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Integrating Macular Ganglion Cell Inner Plexiform Layer and Parapapillary Retinal Nerve Fiber Layer Measurements to Detect Glaucoma Progression

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Purpose: To investigate the temporal relationship among progressive macular ganglion cell inner plexiform layer (GCIPL) thinning, progressive parapapillary retinal nerve fiber layer (RNFL) thinning, and visual field (VF) progression in patients with primary open-angle glaucoma (POAG).

Design: Prospective study.

Participants: One hundred thirty-six POAG patients (231 eyes) followed up for ≥5 years.

Methods: OCT imaging of the macular GCIPL and parapapillary RNFL and perimetry were performed at ~ 4-month intervals. Progressive GCIPL and RNFL thinning were determined by Guided Progression Analysis (GPA) of serial GCIPL and RNFL thickness maps. The specificities of GPA were calculated from the proportions of eyes with progressive GCIPL or RNFL thinning in 67 eyes of 36 healthy individuals followed up for ≥5 years. Visual field progression (likely or possible) was determined by the Early Manifest Glaucoma Trial criteria.

Main Outcome Measures: Hazard ratios for VF progression, progressive RNFL thinning, and progressive GCIPL thinning, as determined by time-varying Cox models.

Results: GPA detected 57 eyes (24.7%) with progressive GCIPL thinning and 66 eyes (28.6%) with progressive RNFL thinning at a specificity of 95.5% and 91.0%, respectively. Thirty-five eyes (15.2%) demonstrated progressive RNFL and GCIPL thinning, whereas 53 eyes (22.9%) demonstrated progressive RNFL or GCIPL thinning. Eyes with progressive GCIPL thinning had a higher risk for progressive RNFL thinning (HR, 5.27; 95% confidence interval [CI], 2.89−9.62), whereas eyes with progressive RNFL thinning were also at a higher risk for progressive GCIPL thinning (HR, 2.99; 95% CI, 1.48−6.02), after adjusting for baseline covariates. The HRs for likely and possible VF progression were 3.48 (95% CI, 1.51−8.01) and 2.74 (95% CI, 1.26−5.98), respectively, on detection of progressive GCIPL thinning and 3.66 (95% CI, 1.68−7.97) and 2.54 (95% CI, 1.23−5.21), respectively, on detection of progressive RNFL thinning after adjusting for baseline covariates. Eyes with VF progression were not at risk of progressive RNFL or GCIPL thinning ($P \geq 0.493$).

Conclusions: Progressive macular GCIPL thinning and progressive parapapillary RNFL thinning are mutually predictive. Because progressive RNFL thinning and progressive GCIPL thinning are both indicative of VF progression, integrating macular GCIPL and parapapillary RNFL measurements is relevant to facilitate early detection of disease deterioration in glaucoma patients. *Ophthalmology 2018;■:1−10 © 2017 by the American Academy of Ophthalmology*

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Glaucoma is a leading cause of irreversible blindness.[1,2] Early detection of disease progression is germane to the determination of target intraocular pressure (IOP) and formulation of a treatment plan to prevent progressive loss in visual function. Characterized by chronic degeneration of retinal ganglion cells (RGCs), tracking changes of the retinal nerve fiber layer (RNFL) and the ganglion cell inner plexiform layer (GCIPL), where the axons and the dendrites and soma of RGCs reside, respectively, with OCT has been shown to be effective in monitoring glaucoma progression.[3−13] Measurement of the RNFL thickness has been centered on the parapapillary region because all the axons of RGCs converge at the optic disc. Measurement of the GCIPL thickness, by contrast, has been focused on the macula because the macula has the highest density of RGCs. Although a few studies have compared progressive parapapillary RNFL thinning and progressive macular GCIPL thinning for detection of glaucoma progression,[5,11,13] whether parapapillary RNFL thickness or macular GCIPL thickness or both should be measured in the monitoring of disease progression for glaucoma patients remains poorly understood. Whereas progressive RNFL thinning has been

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shown to be predictive of visual field (VF) progression,[4,9,12] how progressive GCIPL thinning relates to VF progression and progressive RNFL thinning remains obscure. In this prospective study, we investigated the roles of OCT measurements of macular GCIPL thickness and parapapillary RNFL thickness for detection of glaucoma progression by interrogating the temporal relationship among VF progression, progressive GCIPL thinning, and progressive RNFL thinning determined by Guided Progression Analysis (GPA; Carl Zeiss Meditec, Dublin, CA)—an event-based change-detection algorithm—in 136 patients with primary open-angle glaucoma who had been followed-up at approximately 4-month intervals for at least 5 years. We hypothesized that integrating the macula and the parapapillary region for evaluation of progressive GCIPL thinning and progressive RNFL thinning can facilitate early detection of disease deterioration in glaucoma patients and that progressive GCIPL thinning, in addition to progressive RNFL thinning, would be predictive of VF progression.

