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Detecting Structural Progression in Glaucoma with Optical Coherence Tomography

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Optical coherence tomography (OCT) is increasingly used to obtain objective measurements of the retinal nerve fiber layer (RNFL), optic nerve head, and macula for assessing glaucoma progression. Although OCT has been adopted widely in clinical practice, uncertainty remains concerning its optimal role. Questions include: What is the best structure to measure? What quantity of change is significant? Are structural changes relevant to the patient? How are longitudinal measurements affected by aging? How can changes resulting from aging be differentiated from true progression? How best should OCT be used alongside visual fields, and how often should OCT be performed? Recent studies have addressed some of these questions. Important developments include appreciation of the need to use a consistent point of reference for structural measurements, leading to the introduction of Bruch's membrane opening (BMO)–based measurements, including BMO–minimum rim width and BMO–minimum rim area. Commercially available OCT devices also permit analysis of macular changes over time, for example, changes in the ganglion cell and inner plexiform layers, the sites of the retinal ganglion cell bodies and dendrites, respectively. Several longitudinal studies have compared rates of change in RNFL and macular measurements, with some suggesting that the relative value of each parameter may differ at different stages of disease. In early disease, looking for change over time also may be useful for glaucoma diagnosis, with advantages over classifying eyes using cross-sectional normative databases. Optimal glaucoma management requires information from imaging and visual fields, and efforts have been made to combine information, reducing the noise inherent in both tests to benefit from their different performances according to the stage of disease. Combining information from different structural measurements may also be useful. There is now substantial evidence that progressive structural changes are of direct clinical relevance, with progressive changes on OCT often preceding functional loss and patients with faster change on OCT at increased risk of worsening visual losses. Identification of such patients offers the possibility of commencing or escalating treatment at an earlier stage. This review appraises recent developments in the use of OCT for assessing glaucoma progression. *Ophthalmology 2017;124:S57-S65 © 2017 by the American Academy of Ophthalmology*

Detecting and assessing rates of progression are indispensable constituents of glaucoma management as they provide a means to identify rapidly progressing patients who are at high risk of visual disability and who may require escalation in treatment. Progression is measured conventionally by monitoring for changes in visual field sensitivity; however, many patients have changes to the optic disc or retinal nerve fiber layer (RNFL) in the absence of deterioration on automated perimetry, providing an opportunity to commence or increase treatment before significant decline in vision.[1,2]

Detecting structural change over time is also useful for diagnosing glaucoma, with advantages over classifying an eye as normal, abnormal, or borderline by comparing a single scan with a normative database. Normative databases have strict inclusion criteria, consist largely of patients of European ancestry, and exclude those with high refractive error or ocular comorbidities. Normal structural measurements vary widely between individuals, increasing the chances of misclassification. In some cases, because of the wide range of normal, significant neural losses may occur before a patient is deemed to be outside normal limits. Establishing baseline structural measurements and observing for change over time has great value as an aid to diagnosis, particularly in glaucoma suspects.

Detection of glaucomatous structural changes traditionally has relied on assessment of optic disc photographs; however, agreement among glaucoma specialists in judging change on disc photographs is only slight to fair, and photographs do not allow quantification of rates of change.[3] Optical coherence tomography (OCT) overcomes some of the limitations of optic disc photography and can be used to provide objective measurements of the RNFL, optic nerve head (ONH), and macula, useful for glaucoma diagnosis and progression analysis. Although OCT has been adopted widely in glaucoma clinics, uncertainty remains concerning how best to use OCT to detect glaucoma progression. Pertinent, and only partially answered, questions include: What is the best structure to measure? What quantity of change is significant? Are structural changes relevant to the patient? How are

Statement of Potential Conflict of Interest and Funding/Support: See page S65.

http://dx.doi.org/10.1016/j.ophtha.2017.07.015
ISSN 0161-6420/17

longitudinal measurements affected by aging, and how can changes resulting from aging be differentiated from true progression? What are the best ways to use OCT alongside visual fields and how often should OCT be performed?

What Is the Best Structure to Measure?

