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# Macular assessment using optical coherence tomography for glaucoma diagnosis

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Accepted 29 August 2012

Published Online First 27 September 2012

## ABSTRACT

Optical coherence tomography (OCT) is an interferometry-based imaging modality that generates high-resolution cross-sectional images of the retina. Circumpapillary retinal nerve fibre layer (cpRNFL) and optic disc assessments are the mainstay of glaucomatous structural measurements. However, because these measurements are not always available or precise, it would be useful to have another reliable indicator. The macula has been suggested as an alternative scanning location for glaucoma diagnosis. Using time-domain (TD) OCT, macular measurements have been shown to provide good glaucoma diagnostic capabilities. Performance of cpRNFL measurement was generally superior to macular assessment. However, macular measurement showed better glaucoma diagnostic performance and progression detection capability in some specific cases, which suggests that these two measurements may be combined to produce a better diagnostic strategy. With the adoption of spectral-domain OCT, which allows a higher image resolution than TD-OCT, segmentation of inner macular layers becomes possible. The role of macular measurements for detection of glaucoma progression is still under investigation. Improvement of image quality would allow better visualisation, development of various scanning modes would optimise macular measurements, and further refining of the analytical algorithm would provide more accurate segmentation. With these achievements, macular measurement can be an important surrogate for glaucomatous structural assessment.

## INTRODUCTION

Glaucoma is an optic neuropathy that is characterised by progressive loss of the retinal ganglion cells (RGC) and their axons in the retinal nerve fibre layer (RNFL), thinning of the neuroretinal rim in the optic nerve head (ONH) and visual field (VF) deficit. Therefore, glaucomatous structural change is assessed by careful examination of ONH and peripapillary retinal nerve fibre. Complicating this assessment is the high variability of the ONH size and shape even among healthy individuals: a wide range of optic disc and cup sizes, variable size and configuration of the blood vessels, variable angle of penetration into the eyeball of the optic nerve (titled disc) and peripapillary changes, such as atrophy and others. Taking into consideration this marked variability of ONH size and shape, it is not surprising that the ability to detect glaucoma, especially at an early stage of the disease, varies considerably among clinicians. In the past two decades, a few ocular imaging devices have

been introduced to allow micron scale quantification of ocular structures. Optical coherence tomography (OCT) is an interferometry-based ocular imaging modality that generates high-resolution cross-sectional images of the retina. This device has been shown to be valuable in the diagnosis and monitoring of retinal diseases and glaucoma.<sup>1-7</sup> The clinical utility of OCT in glaucoma is predominantly based on assessment of the circumpapillary RNFL<sup>8-12</sup> because it allows a thorough sample of all retinal axons as they approach the ONH. However, the variability of ONH size and shape described above, along with pathological features, such as large peripapillary atrophy, papilledema and others, might affect the reliability of the circumpapillary RNFL measurements. Zeimer *et al*<sup>13</sup> first suggested imaging of the macula as a potential location for glaucoma evaluation. In this paper, we review the clinical significance, previous works and future direction of macular imaging by OCT in glaucoma.

## WHY IS MACULAR IMAGING BY OCT MEANINGFUL IN GLAUCOMA?

Compared to the ONH, the macula is a relatively simple structure that is devoid of large vessels. It has multiple cellular and plexiform layers and a central depression (fovea) devoid of RGC. The macula offers several potential physiological and anatomical advantages for glaucoma evaluation. First, the retinal nerve fibre is composed of the RGC axons, and therefore assessment of the RGC may be a more direct method for measuring glaucomatous damage than circumpapillary RNFL thickness. In addition, the macula is the only place in the retina where more than a single RGC body exists in the ganglion cell layer. Because the cell body is substantially larger than the soma of the cell, this might improve the ability to detect damage to these cells.<sup>13-16</sup> Furthermore, more than 50% of the RGC of the entire retina are located within the macula; thus scanning of the macula allows sampling of the majority of the RGC. The macula shape, more specifically the RGC layer, is generally less variable among healthy individuals than other diagnostically important structures, such as the RNFL and ONH. Sensitivity of the RGC could potentially be higher than that of the RNFL because changes in this layer would more likely be the result of a pathological process rather than of normal variation.<sup>17</sup>

Although glaucomatous macular changes are difficult to detect clinically, OCT allows accurate quantitative assessment. Imaging of this region is easier for patients because macular imaging needs

central fixation while ONH imaging should be performed through eccentric fixation.

