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Diagnostic Accuracy of Spectralis SD OCT Automated Macular Layers Segmentation to Discriminate Normal from Early Glaucomatous Eyes

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Purpose: To evaluate the accuracy of the macular retinal layer segmentation software of the Spectralis spectral-domain (SD) optical coherence tomography (OCT) device (Heidelberg Engineering, Inc., Heidelberg, Germany) to discriminate between healthy and early glaucoma (EG) eyes.

Design: Prospective, cross-sectional study.

Participants: Forty EG eyes and 40 healthy controls were included.

Methods: All participants were examined using the standard posterior pole and the peripapillary retinal nerve fiber layer (pRNFL) protocols of the Spectralis OCT device. Using an Early Treatment Diagnostic Retinopathy Study circle at the macular level, the automated retinal segmentation software was applied to determine thicknesses of the following parameters: total retinal thickness, inner retinal layer (IRL), macular retinal nerve fiber layer (mRNFL), macular ganglion cell layer (mGCL), macular inner plexiform layer (mIPL), macular inner nuclear layer (mINL), macular outer plexiform layer (mOPL), macular outer nuclear layer (mONL), photoreceptors (PR), and retinal pigmentary epithelium (RPE). The ganglion cell complex (GCC) was determined by adding the mRNFL, mGCL, and mIPL parameters and the ganglion cell layer–inner plexiform layer (mGCL-IPL) was determined by combining the mGCL and mIPL parameters. Thickness of each layer was compared between the groups, and the layer and sector with the best area under the receiver operating characteristic curve (AUC) were identified.

Main Outcome Measures: Comparison of pRNFL, IRL, mRNFL, mGCL, mIPL, mGCC, mGCL-IPL, mINL, mOPL, mONL, PR, and RPE parameters and total retinal thicknesses between groups for the different areas and their corresponding AUCs.

Results: Peripapillary RNFL was significantly thinner in the EG group globally and in all 6 sectors assessed ($P < 0.0005$). For the macular variables, retinal thickness was significantly reduced in the EG group for total retinal thickness, mIRL, mRNFL, mGCL, and mIPL. The 2 best isolated parameters to discriminate between the 2 groups were pRNFL (AUC, 0.956) and mRNFL (AUC, 0.906). When mRNFL, mGCL, and mIPL measurements were combined (mGCC and mGCL plus mIPL), then its diagnostic performance improved (AUC, 0.940 and 0.952, respectively).

Conclusions: Macular RNFL, mGCL-IPL, and mGCC measurements showed a high diagnostic capability to discriminate between healthy and EG participants. However, macular intraretinal measurements still have not overcome standard pRNFL parameters. *Ophthalmology 2017;■:1–11 © 2017 by the American Academy of Ophthalmology*

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Glaucoma is an acquired, multifactorial, and progressive optic neuropathy that is clinically diagnosed as a cupped optic disc associated with a corresponding functional defect in the visual field (VF).[1–4] However, the underlying disease process is the loss of retinal ganglion cells (RGCs) and their axons (the retinal nerve fiber layer [RNFL]).[1–4] In fact, when a glaucomatous visual defect is detected, approximately 28%[5] of RGCs and 17%[6] of RNFL thickness already have been damaged irreversibly.

Between one third and one half of this RGC population resides within the posterior pole. Glaucoma preferentially affects what is called the ganglion cell complex (GCC), which represents 30% to 35% of the total retinal thickness and includes the 3 innermost layers of the macula: the macular RNFL (mRNFL), macular ganglion cell layer (mGCL), and macular inner plexiform layer (mIPL). These layers contain, respectively, the axons, cell bodies, and dendrites of the RGCs. In the macula, the ganglion cell layer

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(GCL) is thicker than the RNFL, with an RGC body diameter approximately 10 to 20 times larger compared with their axons.[7] In addition, the central retina has less variability in cell density compared with peripheral retina or optic nerve head parameters or even peripapillary RNFL (pRNFL) thickness.[7,8] Thus, quantifying RGC loss in the macula has been shown to allow early detection of glaucomatous damage, in some cases even 5 years before functional damage can be detected.[9] In this regard, in vivo thickness measurement of the GCC and GCL plus inner plexiform layer (IPL; GCL-IPL) with spectral-domain (SD) optical coherence tomography (OCT) devices have shown very good discriminative diagnostic ability, especially in early glaucoma (EG),[10–12] but also in moderate to severe glaucoma.[13] The new segmentation software designed for the Spectralis SD OCT (Heidelberg Engineering, Inc., Heidelberg, Germany) enables the independent quantification of all the retinal layers in the macula, including separate measurements of the 3 layers most affected by glaucoma: the mRNFL, mGCL, and mIPL. This differentiation also may contribute to improving our knowledge of the pathogenesis early in the disease in terms of which layer is affected first (cell body vs. axons).

