

UC San Diego

UC San Diego Previously Published Works

Title

Optic nerve head deformation in glaucoma: The temporal relationship between optic nerve head surface depression and retinal nerve fiber layer thinning

Permalink

<https://escholarship.org/uc/item/52t4412w>

Journal

Ophthalmology, 121(12)

ISSN

0161-6420

Authors

Xu, G
Weinreb, RN
Leung, CKS

Publication Date

2014-12-01

DOI

10.1016/j.opthta.2014.06.035

Peer reviewed

Optic Nerve Head Deformation in Glaucoma

The Temporal Relationship between Optic Nerve Head Surface Depression and Retinal Nerve Fiber Layer Thinning

Guihua Xu, BM,^{1,2} Robert N. Weinreb, MD,³ Christopher K. S. Leung, MD, MB ChB¹

Objective: To investigate the temporal relationship between optic nerve head (ONH) surface depression and retinal nerve fiber layer (RNFL) thinning measured by confocal scanning laser ophthalmoscopy (CSLO) and spectral-domain optical coherence tomography (SD-OCT), respectively, during the course of glaucoma progression.

Design: Prospective, longitudinal study.

Participants: A total of 146 eyes of 90 patients with glaucoma and 70 normal eyes of 35 healthy individuals followed for an average of 5.4 years (range, 48.0–76.6 months).

Methods: Eyes were imaged by CSLO (Heidelberg Retinal Tomograph [HRT]; Heidelberg Engineering, GmbH, Dossenheim, Germany) and SD-OCT (Cirrus HD-OCT; Carl Zeiss Meditec AG, Dublin, CA) at approximately 4-month intervals for measurement of ONH surface topography and RNFL thickness, respectively. Significant ONH surface depression and RNFL thinning were defined with reference to Topographic Change Analysis (TCA) with HRT and Guided Progression Analysis (GPA) with Cirrus HD-OCT, respectively. The survival probabilities were compared with a Cox proportional hazards model.

Main Outcome Measures: Number of eyes with progressive ONH and RNFL changes and the sequence of changes.

Results: A total of 3238 OCT and 3238 CSLO images obtained in the same follow-up visits were analyzed. At a specificity of 94.3% (4 eyes showed ONH surface depression and 4 eyes showed RNFL thinning in the normal group), 57 eyes (39.0%) had ONH surface depression, 46 eyes (31.5%) had RNFL thinning, and 23 eyes (15.8%) had evidence of both in the glaucoma group. Among these 23 eyes, 19 (82.6%) had ONH surface depression detected before RNFL thinning, with a median lag time of 15.8 months (range, 4.0–40.8 months). Although only 7.0% of eyes (4/57) had RNFL thinning at the onset of ONH surface depression, 45.7% (21/46) had ONH surface depression at the onset of RNFL thinning. The survival probability of eyes with ONH surface depression was significantly worse than eyes with RNFL thinning ($P = 0.002$).

Conclusions: With reference to the HRT TCA and OCT GPA, ONH surface depression occurred before RNFL thinning in a significant proportion of patients with glaucoma. A time window for therapeutic intervention may exist on detection of ONH surface depression before there is observable RNFL thinning in glaucoma. *Ophthalmology* 2014;121:2362–2370 © 2014 by the American Academy of Ophthalmology.

Although all forms of optic neuropathies exhibit loss of retinal ganglion cells and their axons, glaucoma is unique in having both retinal ganglion cell degeneration and chronic progressive deformation and remodeling of the optic nerve head (ONH). Characteristic features of ONH changes in glaucoma include narrowing of the neuroretinal rim, excavation of the optic cup, loss of prelaminar neural tissue, and deformation of the lamina cribrosa. Quantifying both ONH deformation and retinal nerve fiber layer (RNFL) thinning, a surrogate of loss of retinal ganglion cell axons is relevant to evaluate glaucoma progression. With the advent of digital imaging technologies, reproducible measurements of the ONH and RNFL thickness become feasible.^{1–8} Confocal scanning laser ophthalmoscopy (CSLO) quantifies the surface topography of the ONH, whereas optical coherence tomography (OCT) is most widely used to measure the

RNFL thickness. Although both CSLO and OCT are capable of detecting longitudinal changes of the ONH and RNFL, respectively, the sequence of change in glaucoma progression remains obscure. Specifically, it is unclear whether the topographic changes of the ONH are a cause or a consequence of RNFL thinning. Furthermore, there is no consensus regarding whether ONH topography or RNFL thickness is better for tracking glaucoma progression. Investigating the sequence of ONH and RNFL changes is thus not only relevant to understanding the role of ONH remodeling and deformation in glaucomatous optic nerve damage but also pertinent in devising optimal strategies for detection of disease progression.

Experimental glaucoma studies in nonhuman primates have provided valuable insights into the sequence of ONH and RNFL changes in glaucoma.^{9–12} The studies by Fortune

et al^{9,10} and Strouthidis et al¹¹ suggested that ONH surface height changes measured by CSLO occurred before reduction of RNFL thickness measured by OCT. However, the relatively short follow-up duration (in months rather than in years) and nonphysiologic intraocular pressure (IOP) fluctuation after laser photocoagulation of the trabecular meshwork (with peak IOP up to 50–60 mmHg^{9–11}) may limit the generalizability of the studies to human glaucoma. In the current study, we compared the performance of CSLO and OCT for detection of ONH and RNFL changes and investigated whether ONH surface depression developed before RNFL thinning during the course of glaucoma progression.

Methods

Subjects

A total of 125 subjects, including 90 patients with glaucoma and 35 normal healthy individuals, were consecutively enrolled and followed during the period from June 2007 to November 2013 at the University Eye Center, the Chinese University of Hong Kong. All subjects underwent a full ophthalmic examination, including measurement of visual acuity, refraction and IOP, gonioscopy, and fundus examination. The optic disc was examined with slit-lamp biomicroscopy, and color optic disc stereophotographs were captured. Eyes were included if the visual acuity was at least 20/40 and excluded if there was macular disease, refractive or retinal surgery, or neurologic disease. No subjects had diabetes mellitus. Patients with glaucoma were identified on the basis of the presence of visual field defects (described later) with corresponding optic disc and RNFL changes in at least 1 eye independent of the level of IOP. During the follow-up, patients were treated at the discretion of the attending ophthalmologists with reference to the target IOP. Fourteen eyes (9.6%) had trabeculectomy, and 116 eyes (79.5%) were on at least 1 glaucoma medication at the latest follow-up visit. Normal individuals had no structural optic disc abnormalities and no RNFL defects, no history of IOP >21 mmHg, no visual field defect, and no history of ocular disease, neurologic disease, or major systemic illness. Both eyes had OCT RNFL imaging (Cirrus HD-OCT; Carl Zeiss Meditec AG, Dublin, CA), CSLO optic disc imaging (Heidelberg Retinal Tomograph [HRT]; Heidelberg Engineering, GmbH, Dossenheim, Germany), and visual field testing (Humphrey Field Analyzer II-I; Carl Zeiss Meditec AG) in the same visit at approximately 4-month intervals for at least 48 months. The study was conducted in accordance with the ethical standards stated in the 1964 Declaration of Helsinki and approved by local research ethics committee with written informed consent obtained.