The ideal parameter for measuring glaucoma progression should be highly reproducible and useful at all stages of disease. OCT measurements of rates of change in glaucoma have focused largely on circumpapillary RNFL (cpRNFL) thickness, which is also the most widely used parameter in clinical practice. However, recent studies have indicated that additional information can be gleaned from examining changes in RNFL in other regions, for example, by examining the topography of RNFL loss across a 6×6-mm^2 optic disc cube scan RNFL map.[4] OCT devices now also provide the ability to quantify changes to the glaucomatous macula using measurements such as ganglion cell inner plexiform layer and ganglion cell complex thickness, which includes the ganglion cell layer, inner plexiform layer, and RNFL—the sites of retinal ganglion cell bodies, dendrites, and axons, respectively. Macular measures are of special interest because of the density of retinal ganglion cells located in this region and the realization that, contrary to conventional teaching, the macula often is involved early in the glaucomatous process.[5,6] Some OCT devices now also include the ability to obtain novel ONH metrics such as Bruch's membrane opening (BMO)−minimum rim width (MRW) and BMO−minimum rim area,[7–9] which use BMO as an anatomic point of reference for measurements and are discussed in more detail below.

The first report of OCT to examine glaucoma progression used a prototype time-domain OCT device to measure changes in RNFL thickness over time.[10] The device was limited by poor reproducibility, which may have resulted in false-positive assumptions of progression; however, the study demonstrated the potential of OCT for detecting longitudinal change. Using a commercially available time-domain OCT device (Stratus OCT; Carl Zeiss Meditec, Inc, Dublin, CA), Medeiros et al[11] compared the ability of cpRNFL, ONH, and macular measurements to differentiate eyes progressing on standard automated perimetry (SAP) and optic disc stereophotographs from those that remained stable using conventional tests. Circumpapillary RNFL performed significantly better than ONH and macular parameters at discriminating progressing and stable eyes, with faster rates of cpRNFL thinning observed in progressing eyes (−0.72 μm/year vs. 0.14 μm/year; $P = 0.004$).

Time-domain OCT now has been superseded by spectral-domain (SD) OCT, which has an improved scan speed and a higher resolution, and incorporates innovations such as real-time eye tracking to compensate for eye movements during data acquisition and to reduce motion artifacts. Time-domain OCT was limited by its inability to register images on follow-up scans, meaning measurements from disparate retinal locations could be included in analyses of change over time. In contrast, SD OCT devices can center follow-up scans automatically on previously scanned locations by identifying retinal landmarks, which results in improved reproducibility and better ability to detect progression compared with time-domain OCT.[12,13]

Several studies have used SD OCT to evaluate the role of cpRNFL and macular measurements for assessing glaucoma progression (Table 1).[14–23] However, it is difficult to determine whether one parameter is better than another because of the lack of a gold standard, and although all glaucomatous changes reflect loss of retinal ganglion cells, there is still poor understanding of the temporal relationship between changes to the ONH, RNFL, and macula. Studies either have compared rates of structural change occurring in glaucomatous eyes with rates in healthy participants[17,18,20,22–25] or have examined the association between rates of change on OCT and contemporaneous or future changes on conventional structural or functional assessments.[14,16,19,26–28] Overall, both cpRNFL and macular measures show faster rates of loss in glaucomatous eyes compared with controls; however, there is wide variation in reported rates of change. This is to be expected, however, because trend-based analyses of visual field sensitivities also have demonstrated disparate slopes among different individuals.[29] It is also inappropriate to compare rates of change directly between studies and between parameters because of different baseline thicknesses and dynamic ranges. One approach that helps overcome this problem is to examine rates of change with values normalized for dynamic range. Using this approach to study 97 glaucomatous eyes followed up for an average of 3.2 years, Hammel et al[23] found normalized cpRNFL thickness to decrease by 1.7% per year compared with only a 1.3% per year decrease in macular ganglion cell inner plexiform layer (mGCIPL) thickness. This 1.3-fold faster rate of cpRNFL loss suggests that cpRNFL may be a more sensitive index of progression; however, among eyes with advanced glaucoma, where no further change in cpRNFL was observed, there was significant downward slope in mGCIPL thickness. Therefore, the relative value of cpRNFL and mGCIPL measurements may vary at different stages of disease, with macular measurements possibly of value for monitoring eyes with advanced glaucoma, beyond the floor observed in cpRNFL measurements.[30] These findings also were supported by Sung et al,[16] who found eyes with advanced glaucoma with visual field progression had significantly faster rates of macular thickness loss compared with nonprogressing eyes, whereas there was no significant difference in rate of cpRNFL change between groups. However, it is important to exercise caution in interpreting the results of these studies because the rate of change is not the only variable of importance in determining which parameter could be of most value for detecting progression. For example, a faster rate of change in cpRNFL compared with mGCIPL may be offset by differences in reproducibility of cpRNFL and mGCIPL measurements.

With an increasing number of OCT parameters available to monitor glaucoma progression, there may be confusion as to which parameter to use. To date, evidence suggests that