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Retinal Nerve Fiber Layer Atrophy Is Associated with Visual Field Loss over Time in Glaucoma Suspect and Glaucomatous Eyes

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Abstract

Purpose—To prospectively compare detection of progressive retinal nerve fiber layer thickness (RNFL) atrophy identified using time-domain optical coherence tomography (OCT) with visual field progression using standard automated perimetry (SAP) in glaucoma suspect and preperimetric glaucoma and perimetric glaucoma patients.

Design—Prospective longitudinal clinical trial

Methods—Eligible eyes with 2 years of follow-up underwent time-domain OCT and SAP every 6 months. The occurrence of *visual field progression* was defined as the first follow-up visit reaching a significant ($p < 0.05$) negative visual field index (VFI) slope over time. RNFL progression/improvement was defined as a significant negative/positive slope over time. Specificity was defined as the number of eyes with neither progression nor improvement, divided by the number of eyes without progression. Cox proportional hazard ratios (HR) were calculated using univariate and multivariate models with RNFL loss as a time-dependent covariate.

Results—310 glaucoma suspect and preperimetric glaucoma, and 177 perimetric glaucoma eyes were included. Eighty-nine eyes showed visual field progression and 101 eyes showed RNFL progression. The average time to detect visual field progression in those 89 eyes was 35 ± 13 months; and to detect RNFL progression in those 101 eyes was 36 ± 13 months. In multivariate Cox models, average and superior RNFL losses were associated with subsequent VFI loss in the entire cohort (every $10 \mu\text{m}$ loss, $\text{HR} = 1.38, p = 0.03$; $\text{HR} = 1.20, p = 0.01$ respectively). Among the entire cohort of 487 eyes, 42 had significant VFI improvement and 55 had significant RNFL improvement (specificity 91.4% and 88.7%, respectively).

Conclusion—Structural progression is associated with functional progression in glaucoma suspect and glaucomatous eyes. Average and superior RNFL thickness may predict subsequent SAP loss.

Keywords

retinal nerve fiber layer; visual field; glaucoma progression; hazard ratio

Introduction

Glaucoma is a multifactorial optic neuropathy characterized by progressive neurodegeneration of retinal ganglion cells (RGCs) and their axons characterized by retinal nerve fiber layer (RNFL) attenuation, a specific pattern of damage to the optic nerve head (ONH), and visual field loss.^{1,2} Although both structural and functional damage occur in glaucoma, controversy exists regarding whether substantial RNFL attenuation precedes functional loss measured by standard automated perimetry.^{3–11} It is widely recognized that both structure and function are useful to detect glaucoma progression given discordance in the timing of detecting longitudinal changes in the optic nerve and visual field.^{2,3,8,12–19} The relationship between signal-to-noise²⁰, stage of glaucomatous damage²¹, and the technique and region of visual field studied have significant impacts on the comparison of structure and function for the progression of glaucoma.^{3,22,23}

Novel imaging technologies have been developed that are capable of quantifying early glaucomatous damage at the micron level using structural measures. Time-domain optical coherence tomography (TD-OCT; Stratus OCT, Carl Zeiss Meditec, Dublin, CA) is a high-resolution, micron scale, cross-sectional imaging modality that provides quantitative assessments of the retina and optic nerve head,^{24,25} and is capable to discriminate between normal and glaucomatous eyes, and detect longitudinal loss of RNFL thickness in glaucoma.^{1,26–29}

The visual field index (VFI) is a calculated index allocated to each visual field that determines the level of abnormality of the field. The VFI uses the pattern deviation (PD) probability map to identify the test locations that are considered either normal and scored as 100%, or absolute defect and scored as 0%. The remaining test locations with relative loss on PD plot are scored in percentage based on their total deviation (TD) value and age-corrected normal threshold.³⁰ Since VFI uses PD probability maps, it is less affected by cataract. A weighting procedure is applied to each test location using an estimate of the spatial magnification present in the occipital cortex that divides the test pattern into five concentric rings of increasing eccentricity.³¹ The four test central locations not including measurement of foveal threshold are allotted the highest weight and the weights decrease with increasing eccentricity. The VFI is the mean of all weighted scores in percent.

The VFI scoring system masks early glaucomatous damage by assigning a perfect score to the test locations that are considered normal on the PD plot but may have decreased TD values. The purpose of this study was to prospectively compare the detection of progressive RNFL loss identified using TD-OCT with visual field progression measured using standard automated perimetry in glaucoma suspect and preperimetric glaucoma, and perimetric glaucoma patients.

Methods

Study Population

This was a prospective, non-randomized, longitudinal clinical trial. Participants consisted of glaucoma suspect and preperimetric glaucoma, and perimetric glaucoma patients with 28 months of follow-up who were enrolled in Advanced Imaging for Glaucoma Study (AIGS) conducted at Bascom Palmer, Casey and Doheny Eye Institutes and UPMC Eye Center. Inclusion criteria common to both groups consisted of spherical equivalent refractive error between -7.00 and $+3.00$ diopters sphere, best-corrected visual acuity (BCVA) of 20/40 or better, age between 40 and 80 years, and no prior history of intraocular surgery except for uncomplicated cataract extraction. Subjects with ocular disease other than glaucoma or cataract, parapapillary atrophy extending to 1.7 mm from the center of the optic disc, unreliable visual field, or poor quality ONH or RNFL images were excluded.