Optical Coherence Tomography Retinal Nerve Fiber Layer Imaging

The details of the principles of spectral-domain OCT have been described,¹³ and the methods of OCT RNFL imaging have been described in our earlier studies.^{1,14} The acquisition rate of the Cirrus HD-OCT was 27 000 A-scans per second, and the transverse and axial resolutions were 15 μ m and 5 μ m, respectively. An “optic disc cube” scan protocol was used to measure the RNFL thickness in a 6×6 mm² region (200×200 pixels) centered at the optic disc, and an RNFL thickness map was generated. Only images with signal strength ≥ 7 were included in the analysis. Saccadic eye movement was detected with the line-scanning ophthalmoscope overlaid with OCT en face images. Images with motion artifact, poor centration, poor focus or missing data were detected by the

operator at the time of imaging, and re-scanning was performed in the same visit.^{1,14}

Detection of Progressive Retinal Nerve Fiber Layer Thinning

The Cirrus HD-OCT Guided Progression Analysis (GPA) (Carl Zeiss Meditec AG) was used to analyze serial RNFL thickness maps (200×200 pixels) for detection of progressive RNFL thinning.¹⁵ Guided Progression Analysis automatically aligned and registered 2 baseline and the follow-up OCT images so that the same superpixel (1 superpixel = 4×4 pixels) locations could be analyzed for detection of change. The difference in RNFL measurement of an individual superpixel between the baseline and the follow-up RNFL thickness maps was compared with an estimate of test–retest variability of that particular superpixel (proprietary database from Carl Zeiss Meditec AG). Superpixels with an RNFL measurement difference exceeding the test–retest variability between a follow-up and the first and second baseline images would be encoded in yellow in the OCT RNFL thickness change map (50×50 superpixels). If the same changes were evident in an additional consecutive follow-up image, the superpixels would be encoded in red. In this study, the 2 baseline images were separated by approximately 4 months and progressive RNFL thinning was confirmed when an area of more than 20 superpixels (factory default) was encoded in red in the RNFL thickness change map for at least 2 consecutive visits. At least 3 consecutive follow-up visits showing significant RNFL thickness reduction were required to confirm progressive RNFL thinning.

Confocal Scanning Laser Ophthalmoscopy of the Optic Nerve Head

Optic disc imaging was performed with the HRT 3 (Heidelberg Engineering). A 3-dimensional topographic image consisting of up to 384×384×64 pixels was constructed from multiple focal planes axially along the ONH. An average of 3 consecutive scans was obtained and aligned to compose a single mean topography for analysis. The optic disc margin was outlined by an experienced examiner on the mean topographic image. Once the contour line was drawn, the software automatically calculated all the optic disc measurements. The area above the reference plane was defined as the rim, and the area below was defined as the cup. The reference plane was defined at 50 μ m posterior to the mean retinal height between 350° and 356° along the contour line. Re-scanning was performed in the same visit if motion artifacts were detected immediately after the imaging. All eyes included in the analysis had an image quality standard deviation ≤ 30 μ m.

Detection of Progressive Optic Nerve Head Surface Depression

The HRT Topographic Change Analysis (TCA, Heidelberg Engineering) was used to analyze serial ONH topography images (96×96 superpixels; 1 superpixel = 4×4 pixels) for detection of ONH surface depression.¹⁶ Individual superpixel ONH surface height measurements were compared between the baseline and each of the follow-up examinations with an F test. The pooled variability of the baseline and the follow-up examinations of a particular pixel was compared with the within variability of the baseline and the follow-up examinations (with an error probability of the F-test <5%). If significant ONH surface depression was detected in a superpixel and confirmed with ≥ 2 consecutive follow-up visits, the superpixel would be encoded in red in the significance map. The saturation of the color increased with the magnitude of surface height change. Progressive ONH surface

depression was defined using 3 criteria (liberal, moderate, and conservative) with reference to the area and depth of ONH surface depression adopted from the studies by Chauhan and colleagues.^{17,18} The liberal criterion required a cluster of $\geq 0.5\%$ of the disc area and a depth change of ≥ 20 μm ; the moderate criterion a cluster of $\geq 1\%$ of the disc area and a depth change of ≥ 50 μm ; and the conservative criterion a cluster of $\geq 2\%$ of the disc area and a depth change of ≥ 100 μm . The change had to occur in at least 3 of 4 consecutive follow-up examinations. These criteria were validated in 34 normal eyes and the specificities were 81% (95% confidence interval [CI], 67.8–94.2), 94% (95% CI, 86.0–100), and 97% (95% CI, 91.3–100), respectively, at 5 years.^{17,18}

To standardize the criteria for defining ONH and RNFL progression in this study, ≥ 3 consecutive follow-up visits showing significant changes were required to confirm ONH surface depression and RNFL thinning. The first follow-up visit in which the ONH significance map/RNFL thickness change map was encoded in red with the required area/number of superpixels (i.e., the consecutive visit when significant changes were detected) was considered as the time when ONH surface depression/RNFL thinning was initially detected, which was determined at or after the fourth follow-up visit. Optic nerve head surface depression/RNFL thinning was determined at or after the fourth visit because at least 4 visits (2 baseline and 2 follow-up) were required to detect significant changes encoded in red in the RNFL thickness change map, whereas only a minimum of 3 visits (1 baseline and 2 follow-up) were required to detect significant changes encoded in red in the ONH significance map. Determining progression at or after the fourth follow-up visit would eliminate potential bias favoring HRT TCA over OCT GPA for detection of change.

Correspondence in location of progression between HRT and OCT was examined at the time when ONH and RNFL changes were initially detected. The number of eyes with corresponding ONH and RNFL changes in the superior (0–179 degrees) or inferior (180–359 degrees) sector(s) of the optic disc was recorded.

