOP. At present there is no consensus as to which IOP parameter is the most relevant for monitoring in patients with glaucoma, and clinicians will often consider each of them in assessing their patients.⁴² Randomized clinical trials in persons with glaucoma have clearly demonstrated elevated IOP as a risk factor for progressive optic nerve and visual field loss.^{42–47} A recent study reported that higher levels of IOP are significantly related to higher rates of progressive RNFL loss detected by the GDxECC; each 1-mmHg higher IOP was associated with an additional loss of 0.05 microns per year of RNFL.²⁶ The present study adds further to the growing body of evidence that suggests that elevated IOP is associated with progressive RNFL loss in persons with glaucoma.

It is important to consider variables that may influence RNFL thickness measurements over time using time-domain OCT. Longitudinal variability of average RNFL thickness using Stratus OCT has been demonstrated to be 11.7 μm .⁴⁸ Clinicians must be careful to exclude images obtained that are poorly focused or characterized by weak or variable signal strength.^{49,50} Vizzeri et al⁵¹ have reported that for each unit of decrease in signal strength compared to baseline, the average RNFL thickness is reduced by 2 μm . Images obtained during eye movement, or images in which the OCT beam is poorly centered around the optic disc^{51–53} will have greater variability in RNFL thickness measurements. Failure of the RNFL segmentation algorithm will contribute significant bias to the assessment of glaucoma progression over time.⁴⁹ Finally, variability in RNFL thickness between OCT instruments exceeds the inter-operator variability of two well trained individuals in the same practice and should be carefully considered when comparing RNFL thickness values obtained on different Stratus™ OCT instruments.⁵⁴

Glaucoma is a slowly progressive disease, and many subjects in the present study were treated with ocular hypotensive therapy thereby reducing the risk of progression. Our study has other limitations including a relatively limited sample size and follow-up interval. Longer follow-up is warranted to further investigate differences in the velocity of progression among individuals in this cohort, and risk factors associated with RNFL progression.

In conclusion, OCT may be useful for detection of glaucomatous structural progression and quantifying the velocity of progressive RNFL loss. The present study demonstrates that despite differences in the criteria used to judge functional progression, progressing eyes have a significantly greater rate of RNFL loss compared to non-progressing eyes. Non-progressing eyes have a similar rate of RNFL loss as age-matched normal eyes. The current findings provide additional support for the use of longitudinal RNFL thickness measurements as an endpoint in clinical trials for detection of progressive glaucomatous structural atrophy.