The glaucoma suspect and preperimetric glaucoma eyes consisted of eyes with ocular hypertension characterized by intraocular pressure (IOP) ≥ 24 mmHg with normal optic discs, and normal standard automated perimetry defined as glaucoma hemifield test (GHT) within normal limits and MD and PSD within 95% CI limits; or patients with glaucomatous optic neuropathy on funduscopic examination and review of stereoscopic optic disc photographs but normal visual field. Glaucomatous optic neuropathy was defined as neuroretinal rim narrowing to the optic disc margin, notching, excavation, or RNFL defect. The perimetric glaucoma patients had glaucomatous optic nerve damage and corresponding abnormal visual field defined as abnormal glaucoma hemifield test, and pattern standard deviation (PSD) outside 95% normal limits. Patients with visual field abnormalities had at least one confirmatory visual field examination. 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, standard automated perimetry, and RNFL imaging. The RNFL imaging was performed using TD-OCT (Stratus OCT; software version 5.0.1; Carl Zeiss Meditec, Dublin, CA) every six months. During the follow-up period, each patient was treated at the discretion of the attending physician.

Time-Domain Optical Coherence Tomography (TD-OCT)

The TD-OCT was employed to measure the RNFL thickness. The software determines the RNFL thickness as the distance between the vitreoretinal interface and a posterior border based on a predefined reflectivity signal level. The calibration was checked annually in accordance with the manufacturer's guidelines by authorized technicians. At each visit, two images were acquired from each subject. Each image consisted of three sets of 256 A-scans along a 3.4-mm-diameter circumpapillary scan centered at the ONH. The fast-scanning mode was used, in which all scans are acquired and aligned automatically after initial positioning and acquisition by the operator. The "Repeat Scan" option incorporated in TD-OCT was used to optimize the alignment of the follow-up scan circle and the baseline image. 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. 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 Definition of Progression

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

Both eyes of eligible patients enrolled in the AIGS with > 28 months of follow-up and reliable visual field were included. TD-OCT and standard automated perimetry were measured every 6 months. *Progression* was defined as a significant ($p < 0.05$) negative slope in the annual rate of change in VFI and RNFL. The occurrence of *visual field progression* was defined as the first follow-up visit reaching a significant ($p < 0.05$) negative VFI slope over time. Improvement was defined as a significant ($P < 0.05$) positive slope in the annual rate of change in VFI and RNFL. Specificity was defined as the number of eyes with neither progression nor improvement, divided by the number of eyes without progression.

Statistical Analysis

Statistical analysis was performed using SAS software version 9.2 (SAS Inc., Cary, NC, USA) to detect progressive RNFL loss and visual field progression in glaucoma suspect and preperimetric glaucoma, and perimetric glaucoma patients. All tests were two-sided and a p-value of < 0.05 was considered significant. The average of two high quality measurements that met the inclusion criteria was used for the statistical analysis. Analysis of variance (ANOVA) was used to compare the continuous variables and chi-square test for the categorical variables. When applicable, general estimating equation (GEE) method was used to adjust for correlation between the two eyes of the same patient.³² Univariate and multivariate Cox proportional hazard ratios (HR) with 95% confidence intervals were calculated using univariate and multivariate models with RNFL loss as a time-dependent covariate in order to identify the risk factors predictive of visual field progression.

Univariate Cox proportional hazard regression models examined the HRs for the individual parameters and were not adjusted for the presence of other factors. Predictors with a p-value of 0.1 or less were evaluated for the multivariate models through stepwise selection. Separate models were constructed for multivariate analyses. Each model included one imaging parameter, and age and visual field PSD at baseline. For Cox models, a technique called "robust sandwich covariance estimate" was used in the Wald tests to adjust for

correlation between two eyes from the same patient.³³ Three types of Kaplan-Meier curves were created to compare the survival times for: Perimetric Glaucoma eyes vs. glaucoma suspect and preperimetric glaucoma eyes (Figure 1), the eyes that had significant loss of RNFL vs. those that did not (Figure 2), and RNFL loss vs. VFI loss (explained in the results).

Results

487 eyes of 246 patients (310 glaucoma suspect and preperimetric glaucoma and 177 perimetric glaucoma) were included, of which 131 patients were glaucoma suspect and preperimetric glaucoma in both eyes, 65 patients were perimetric glaucoma in both eyes and 50 patients were perimetric glaucoma in one eye and glaucoma suspect or preperimetric glaucoma in the other eye. Table 1 demonstrates demographics and baseline characteristics of two groups of perimetric glaucoma eyes, and glaucoma suspect and preperimetric glaucoma eyes. Mean age of the entire study group was 60.3 ± 9.5 years (range 40–80). Each eye underwent both visual field and TD-OCT examinations at every visit. The average number of visual fields/OCT examinations for each eye was 8.6 ± 2 with the minimum of 4 and maximum of 12 measurements. Only two patients had 4 measurements within a time span of 30 and 36 months respectively. The mean VFI, MD, and PSD were $88.77 \pm 13.08\%$, $-3.82 \pm 4.28\text{dB}$ and $5.37 \pm 4.21\text{dB}$ respectively in perimetric glaucoma; and $99.07 \pm 1.14\%$, $-0.23 \pm 1.04\text{dB}$, and $1.61 \pm 0.38\text{dB}$ in glaucoma suspect/preperimetric glaucoma (all $p < 0.001$). The average RNFLT was $76.44 \pm 13.57\mu\text{m}$ and $92.74 \pm 12.20\mu\text{m}$ ($p < 0.001$) in perimetric glaucoma and glaucoma suspect/preperimetric glaucoma respectively. Mean follow-up time was 36.4 ± 13.8 and 40.6 ± 11.5 months ($p < 0.001$) in perimetric glaucoma and glaucoma suspect/preperimetric glaucoma respectively. Mean IOP was 14.7 ± 3.7 and $16.8 \pm 3.8\text{mmHg}$ in perimetric glaucoma and GLAUCOMA SUSPECT/PREPERIMETRIC GLAUCOMA respectively ($p < 0.001$).