Optical Coherence Tomography and Confocal Scanning Laser Ophthalmoscopy Images Included for Progression Analysis

A total of 3274 OCT and 3412 CSLO images were collected from the same OCT and CSLO instruments. After excluding images with inadequate image quality (144 HRT images had image quality standard deviation >30 ; 27 images had signal strength <7), motion artifact (6 OCT images), and failure to register with the baseline images for GPA (3 OCT images), 3238 OCT and 3268 CSLO images were qualified for inclusion. To ensure a fair comparison between GPA and TCA, we included only eyes that had both qualified OCT and CSLO images available in the same visit. Thus, 3238 OCT and 3238 CSLO images from 216 eyes (90 patients with glaucoma and 35 normal subjects) were finally included for GPA and TCA.

Visual Field Examination

The details of visual field examination have been described in our previous studies.^{1,14} Visual field was obtained with the white-on-white SITA standard 24-2 strategy in Humphrey Field Analyzer II-i (Carl Zeiss Meditec AG). All visual fields included in the study had fixation losses, false-positive errors, and false-negative errors less than 20%. Average visual field sensitivity was expressed in mean deviation (MD), as calculated by the perimetry software. A visual field defect was defined as having ≥ 3 significant ($P < 0.05$) nonedge contiguous points with at least 1 at the $P < 0.01$ level on

the same side of horizontal meridian in the pattern deviation plot and confirmed with at least 2 consecutive examinations.^{1,14}

Detection of Visual Field Progression

Visual field progression was analyzed with event analysis using the GPA, according to the Early Manifest Glaucoma Trial (EMGT) criteria.¹⁹ Progression was defined when there were ≥ 3 points that showed significant change (greater than the test–retest variabilities) compared with 2 baseline examinations (separated by ~ 4 months in this study) for ≥ 3 consecutive tests (i.e., “likely progression” was noted in the GPA printout in the latest follow-up visit).

Statistical Analysis

Statistical analyses were performed using Stata version 12.0 (StataCorp LP, College Station, TX). Differences in demographics, visual field, ONH, and RNFL measurements between the normal and glaucoma groups were compared with linear mixed models after adjustment of correlation between fellow eyes. The survival probability of the structural parameters in the progression analysis was compared with the Cox proportional hazards model, and the correlation between fellow eyes was adjusted with a shared-frailty model.²⁰ The agreement between ONH surface depression and RNFL thinning, and between visual field progression and RNFL/ONH progression was calculated with kappa statistics. A value between 0.0 and 0.2 indicates slight agreement, 0.21 and 0.40 indicates fair agreement, 0.41 and 0.60 indicates moderate agreement, 0.61 and 0.80 indicates substantial agreement, and 0.81 and 1 indicates almost perfect agreement.²¹ $P < 0.05$ was considered statistically significant.

Results

A total of 2215 CSLO and 2215 OCT images of 146 eyes of 90 patients with glaucoma followed at a mean of 4.1-month intervals for an average of 5.4 years (range, 48.3–76.6 months) were included in the analysis. The IOP was 18.1 ± 3.7 mmHg (range, 9.0–29.0 mmHg) at the baseline and 16.7 ± 4.2 mmHg (8.0–35.0 mmHg) at the latest follow-up visit. At the baseline examination, there were 68.7% mild ($\text{MD} \geq -6$ dB), 22.5% moderate (-6 dB $> \text{MD} > -12$ dB) and 8.8% advanced ($\text{MD} \leq -12$ dB) glaucomatous eyes. The demographics and baseline visual field, ONH, and RNFL measurements of the glaucoma and normal groups are presented in Table 1.

Optic Nerve Head Surface Depression and Retinal Nerve Fiber Layer Thinning in Patients with Glaucoma

At the latest follow-up visit, 64 eyes (43.8%; 48 patients), 57 eyes (39.0%; 43 patients), and 23 eyes (15.8%; 19 patients) developed progressive ONH surface depression detected by CSLO using the liberal, moderate, and conservative criteria, respectively. Progressive RNFL thinning was detected by OCT in 46 eyes (31.5%; 38 patients). All eyes with confirmed progressive RNFL thinning or ONH surface depression during the follow-up also had significant changes evident in the latest visit. Concomitant ONH and RNFL progression were found in 24 eyes (16.4%; 19 patients) using the liberal criterion, 23 eyes (15.8%; 18 patients) using the moderate criterion, and 10 eyes (6.8%; 7 patients) using the conservative criterion (Fig 1).

Table 1. Demographics, Visual Field, Optical Coherence Tomography, and Confocal Scanning Laser Ophthalmoscopy Measurements of Patients with Glaucoma and Normal Subjects (Mean $\pm$ Standard Deviation)

	Glaucoma	Normal	P Value
Subjects/eyes	90/146	35/70	-
Age (yrs)	54.05 $\pm$ 15.11	58.34 $\pm$ 6.84	0.018
Refraction (D)	-2.93 $\pm$ 4.03	-0.56 $\pm$ 1.92	0.001
Axial length (mm)	24.78 $\pm$ 2.07	23.52 $\pm$ 1.22	<0.001
Baseline visual field MD (dB)	-4.90 $\pm$ 5.00	-0.95 $\pm$ 1.64	<0.001
Baseline average RNFL thickness (μ m) (OCT)	75.88 $\pm$ 13.77	97.85 $\pm$ 11.27	<0.001
Baseline disc area (mm ²) (CSLO)	2.22 $\pm$ 0.53	2.03 $\pm$ 0.39	0.029
Baseline cup area (mm ²) (CSLO)	1.02 $\pm$ 0.58	0.42 $\pm$ 0.26	<0.001
Baseline rim area (mm ²) (CSLO)	1.20 $\pm$ 0.39	1.61 $\pm$ 0.31	<0.001
Baseline vertical cup disc ratio (CSLO)	0.62 $\pm$ 0.02	0.28 $\pm$ 0.02	<0.001

CSLO = confocal scanning laser ophthalmoscopy; D = diopter; dB = decibel; MD = mean deviation; OCT = optical coherence tomography; RNFL = retinal nerve fiber layer.