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References

1. Huang D, Swanson E, Lin C, et al. Optical coherence tomography. *Science*. 1991; 254:1178–1181. [PubMed: 1957169]

2. Hee MR, Puliafito CA, Wong C, et al. Optical coherence tomography of macular holes. *Ophthalmology*. 1995; 102:748–756. [PubMed: 7777274]
3. Schuman JS, Pedut-Kloizman T, Hertzmark E, et al. Reproducibility of nerve fiber layer thickness measurements using optical coherence tomography. *Ophthalmology*. 1996; 103:1889–1898. [PubMed: 8942887]
4. Mistlberger A, Liebmann JM, Greenfield DS, et al. Heidelberg retina tomography and optical coherence tomography in normal, ocular-hypertensive, and glaucomatous eyes. *Ophthalmology*. 1999; 106:2027–2032. [PubMed: 10519603]
5. Bowd C, Weinreb RN, Williams JM, Zangwill LM. The Retinal Nerve Fiber Layer Thickness in Ocular Hypertensive, Normal, and Glaucomatous Eyes With Optical Coherence Tomography. *Arch Ophthalmol*. 2000; 118:22–26. [PubMed: 10636409]
6. Huang Y, Cideciyan AV, Papastergiou GI, et al. Relation of optical coherence tomography to microanatomy in normal and rd chickens. *Invest Ophthalmol Vis Sci*. 1998; 39:2405–2416. [PubMed: 9804149]
7. Hoh ST, Greenfield DS, Mistlberger A, et al. Optical coherence tomography and scanning laser polarimetry in normal, ocular hypertensive, and glaucomatous eyes. *Am J Ophthalmol*. 2000; 129:129–135. [PubMed: 10682963]
8. Zangwill LM, Bowd C, Berry CC, et al. Discriminating between normal and glaucomatous eyes using the Heidelberg Retina Tomograph, GDx Nerve Fiber Analyzer, and Optical Coherence Tomograph. *Arch Ophthalmol*. 2001; 119:985–993. [PubMed: 11448320]
9. Leung, CK-s; Cheung, CY.; Weinreb, RN., et al. Evaluation Of Retinal Nerve Fiber Layer Progression In Glaucoma With Optical Coherence Tomography Guided Progression Analysis (GPA). *Invest. Ophthalmol. Vis. Sci*. 2009 09-3468.
10. Medeiros FA, Zangwill LM, Alencar LM, et al. Detection of Glaucoma Progression with Stratus OCT Retinal Nerve Fiber Layer, Optic Nerve Head, and Macular Thickness Measurements. *Invest. Ophthalmol. Vis. Sci*. 2009; 50:5741–5748. [PubMed: 19815731]
11. Wollstein G, Schuman JS, Price LL, et al. Optical Coherence Tomography Longitudinal Evaluation of Retinal Nerve Fiber Layer Thickness in Glaucoma. *Arch Ophthalmol*. 2005; 123:464–470. [PubMed: 15824218]
12. Lee EJ, Kim TW, Park KH, et al. Ability of Stratus OCT to detect progressive retinal nerve fiber layer atrophy in glaucoma. *Invest Ophthalmol Vis Sci*. 2009; 50:662–668. [PubMed: 18824734]
13. Budenz DL, Fredette M-J, Feuer WJ, Anderson DR. Reproducibility of Peripapillary Retinal Nerve Fiber Thickness Measurements with Stratus OCT in Glaucomatous Eyes. *Ophthalmology*. 2008; 115:661–666. [PubMed: 17706287]
14. Leske MC, Heijl A, Hyman L, Bengtsson B. Early Manifest Glaucoma Trial: design and baseline data. *Ophthalmology*. 1999; 106:2144–2153. [PubMed: 10571351]
15. Viswanathan AC, Fitzke FW, Hitchings RA. Early detection of visual field progression in glaucoma: a comparison of progressor and statpac 2. *Br J Ophthalmol*. 1997; 81:1037–1042. [PubMed: 9497460]
16. Viswanathan AC, Crabb DP, McNaught AI, et al. Interobserver agreement on visual field progression in glaucoma: a comparison of methods. *Br J Ophthalmol*. 2003; 87:726–730. [PubMed: 12770970]
17. Strouthidis NG, Scott A, Peter NM, Garway-Heath DF. Optic Disc and Visual Field Progression in Ocular Hypertensive Subjects: Detection Rates, Specificity, and Agreement. *Invest. Ophthalmol. Vis. Sci*. 2006; 47:2904–2910. [PubMed: 16799032]
18. Ahrlich KG, De Moraes CG, Teng CC, Prata TS, Tello C, Ritch R, Liebmann JM. Visual field progression differences between normal-tension and exfoliative high-tension glaucoma. *Invest Ophthalmol Vis Sci*. 2010; 51:1458–1463. [PubMed: 20042657]
19. De Moraes CG, Prata TS, Liebmann CA, Tello C, Ritch R, Liebmann JM. Spatially consistent, localized visual field loss before and after disc hemorrhage. *Invest Ophthalmol Vis Sci*. 2009; 50:4727–4733. [PubMed: 19458330]
20. Folgar FA, de Moraes CG, Prata TS, Teng CC, Tello C, Ritch R, Liebmann JM. Glaucoma surgery decreases the rates of localized and global visual field progression. *Am J Ophthalmol*. 2010; 149:258–264. [PubMed: 20103054]