89 (18%) eyes (41 glaucoma suspect/preperimetric glaucoma, and 48 perimetric glaucoma, $p < 0.001$) showed visual field progression, and 101 (21%) eyes (56 glaucoma suspect/preperimetric glaucoma, and 45 perimetric glaucoma; $p = 0.07$) showed RNFL progression, of which, five (1%) eyes showed visual field and RNFL progression simultaneously, 63 (12.9%) eyes showed visual field progression without RNFL progression and 7 (1.4%) eyes showed visual field progression preceding RNFL progression. The average time to detect functional loss using visual fields in these 70 eyes was 35.0 ± 13.2 months.

75 (15.4%) eyes showed RNFL progression without visual field progression, 63 (12.9%) eyes showed VFI progression without RNFL progression, and 26 eyes demonstrated progression using both methods ($p = 0.35$; McNemar's test).

Among the 26 eyes that demonstrated progression using both methods, 14 (3%) eyes showed RNFL progression preceding visual field progression, 7 (1.4%) eyes showed visual field progression preceding RNFL progression and 5 (1.03%) eyes showed simultaneous progression using both methods ($p = 0.18$, McNemar's test). The average time to detect structural loss using TD-OCT in these 89 eyes was 35.8 ± 13.1 ($p = 0.9$). 323 eyes showed no RNFL or visual field progression.

Table 2 demonstrates the number of eyes showing progression by VFI criteria in each of the glaucoma suspect, preperimetric glaucoma and perimetric glaucoma groups. The highest rate of visual field progression was observed in the perimetric glaucoma group (48/177 or 27%). Table 3 demonstrates the annual rates of loss in visual field indices calculated using linear regression analysis over time in the entire cohort accounting for the inclusion of both eyes. The rates of loss were significantly steeper in perimetric glaucoma group

compared with glaucoma suspect/preperimetric glaucoma group for all three visual field indices of VFI, MD and PSD. Table 4 demonstrates the annual rates of loss in RNFL parameters measured by time-domain optical coherence tomography using linear regression analysis technique. The annual rate of RNFL loss was significantly steeper in perimetric glaucoma group compared with glaucoma suspect/preperimetric glaucoma group for average, superior, inferior and temporal RNFL thickness values. Table 5 demonstrates that the rate of VFI loss per year was significantly steeper in the eyes that had significant RNFL loss compared with those that did not have RNFL loss in the perimetric glaucoma group. Table 6 compares baseline visual field and RNFL parameters in two groups of eyes that showed progression using significant VFI slope versus the eyes that showed significant RNFL slope. Tables 7, 8, and 9 demonstrate the results of the univariate and multivariate Cox models for the calculation of proportional hazard ratios to identify the risk factors predictive of visual field progression.

Using univariate Cox proportional hazard models, the following time-dependent parameters were predictive of VFI loss: loss of average RNFL (every $-10\mu\text{m}$, $\text{HR}=1.40$, $p=0.02$); loss of average superior RNFL (every $-10\mu\text{m}$, $\text{HR}=1.15$, $p=0.01$), and whether the slope of RNFL is significantly negative over the entire follow-up (yes vs. no, $\text{HR}=1.86$, $p=0.01$). In multivariate Cox models including baseline PSD, progressive loss of average and superior RNFL was associated with subsequent VFI loss in the entire cohort (for every $10\mu\text{m}$ RNFL thickness reduction, $\text{HR}=1.38$, $p=0.03$; $\text{HR}=1.20$, $p=0.01$ respectively). Among the entire cohort of 487 eyes, 42 (8.6%) had significant VFI improvement and 55 (11.3%) had significant RNFL improvement (specificity 91.4% and 88.7%, respectively, $p = 0.80$). Figure 1 demonstrates a Kaplan-Meier analysis that indicates that cumulative probability of visual field progression was significantly higher in perimetric glaucoma than glaucoma suspect/preperimetric glaucoma eyes (Log rank test $p < 0.001$). Figure 2 demonstrates a Kaplan-Meier analysis that indicates that cumulative probability of visual field progression was significantly higher in eyes that showed loss of average RNFL over follow-up period compared with eyes that did not show RNFL loss, (Log rank test $p = 0.014$). We also conducted a third Kaplan-Meier analysis to compare the times of progression and found that there was no significant difference ($p = 0.28$) between the times of progression using significant negative slopes of average RNFL vs. VFI.

Discussion

In the present study, we used a trend-based analysis employing the linear regression of RNFL and VFI values, and defined the visual field progression based upon a significant negative rate of VFI loss. As previously mentioned, the VFI scoring system masks early glaucomatous damage. Among 177 perimetric glaucoma eyes, 48 eyes showed visual field progression and 45 eyes showed average RNFL progression. Among 310 glaucoma suspect/preperimetric glaucoma eyes, 41 eyes showed visual field progression and 56 eyes showed average RNFL progression. These facts add to the body of evidence that VFI is less sensitive to progression in glaucoma suspect and early preperimetric glaucoma. It seems that using visual field loss as the only endpoint in clinical trials limits the interpretation of the behavior of disease, as it is a subjective test with large variability and limited range, and requires longer follow-up time, and there is no consensus on the best method of progression judgment³⁴ or alternatively, one might conclude that TD-OCT has high rate of false positive calls.