Specificity of Confocal Scanning Laser Ophthalmoscopy and Spectral-Domain Optical Coherence Tomography for Detection of Progression

A total of 1023 CSLO and 1023 OCT images of 70 eyes of 35 normal individuals followed at a mean of 4.5-month intervals for an average of 5.2 years (range, 48.0–72.8 months) were included for calculation of the specificities of CSLO and spectral-domain OCT. A total of 10, 4, and 2 eyes showed ONH surface depression using the liberal, moderate, and conservative criteria, respectively, and 4 eyes showed RNFL thinning. The estimated specificities were 85.7% (95% CI, 75.7–92.1), 94.3% (95% CI, 86.2–97.8), 97.1% (95% CI, 90.1–99.2), and 94.3% (95% CI, 86.2–97.8), respectively. By using the moderate criterion, the specificity of CSLO for detection of ONH surface depression (94.3%) would be comparable to the specificity of OCT for detection of RNFL thinning (94.3%).

Temporal and Spatial Relationship of Optic Nerve Head Surface Depression and Retinal Nerve Fiber Layer Thinning

Among the 23 eyes with both ONH surface depression and RNFL thinning evident at the latest follow-up visit using the moderate criterion (Fig 1), 8.7% (2 eyes) had RNFL thinning detected before ONH surface depression, 8.7% (2 eyes) had RNFL thinning and ONH surface depression in the same visit, and 82.6% (19 eyes) had ONH surface depression detected before RNFL thinning. The lag time between the onsets of RNFL thinning and ONH surface depression for these 19 eyes ranged from 4.0 to 40.8 months, with a median of 15.8 months (Fig 2). At the same level of specificity (94.3%), 7.0% of eyes (4/57) showed RNFL thinning at the onset of ONH surface depression. By contrast, 45.7% (21/46) demonstrated ONH surface depression at the onset of RNFL thinning. The survival probability of eyes with ONH surface depression was significantly worse than those with RNFL thinning ($P = 0.002$) (Fig 3); 65.2% (15/23) of eyes showed correspondence in the location of ONH and RNFL changes; 26.7% had superior, 60.0% had inferior, and 13.3% had diffuse ONH surface depression and RNFL thinning.

Agreement with Visual Field Progression

A total of 22 eyes (15.1%) had visual field progression defined by the EMGT criteria. The agreement with visual field progression was equally poor for both RNFL thinning (kappa = 0.076; 95% CI, -0.077 to 0.230) and ONH surface depression (kappa = 0.175; 95% CI, 0.034–0.316). Of note, for eyes with concomitant ONH surface depression, RNFL thinning, and visual field loss (6 eyes), ONH surface depression preceded visual field progression in all eyes (Fig 2).

Case Examples

Figures 4 and 5 illustrate the temporal and spatial relationships of ONH surface depression and RNFL thinning in 2 glaucomatous eyes from 2 patients. In the first example (Fig 4), diffuse ONH surface depression was first noticed on November 2, 2009, which was then followed by superior (June 25, 2010) and inferior

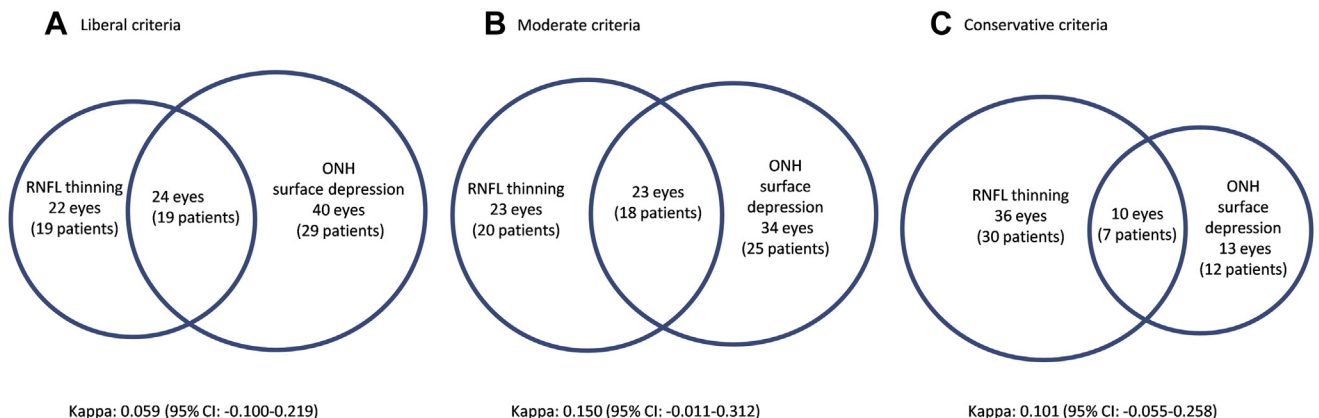


Figure 1. Venn diagrams showing the number of eyes with retinal nerve fiber layer (RNFL) thinning detected by optical coherence tomography (OCT) and optic nerve head (ONH) surface depression detected by confocal scanning laser ophthalmoscopy (CSLO) using the liberal (A), moderate (B), and conservative (C) criteria in patients with glaucoma. CI = confidence interval.

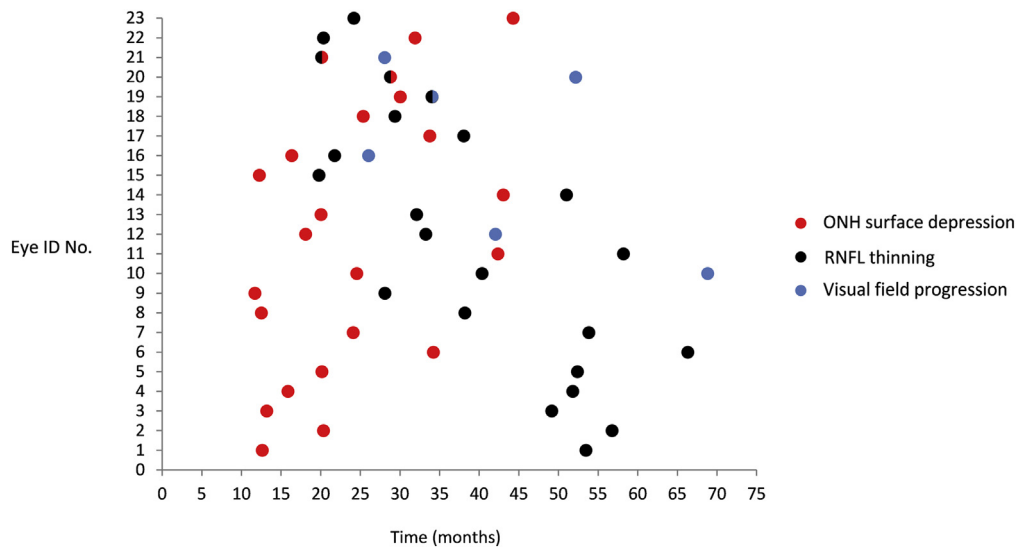


Figure 2. Temporal sequence of optic nerve head (ONH) surface depression (red dots) and retinal nerve fiber layer (RNFL) thinning (black dots) in the 23 glaucomatous eyes detected with both ONH and RNFL progression at the latest follow-up visit. Six eyes also showed visual field progression (blue dots) during the follow-up. ID No. = identification number.

