

BEYOND THE RETINAL NERVE FIBER LAYER



Recent data support macular ganglion cell analysis as a useful adjunct to monitor glaucomatous progression.

BY ERIN SIECK, MD, AND ANJALI BHORADE, MD, MSCI

CAN MACULA AND OPTIC NERVE HEAD PARAMETERS DETECT GLAUCOMA PROGRESSION IN EYES WITH ADVANCED CIRCUMPAPILLARY RETINAL NERVE FIBER LAYER DAMAGE?

Lavinsky F, Wu M, Schuman JS, et al¹

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ABSTRACT SUMMARY

Investigators assessed whether and to what extent optic nerve head (ONH) and macular parameters on OCT could be used to identify disease progression in patients with glaucoma who exhibited advanced structural damage to the circumpapillary retinal nerve fiber layer (CRNFL). In this longitudinal study, 44 eyes of 37 patients with advanced glaucoma were observed for a mean 4 years. The mean age of patients in this study was 67.0 ± 11.4 years; 57% of the patients were women, and 70% were White.

Visual field testing using a 24-2 strategy and OCT analysis of the CRNFL, ganglion cell–inner plexiform layer (GCIPL), and ONH parameters were performed at a minimum of four visits spaced at least 5 months apart. A diagnosis of advanced glaucoma was based on a mean CRNFL thickness of 60 μ m or less,

as measured with spectral-domain OCT. Guided progression analysis (GPA) data from the OCT machine algorithm were used to compare progression rates in CRNFL and GCIPL measurements. The rates of change in visual field mean deviation and visual field index were also analyzed.

Median visual field deviation was -10.18 dB, and mean CRNFL thickness was 54.55 ± 3.42 μ m. The rates of change in visual field mean deviation (-0.48 ± 0.07 dB/y) and visual field index ($-1.80 \pm 0.26\%$ /y) were significant ($P < .001$). OCT analysis of the GCIPL also showed a significant rate of change (-0.57 ± 0.05 μ m/y, $P < .001$). In addition, the rate of change was significant ($P < .001$) for the following ONH parameters: rim

area, cup volume, and average and vertical cup-to-disc ratios. GPA software did not detect a significant rate of change in CRNFL thickness.

DISCUSSION

Why is it important to monitor patients who have advanced glaucoma?

Patients with advanced glaucoma are at increased risk of falls, motor vehicle collisions, and visual disability compared to patients who do not have glaucoma and those whose disease is less severe.³ These adverse events can increase patients' depression, social isolation, morbidity, and mortality⁴ and put a significant financial burden on society.⁵ Small changes in vision can produce large changes in visual function in

STUDY IN BRIEF

- In this longitudinal study of patients with early glaucoma, clinical measures were used to predict whether disease progression was evident first with OCT analysis of the peripapillary retinal nerve fiber layer (PRNFL) or the macular ganglion cell–inner plexiform layer. Lower pretreatment IOP and a thinner baseline PRNFL predicted progression on macular ganglion cell–inner plexiform layer analysis before progression was evident on PRNFL analysis.

WHY IT MATTERS

Minimizing glaucomatous progression in the eyes of patients with advanced disease is important because of their high risk of visual disability. Detecting progression, however, is challenging in this population owing to the poor reliability of visual fields and the well-known floor effect of OCT circumpapillary retinal nerve fiber layer analysis.²

patients who have advanced glaucoma and profoundly decrease their quality of life. Careful monitoring of these patients is therefore critically important.

Why is it difficult to monitor patients with advanced glaucoma?

Traditional thinking holds that functional measurements are superior to structural measurements for the monitoring of disease progression when glaucoma has reached an advanced stage.⁶ Small structural changes in the optic nerve become difficult to detect on examination. Additionally, OCT CRNFL analysis has a well-known floor effect below which changes in CRNFL are not informative.⁷ Even functional measures (visual

field tests), however, are not ideal for monitoring the progression of advanced disease owing to poor fixation and variability at lower threshold sensitivities.⁸

In this study, CRNFL analysis reached a floor effect with a mean of $54.55 \pm 3.42 \mu\text{m}$, and no significant rate of change was detected in the CRNFL. In contrast, GCIPL and ONH parameters on OCT exhibited a significant rate of change over time, as did the visual field tests. Because approximately 50% of retinal ganglion cells (RGCs) reside in the macula,⁹ monitoring the progression of RGC loss in the macula may be more effective than monitoring RGC loss in the peripapillary retinal nerve fiber layer (PRNFL).

How can these findings be incorporated into clinical practice?

Although OCT scans of the CRNFL are effective for measuring glaucomatous progression, their use for detecting changes in CRNFL thickness is limited below $60 \mu\text{m}$. At this stage, clinicians can use OCT scans to monitor changes in ONH parameters. Although the CRNFL scans reach a floor effect, clinicians may continue to use OCT GCIPL analysis to detect progressive RGC loss. Unfortunately, at this time, OCT macular GCIPL analysis is not approved for reimbursement in patients with glaucoma. It is to be hoped that this will change if future studies support the use of GCIPL analysis for patients with advanced glaucoma.