We found that structural progression is associated with subsequent functional progression in glaucoma suspect and glaucomatous eyes. Several studies have found similar results using different techniques of structural and functional progression.^{35–38} Our data is consistent with previous studies that reported that discordant exists between different methods of

progression detection using structural and functional measures.^{5,39,40} Different attempts have been made to generate models that predict visual function from RNFL structure.^{6,8,41} The purpose of this study was not to evaluate the agreement between structural and functional progression methods, but our aim was to prospectively compare RNFL progression with visual field progression using trend-based analysis, and explore whether RNFL loss is predictive of subsequent visual field loss. Quite often the structural and functional progression do not happen simultaneously within a certain period of time, but if the patient is followed up long enough, eventually both structural and functional progression will confirm the findings of the other method.

In this study, of the total of 190 progressing eyes using significant rate of loss in RNFL or VFI, 70 eyes (37%) showed visual field progression without or prior to RNFL progression. This result is very similar to that of the Ocular Hypertension Treatment Study (OHTS) that showed 35% of patients with visual field loss without any sign of structural progression.⁴² Medeiros and colleagues²⁶ also showed that 34% of all glaucoma suspect converters developed visual field defects without structural progression. It is not quite clear why functional progression precedes structural progression in some patients and vice versa. Future studies that target more detailed and objective functional tests and alternative structural parameters may succeed in responding to this question.

We found that average and superior RNFL as time dependent covariates are significant predictors of subsequent visual field loss in the entire cohort, so that every 10 μ m attenuation of average RNFL, is associated with a 38% higher chance and every 10 μ m attenuation of superior RNFL is associated with a 20% higher chance of visual field progression. Previous studies have similarly suggested that RNFL thinning may be a predictor of subsequent visual field loss.^{38,39}

Our study has potential limitations. One of the limitations of the study is that this glaucoma cohort was treated at the discretion of the attending physician to the best possible. We did not have an untreated arm in the study; therefore judging the true rate of progression in structure and function and deciding which one occurs first if untreated remains unknown. The second limitation of this study is the lack of specificity coming from healthy subjects. Another limitation of the study is that there were not many progressing eyes in glaucoma suspect/preperimetric glaucoma. The glaucoma suspect/preperimetric glaucoma patients do not progress as fast as perimetric glaucoma patients and need longer follow-up time to show significant visual loss especially if they are diagnosed early and treated to the best possible. Visual field progression occurred in 27% (48/177) of perimetric glaucoma eyes, whereas only in 13% (41/310) of glaucoma suspect/preperimetric glaucoma eyes visual field progression was identified. Two characteristics of the study cohort cause smaller number of cases with visual field progression in the glaucoma suspect/preperimetric glaucoma group. A) The number of glaucoma suspect eyes in this study was twice as high as the number of glaucomatous eyes; and the baseline visual field damage in glaucoma suspect/preperimetric glaucoma was not enough to see future visual field progression. The visual field inclusion criteria for the glaucoma suspect/preperimetric glaucoma eyes required GHT within normal limits and MD and PSD indices within 95% CI. It has been demonstrated that patients with worse baseline visual field MD or PSD are more likely to undergo a more rapid subsequent rate of functional change in the future among those with early or suspected glaucoma.^{43–45}; B) The follow-up time was not long enough to allow a significant rate of VFI loss in the glaucoma suspect/preperimetric glaucoma group.

In conclusion, structural progression measured using TD-OCT was associated with functional progression in glaucoma suspect/preperimetric glaucoma and glaucomatous eyes. Average and superior RNFL attenuations were the most important risk factors for visual

field progression. The annual rate of RNFL loss was significantly steeper in glaucomatous eyes compared with glaucoma suspect/preperimetric glaucoma eyes for average, superior, inferior and temporal RNFL thickness values.