Measurement variability of macular thickness was better than that of circumpapillary RNFL thickness in previous publications.<sup>18–20</sup> Test–retest variability ranged from 2.3 to 10.1  $\mu\text{m}$  in macular thickness and 5.8–18.9  $\mu\text{m}$  in RNFL thickness when assessed by OCT.<sup>19</sup> As macular and circumpapillary RNFL thickness have different dynamic ranges (macular, approximately 280–300  $\mu\text{m}$  in healthy eyes, 250–280  $\mu\text{m}$  in glaucomatous eyes; circumpapillary RNFL, 80–100  $\mu\text{m}$  in healthy eyes, 60–80  $\mu\text{m}$  in glaucomatous eyes),<sup>18 21 22</sup> it would be more desirable to use coefficient of variation (COV), which is the ratio of SD to the mean, for the assessment of measurement variability rather than the test–retest variability value itself. Mean COV was 1.2% in macular thickness and 4.4% in RNFL thickness according to the study of Garcia-Martin *et al.*<sup>18</sup> In the study of Nakatani *et al.*,<sup>19</sup> COV of macular thickness ranged from 0.4 to 2.8% while those of RNFL thickness ranged from 3.0 to 11.7% in normal and glaucomatous eyes.

The recent development of spectral-domain (SD) OCT technology allows image acquisition at faster speeds than was possible with conventional time-domain (TD) OCT. As a result, more scans can be acquired and combined to create three-dimensional (3D) macular images.<sup>23</sup> Due to the relatively slow acquisition rate of TD-OCT, the conventional scanning pattern used for the macula was six evenly distributed radial scans with interpolation between neighbouring scans. The interpolation mostly affected the outer part of the macula, where the scans are further apart, which is also the location of most glaucomatous damage. SD-OCT scans either employ a raster scan pattern or a denser collection of radial scans with less interpolation than was employed for TD-OCT images.

**Table 1** Comparison of macular and circumpapillary RNFL thickness measurement for glaucoma detection using OCT

Authors	OCT device	Main finding
Wollstein <i>et al</i> <sup>1</sup>	Prototype OCT	RNFL thickness had higher sensitivity and specificity for the detection of visual field abnormalities than macular thickness
Leung <i>et al</i> <sup>6</sup>	Stratus OCT	RNFL thickness outperformed both total macular and macular nerve fibre layer thickness in terms of glaucoma detection and visual function correlation
Medeiros <i>et al</i> <sup>7</sup>	Stratus OCT	The RNFL parameter inferior thickness was significantly better than the macular thickness parameter
Na <i>et al</i> <sup>22</sup>	Cirrus OCT	RNFL thickness measurements were generally superior to those of macular thickness
Seong <i>et al</i> <sup>27</sup>	RTVue OCT	Macular inner retinal thickness showed glaucoma discrimination ability comparable to that of RNFL thickness in patients with early visual field defects In eyes with advanced or peripheral defect, RNFL measurement showed a better glaucoma diagnostic ability than did macular inner retinal layer measurement
Huang <i>et al</i> <sup>20</sup>	RTVue OCT	Average RNFL thickness is the optimal individual OCT parameter to detect perimetric glaucoma Simultaneous evaluation on disc morphology, RNFL and macular inner retinal thickness can improve the diagnostic accuracy in diagnosing glaucoma
Nakatani <i>et al</i> <sup>19</sup>	Topcon 3D OCT	For the diagnosis of early glaucoma, macular parameters had high discriminating power and high reproducibility comparable with RNFL parameters

OCT, optical coherence tomography; RNFL, retinal nerve fibre layer; 3D, three dimensional.

