Evaluation of macular ganglion cell analysis compared to retinal nerve fiber layer thickness for pre-perimetric glaucoma diagnosis

The National Program for Control of Blindness survey, 2001, found glaucoma to be one the most common causes of irreversible blindness in India.[1] Long-term, randomized control studies have established that glaucomatous neuropathy can be stabilized in a large percentage of patients; however, some continue to progress despite therapy.[2-4] Therefore, accurately diagnosing preperimetric glaucoma would enable an ophthalmologist to start treatment at an appropriate time, and prevent/delay the occurrence of visual field loss.

Studies have looked for perimetric strategies such as blue on yellow and motion detection to look for preperimetric or very early signs of Glaucoma, but found shortcomings due to subjectivity, interindividual variability, effect of nuclear sclerosis, etc. The advent of objective imaging, especially optical coherence tomography (OCT), in glaucoma was welcomed, hoping that it would enable the diagnosis of preperimetric or early glaucoma. An average of retinal nerve fiber layer (RNFL), measurements in groups of patients having early glaucoma showed a statistical difference in RNFL assessment, compared to healthy controls. Yet, it was not possible to extrapolate this to an individual patient due to interindividual variability in optic nerve head (ONH) size and shape in patients as well as in measurements by different instruments, leading to difficulty in interpretation, when used alone. Histopathology in experimental glaucoma models has shown substantial ganglion cell loss in the perifoveal and parafoveal regions.[5,6] Improved spectral domain OCTs with additional postprocessing of scans, has made it possible to delineate individual layers in the retina, of which RNFL, ganglion cell layer (GCL), and inner plexiform layer (IPL) are significantly affected in glaucoma. Compared to RNFL measurements around the optic nerve head, assessment at the macular area shows less inter-subject anatomic variability, and also has a greater number of ganglion cells, so that small changes can be definitively diagnosed.

Oddone *et al.*, in a systematic review of published studies, to find out the relative diagnostic accuracy of RNFL versus different macular measurements for glaucoma, observed that the sensitivity summary of most parameters for both RNFL and macular ganglion cell complex (GCC) was between 0.65 and 0.75, making each of these unsatisfactory as a single parameter to be used in clinical setting. A meta-analysis looking at different OCT instruments and differing GCC parameters showed that OCT RNFL parameters are still preferable to macular measurements for diagnosis of manifest glaucoma, though differences may be small [Table 1].[7-10]

Kansal *et al.* reported a meta-analysis of 5 OCT devices and found a diagnostic accuracy of RNFL and segmented macular regions (ganglion cell IPL [GCIPL], GCC) scans to be similar, and higher than total macular thickness.[11] More diagnostically favorable areas under the receiver operating characteristic curves were demonstrated in patients with increased glaucoma severity. Kim *et al.*[12] have suggested that a larger macular grid 3 mm × 6 mm has better diagnostic ability for early glaucoma.

GCIPL, GCCIPL, thickness on high definition OCT has been evaluated in the diagnosis of preperimetric and early glaucoma and found that the diagnostic ability of GCCIPL in preperimetric glaucoma was less than ONH and RNFL parameters, while it was similar in perimetric glaucoma.[13-15]

However, macular parameters such as the GCC may be more reliable in certain clinical settings, for example, in pathological myopia (with disc tilting and peripapillary atrophy), optic disc size variability or deformation like ONH hypoplasia or coloboma, the conditions which lower the accuracy of peripapillary RNFL.[16,17] Macular pathology that causes abnormal thickening of the inner retina such as macular edema or retinal fibrosis will interfere with GCC measurements. This prevents accurate comparison with the normative database, as well as interfering with detection of change over time.