(November 29, 2012) RNFL thinning. In the second example (Fig 5), inferotemporal ONH surface depression (September 29, 2009) preceded inferotemporal RNFL thinning (January 28, 2010), and there was correspondence in the location of ONH and RNFL progression.

Discussion

In this prospective study, we followed 146 eyes of 90 patients with glaucoma for an average of 5.4 years and showed that ONH surface depression generally occurred before RNFL thinning. This is supported by the observation that at a comparable level of specificity (94.3%), 82.6% of the 23 eyes with evidence of both progressive ONH and RNFL changes had ONH surface depression detected before RNFL

thinning. Furthermore, the survival probability of eyes with ONH surface depression was significantly worse than those with RNFL thinning ($P = 0.002$). At the onset of ONH surface depression, only 7.0% of eyes showed RNFL thinning, whereas at the onset of RNFL thinning, 45.7% already had ONH surface depression. These findings underscore the importance of detecting ONH surface depression for evaluation of glaucoma progression and provide insights of the impact of ONH deformation on retinal ganglion cell degeneration in glaucoma.

Although glaucoma is characterized by both ONH deformation and RNFL thinning, the temporal sequence of ONH and RNFL changes has remained obscure. Animal studies have suggested that ONH surface depression precedes RNFL thinning.^{9–12} By imaging the ONH with CSLO and RNFL with SD-OCT in 9 rhesus macaques that developed IOP elevation after laser photocoagulation of the trabecular meshwork, Strouthidis et al¹¹ reported no significant change in RNFL thickness at the onset of CSLO-detected ONH surface depression at 1.2 to 5.8 months after laser photocoagulation. Significant RNFL thinning was detected only at 7.1 to 14.0 months. Two recent studies by Fortune et al^{9,10} confirmed this observation with a larger sample size using the same imaging instruments. In a study examining 33 rhesus macaques for approximately 200 days, RNFL thickness did not significantly decrease until 15 days after the onset of ONH surface depression at 5 to 32 weeks post-laser photocoagulation of the trabecular meshwork.¹⁰ In another study following 68 rhesus macaques for an average of 10.0 ± 7.4 months, ONH surface depression was detected approximately 1 to 2 months earlier than RNFL thinning.⁹ These studies provided an important foundation for investigation of ONH and RNFL changes in glaucoma. Yet, there are limitations inherent to the animal models. Specifically, IOP elevation induced by laser photocoagulation of the trabecular meshwork would not recapitulate the

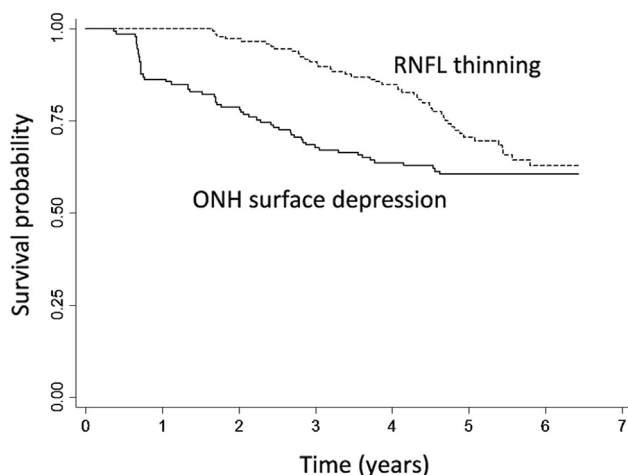


Figure 3. Survival function of eyes with optic nerve head (ONH) surface depression and retinal nerve fiber layer (RNFL) thinning.