## MACULA THICKNESS PERFORMANCE WITH TD-OCT

Several studies have evaluated the diagnostic capability of the macular thickness.<sup>1–7</sup> Some reports have compared the diagnostic abilities of macular thickness, RNFL thickness and ONH parameters. Using an early version of TD-OCT, Giovannini *et al*<sup>2</sup> showed that volumetric analysis of the macula correlated significantly with glaucoma status. Greenfield *et al*<sup>3</sup> reported that macular thickness changes correlated with changes in visual function and circumpapillary RNFL in glaucoma and may be a surrogate indicator of RGC loss. Wollstein *et al*<sup>1</sup> reported that macular thickness, as measured by OCT, was capable of detecting glaucomatous damage and corresponded with the circumpapillary RNFL thickness; however, circumpapillary RNFL thickness had a higher sensitivity and specificity for the detection of VF abnormalities. Leung *et al*<sup>6</sup> also showed that circumpapillary RNFL thickness outperformed both total macular and macular nerve fibre layer thickness in terms of glaucoma detection and visual function correlation. Medeiros *et al*<sup>7</sup> reported that RNFL and ONH measurements had better discriminating performance than macular measurements when assessed by a later version of TD-OCT. Study outcomes comparing RNFL and macular thickness measurements are summarised in table 1. These studies indicated that although macular thickness has good glaucoma diagnostic capabilities, circumpapillary RNFL measurement performance is superior. One possible explanation might be the use of total macular thickness, which contains all retinal layers. Some of the retinal layers are not involved in the glaucomatous process and thus may reduce the sensitivity and specificity of diagnosis. This leads to concrete efforts in further segmenting the macula to allow quantification of inner retinal layers that are more specifically affected by glaucomatous damage.

## SEGMENTATION OF MACULAR LAYERS

The macula is composed of multiple layers organised from innermost to outermost: inner limiting, nerve fibre, RGC, inner plexiform, inner nuclear, outer plexiform, outer nuclear and the retinal pigment epithelial layers. Glaucoma primarily affects the axon and body of RGC, which constitutes the inner retina.

Differentiation of individual retinal layers by ocular imaging requires a high level of resolution and an advanced segmentation algorithm. Ishikawa *et al*<sup>16</sup> developed a customised segmentation algorithm for macular segmentation using TD-OCT images. They demonstrated comparable glaucoma diagnostic capability of the inner retinal layers with circumpapillary RNFL. Moreover, inner retinal layer thickness was statistically significantly better in discriminating between healthy and glaucomatous eyes than total macular thickness. Wang *et al*<sup>24</sup> measured the RGC layer thickness in glaucomatous eyes with an SD-OCT device, using a computer-aided manual segmentation procedure. They reported that it was feasible to obtain local measurements of RGC thickness that corresponded to functional findings.

Manufacturers of SD-OCT devices incorporated automatic macular segmentation analysis into their operating system. The ganglion cell complex (GCC) was designated for thickness measurements from the internal limiting membrane to the inner nuclear layer, which is composed of RGC, along with their axons and dendrites. Other manufacturers segmented the inner retina into the ganglion cell inner plexiform layer. Cho *et al*<sup>25</sup> examined the relationship between VF mean sensitivity and macular GCC thickness, and reported a similar level of correlation as with circumpapillary RNFL thickness. Rao *et al*<sup>26</sup> also evaluated the association between the various SD-OCT-derived

structural measurements and VF. They reported that the stronger relationships were found for segmented inner retinal thickness than full retinal thickness measurement.