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References

- Schuman JS, Hee MR, Arya AV, et al. Optical coherence tomography: a new tool for glaucoma diagnosis. *Curr Opin Ophthalmol*. 1995; 6(2):89–95. [PubMed: 10150863]
- Hood DC, Kardon RH. A framework for comparing structural and functional measures of glaucomatous damage. *Prog Retin Eye Res*. 2007; 26(6):688–710. [PubMed: 17889587]
- Artes PH, Chauhan BC. Longitudinal changes in the visual field and optic disc in glaucoma. *Prog Retin Eye Res*. 2005; 24(3):333–54. [PubMed: 15708832]
- Greenfield DS. Optic nerve and retinal nerve fiber layer analyzers in glaucoma. *Curr Opin Ophthalmol*. 2002; 13(2):68–76. [PubMed: 11880718]
- Zhu H, Crabb DP, Fredette MJ, Anderson DR, Garway-Heath DF. Quantifying Discordance Between Structure and Function Measurements in the Clinical Assessment of Glaucoma. *Arch Ophthalmol*. 2011; 129(9):1167–74. [PubMed: 21555599]
- Zhu H, Crabb DP, Schlottmann PG, et al. Predicting visual function from the measurements of retinal nerve fiber layer structure. *Invest Ophthalmol Vis Sci*. 2010; 51(11):5657–66. [PubMed: 20505207]
- Falsini B, Marangoni D, Salgarello T, et al. Structure-function relationship in ocular hypertension and glaucoma: interindividual and interocular analysis by OCT and pattern ERG. *Graefes Arch Clin Exp Ophthalmol*. 2006; 44(8):1153–62. [PubMed: 18386035]
- Strouthidis NG, Vinciotti V, Tucker AJ, Gardiner SK, Crabb DP, Garway-Heath DF. Structure and function in glaucoma: The relationship between a functional visual field map and an anatomic retinal map. *Invest Ophthalmol Vis Sci*. 2006; 47(12):5356–62. [PubMed: 17122124]
- Harwerth RS, Quigley HA. Visual field defects and retinal ganglion cell losses in patients with glaucoma. *Arch Ophthalmol*. 2006; 124(6):853–9. [PubMed: 16769839]
- Johnson CA, Sample PA, Zangwill LM, et al. Structure and function evaluation (SAFE): II. Comparison of optic disk and visual field characteristics. *Am J Ophthalmol*. 2003; 135(2):148–54. [PubMed: 12566017]
- Johnson CA, Cioffi GA, Liebmann JR, Sample PA, Zangwill LM, Weinreb RN. The relationship between structural and functional alterations in glaucoma: a review. *Semin Ophthalmol*. 2000; 15(4):221–33. [PubMed: 17585436]
- Zhu H, Crabb DP, Anderson D, Fredette MJ, Garway-Heath DF. Combining Structural and Functional Measurements to Improve Reproducibility of Follow Up Data in Glaucoma. *Invest Ophthalmol Vis Sci*. 2009; 50(5):2572. [PubMed: 19151381]
- Hood DC, Anderson SC, Wall M, Kardon RH. Structure versus function in glaucoma: an application of a linear model. *Invest Ophthalmol Vis Sci*. 2007; 48(8):3662–8. [PubMed: 17652736]
- Harwerth RS, Carter-Dawson L, Smith EL 3rd, Barnes G, Holt WF, Crawford ML. Neural losses correlated with visual losses in clinical perimetry. *Invest Ophthalmol Vis Sci*. 2004; 45(9):3152–60. [PubMed: 15326134]
- 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(4):464–70. [PubMed: 15824218]

16. Medeiros FA, Zangwill LM, Girkin CA, Liebmann JM, Weinreb RN. Combining Structural and Functional Measurements to Improve Estimates of Rates of Glaucomatous Progression. *Am J Ophthalmol.* 2012; 153(6):1197–1205. [PubMed: 22317914]
17. Sample PA, Johnson CA. Functional assessment of glaucoma. *J Glaucoma.* 2001; 10(5, Suppl 1):S49–52. [PubMed: 11890275]
18. Spaeth GL, Lopes JF, Junk AK, Grigorian AP, Henderer J. Systems for staging the amount of optic nerve damage in glaucoma: a critical review and new material. *Surv ophthalmol.* 2006; 51(4):293–315. [PubMed: 16818081]
19. Zangwill LM, Bowd C. Retinal nerve fiber layer analysis in the diagnosis of glaucoma. *Curr Opin Ophthalmol.* 2006; 17(2):120–31. [PubMed: 16552246]
20. Budenz DL, Fredette MJ, Feuer WJ, Anderson DR. Reproducibility of peripapillary retinal nerve fiber thickness measurements with stratus OCT in glaucomatous eyes. *Ophthalmology.* 2008; 115(4):661–6. e4. [PubMed: 17706287]
21. DeLeon Ortega JE, Sakata LM, Kakati B, et al. Effect of glaucomatous damage on repeatability of confocal scanning laser ophthalmoscope, scanning laser polarimetry, and optical coherence tomography. *Invest Ophthalmol Vis Sci.* 2007; 48(3):1156–63. [PubMed: 17325159]
22. Boden C, Blumenthal EZ, Pascual J, et al. Patterns of glaucomatous visual field progression identified by three progression criteria. *Am J Ophthalmol.* 2004; 138:1029–36. [PubMed: 15629296]
23. Sample PA, Bosworth CF, Weinreb RN. The loss of visual function in glaucoma. *Semin Ophthalmol.* 2000; 15(4):182–93. [PubMed: 17585433]
24. Huang D, Swanson EA, Lin CP, et al. Optical coherence tomography. *Science.* 1991; 254(5035):1178–81. [PubMed: 1957169]
25. Schuman JS, Pedut-Kloizman T, Hertzmark E, et al. Reproducibility of nerve fiber layer thickness measurements using optical coherence tomography. *Ophthalmology.* 1996; 103(11):1889–98. [PubMed: 8942887]
26. Medeiros FA, Alencar LM, Zangwill LM, Bowd C, Sample PA, Weinreb RN. Prediction of functional loss in glaucoma from progressive optic disc damage. *Arch Ophthalmol.* 2009; 127(10):1250–6. [PubMed: 19822839]
27. Strouthidis NG, Fortune B, Yang H, Sigal IA, Burgoyne CF. Longitudinal change detected by spectral domain optical coherence tomography in the optic nerve head and peripapillary retina in experimental glaucoma. *Invest Ophthalmol Vis Sci.* 2011; 52(3):1206–19. [PubMed: 21217108]
28. Schuman JS, Pedut-Kloizman T, Pakter H, et al. Optical coherence tomography and histologic measurements of nerve fiber layer thickness in normal and glaucomatous monkey eyes. *Invest Ophthalmol Vis Sci.* 2007; 48(8):3645–54. [PubMed: 17652734]
29. Budenz DL, Chang RT, Huang X, Knighton RW, Tielsch JM. Reproducibility of retinal nerve fiber thickness measurements using the stratus OCT in normal and glaucomatous eyes. *Invest Ophthalmol Vis Sci.* 2005; 46(7):2440–3. [PubMed: 15980233]
30. Bengtsson B, Heijl A. A visual field index for calculation of glaucoma rate of progression. *Am J Ophthalmol.* 2008; 145(2):343–53. [PubMed: 18078852]
31. Levi DM, Klein SA, Aitsebaomo AP. Vernier acuity, crowding and cortical magnification. *Vision research.* 1985; 25(7):963–77. [PubMed: 4049746]
32. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics.* 1986; 42(1):121–30. [PubMed: 3719049]
33. Guo SW, Lin DY. Regression analysis of multivariate grouped survival data. *Biometrics.* 1994; 50(3):632–9. [PubMed: 7981390]
34. Katz J, Congdon N, Friedman DS. Methodological variations in estimating apparent progressive visual field loss in clinical trials of glaucoma treatment. *Arch Ophthalmol.* 1999; (9):117, 1137–42. [PubMed: 9930173]
35. Sung KR, Kim S, Lee Y, Yun SC, Na JH. Retinal nerve fiber layer normative classification by optical coherence tomography for prediction of future visual field loss. *Invest Ophthalmol Vis Sci.* 2011; 52(5):2634–9. [PubMed: 21282570]