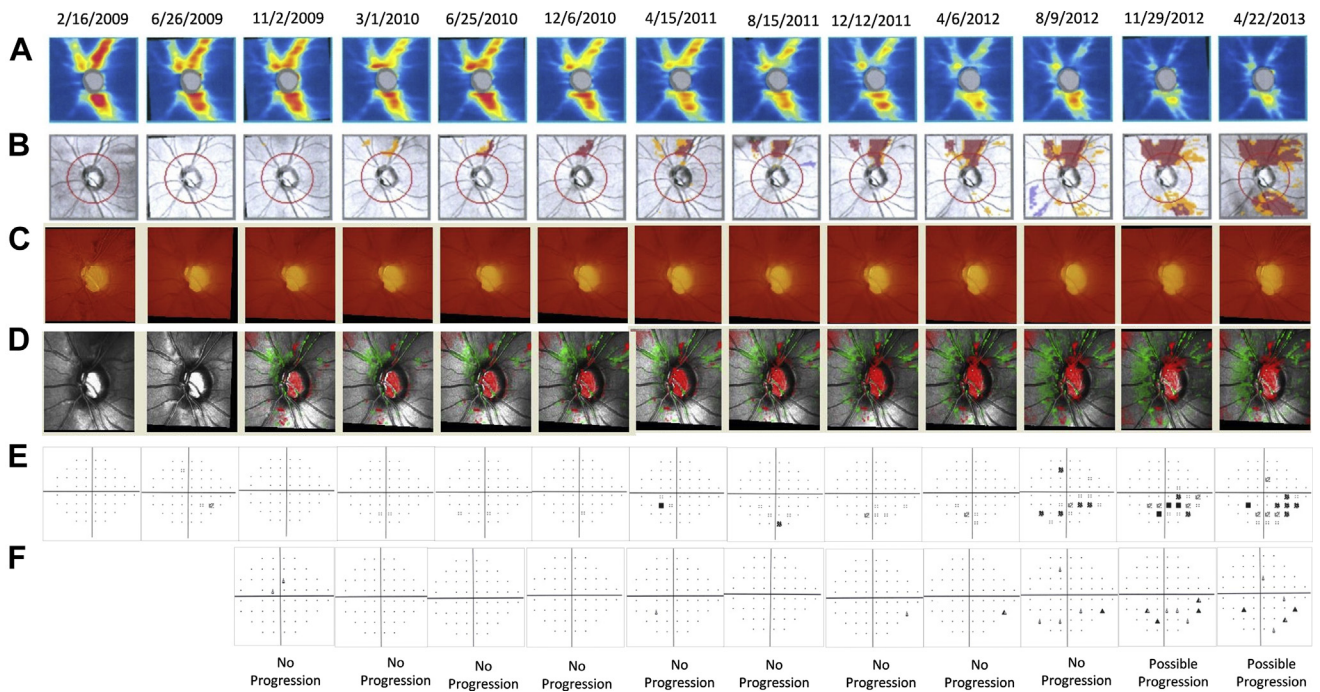


Figure 4. Serial retinal nerve fiber layer (RNFL) thickness maps (A), RNFL thickness change maps (B), optic nerve head (ONH) surface topology (C), ONH significance maps (D), pattern deviation plots (E), and Guided Progression Analysis (GPA) (Early Manifest Glaucoma Trial [EMGT] criteria) (F) of the left eye of a 27-year-old patient with primary open angle glaucoma followed for 50.4 months. Diffuse ONH surface depression was detected on November 2, 2009, which was then followed by superior (June 25, 2010) and inferior (November 29, 2012) RNFL thinning and visual field progression.

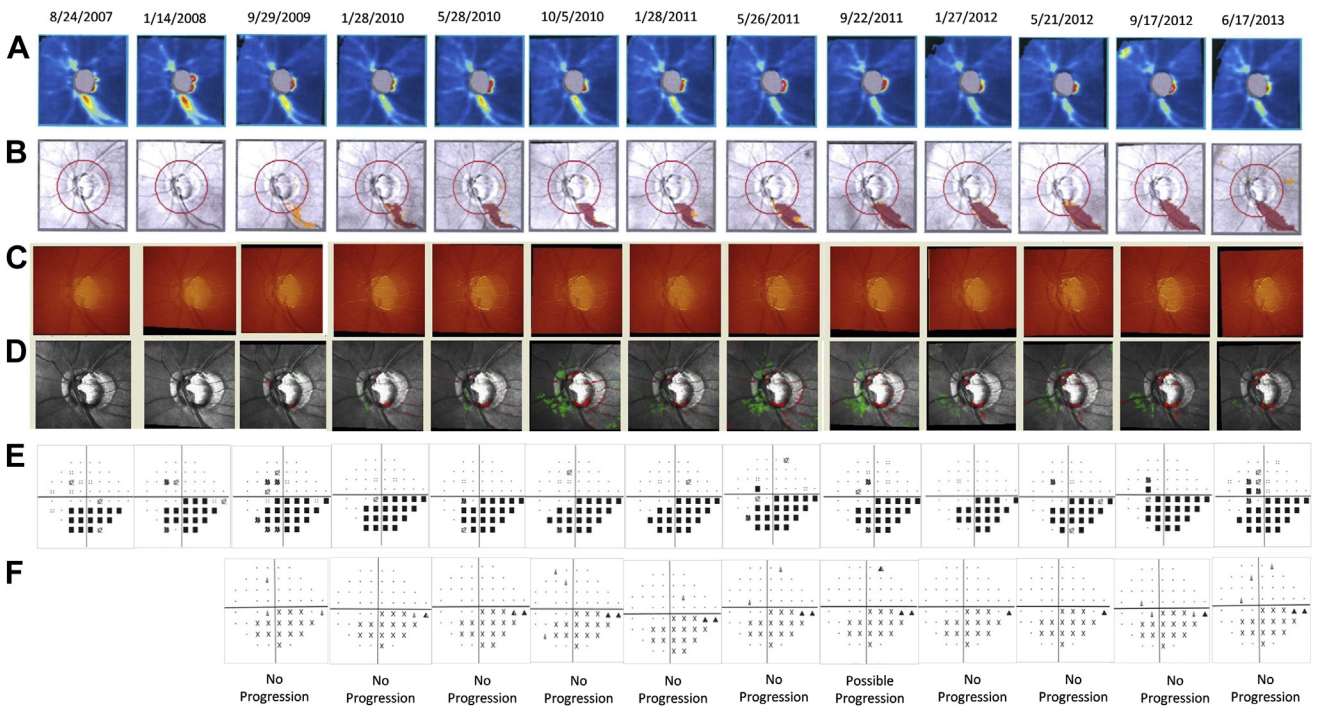


Figure 5. Serial retinal nerve fiber layer (RNFL) thickness maps (A), RNFL thickness change maps (B), optic nerve head (ONH) surface topology (C), ONH significance maps (D), pattern deviation plots (E), and Guided Progression Analysis (GPA) (Early Manifest Glaucoma Trial [EMGT] criteria) (F) of the left eye of a 48-year-old patient with primary open angle glaucoma followed for 70.2 months. The ONH surface depression was first noted on September 29, 2009, at the inferotemporal neuroretinal rim. Inferotemporal RNFL thinning was then detected on January 28, 2010.

IOP profiles in patients with glaucoma. High IOP spikes after laser photocoagulation (up to 50–60 mmHg in some studies) are not uncommon.^{9–11} Structural changes of the ONH consequential to an acute IOP effect remain a potential concern.¹¹ Although ONH surface depression and RNFL thinning were detected in weeks to months in experimental glaucoma, most patients with glaucoma progress in years and a longer follow-up duration would be needed to capture ONH deformation. Therefore, a long-term clinical study is relevant to decipher the relationship between ONH and RNFL changes in glaucoma.

Our clinical data corroborate previous experimental findings that ONH surface depression can be detected before RNFL loss. In contrast to the experimental glaucoma studies in which the lag time between RNFL and ONH surface changes was approximately 2 to 8 weeks, we found that ONH surface depression preceded RNFL thinning by up to 41 months (with a median of 16 months) in patients with glaucoma (Fig 2). This is a significant finding suggesting that ONH deformation and remodeling is a chronic process and that a time window might be available for therapeutic intervention in many patients on detection of ONH surface depression (i.e., before irreversible loss of the RNFL). Of note, in eyes with concomitant ONH surface depression, RNFL thinning, and visual field progression during the follow-up period, ONH surface depression always preceded visual field progression (Fig 2). Clinical trials investigating the impact of additional IOP lowering on detection of ONH surface depression on preserving visual function of patients with glaucoma are warranted.