Assessing the diagnostic performance of GCC thickness, Seong *et al*<sup>27</sup> reported that GCC thickness was comparable to circumpapillary RNFL thickness in terms of glaucoma diagnostic capability. Sakamoto *et al*<sup>28</sup> compared macular RNFL images obtained by 3D SD-OCT with those obtained by colour and red-free fundus photography. They found that more macular RNFL defects were detected on 3D SD-OCT images than on colour fundus photographs. Kim *et al*<sup>29</sup> classified glaucoma into three disease severity groups based on the mean deviation of the VF. They reported that the macular GCC and circumpapillary RNFL thicknesses showed similar diagnostic performances in detecting early, moderate and severe glaucoma. Kotera *et al*<sup>30</sup> showed that the mean macular inner retinal thickness was significantly thinner in suspected glaucoma and preperimetric glaucomatous eyes than in healthy eyes, while mean total retinal and macular nerve fibre layer thicknesses were not. This report might demonstrate the utility of macular inner retinal measurements as an early indicator of glaucomatous change.

Assessing covariability associated with macular inner retinal thickness, Kim *et al*<sup>31</sup> showed that thin GCC thickness correlated with older age and longer axial length. Similarly, Mwanza *et al*<sup>32</sup> reported that a thinner ganglion cell inner plexiform layer was associated with thinner RNFL, older age, longer ocular axial length and male sex.

Taken together, published studies indicated that the segmented macular inner retinal layer thickness performs better than the total macular thickness and similar to (but not better than) the circumpapillary RNFL thickness in glaucoma diagnosis.

## CLINICAL APPLICATION

In clinical practice, situations in which glaucomatous changes were detected in the circumpapillary RNFL without corresponding damage in the macula or vice versa have been encountered. Na *et al*<sup>33</sup> classified cases according to whether they were better diagnosed by macular thickness or circumpapillary RNFL measurement. Overall, more eyes were diagnosed by circumpapillary RNFL than by macular measurements. Eyes with exclusive macular damage tended to have larger ONH sizes than eyes that had solely abnormal circumpapillary RNFL measurements. It was suggested that this difference in diagnostic capability was due to measuring circumpapillary RNFL thickness in a fixed-sized circumpapillary diameter (3.4 mm), which brought the sampling circle closer to the disc margin in a larger ONH. As RNFL thickness measured close to the disc margin tends to be thicker, this might mask early glaucomatous structural abnormalities.

The papillomacular bundle has been shown to be resistant to glaucomatous damage until the end stage of the disease. Therefore, measurement of the posterior pole macular thickness may be a strategy to measure advanced glaucomatous function. However, progressive RNFL loss is not easy to detect in advanced glaucoma because most of the RNFL is already lost at this stage. Sung *et al*<sup>21</sup> reported that more than half of their advanced glaucoma participants (VF mean deviation < -10 dB) could not be evaluated by photographic assessment of the ONH and RNFL because these structures exhibited advanced glaucomatous abnormalities that precluded clinical assessment of structural changes. The participants showed a much higher rate of progression in macular thickness than with circumpapillary RNFL thickness and a better agreement with progression by VF.

Glaucoma is typically described as causing a focal abnormality, especially in the early stages of the disease. In order to

exploit this in a fashion similar to that employed by the glaucoma hemifield test in VF, Um *et al*<sup>34</sup> categorised the posterior-pole macular area into five regions in each hemifield. The difference between corresponding locations was compared to the difference between these locations in healthy eyes. The asymmetry in hemifield macular thickness showed better glaucoma diagnostic capability than the average circumpapillary RNFL thickness in early glaucomatous eyes.

## PROGRESSION DETECTION

The clinical utility of ocular imaging devices could be further amplified by detecting disease progression in glaucoma. Most OCT progression studies conducted so far were confined to circumpapillary RNFL measurements and only a few studies have evaluated macular thickness measurements. Medeiros *et al*<sup>35</sup> reported that circumpapillary RNFL thickness outperformed macular thickness and optic disc parameters in detecting glaucoma progression using TD-OCT.