21. Teng CC, De Moraes CG, Prata TS, Tello C, Ritch R, Liebmann JM. Beta-Zone parapapillary atrophy and the velocity of glaucoma progression. *Ophthalmology*. 2010; 117:909–915. [PubMed: 20132988]
22. Gardiner SK, Crabb DP. Examination of different pointwise linear regression methods for determining visual field progression. *Invest Ophthalmol Vis Sci*. 2002; 43(5):1400–1407. [PubMed: 11980853]
23. Bengtsson B, Heijl A. A Visual Field Index for Calculation of Glaucoma Rate of Progression. *Am J Ophthalmol*. 2008; 145:343–353. [PubMed: 18078852]
24. Medeiros FA, Moura FC, Vessani RM, Susanna R. Axonal loss after traumatic optic neuropathy documented by optical coherence tomography. *Am J Ophthalmol*. 2003; 135:406–408. [PubMed: 12614771]
25. Wollstein G, Schuman JS, Price LL, et al. Optical coherence tomography longitudinal evaluation of retinal nerve fiber layer thickness in glaucoma. *Arch Ophthalmol*. 2005; 123:464–470. [PubMed: 15824218]
26. Costello F, Coupland S, Hodge W, et al. Quantifying axonal loss after optic neuritis with optical coherence tomography. *Ann Neurol*. 2006; 59:963–969. [PubMed: 16718705]
27. Trip SA, Schlottmann PG, Jones SJ, et al. Optic nerve atrophy and retinal nerve fibre layer thinning following optic neuritis: evidence that axonal loss is a substrate of MRI-detected atrophy. *Neuroimage*. 2006; 31:286–293. [PubMed: 16446103]
28. Vesti E, Johnson CA, Chauhan BC. Comparison of different methods for detecting glaucomatous visual field progression. *Invest Ophthalmol Vis Sci*. 2003; 44:3873–3879. [PubMed: 12939303]
29. Kovalska M, Grieshaber MC, Schötzau A, Katamay R, Hauenstein D, Flammer J, Orgül S. Detection of visual field progression in glaucoma. *Klin Monbl Augenheilkd*. 2008; 225:342–345. [PubMed: 18454368]
30. Heijl A, Bengtsson B, Lindgren G. Visual field progression in glaucoma. *Br J Ophthalmol*. 1998; 82:1097–1098. [PubMed: 9893615]
31. Leung, CK-s; Cheung, CYL.; Weinreb, RN., et al. Evaluation of retinal nerve fiber layer progression in glaucoma: a study on optical coherence tomography guided progression analysis. *Invest Ophthalmol Vis Sci*. 2010; 51:217–222. [PubMed: 19684001]
32. Arnalich-Montiel F, Casas-Llera P, Muñoz-Negrete F, Rebolleda G. Performance of glaucoma progression analysis software in a glaucoma population. *Graefes Arch Clin Exp Ophthalmology*. 2009; 247:391–397.
33. Medeiros FA, Alencar LM, Zangwill LM, et al. The Relationship between Intraocular Pressure and Progressive Retinal Nerve Fiber Layer Loss in Glaucoma. *Ophthalmology*. 2009; 116:1125–1133. [PubMed: 19376584]
34. Wesselink C, Heeg GP, Jansonius NM. Glaucoma Monitoring in a Clinical Setting: Glaucoma Progression Analysis vs Nonparametric Progression Analysis in the Groningen Longitudinal Glaucoma Study. *Arch Ophthalmol*. 2009; 127:270–274. [PubMed: 19273789]
35. Casas-Llera P, Rebolleda G, Munoz-Negrete FJ, et al. Visual field index rate and event-based glaucoma progression analysis: comparison in a glaucoma population. *British Journal of Ophthalmology*. 2009; 93:1576–1579. [PubMed: 19535357]
36. Strouthidis NG, Scott A, Viswanathan AC, et al. Monitoring glaucomatous visual field progression: the effect of a novel spatial filter. *Invest Ophthalmol Vis Sci*. 2007; 48:251–257. [PubMed: 17197540]
37. Medeiros FA, Alencar LM, Zangwill LM, et al. Detection of Progressive Retinal Nerve Fiber Layer Loss in Glaucoma Using Scanning Laser Polarimetry with Variable Corneal Compensation. *Invest Ophthalmol Vis Sci*. 2009; 50:1675–1681. [PubMed: 19029038]
38. Alencar LM, Medeiros FA, Weinreb R. Progressive localized retinal nerve fiber layer loss following a retinal cotton wool spot. *Semin Ophthalmol*. 2007; 22:103–104. [PubMed: 17564932]
39. Lopes de Faria JM, Russ H, Costa VP. Retinal nerve fibre layer loss in patients with type 1 diabetes mellitus without retinopathy. *Br J Ophthalmol*. 2002; 86:725–728. [PubMed: 12084737]
40. Kee C, Hwang JM. Optical coherence tomography in a patient with tobacco-alcohol amblyopia. *Eye*. 2008; 22:469–470. [PubMed: 17435689]