Methods

Participants

This study included 136 primary open-angle glaucoma patients consecutively recruited from the Caritas Medical Center, Hong Kong Eye Hospital, and the University Eye Center of the Chinese University of Hong Kong, who had been followed up at approximately 4-month intervals with OCT imaging of the macular GCIPL and the parapapillary RNFL and standard automated perimetry between July 2007 and July 2016. These patients were recruited in a previous study investigating the impact of progressive RNFL thinning on VF progression.[9] All participants underwent a comprehensive ophthalmic examination including measurements of best-corrected visual acuity, refraction, axial length, central corneal thickness, IOP (Goldmann applanation tonometry), gonioscopy, and biomicroscopy examination of the optic disc and retina. All participants had visual acuity of 20/40 or better. Patients with VF loss or RNFL thinning unrelated to glaucoma were excluded. Glaucoma was diagnosed by the presence of narrowed neuroretinal rim and RNFL defects with corresponding VF defects in standard automated perimetry in at least 1 eye. Intraocular pressure was not a diagnostic criterion. Glaucoma patients were managed during the study follow-up with reference to the target IOP determined by the attending ophthalmologists without taking into consideration the OCT analysis of progressive RNFL or GCIPL thinning (RNFL and GCIPL thickness analysis reports were not masked). To determine the specificity of GPA for detection of progressive RNFL and GCIPL thinning, 67 eyes of 36 healthy individuals recruited between January 2008 and December 2016 who were followed up at approximately 4-month intervals for OCT imaging of the RNFL and GCIPL and standard automated perimetry for more than 5 years and 26 eyes of 26 healthy individuals recruited between October 2008, and January 2009, who were followed up weekly for 8 consecutive weeks for OCT imaging of the RNFL and GCIPL were included. Healthy individuals showed no optic disc or RNFL abnormalities on clinical examination, no VF abnormalities, and no history of ocular disease (except for mild cataract), neurologic disease, or major systemic illness. The study was conducted in accordance with the ethical standards stated in the 1964 Declaration of Helsinki and approved by Hong Kong Kowloon Central Research Ethics Committee with informed consent obtained.

OCT Imaging of the Macular Ganglion Cell Inner Plexiform Layer and Parapapillary Retinal Nerve Fiber Layer

The Cirrus HD-OCT (software version 9.5; Carl Zeiss Meditec) measured the RNFL thicknesses from the optic disc cube scan (200 × 200 pixels) and the GCIPL thicknesses from the macula cube scan (200 × 200 pixels), generating the RNFL thickness map at the parapapillary region (6 × 6 mm^2) and the GCIPL thickness map in an elliptical annulus (inner vertical and horizontal axes of 1.0 mm and 1.2 mm, respectively; outer vertical and horizontal axes of 4.0 mm and 4.8 mm, respectively) centered at the fovea. All OCT scans had a signal strength of 6 or more. OCT scans with motion artifact, poor centration, or missing data were discarded with rescanning performed in the same visit. Both the optic disc cube scan and the macula cube scan had to meet the image quality requirement in the same visit for inclusion in the progression analysis. If only the optic disc cube scan or the macular cube scan of an eye met the image quality requirement in a follow-up visit, both scans would be removed from the longitudinal series. An eye would be excluded if (1) optic disc or macula cube scans from 4 or more visits showed segmentation failure of the RNFL or GCIPL during the study follow-up (6 eyes were excluded); (2) the total follow-up duration was less than 5 years after exclusion of OCT scans with suboptimal image quality (1 eye was excluded); (3) macular disease (e.g., epiretinal membrane, macular edema) developed during the study follow-up (2 eyes were excluded); or (4) registration failure for GPA (10 eyes were excluded). For the 231 eyes included in the analysis, 10 pairs of RNFL and GCIPL thickness maps from 5 eyes were excluded because of segmentation errors, and 27 pairs of RNFL and GCIPL thickness maps from 10 eyes were excluded because of signal strength of less than 6. After excluding the 37 pairs of RNFL and GCIPL thickness maps, 3883 pairs of RNFL and GCIPL thickness maps were available for progression analysis.

Guided Progression Analysis for Detection of Progressive Retinal Nerve Fiber Layer and Ganglion Cell Inner Plexiform Layer Thinning

Guided Progression Analysis (GPA; Carl Zeiss Meditec) is an event-based algorithm for detection of progressive RNFL thinning and progressive GCIPL thinning. Guided Progression Analysis aligned, registered, and compared changes in RNFL and GCIPL thicknesses at the individual superpixels (1 superpixel = 4 × 4 pixels) between the follow-up and 2 baseline RNFL and GCIPL thickness maps (separated by approximately 4 months in this study). A superpixel was encoded in yellow in the RNFL and GCIPL thickness change map when the differences in RNFL and GCIPL thickness between the follow-up and the first and the second baseline RNFL and GCIPL thickness maps were greater than the test–retest variability of that superpixel location and in red if the differences were observed in a consecutive follow-up visit (Fig 1). In this study, progressive RNFL and GCIPL thinning were defined when 20 or more contiguous superpixels were encoded in red in the RNFL and GCIPL thickness change map outside the region of peripapillary atrophy (if any) and the same changes also were detected in all the subsequent follow-up visits.

Specificities of Guided Progression Analysis for Detection of Progressive Retinal Nerve Fiber Layer and Ganglion Cell Inner Plexiform Layer Thinning

The specificity of GPA for detection of progressive RNFL and GCIPL thinning was determined from the proportion of eyes with

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