MACULAR GANGLION CELL-INNER PLEXIFORM LAYER LOSS PRECEDES PERIPAPILLARY RETINAL NERVE FIBER LAYER LOSS IN GLAUCOMA WITH LOWER INTRAOCULAR PRESSURE

Marshall HN, Andrew NH, Hassall M, et al¹⁰
Industry support: No

ABSTRACT SUMMARY

A prospective, longitudinal cohort study assessed the ability of OCT analysis of ONH and macular parameters to identify disease progression in patients with glaucoma who exhibited advanced structural damage to the CRNFL. The study included 271 eyes of 207 patients for whom there was statistically significant evidence of glaucomatous progression using OCT GPA software. Disease progression was first observed in the macular ganglion cell–inner plexiform layer (MGCIP) in 134 eyes and in the PRNFL in 111 eyes. Eyes ($n = 26$) that exhibited progression in the MGCIP and PRNFL at the same time were excluded. Baseline patient characteristics and clinical parameters such as pretreatment IOP, PRNFL and

MGCIP thickness, central corneal thickness, and optic disc area were recorded.

The mean age of patients was 66.72 ± 9.15 years, with no difference in age or sex between the MGCIP-first and PRNFL-first groups. The MGCIP-first group had a thinner baseline PRNFL thickness, lower maximum recorded

pretreatment IOP, and lower maximum recorded IOP (all $P < .001$) compared to eyes in the PRNFL-first group. The MGCIP-first group was also 3.03 times more likely to develop paracentral visual field defects or to show progression of these defects.

Among eyes that exhibited disease progression in both the

STUDY IN BRIEF

- In this longitudinal study of patients with early glaucoma, clinical measures were used to predict whether disease progression was evident first with OCT analysis of the peripapillary retinal nerve fiber layer (PRNFL) or the macular ganglion cell–inner plexiform layer (MGCIP). Lower pretreatment IOP and a thinner baseline PRNFL predicted progression on MGCIP analysis before progression was evident on PRNFL analysis.

WHY IT MATTERS

OCT analysis of both the PRNFL and the MGCIP assists with the monitoring of glaucomatous progression in patients with early disease.¹¹ It is not clear, however, whether certain clinical measures predict progression earlier on one scan versus another. This study suggests that patients with early glaucoma who have lower pretreatment IOPs and thinner baseline PRNFL measurements show progression earlier on MGCIP scans than on PRNFL scans. Moreover, eyes for which progression is evident on MGCIP scans first appear to be at increased risk of developing a paracentral visual field defect.

MGCIPL and PRNFL, those with a pretreatment IOP lower than 14 mm Hg exhibited MGCIPL progression 12.02 ± 8.40 months before PRNFL progression on average. Eyes with a maximum pretreatment IOP higher than 30 mm Hg showed progression on PRNFL analysis 31.29 ± 2.41 months before progression on MGCIPL analysis.

DISCUSSION

Is MGCIPL or PRNFL analysis a better choice for monitoring patients with early glaucoma and glaucoma suspects?

This study supports the use of both MGCIPL and PRNFL scans to optimize the detection of glaucoma in its early stages and its progression. Both assessments measure different parts of the eye and may provide different information regarding the location of glaucomatous progression. Although a majority of eyes in this study first exhibited progression in either the MGCIPL or the PRNFL, 26 eyes experienced concurrent progression on the PRNFL and MGCIPL scans, which suggests a possible overlap in the use of these tests.

This study suggests that patients who have early glaucoma and glaucoma suspects with lower pretreatment IOPs and thinner baseline PRNFL thickness may benefit from closer monitoring using MGCIPL analysis and close follow-up for paracentral defects. There was a two-and-a-half times greater risk of progression in the PRNFL first for every 5-mm Hg increase in maximum pretreatment IOP, which suggests that patients with a higher pretreatment IOP may benefit from close monitoring with PRNFL analysis.

Does this study suggest that low-tension and high-tension glaucoma are different disease processes?

In this study, patients who exhibited progression on MGCIPL analysis first tended to have a lower baseline IOP and to develop or show worsening of a paracentral visual field defect. According to Marshall and colleagues, it is plausible that these individuals have an endophenotype of glaucoma in which thinning of the MGCIPL occurs before PRNFL thinning at lower IOPs. Interestingly, lower maximum IOPs and smaller visual field defects closer to fixation are often described in patients with normal-tension glaucoma, whereas higher IOPs and peripheral visual field defects are often observed in patients with high-tension glaucoma.¹²

Figure 3 from the study elegantly displays the relationship between maximum pretreatment IOP and the mean interval between progression on MGCIPL and PRNFL scans. There is an overlap of MGCIPL and PRNFL progression at an IOP of around 21 to 22 mm Hg, which is similar to the relative cutoffs between normal-tension and high-tension glaucoma. Although these results cannot clarify

whether low- and high-tension glaucoma are different disease processes, the results suggest that IOP levels may be associated with damage to different parts of the eye. The PRNFL analysis measures ganglion cell axons, which are susceptible to compression against the lamina cribrosa when IOP is elevated.¹³ The MGCIPL analysis measures ganglion cell bodies, but the mechanism of death in this location is unclear. Continued research into the relationship between clinical parameters such as IOP and disease progression in the MGCIPL and PRNFL is needed to better understand the pathophysiology of potential different glaucoma subtypes. ■

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