36. Lalezary M, Medeiros FA, Weinreb RN, et al. Baseline optical coherence tomography predicts the development of glaucomatous change in glaucoma suspects. *Am J Ophthalmol*. 2006; 142(4):576–82. [PubMed: 17011848]
37. Mansouri K, Leite MT, Medeiros FA, Leung CK, Weinreb RN. Assessment of rates of structural change in glaucoma using imaging technologies. *Eye (Lond)*. 2011; 25(3):269–77. [PubMed: 21212798]
38. Leung CK, Chiu V, Weinreb RN, et al. Evaluation of Retinal Nerve Fiber Layer Progression in Glaucoma A Comparison between Spectral-Domain and Time-Domain Optical Coherence Tomography. *Ophthalmology*. 2011; 118:1558–62. [PubMed: 21529954]
39. Leung CK, Liu S, Weinreb RN, et al. Evaluation of retinal nerve fiber layer progression in glaucoma a prospective analysis with neuroretinal rim and visual field progression. *Ophthalmology*. 2011; 118(8):1551–7. [PubMed: 21529958]
40. Xin D, Greenstein VC, Ritch R, Liebmann JM, De Moraes CG, Hood DC. A comparison of functional and structural measures for identifying progression of glaucoma. *Invest Ophthalmol Vis Sci*. 2011; 52(1):519–26. [PubMed: 20847115]
41. Strouthidis NG, Gardiner SK, Owen VM, Zuniga C, Garway-Heath DF. Predicting progression to glaucoma in ocular hypertensive patients. *J Glaucoma*. 2010; 19(5):304–9. [PubMed: 19730117]
42. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002; 120(6):701–13. [PubMed: 12049574]
43. Gardiner SK, Demirel S, Johnson CA. Perimetric indices as predictors of future glaucomatous functional change. *Optom Vis Sci*. 2011; 88(1):56–62. [PubMed: 20966804]
44. Leske MC, Heijl A, Hussein M, Bengtsson B, Hyman L, Komaroff E. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. *Arch Ophthalmol*. 2003; 121(1):48–56. [PubMed: 12523884]
45. 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(6):714–20. [PubMed: 12049575]

Biography

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Figure 1.

Cumulative probability of visual field progression over follow-up period was significantly higher for eyes with perimetric glaucoma versus eyes that were diagnosed as glaucoma suspect or preperimetric glaucoma (Kaplan-Meier analysis, Logrank test $p < 0.001$).

Figure 2.

Cumulative probability of visual field progression was significantly higher for eyes that had overall retinal nerve fiber layer (RNFL) progression over follow-up period versus those that did not (Kaplan-Meier analysis, Logrank test $p = 0.014$).

Table 1

Clinical characteristics of two groups of perimetric glaucoma, and glaucoma suspect and preperimetric glaucoma eyes at baseline. For continuous variables, mean $\pm$ standard deviation (minimum - maximum) have been presented.