41. Siepmann TA, Wefers Bettink-Remeijer M, Hintzen RQ. Retinal nerve fiber layer thickness in subgroups of multiple sclerosis, measured by optical coherence tomography and scanning laser polarimetry. *J Neurol*. Epub ahead of print.
42. Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. *Arch Ophthalmol*. 2002; 120:1268–1279. [PubMed: 12365904]
43. Leske MC, Heijl A, Hussein M, et al. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. *Arch Ophthalmol*. 2003; 121:48–56. [PubMed: 12523884]
44. Gordon MO, Beiser JA, Brandt JD, et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002; 120:714–720. [PubMed: 12049575]
45. Miglior S, Zeyen T, Pfeiffer N, et al. Results of the European Glaucoma Prevention Study. *Ophthalmology*. 2005; 112:366–375. [PubMed: 15745761]
46. Musch DC, Gillespie BW, Lichter PR, et al. Visual field progression in the Collaborative Initial Glaucoma Treatment Study the impact of treatment and other baseline factors. *Ophthalmology*. 2009; 116:200–207. [PubMed: 19019444]
47. Lee PP, Sultan MB, Grunden JW, Cioffi GA. Assessing the Importance of IOP Variables in Glaucoma Using a Modified Delphi Process. *J Glaucoma*. 2009 Epub ahead of print.
48. Leung, CK-s; Cheung, CY.; Lin, D., et al. Longitudinal Variability of Optic Disc and Retinal Nerve Fiber Layer Measurements. *Invest. Ophthalmol. Vis. Sci*. 2008; 49:4886–4892. [PubMed: 18539940]
49. Wu Z, Vazeen M, Varma R, et al. Factors associated with variability in retinal nerve fiber layer thickness measurements obtained by optical coherence tomography. *Ophthalmology*. 2007; 114:1505–1512. [PubMed: 17367862]
50. Cheung CYL, Leung CKS, Lin D, et al. Relationship between retinal nerve fiber layer measurement and signal strength in optical coherence tomography. *Ophthalmology*. 2008; 115:1347–1351. [PubMed: 18294689]
51. Vizzeri G, Bowd C, Medeiros FA, et al. Effect of signal strength and improper alignment on the variability of stratus optical coherence tomography retinal nerve fiber layer thickness measurements. *Am J Ophthalmol*. 2009; 148:249–255. [PubMed: 19427621]
52. Gabriele ML, Ishikawa H, Wollstein G, et al. Optical coherence tomography scan circle location and mean retinal nerve fiber layer measurement variability. *Invest Ophthalmol Vis Sci*. 2008; 49:2315–2321. [PubMed: 18515577]
53. Vizzeri G, Bowd C, Medeiros FA, et al. Effect of improper scan alignment on retinal nerve fiber layer thickness measurements using Stratus optical coherence tomograph. *J Glaucoma*. 2008; 17:341–349. [PubMed: 18703942]
54. Sehi M, Guaqueta DC, Feuer WJ, Greenfield DS. A comparison of structural measurements using 2 Stratus optical coherence tomography instruments. *J Glaucoma*. 2007; 16:287–292. [PubMed: 17438421]

Figure 1.