Table 1: Relative diagnostic odds ratio for ganglion cell complex and ganglion cell inner plexiform layer studies in diagnosing manifest glaucoma

Parameter	Studies (number of patients)	Sensitivity (95% CI)	Specificity (95% CI)	Relative DOR (95% CI)
RNFL average GCIPL average (on cirrus)	9 (1454)	0.69 (0.60-0.77) 0.62 (053-0.71)	0.94 (0.91-0.96) 0.92 (0.89-0.94)	Reference 32.29 (19.85-59.24) 0.54 (0.35-0.84)
RNFL inferior GCIPL minimum (on cirrus)	7 (1178)	0.79 (0.67-0.87) 0.79 (0.68-0.88)	0.94 (0.92-0.96) 0.90 (0.87-0.93)	Reference 60.62 (29.04-126.56) 0.59 (0.35-0.98)
RNFL average GCC average (on cirrus)	9 (1454)	0.69 (0.60-0.77) 0.62 (053-0.71)	0.94 (0.91-0.96) 0.92 (0.89-0.94)	Reference 32.29 (19.85-59.24) 0.54 (0.35-0.84)

Relative DORs are based only on studies that measure both parameters (i.e., on direct comparisons). Relative DORs are obtained from hierarchical summary receiver operating characteristic. Adapted from Oddone *et al.*, 2016.[8] CI: Confidence interval, DORs: Diagnostic odds ratios, RNFL: Retinal nerve fiber layer, GCIPL: Ganglion cell inner plexiform layer, GCC: Ganglion cell complex

Pierro *et al.*[18] found that the definition of the GCC across manufacturers varies, with most considering the GCC to be made up of the IPL + GCL + nerve fiber layer (NFL) (Optovue; Nidek) while Carl Zeiss Meditec uses only IPL + GCL and ignores the NFL, and Topcon gives three different maps with varying combinations of IPL/GCL/NFL. Depending on the OCT machine used, average GCC thickness is approximately 95–100 μ. As the technique is new, along with a lack of standardization between OCT units, it is difficult to compare GCC instruments to each other, or to existing glaucoma instruments in terms of sensitivity and specificity for glaucoma detection and diagnosis.[2] Tan *et al.* noted that more than one-third of their scans on glaucomatous eyes had to be excluded from segmentation analysis owing to poor quality scans related to speckle noise and uneven tissue reflectivity.[10]

The ganglion cell analysis, GCA, published in this issue, done in early glaucomatous eyes, glaucoma suspects, ocular hypertensives and normal eyes, also shows that analyzing GCA, a combination of GCL and IPL, is not better than RNFL measurements in the detection of preperimetric glaucoma.[19]

Most importantly, there is no standard accepted definition of preperimetric glaucoma itself, making diagnostic evaluations arbitrary. Further, to know the difference between the diagnostic accuracy of RNFL versus GCC or GCCIPL, direct comparative or randomized studies are needed to obviate the heterogeneity in the sensitivity analysis of recent studies.

Ramanjit Sihota, Shikha Gupta, Dewang Angmo

Dr. Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, India.
E-mail: rjsihota@gmail.com

References

1. Murthy GV, Gupta SK, Bachani D, Jose R, John N. Current estimates of blindness in India. Br J Ophthalmol 2005;89:257-60.

2. Musch DC, Gillespie BW, Niziol LM, Lichter PR, Varma R; CIGTS Study Group, *et al.* Intraocular pressure control and long-term visual field loss in the collaborative initial glaucoma treatment study. Ophthalmology 2011;118:1766-73.

3. Öhnell H, Heijl A, Brenner L, Anderson H, Bengtsson B. Structural and functional progression in the early manifest glaucoma trial. Ophthalmology 2016;123:1173-80.

4. The advanced glaucoma intervention study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. The AGIS investigators. Am J Ophthalmol 2000;130:429-40.

5. Desatnik H, Quigley HA, Glovinsky Y. Study of central retinal ganglion cell loss in experimental glaucoma in monkey eyes. J Glaucoma 1996;5:46-53.

6. Frishman LJ, Shen FF, Du L, Robson JG, Harwerth RS, Smith EL 3rd, *et al.* The scotopic electroretinogram of macaque after retinal ganglion cell loss from experimental glaucoma. Invest Ophthalmol Vis Sci 1996;37:125-41.

7. Oddone F, Lucenteforte E, Michelessi M, Rizzo S, Donati S, Parravano M, *et al.* Macular versus retinal nerve fiber layer parameters for diagnosing manifest glaucoma: A Systematic review of diagnostic accuracy studies. Ophthalmology 2016;123:939-49.