Needless to say, measurement repeatability is of paramount importance in progression detection. Mwanza *et al*<sup>17</sup> recently demonstrated higher measurement reproducibility of macular ganglion cell layer thickness by the use of SD-OCT than TD OCT. Recently, Na *et al*<sup>22</sup> reported the glaucoma progression detection capability of macular ganglion cell layer thickness. According to their results, ganglion cell layer thickness showed similar sensitivity to RNFL or total macular thickness in terms of agreement with progression determined by optic disc/RNFL photographic or VF assessment.

The denser scanning and improved measurement reproducibility offered by SD-OCT hold promise to improve the detection of structural progression. However, more studies to confirm this hypothesis are yet to be published.

## LIMITATIONS

In the meantime, macular thickness measurement has some limitations when used for diagnosing glaucoma. One of the factors that may influence macular measurements for glaucoma detection and the relationship with functional tests is the spatial summation within central vision. The spatial summation becomes a significant factor affecting the structure-function relationship within macular. When standard automated perimetry (SAP) is used as a functional test, while the inner retinal layer is thinning, the enlargement of the area of complete summation, ie, Ricco's area, compensates reduced SAP sensitivity especially in early glaucoma to maintain a constant threshold at this area.<sup>36</sup> This may induce a disrupted structure-function relationship between macular thickness and SAP sensitivity and thus affect the diagnostic performance of macular measurement.

## FUTURE DIRECTIONS

To enhance the clinical utility of macular measurements obtained by OCT in glaucoma diagnosis, the image quality itself must be improved because the analytical outcome depends heavily on image quality. In particular, segmentation of inner and outer macular layers demands a high quality image. Enhanced image quality facilitates the precise segmentation of various cellular layers of the macula. An effort has been made to improve image quality using various techniques. Nakano *et al*<sup>37</sup> suggested that speckle noise was the primary artefact in OCT images, and a speckle noise-reducing technique was adopted by using eye-tracking and averaging, which allowed clearer visualisation and measurement of the macular ganglion cell layer. Development of various applications of scanning modes to optimise macular

measurements is warranted, as is the further refining of the analytical algorithm for accurate segmentation.

## CONCLUSION

Circumpapillary RNFL and ONH assessments are the mainstay of glaucomatous structural measurements. However, because these measurements cannot always be obtained, it would be useful to have another reliable indicator for glaucomatous structural assessment by OCT. The performance of circumpapillary RNFL measurement was generally superior to macular assessment. In the meantime, macular thickness measurement showed better glaucoma diagnostic performance and progression detection capability in some specific cases, which suggests that these two measurements may be combined to produce a better diagnostic strategy. Several studies show that the macular inner retinal layer acts comparably to circumpapillary RNFL in glaucoma diagnosis. Investigations are ongoing into its use for the detection of glaucoma progression. More sophisticated measurement and analysis tools that can amplify the advantages of macular measurements are expected. With these achievements, macular measurement can be an important clinical surrogate for glaucomatous structural assessment.

**Contributors** KRS: conception and design, acquisition of data, analysis and interpretation of data, drafting the article, critical revision, final approval of the version for publication. GW: drafting the article, critical revision, final approval of the version for publication. NRK: drafting the article, critical revision. JHN: drafting the article. JEN: critical revision. CYK: drafting the article, critical revision. JSS: critical revision, final approval of the version for publication.

**Funding** This study was supported by a grant of the Korea Health technology R&D Project, Ministry of Health & Welfare, Republic of Korea (A101727).

**Competing interests** JSS has intellectual property licensed by Massachusetts Institute of Technology to Carl Zeiss Meditec. All other authors declare they have no conflicts of interest.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Correction notice** This article has been corrected since it was published Online First. The spelling of 'Macula' has been corrected to 'Macular' in the article title.

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*Br J Ophthalmol* 2012 96: 1452-1455 originally published online September 27, 2012  
doi: 10.1136/bjophthalmol-2012-301845

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