The likelihood of detecting RNFL thinning versus ONH surface depression during the course of glaucoma progression may vary with the intrinsic properties of individual eyes and the specificity of the imaging instruments. It is notable that 23 eyes had RNFL thinning without ONH surface depression and 34 eyes had ONH surface depression without RNFL thinning using the moderate criterion (Fig 1B). It has been shown that a smaller corneal hysteresis is associated with a larger and deeper cup in glaucomatous eyes^{22,23} and correlates with greater pressure-related rim and cup volume/area changes.²⁴ Eyes with a smaller corneal hysteresis may signify a reduced viscous dampening of the cornea and an increased deformability of the ONH.²⁵ Detecting ONH surface depression might be more difficult in eyes with an increased corneal hysteresis. Retinal nerve fiber layer thinning may occur earlier than ONH surface depression in these eyes during the course of glaucoma progression. The biomechanical response of the lamina cribrosa in ONH remodeling also can be age related. The anterior laminar surface has been shown to be shallower in older than in younger eyes at a given level of glaucomatous visual field loss.²⁶ The lamina cribrosa also is less compliant to IOP reduction in older than in younger eyes.^{27,28} In this study, eyes detected with ONH surface depression only (33 eyes) were younger (48.6 ± 14.9 years) than eyes detected with RNFL thinning only (23 eyes) (50.2 ± 16.2 years), but the difference was not statistically significant ($P = 0.600$). We are conducting another study to investigate potential factors contributing to the predilection in detection of ONH and RNFL changes in glaucoma progression.

The ability to detect ONH and RNFL changes also is related to the desired level of specificity of CSLO and OCT. The 3 criteria (liberal, moderate, and conservative) selected for detection of ONH surface changes were adopted from the studies by Chauhan and colleagues.^{17,18} They followed 34 normal subjects for 5 years and showed the specificities to be 81%, 94%, and 97%, respectively. These values are close to our estimates (85.7%, 94.3%, and 97.1%, respectively) derived from 70 normal eyes followed for an average of 5.2 years. The specificity for analysis of RNFL thinning with GPA was 94.3%. With the same level of specificity (94.3%), we therefore selected the moderate criterion for comparison of ONH surface depression and RNFL thinning and their survival probabilities.

Although the survival function was significantly worse for eyes with ONH surface depression compared with eyes with RNFL thinning, the respective survival curves converged by 6 years (Fig 3), suggesting that RNFL thinning followed ONH surface depression (Fig 2) and that the proportions of eyes with ONH surface depression and RNFL thinning were similar at the end of follow-up. Although the agreement between ONH surface depression and RNFL thinning remain poor by the end of the study (Fig 1), we speculate that it will improve with follow-up time. Confocal scanning laser ophthalmoscopy and OCT can provide complementary information for monitoring of glaucoma progression.

Study Limitations

There are potential inherent limitations of the imaging instruments and study design that may affect the interpretation of our results. We used CSLO to capture ONH surface change because CSLO has been used to assess ONH topography in clinical practice for more than 2 decades. However, CSLO-detected ONH surface depression may represent posterior displacement of pre-laminar surface, posterior displacement of the lamina cribrosa, loss of the neuroretinal rim, loss of the prelaminar tissue, or a combination of these. Confocal scanning laser ophthalmoscopy is not able to discern the individual components of ONH changes. Although SD-OCT imaging of the deep ONH structures would be useful for the differentiation, no algorithm has been validated to detect ONH changes. We used TCA and GPA for change analysis because they are validated, event-based algorithms widely adopted in clinical practice. Because there is no reference standard for evaluation of ONH and RNFL progression in glaucoma, we standardized the specificities of TCA and GPA at a relatively high level (94.3%) for comparison of ONH and RNFL changes. However, this might reduce the sensitivity to detect change. Patients being followed in the study were treated at the discretion of the attending ophthalmologists with reference to the target IOP. Although IOP-lowering treatment may lead to anterior displacement of the lamina cribrosa,^{27–29} more eyes had ONH surface depression than RNFL thinning using the moderate and liberal criteria. In a prospective study with a mean follow-up duration of more than 5 years examining a group of patients with glaucoma with an average age >50 years, it is inevitable that a significant portion of patients

would require intraocular surgery (e.g., 9.6% of eyes in this study had a history of trabeculectomy, and 9.6% had cataract extraction). Excluding these patients would not only decrease the power of analysis but also limit the generalizability of our findings to real-life clinical settings where surgical intervention is often needed to prevent visual loss. Intraocular surgery could change the signal-to-noise ratio of the OCT and HRT images, which may in turn confound the detection of change. Therefore, we included only images with a high signal-to-noise ratio (signal strength ≥ 7 for OCT; image quality standard deviation ≤ 30 μm for HRT) for analysis. Last, it is worth noting that the EMGT criteria may not be sensitive to detect visual field progression in eyes with extensive field loss. Likewise, detecting RNFL thinning and ONH surface depression could be difficult in advanced glaucoma. Nevertheless, including patients with both mild and advanced diseases is important for the study because the performance of OCT and HRT may vary with the stages of glaucoma.

In conclusion, with reference to the HRT TCA and OCT GPA, ONH surface depression can be detected before RNFL thinning during the course of glaucoma progression with a lag time of more than 3 years. Devising strategies for early detection of ONH deformation might be informative to predict and prevent irreversible RNFL and visual field loss in glaucoma.