Criteria used for judgement of visual field progression. Guided Progression Analysis (GPA, left) identifies *Likely Progression* when a significant change in sensitivity is detected in ≥ 3 points and repeated in the same points (black triangles), on 3 consecutive follow-up tests. Progressor™ (center) identifies progression (red square) as a test point with significant ($p < 0.01$) sensitivity loss > 1 dB loss per year (non-edge points) or > 2 dB loss per year (edge points). A significant ($p < 0.05$) decline in the slope of the Visual Field Index (VFI, right) is defined as progression.

Figure 2. Scatterplot demonstrating relationship between the change of average retinal nerve fiber layer thickness (RNFLT) and mean visual field slope using Progressor™ among glaucomatous eyes ($n = 46$). The rate of RNFLT change ($\mu\text{m}/\text{year}$) was significantly ($p < 0.001$) correlated with the rate of visual field change (dB/year).

Table 1

Clinical characteristics of the study population (n = 76 eyes).

Mean $\pm$ SD (Range)	Normal (n=30)	Glaucoma (n=46)	p-value
Age (years)	66.73 $\pm$ 8.45 (50 to 77)	68.9 $\pm$ 8.8 (46 to 79)	0.30 *
Gender			
Male	10	22	0.24 [‡]
Female	20	24	
Race			
White	30	40	0.24 [‡]
Hispanic	0	2	
Black	0	2	
Asian	0	2	
CCT (μ m)	544.67 $\pm$ 21.16 (506 to 586)	541 $\pm$ 43.10 (448 to 654)	0.67 *
IOP (mmHg)	13.8 $\pm$ 2.9 (9.5 to 20)	15.3 $\pm$ 3.7 (8 to 23)	0.052 *
SAP			
MD (dB)	0.15 $\pm$ 0.52 (-0.97 to 1)	-3.87 $\pm$ 4.27 (-15.2 to 0.73)	<0.001 *
PSD (dB)	1.46 $\pm$ 0.28 (0.76 to 2.03)	4.87 $\pm$ 3.88 (1.37 to 13.95)	<0.001 *
OCT RNFLT (μ m)			
Average RNFL	92.05 $\pm$ 10.20 (67.30 to 109.88)	77.64 $\pm$ 18.97 (40.19 to 117.21)	<0.001 *
Superior average	106.73 $\pm$ 20.10 (66 to 145)	91.67 $\pm$ 26.16 (40 to 153)	0.009 *
Inferior average	118.53 $\pm$ 14.41 (93 to 139)	95.88 $\pm$ 27.01 (47 to 175)	<0.001 *

* Independent samples T-test;

[‡] Chi-square; CCT = central corneal thickness; IOP = intraocular pressure; MD = mean deviation; PSD = pattern standard deviation; SAP = standard automated perimetry; OCT = optical coherence tomography; RNFLT = retinal nerve fiber layer thickness

Table 2

Baseline optical coherence tomography retinal nerve fiber layer thickness measurements in progressing and non-progressing glaucomatous eyes

SAP Criterion	OCT RNFLT (μm)	Progressing Eyes (n)	Non-progressing Eyes (n)	p-value *
VFI	Average	72.5 ± 23.6 (5)	78.5 ± 19.3 (41)	0.52
	Superior Average	80.0 ± 35.1 (5)	93.8 ± 26.6 (41)	0.30
	Inferior average	87.2 ± 31.4 (5)	96.7 ± 27.1 (41)	0.47
Progressor™	Average	72.0 ± 15.7 (11)	79.5 ± 20.5 (35)	0.29
	Superior Average	84.3 ± 23.9 (11)	94.6 ± 28.4 (35)	0.30
	Inferior average	91.1 ± 18.9 (11)	97.0 ± 29.5 (35)	0.55
EMGT	Average	55.7 ± 10.8 (2)	78.8 ± 19.4 (44)	0.10
	Superior Average	57.5 ± 20.5 (2)	93.9 ± 26.9 (44)	0.27
	Inferior average	70.0 ± 15.5 (2)	96.9 ± 27.3 (44)	0.18
3-Omitting Method	Average	61.0 ± 18.3 (2)	78.6 ± 19.5 (44)	0.22
	Superior Average	62.0 ± 26.9 (2)	93.7 ± 27.0 (44)	0.11
	Inferior average	76.0 ± 24.0 (2)	96.6 ± 27.4 (44)	0.30

