Point-Counterpoint

Is optical coherence tomography glaucoma macular analysis useful for managing and diagnosing glaucoma?

Justo Manuel A. Orros, Jr., MD[1,2,3,4], Carlo Josemaria Rubio, MD[1,4,5],
Joseph Anthony Tumbocon, MD[1,4,6]

[1]Philippine Glaucoma Society
[2]Mariano Marcos Memorial Hospital and Medical Center, Batac City, Ilocos Norte
[3]The Black Nazarene Specialty Hospital, San Nicolas, Ilocos Norte
[4]St. Luke's Medical Center, Quezon City
[5]Peregrine Eye and Laser Institute, Makati City
[6]St. Luke's Medical City, Global City, Taguig

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Ganglion Cell Analysis: A Yes Perspective

Justo Manuel A. Orros, Jr., MD

Since the introduction of spectral-domain optical coherence tomography (OCT), we are now able to obtain detailed cross-sections of the macula as well as identify and measure the ganglion cell complex. The ganglion cell is central to glaucoma as its gradual loss or death defines the disease. Macular ganglion cell complex scanners analyze a specified area of the macula ranging from 5 to 12 mm in size with the fovea at its center. Unfortunately, these scan only about half of all the total ganglion cell complexes in the eye. Yet, developers justified the adequacy of macular scans because majority of ganglion cell complexes are located in the macula, where the earliest glaucoma damage occurs.[1-3] Also, peripheral ganglion cell complexes are too thin to reliably scan.[1]

Glaucomatous eyes have thinner ganglion cell complexes than normal eyes. Various manufacturers developed different programs and algorithms in analyzing these data. The ganglion cell complex can be analyzed using either the whole macular thickness or only the inner plexiform layer thickness, or a combination of both and other parameters.

Analysis of the retinal nerve fiber layer (RNFL), examination of the optic disc, and evaluation of the visual fields provide structure-function correlation. Will ganglion cell complex analysis offer additional information and advantages in clinical practice?

Ganglion cell complex (GCC) analysis does offer several advantages over circumpapillary RNFL analysis. It may aid in earlier detection of glaucoma and disease progression. It also has a role in differential diagnosis and in special cases of abnormal optic nerve head appearance such as tilted disc, optic nerve coloboma, and in the presence of posterior staphylomas.[2,3]

It is important to determine the temporal association of how a ganglion cell is injured to understand the progression of glaucoma as a disease, especially in its early stages. It is still uncertain whether axonal pathology precedes or follows retinal ganglion cell body loss in glaucoma. Several authors have suggested that individual ganglion cells are first injured at the level of the lamina cribrosa and damage proceeds in a retrograde fashion towards the cell bodies.[4] Others suggest an antegrade course with ganglion cell bodies and dendrites showing signs of injury first followed by the axons.[5,6] Because of this, assessing changes in the cell bodies of ganglion cells, along with RNFL changes, has now become important.[3]

In theory, current circumpapillary RNFL scanners are able to detect RNFL changes before visual field changes occur. Is it also now possible to detect ganglion cell death or loss? According to the glaucoma disease continuum, this event occurs before RNFL thinning.

There are a number of studies that show GCC analysis to be superior over RNFL analysis in determining early glaucoma.[7-9] In addition, significantly thinner macular ganglion cell complexes in the perimetrically normal hemifield have been demonstrated in glaucomatous eyes.[10,11] This may be evidence of preperimetric glaucoma detected by GCC analysis alone.

Among eyes with advanced glaucoma, GCC analysis may be a better alternative over RNFL analysis in monitoring progression.[4,12-14]

Another possible advantage of GCC scans over RNFL OCT is ease of data acquisition. RNFL OCT requires the subject to maintain fixation medially (off-center) which may cause motion artifacts. On the other hand, scanning the macula places the eye in the primary position, the most relaxed position of the eye. This may be easier for children and patients with poor central fixation.[1,2] Patients with axial myopia may benefit from macula scans as well since there are less distortion artifacts than circumpaillary RNFL scans due to the neutral position of the eyes during data acquisition. Myopic eyes have thinner maculas, but since the ganglion cell layer is several cells thick in the macula, it may be better to measure this than a very thin circumpapillary RNFL in determining disease and progression.[2,3]

So yes, ganglion cell analysis is useful in clinical practice as it has its advantages over RNFL analysis. Disadvantages and limitations include scanning only about half of the ganglion cells and limited reliability in the presence of macular conditions such as age-related macular degeneration and epiretinal membrane. With these in mind, it is still advisable to use all available data including visual field tests and RNFL OCT in the diagnosis and monitoring of glaucoma. Technology is still improving. Better scanning protocols, databases, and algorithms may be available in the near future.