8. Wojtkowski M, Srinivasan V, Fujimoto JG, Ko T, Schuman JS, Kowalczyk A, *et al.* Three-dimensional retinal imaging with high-speed ultrahigh-resolution optical coherence tomography. Ophthalmology 2005;112:1734-46.

9. Chen TC, Cense B, Pierce MC, Nassif N, Park BH, Yun SH, *et al.* Spectral domain optical coherence tomography: Ultra-high speed, ultra-high resolution ophthalmic imaging. Arch Ophthalmol 2005;123:1715-20.

10. Tan O, Chopra V, Lu AT, Schuman JS, Ishikawa H, Wollstein G, *et al.* Detection of macular ganglion cell loss in glaucoma by fourier-domain optical coherence tomography. Ophthalmology 2009;116:2305-140.

11. Kansal V, Armstrong JJ, Pintwala R, Hutnik C. Optical coherence tomography for glaucoma diagnosis: An evidence based meta-analysis. PLoS One 2018;13:e0190621.

12. Kim NR, Lee ES, Seong GJ, Kim JH, An HG, Kim CY, *et al.* Structure-function relationship and diagnostic value of macular ganglion cell complex measurement using fourier-domain OCT in glaucoma. Invest Ophthalmol Vis Sci 2010;51:4646-51.

13. Begum VU, Addepalli UK, Yadav RK, Shankar K, Senthil S, Garudadri CS, *et al.* Ganglion cell-inner plexiform layer thickness of high definition optical coherence tomography in perimetric and preperimetric glaucoma. Invest Ophthalmol Vis Sci 2014;55:4768-75.

14. Kim HJ, Lee SY, Park KH, Kim DM, Jeoung JW. Glaucoma diagnostic ability of layer-by-layer segmented ganglion cell complex by spectral-domain optical coherence tomography. Invest Ophthalmol Vis Sci 2016;57:4799-805.

15. Shin HY, Park HY, Jung KI, Choi JA, Park CK. Glaucoma diagnostic ability of ganglion cell-inner plexiform layer thickness differs according to the location of visual field loss. Ophthalmology 2014;121:93-9.

16. Shoji T, Sato H, Ishida M, Takeuchi M, Chihara E. Assessment of glaucomatous changes in subjects with high myopia using spectral domain optical coherence tomography. Invest Ophthalmol Vis Sci 2011;52:1098-102.

17. Kim NR, Lee ES, Seong GJ, Kang SY, Kim JH, Hong S, *et al.* Comparing the ganglion cell complex and retinal nerve fibre layer measurements by fourier domain OCT to detect glaucoma in high myopia. Br J Ophthalmol 2011;95:1115-21.

18. Pierro L, Gagliardi M, Iuliano L, Ambrosi A, Bandello F. Retinal nerve fiber layer thickness reproducibility using seven different OCT instruments. Invest Ophthalmol Vis Sci 2012;53:5912-20.

19. Kaushik S, Kataria P, Jain V, Joshi G, Raj S, Pandav SS. Evaluation of macular ganglion cell analysis compared to retinal nerve fiber layer thickness for preperimetric glaucoma diagnosis. Indian J Ophthalmol 2018;66:511-6.

Access this article online	
Quick Response Code:	**Website:** www.ijo.in
	DOI: 10.4103/ijo.IJO_235_18

About the author

Prof Ramanjit Sihota, MD, FRCS, FRCOphth, heads the Glaucoma Research Facility and Clinical Services at Dr Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, India.

Prof Sihota has won the World Glaucoma Association Research Recognition Award 2011, and numerous national and international awards for research in glaucoma. She has spearheaded the National Task Force in Glaucoma, which is currently operational across India. She has also taken a lead in rationalizing the treatment of Primary Angle Closure Disease in South East Asia. She is a past president of the Glaucoma Society of India, which she has fondly nurtured to become one of the most impactful professional ophthalmic organizations in India.

Prof Sihota is a powerful teacher and leaves an indelible influence on her residents in training. Her edited version of the legendary book "Parsons' Diseases of the Eye" is very widely followed by the students of ophthalmology.

Prof Sihota is an astute and a compassionate clinician, a consummate surgeon an insightful academician, a teacher par excellence, and an opinion-leader in glaucoma. IJO is proud to have her on the Editorial Board and as a Guest Editor.