The purpose of this study was to assess the diagnostic accuracy of this new macular retinal layer segmentation software to discriminate between healthy participants and participants with EG. This ability also was compared with that shown by the more conventional analysis of pRNFL thickness.

Methods

Study Design

This prospective, cross-sectional, multicenter, observational study complied with the tenets of the Declaration of Helsinki and was approved by the Ethical Committee of Hospital de l'Esperança-Parc de Salut Mar. Informed consent was obtained from all the participants. One eye of each participant was included in this study according to the eligibility criteria described below. If both eyes met the eligibility criteria, one eye was selected randomly.

Participants

The study was undertaken from February 2015 through May 2015. Participants included in this study were recruited consecutively at the Departments of Glaucoma of Hospital de l'Esperança-Parc de Salut Mar, Institut Català de la Retina, and Institut de la Màcula in Barcelona, Spain. All participants underwent a complete ophthalmic examination that included best-corrected visual acuity, pachymetry, slit-lamp biomicroscopy of the anterior and posterior segments, Goldmann applanation tonometry, gonioscopy, optic nerve head retinography, and peripapillary and macular imaging using Spectralis SD OCT (Heidelberg Eye Explorer version 1.9.13.0, Spectralis Viewing Module 6.5.2.0; Heidelberg Engineering). Swedish interactive threshold algorithm standard strategy, program 24-2 of the Humphrey Field Analyzer (Carl Zeiss Meditec, Jena, Germany), was used for VF testing of each eye. Reliability criteria were fixation losses of 20% or less, false-positive results of 15% or less, and false-negative results of 33% or less.

Inclusion criteria were as follows: patients older than 18 years of age, best-corrected visual acuity better than 20/40, refractive error of less than 5 spherical diopters and 2 diopters of cylinder, and open angle on gonioscopy. Exclusion criteria were previous intraocular or laser surgery except uncomplicated cataract surgery 6 months before examination, history or evidence of retinal or macular pathologic features (including drusen), systemic diseases or neurologic disorders that could produce VF or optic disc defects, and failure to obtain reliable standard automated perimetry results.

Test Methods

Reference Standard. The target condition (EG) was defined using both structural and functional evidence as suggested by Foster et al[14] and as usually performed clinically. Glaucomatous VF defects were defined according to the criteria of Anderson[15] in which at least 1 of the following had to be present: having a cluster of 3 or more nonedge points with $P < 0.05$ and at least 1 point with $P < 0.01$ in the pattern deviation probability plot, or pattern standard deviation of less than 5%, or glaucoma hemifield test results outside normal limits. Both EG and healthy participants underwent VF examination at least twice before the study was initiated.

Early glaucoma patients had to have elevated basal intraocular pressure (>21 mmHg), glaucomatous optic disc abnormalities evaluated by 2 glaucoma specialists (M.P. and A.G.; defined as thinning of the neuroretinal rim, notches, peripapillary hemorrhages, or RNFL defects), and glaucomatous VF defects with a mean deviation (MD) of more than −6 dB. Healthy controls had a normal optic nerve head appearance, intraocular pressure of 21 mmHg or less, and normal VF results.

Index Test: Spectral-Domain Optical Coherence Tomography Imaging. All participants were examined using the standard posterior pole and pRNFL protocols of the Spectralis OCT. Images had to have a quality index of at least 20 to be included in the study. Images with artifacts were excluded.

Images were acquired using the automated eye alignment eye-tracking software (TruTrack; Heidelberg Engineering) to obtain perifoveal volumetric retinal scans comprising 61 single lines of 15 frames (30°×25° volume scan centered at the fovea). Peripapillary RNFL thickness (from internal limiting membrane to the inner aspect of the retinal pigment epithelium [RPE]) also was measured in all participants in a standard fashion using the instrument's RNFL protocol (circular 3.5-mm diameter, 768 A-scans) and was segmented automatically using the Spectralis software. Correction for fovea−disc orientation was provided automatically by the software with the Fovea-Disc Alignment system. In all cases, foveal fixation and segmentation were checked to be correct.

Using these specific protocols, images were obtained by 3 experienced operators in 3 different centers and were sent to the main center using the Spectralis raw data sharing system, where all the images were reviewed exhaustively by a glaucoma specialist (M.P.) who was masked to clinical information and then assessed quality, alignment, and artifacts and performed macular segmentation. Layer-by-layer segmentation was executed automatically in this instrument using the new software for the Spectralis OCT (Fig 1), and it was checked to be adequate in the 61 B-scans of each imaged eye using the criteria of Ishikawa et al[16] as a reference. In detail, we excluded eyes with incorrigible segmentation failures, which were defined as obvious disruption of the detected border, border wandering (detected border jumping to and from different anatomic structures), or both within more than 5% consecutively (i.e., an uninterrupted error) or 20% cumulatively (i.e., adding up all errors amounted to 20%