References

- Leung CK, Cheung CY, Weinreb RN, et al. Retinal nerve fiber layer imaging with spectral-domain optical coherence tomography: a variability and diagnostic performance study. *Ophthalmology* 2009;116:1257–63.
- Mwanza JC, Gendy MG, Feuer WJ, et al. Effects of changing operators and instruments on time-domain and spectral-domain OCT measurements of retinal nerve fiber layer thickness. *Ophthalmic Surg Lasers Imaging* 2011;42:328–37.
- Grewal DS, Sehi M, Cook RJ, Greenfield DS; Advanced Imaging in Glaucoma Study Group. The impact of retardance pattern variability on nerve fiber layer measurements over time using GDx with variable and enhanced corneal compensation. *Invest Ophthalmol Vis Sci* 2011;52:4516–24.
- Kim JS, Ishikawa H, Sung KR, et al. Retinal nerve fibre layer thickness measurement reproducibility improved with spectral domain optical coherence tomography. *Br J Ophthalmol* 2009;93:1057–63.
- Yang B, Ye C, Yu M, et al. Optic disc imaging with spectral-domain optical coherence tomography: variability and agreement study with Heidelberg retinal tomograph. *Ophthalmology* 2012;119:1852–7.
- Leung CK, Cheung CY, Lin D, et al. Longitudinal variability of optic disc and retinal nerve fiber layer measurements. *Invest Ophthalmol Vis Sci* 2008;49:4886–92.
- Chauhan BC, LeBlanc RP, McCormick TA, et al. Test-retest variability of topographic measurements with confocal scanning laser tomography in patients with glaucoma and control subjects. *Am J Ophthalmol* 1994;118:9–15.
- Weinreb RN, Lusk M, Bartsch DU, Morsman D. Effect of repetitive imaging on topographic measurements of the optic nerve head. *Arch Ophthalmol* 1993;111:636–8.
- Fortune B, Reynaud J, Wang L, Burgoyne CF. Does optic nerve head surface topography change prior to loss of retinal nerve fiber layer thickness: a test of the site of injury hypothesis in experimental glaucoma. *PLoS One* [serial online] 2013;8: e77831. Available at: <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0077831>. Accessed June 23, 2014.
- Fortune B, Burgoyne CF, Cull G, et al. Structural and functional abnormalities of retinal ganglion cells measured in vivo at the onset of optic nerve head surface change in experimental glaucoma. *Invest Ophthalmol Vis Sci* 2012;53:3939–50.
- Strouthidis NG, Fortune B, Yang H, et al. 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;52:1206–19.
- He L, Yang H, Gardiner SK, et al. Longitudinal detection of optic nerve head changes by spectral domain optical coherence tomography in early experimental glaucoma. *Invest Ophthalmol Vis Sci* 2014;55:574–86.
- Nassif N, Cense B, Park BH, et al. In vivo human retinal imaging by ultrahigh-speed spectral domain optical coherence tomography. *Opt Lett* 2004;29:480–2.
- Yu M, Weinreb RN, Yiu C, et al. Computer simulation of progressive retinal nerve fiber layer loss in glaucoma: performance of event and trend analyses. *Invest Ophthalmol Vis Sci* 2011;52:9674–83.
- Leung CK, Yu M, Weinreb RN, et al. Retinal nerve fiber layer imaging with spectral-domain optical coherence tomography: patterns of retinal nerve fiber layer progression. *Ophthalmology* 2012;119:1858–66.
- Chauhan BC, Blanchard JW, Hamilton DC, LeBlanc RP. Technique for detecting serial topographic changes in the optic disc and peripapillary retina using scanning laser tomography. *Invest Ophthalmol Vis Sci* 2000;41:775–82.
- Chauhan BC, Hutchison DM, Artes PH, et al. Optic disc progression in glaucoma: comparison of confocal scanning laser tomography to optic disc photographs in a prospective study. *Invest Ophthalmol Vis Sci* 2009;50:1682–91.
- Chauhan BC, Nicoletta MT, Artes PH. Incidence and rates of visual field progression after longitudinally measured optic disc change in glaucoma. *Ophthalmology* 2009;116:2110–8.
- Heijl A, Leske MC, Bengtsson B, et al; EMGT Group. Measuring visual field progression in the Early Manifest Glaucoma Trial. *Acta Ophthalmol Scand* 2003;81:286–93.
- Govindarajulu US, Lin H, Lunetta KL, D'Agostino RB Sr. Frailty models: applications to biomedical and genetic studies. *Stat Med* 2011;30:2754–64.
- Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159–74.
- Congdon NG, Broman AT, Bandeen-Roche K, et al. Central corneal thickness and corneal hysteresis associated with glaucoma damage. *Am J Ophthalmol* 2006;141:868–75.
- Prata TS, Lima VC, Guedes LM, et al. Association between corneal biomechanical properties and optic nerve head morphology in newly diagnosed glaucoma patients. *Clin Experiment Ophthalmol* 2012;40:682–8.
- Prata TS, Lima VC, de Moraes CG, et al. Factors associated with topographic changes of the optic nerve head induced by acute intraocular pressure reduction in glaucoma patients. *Eye (Lond)* 2011;25:201–7.
- Wells AP, Garway-Heath DF, Poostchi A, et al. Corneal hysteresis but not corneal thickness correlates with optic nerve surface compliance in glaucoma patients. *Invest Ophthalmol Vis Sci* 2008;49:3262–8.

26. Ren R, Yang H, Gardiner SK, et al. Anterior lamina cribrosa surface depth, age, and visual field sensitivity in the Portland Progression Project. *Invest Ophthalmol Vis Sci* 2014;55:1531–9.
27. Lee EJ, Kim TW, Weinreb RN. Reversal of lamina cribrosa displacement and thickness after trabeculectomy in glaucoma. *Ophthalmology* 2012;119:1359–66.
28. Lee EJ, Kim TW, Weinreb RN, et al. Reversal of lamina cribrosa displacement after intraocular pressure reduction in open-angle glaucoma. *Ophthalmology* 2013;120:553–9.
29. Reis AS, O'Leary N, Stanfield MJ, et al. Laminar displacement and prelaminar tissue thickness change after glaucoma surgery imaged with optical coherence tomography. *Invest Ophthalmol Vis Sci* 2012;53:5819–26.

Footnotes and Financial Disclosures

Originally received: February 5, 2014.

Final revision: February 10, 2014.

Accepted: June 23, 2014.

Available online: August 6, 2014.

Manuscript no. 2014-208.

¹ Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong, PRC.

² HuiZhou Municipal Central Hospital Eye Department, HuiZhou City, Guangdong Province, PRC.

³ Hamilton Glaucoma Center and the Department of Ophthalmology, University of California, San Diego, California.

Financial Disclosure(s):

The author(s) have made the following disclosure(s): G.X.: None. R.N.W. is a consultant to Topcon and receives research support from Carl Zeiss Meditec AG, Heidelberg Engineering, Optovue, Topcon, and Nidek. C.K.S.L. receives speaker honorarium from Carl Zeiss Meditec AG and

Heidelberg Engineering, and research support from Carl Zeiss Meditec AG and Optovue.

Abbreviations and Acronyms:

CI = confidence interval; **CSLO** = confocal scanning laser ophthalmoscopy; **EMGT** = Early Manifest Glaucoma Trial; **GPA** = Guided Progression Analysis; **HRT** = Heidelberg Retinal Tomograph; **IOP** = intraocular pressure; **MD** = mean deviation; **OCT** = optical coherence tomography; **ONH** = optic nerve head; **RNFL** = retinal nerve fiber layer; **SD-OCT** = spectral-domain optical coherence tomography; **TCA** = Topographic Change Analysis.

Correspondence:

Christopher K. S. Leung, MD, MB ChB, Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong, PRC. E-mail: tlims00@hotmail.com.