	Perimetric glaucoma eyes (n=177); Patients (n=115)	Glaucoma suspect/preperimetric glaucoma eyes (n=310); Patients (n=181)	p-value
Age (years) [‡]	62.2 $\pm$ 9.4 (40 – 80)	59.8 $\pm$ 9.6 (40 – 79)	*0.14
Gender			‡0.75
Male	46 (40%)	69 (38.1%)	
Female	69 (60%)	112 (61.9%)	
Ethnicity			‡0.59
Caucasian	62 (62.6%)	116 (64.1%)	
Hispanic	15 (13.0%)	20 (11.1%)	
African American	12 (10.4%)	20 (11.1%)	
Others	16 (13.9%)	25 (13.8%)	
Family history of glaucoma	56 (48.7%)	94 (51.9%)	‡0.60
Follow up duration (month) [‡]	36.4 $\pm$ 13.8 (30 – 66)	40.6 $\pm$ 11.5 (30 – 66)	* <0.001
Diagnosis	POAG 160 Secondary GL 12 PACG 5	OHT 88 ONH/RNFL defect 187 OHT + ONH/RNFL 22 Fellow eye with PG 13	
IOP (mmHg) [‡]	14.73 $\pm$ 3.74 (4.00 – 33.00)	16.78 $\pm$ 3.75 (6.50 – 27.00)	* <0.0001
CCT (μ m) [‡]	542.0 $\pm$ 35.4 (448 – 697)	555.4 $\pm$ 34.19 (460 – 677)	* <0.0001
SAP [‡]			*
MD (dB)	–3.82 $\pm$ 4.28 (–20.7 to 1.59)	–0.23 $\pm$ 1.04 (–7.7 to 3.1)	<0.0001
PSD (dB)	5.37 $\pm$ 4.21 (0 – 16.5)	1.61 $\pm$ 0.38 (0.9 – 4.5)	<0.0001
VFI (%)	88.77 $\pm$ 13.08 (37 – 100)	99.07 $\pm$ 1.14 (93 – 100)	<0.0001
OCT (μ m) [‡]			*
Average	76.44 $\pm$ 13.57 (35.4 – 121.0)	92.74 $\pm$ 12.20 (52.8 – 127.9)	<0.0001
Temporal quadrant	59.23 $\pm$ 15.15 (24 – 95)	67.43 $\pm$ 14.09 (32 – 113)	<0.0001
Superior quadrant	91.39 $\pm$ 21.01 (33 – 147)	111.10 $\pm$ 20.58 (56 – 168)	<0.0001
Nasal quadrant	64.39 $\pm$ 16.98 (31 – 134)	74.14 $\pm$ 17.35 (34 – 146)	<0.0001
Inferior quadrant	90.81 $\pm$ 23.11 (43 – 154)	118.20 $\pm$ 18.79 (71 – 175)	<0.0001

[‡]Data were presented as mean $\pm$ standard deviation (minimum – maximum);

* Analysis of variance adjusted for inter-eye correlation;

[†] Chi-square test; POAG = primary open-angle glaucoma; OHT = ocular hypertension; GL = glaucoma; ONH = optic nerve head; RNFL = retinal nerve fiber layer; PACG = primary angle closure glaucoma; IOP = intraocular pressure; CCT = central corneal thickness; SAP = standard automated perimetry; MD = mean deviation; PSD = pattern standard deviation; VFI = visual field index; OCT = optical coherence tomography.

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Table 2

The number of eyes showing progression by visual field index (VFI) criteria in each of the glaucoma suspect (GS), preperimetric glaucoma (PPG) and perimetric glaucoma (PG) groups.

Patient Group		Visual field Progression	Total
PG	Perimetric Glaucoma patients	48	177
GS	1: OHT (Ocular Hypertension)	15	88
PPG	2: Abnormality in ONH or RNFL	23	187
PPG	3: OHT and ONH or RNFL abnormality	2	22
GS	4: Fellow eye of Perimetric glaucoma	1	13

Table 3

The annual rates of loss in standard automated perimetry indices in two groups of perimetric glaucoma, and glaucoma suspect/preperimetric glaucoma, utilizing all participants' data. The rates (slopes) were estimated using mixed effect models.

SAP parameters	Perimetric Glaucoma	Glaucoma Suspect and Preperimetric Glaucoma	p-value *
VFI %/year	-0.44 ± 0.059	-0.070 ± 0.023	<0.001
MD dB/year	-0.18 ± 0.025	-0.054 ± 0.014	<0.001
PSD dB/year	0.073 ± 0.022	0.017 ± 0.0075	<0.001

SAP = standard automated perimetry; VFI = visual field index; MD = mean deviation; PSD = pattern standard deviation; dB = decibel;

* A random effect for eye was added to the mixed effect model to adjust for the inter-eye correlation.

Table 4

The comparison between the annual rates of loss in RNFL ($\mu\text{m}/\text{year}$) of perimetric glaucoma versus glaucoma suspect/preperimetric glaucoma eyes, utilizing all participants' data. Rates (slopes) were estimated using mixed effect models.

OCT parameters	Perimetric Glaucoma	Glaucoma Suspect and Preperimetric Glaucoma	P-value*
Average RNFL	-0.75 ± 0.09	-0.40 ± 0.064	<0.001
Superior RNFL	-1.25 ± 0.17	-0.66 ± 0.12	<0.001
Inferior RNFL	-0.80 ± 0.14	-0.38 ± 0.11	<0.001
Temporal RNFL	-0.36 ± 0.13	0.073 ± 0.099	0.007
Nasal RNFL	-0.63 ± 0.17	-0.62 ± 0.14	0.99

OCT = optical coherence tomography; RNFL = retinal nerve fiber layer; *

* A random effect for eye was added to the mixed effect model to adjust for inter-eye correlation.

Table 5

In each disease category of perimetric glaucoma and glaucoma suspect/preperimetric glaucoma, the rate of Visual Field Index loss was compared between two groups of eyes that had significant retinal nerve fiber layer (RNFL) loss versus those that did not.

Glaucoma Status	Significant RNFL progression	VFI (%/year)	P value *
Perimetric Glaucoma	Yes	-0.71 ± 0.13	0.006
	No	-0.34 ± 0.065	
Glaucoma Suspect and Preperimetric Glaucoma	Yes	-0.11 ± 0.050	0.27
	No	-0.058 ± 0.026	

RNFL = retinal nerve fiber layer; VFI = Visual Field Index. Rates (slopes) were estimated using mixed effect models.

* A random effect for eye was added to the mixed effect model to adjust for the inter-eye correlation.