* One-way ANOVA; SAP = standard automated perimetry; VFI = visual field index; OCT = optical coherence tomography; RNFL = retinal nerve fiber layer thickness; EMGT = Early Manifest Glaucoma Trial criteria

Table 3

Mean rate of retinal nerve fiber layer thickness loss ($\mu\text{m}/\text{year}$) measured using optical coherence tomography in glaucoma eyes judged to be non-progressing and progressing.

SAP Criterion	Rate of RNFLT Loss ($\mu\text{m}/\text{year}$)	Progressing Eyes	Non-progressing Eyes	p-value*
VFI	Average	-2.1 ± 1.1	-0.002 ± 1.4	0.003
	Superior Average	-2.9 ± 1.0	-0.2 ± 1.8	0.001
	Inferior Average	-3.3 ± 3.0	-0.5 ± 2.4	0.02
Progressor™	Average	-1.0 ± 1.3	0.02 ± 1.6	0.04
	Superior Average	-1.7 ± 1.5	-0.1 ± 1.9	0.01
	Inferior Average	-1.5 ± 2.9	-0.6 ± 2.5	0.36
EMGT	Average	-0.8 ± 1.9	-0.2 ± 1.5	0.75
	Superior Average	-2.0 ± 1.9	-0.4 ± 1.9	0.43
	Inferior Average	-0.4 ± 3.3	-0.8 ± 2.6	0.84
3-Omitting Method	Average	-2.2 ± 0.2	-0.1 ± 1.5	<0.001
	Superior Average	-3.4 ± 0.1	-0.4 ± 1.9	<0.001
	Inferior Average	-3.5 ± 1.1	-0.7 ± 2.5	0.10

* One-way ANOVA; SAP = standard automated perimetry; VFI = visual field index; OCT = optical coherence tomography; RNFLT = retinal nerve fiber layer thickness; EMGT = Early Manifest Glaucoma Trial criteria

Table 4

Mean rate of average, superior, and inferior retinal nerve fiber layer thickness loss ($\mu\text{m}/\text{year}$) measured using optical coherence tomography among normal eyes and non-progressing glaucomatous eyes.

SAP Criterion	Rate of RNFLT Loss ($\mu\text{m}/\text{year}$)	Normal Eyes	Non-progressing Eyes	p-value*
VFI	Average	0.43 ± 0.92	-0.002 ± 1.44	0.34
	Superior Average	0.19 ± 1.85	-0.22 ± 1.80	0.09
	Inferior Average	0.52 ± 2.49	-0.50 ± 2.4	0.15
Progressor™	Average	0.43 ± 0.92	0.02 ± 1.60	0.20
	Superior Average	0.19 ± 1.85	-0.14 ± 1.90	0.48
	Inferior Average	0.52 ± 2.49	-0.6 ± 2.5	0.07
EMGT	Average	0.43 ± 0.92	-0.20 ± 1.55	0.05
	Superior Average	0.19 ± 1.85	-0.44 ± 1.92	0.16
	Inferior Average	0.52 ± 2.49	-0.82 ± 2.56	0.03
3-Omitting Method	Average	0.43 ± 0.92	-0.13 ± 1.52	0.07
	Superior Average	0.19 ± 1.85	-0.38 ± 1.86	0.19
	Inferior Average	0.52 ± 2.49	-0.68 ± 2.53	0.05

* One-way ANOVA; SAP = standard automated perimetry; VFI = visual field index; OCT = optical coherence tomography; RNFLT = retinal nerve fiber layer thickness; EMGT = Early Manifest Glaucoma Trial criteria