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Ganglion Cell Analysis: A No Perspective

Carlo Josemaria Rubio, MD

When glaucomatous damage occurs in the eye, the macula is commonly affected. This glaucomatous damage can be measured as a loss of the ganglion cell layer, the retinal nerve fiber layer of the macula, and the inner plexiform layer. When the aforementioned layers are measured using the optical coherence tomography (OCT), they are usually analyzed together since they are difficult to segment.

In glaucoma, structural loss theoretically precedes functional loss of vision. OCT usually detects structural losses in the layers of the eye before functional loss is detected by perimetry. Ganglion cell analysis (GCA) is done as part of OCT. Ganglion cell loss is thought to occur early in glaucoma.

According to studies by Sung *et al.* and Kotowski *et al.*, GCA and retinal nerve fiber layer (RNFL) analysis of the OCT are equally effective.[1,2] A systematic review by Hood *et al.* analyzed data from 36 studies which compared GCA and RNFL parameters.[3] According to the authors, "RNFL parameters are still favorable to macular parameters in diagnosing manifest glaucoma, but the differences are small."

There are many limitations to GCA. According to Ishikawa *et al.*, GCA analysis only covers 50% of the RNFL, whereas RNFL analysis assesses all RNFLs.[4] GCA has been proposed as a means to measure the presence of glaucoma in myopic eyes. However, according to Takeyama *et al.*, macular thickness in myopic eyes with long axial length can be relatively thin, resulting in a lot of false positives when assessed via GCA.[5] According to the World Glaucoma Association Consensus statements, performing the GCA will require a lot more work compared to simply analyzing the nerve fiber layer.[6] Analyzing the GCA requires measurements of many different segmentations of the retina, whereas reliable RNFL analysis requires only the measurement of two segmentations. Another limitation of the GCA is that while it can measure damage missed by RNFL analysis, it can also miss damage that has occurred outside of the region of the macula.[7,8] GCA is also difficult to interpret when there are pathologies in the macular region.

One caveat to the analysis of GCA versus RNFL parameters is that most studies compared macular thickness parameters to circumpapillary RNFL (cpRNFL) profiles and not RNFL thickness maps. Some cpRNFL analyses can miss damage that RNFL thickness maps can detect.

In summary, most evidence show that GCA is similar to RNFL parameters in diagnosing glaucoma. A systematic review of studies comparing GCA to RNFL parameters suggests that RNFL parameters are favored over macular parameters in assessing glaucoma.[9] Performing the GCA involves more effort for the diagnostic staff. There is a question of whether performing GCA in addition to RNFL analysis is worth the time and effort of the staff, since both parameters are thought to be similar in their ability to diagnose glaucoma. Data is equivocal at this time, thus performing a GCA in addition to obtaining measurements for the RNFL may not be worth the time and effort of the staff involved.

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Consolidating the Evidence

Joseph Anthony Tumbocon, MD

Glaucomatous damage can cause thinning of the macula due to loss of the ganglion cell layer (GCL), inner plexiform layer (IPL) and macular retinal nerve fiber layer, which can be measured in combination or individually by optical coherence tomography (OCT).[1] It is common to measure the GCL and IPL layers together since it is difficult to segment these layers separately and there is no significant difference in the diagnostic capability of GC versus GC+IPL analysis.[2] OCT can also assess for thinning of the peripapillary/circumpapillary retinal nerve fiber layer. It is recommended to utilize the 6x6 mm peripapillary retinal nerve fiber layer (PP-RNFL) thickness and deviation maps since they provide better spatial information on the pattern and probability of RNFL loss.

Current evidence suggests that OCT scans of the macula have similar diagnostic accuracy to that of peripapillary retinal nerve fiber layer (PP-RNFL) thickness analysis.[3] There are some instances that GC+IPL analysis may be more useful than PP-RNFL in diagnosing glaucoma, such as in high myopia, tilted optic discs, or in advanced glaucoma. However, it is preferable to use automated perimetry in monitoring patients with advanced glaucoma due to the "floor effect" of OCT measurements and the wider dynamic range of perimetry in the advanced stages of the disease.

In eyes with or predisposed to macular disease, such as age-related macular degeneration or macular edema, PP-RNFL is recommended over GC+IPL. In monitoring for glaucomatous progression, PP-RNFL may be preferable to GC+IPL due to the robust PP-RNFL progression analysis software in some of the spectral-domain OCT machines that can differentiate true progression from intertest variability.

The next generation of swept-source OCT imaging machines have a wider scanning area that merges the PP-RNFL and GC-IPL measurements in one scan. This combines the advantages of the two scanning protocols, potentially allowing earlier detection and better monitoring of our glaucoma patients in the future.

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