Table 6

Baseline visual field and retinal nerve fiber layer (RNFL) parameters were compared between the two groups of eyes that showed progression using significant visual field index (VFI) slope versus the eyes that showed significant RNFL slope. Values represent mean $\pm$ standard deviation (minimum – maximum).

	VFI progression only (30 eyes diagnosed as glaucoma suspect/preperimetric glaucoma; and 33 eyes diagnosed as perimetric glaucoma)	RNFL progression only (45 eyes diagnosed as glaucoma suspect/preperimetric glaucoma and 30 eyes diagnosed as perimetric glaucoma)	p-value
Number	63	75	0.35
Age	61.5 $\pm$ 8.6 (40 – 77)	61.8 $\pm$ 8.1 (41 – 80)	0.71
Baseline RNFL	83.3 $\pm$ 14.2 (58.0 – 127.9)	89.1 $\pm$ 14.1 (49.1 – 123.6)	0.02 *
Baseline VFI	93.6 $\pm$ 10.6 (60 – 100)	94.2 $\pm$ 10.2 (47 – 100)	0.73 *
Baseline MD	–2.96 $\pm$ 3.88 (–14.7 to 2.0)	–1.96 $\pm$ 2.96 (–15.0 to 1.6)	0.09 *
Baseline PSD	4.17 $\pm$ 4.33 (1.1 – 16.5)	3.17 $\pm$ 2.90 (1.1 – 14.2)	0.11 *

VFI = visual field index; RNFL = retinal nerve fiber layer; MD = mean deviation; PSD = pattern standard deviation.

* General estimating equation method was used to adjust for inter-eye correlation from the same patient.

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Table 7

Univariate Cox proportional hazard ratios to identify the clinical risk factors predictive of visual field progression in glaucoma suspect, preperimetric and perimetric glaucoma eyes.

Univariate					
Covariates (Univariate)	Per Risk Unit	HR	p-value	L95CI	U95CI
Age	10 years older	1.17	0.17	0.94	1.47
Gender	Female	0.95	0.85	0.59	1.55
Race	African Origin	0.67	0.41	0.26	1.73
Family history of glaucoma	Yes	0.91	0.68	0.56	1.45
Central corneal thickness	-40 µm	1.18	0.26	0.89	1.56
IOP at baseline	+1mmHg	0.97	0.36	0.91	1.04
Mean Deviation at baseline	1dB Lower	1.09	0.00	1.03	1.14
Pattern Standard Deviation at baseline	1dB Higher	1.11	0.00	1.05	1.17
VFI at baseline	5 lower	1.09	0.08	0.99	1.20

HR = hazard ratio; L95CI = lower limit of 95% confidence interval; U95CI = upper limit of 95% confidence interval; IOP = intraocular pressure; VFI = visual field index; RNFL = retinal nerve fiber layer

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Table 8

Univariate and multivariate Cox proportional hazard ratios and 95% confidence interval limits to identify the retinal nerve fiber layer thickness risk factors predictive of visual field progression among glaucoma suspect, preperimetric and perimetric glaucoma eyes.

		Univariate				Multivariate			
Covariates (Univariate)	Per Risk Unit	HR	p-value	L95CI	U95CI	HR	p-value	L95CI	U95CI
Overall RNFL thickness at baseline	−10µm	1.18	0.03	1.02	1.37	1.08	0.41	0.90	1.28
Significant RNFL negative slope	Yes	1.85	0.01	1.16	2.95	1.93	0.01	1.21	3.10
Superior RNFL thickness at baseline	−10µm	1.07	0.17	0.97	1.19	1.01	0.76	0.96	1.06
Inferior RNFL thickness at baseline	−10µm	1.15	0.00	1.05	1.26	1.04	0.12	0.99	1.10
Temporal RNFL thickness at baseline	−10µm	1.03	0.71	0.88	1.22	0.99	0.73	0.91	1.07
Nasal RNFL thickness at baseline	−10µm	1.12	0.08	0.99	1.26	1.04	0.22	0.98	1.11

HR = hazard ratio; L95CI = lower limit of 95% confidence interval; U95CI = upper limit of 95% confidence interval; IOP = intraocular pressure; VFI = visual field index; RNFL = retinal nerve fiber layer

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Time dependent covariates that were associated with the risk of visual field progression in glaucoma suspect, preperimetric glaucoma and perimetric glaucoma eyes.

Table 9

Covariates (Univariate)	Per Risk Unit	Univariate				Multivariate			
		HR	p-value	L95CI	U95CI	HR	p-value	L95CI	U95CI
		Time dependent Covariates							
IOP	1mmHg Higher	0.97	0.49	0.91	1.05				
Time dependent Stratus OCT Covariates									
Overall RNFL loss from baseline	-10µm	1.40	0.02	1.05	1.87	1.38	0.03	1.02	1.85
Superior RNFL loss from baseline	-10µm	1.22	0.01	1.06	1.40	1.20	0.01	1.05	1.38
Inferior RNFL loss from baseline	-10µm	1.16	0.10	0.97	1.39	1.16	0.12	0.93	1.40
Temporal RNFL loss from baseline	-10µm	1.11	0.23	0.93	1.33	1.12	0.23	0.93	1.34
Nasal RNFL loss from baseline	-10µm	1.03	0.70	0.88	1.21	1.16	0.72	0.87	1.22

HR = hazard ratio; L95CI = lower limit of 95% confidence interval; U95CI = upper limit of 95% confidence interval; IOP = intraocular pressure; VFI = visual field index; RNFL = retinal nerve fiber layer