Optical Coherence Tomography Longitudinal Evaluation of Retinal Nerve Fiber Layer Thickness in Glaucoma

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Objectives: To longitudinally evaluate optical coherence tomography (OCT) peripapillary retinal nerve fiber layer thickness measurements and to compare these measurements across time with clinical status and automated perimetry.

Methods: Retrospective evaluation of 64 eyes (37 patients) of glaucoma suspects or patients with glaucoma participating in a prospective longitudinal study. All participants underwent comprehensive clinical assessment, visual field (VF) testing, and OCT every 6 months. Field progression was defined as a reproducible decline of at least 2 dB in VF mean deviation from baseline. Progression of OCT was defined as reproducible mean retinal nerve fiber layer thinning of at least 20 µm.

Results: Each patient had a median of 5 usable OCT scans at median follow-up of 4.7 years. The difference in the linear regression slopes of retinal nerve fiber layer thickness between glaucoma suspects and patients with glaucoma was nonsignificant for all variables; however, Kaplan-Meier survival curve analysis demonstrated a higher progression rate by OCT vs VF. Sixty-six percent of eyes were stable throughout follow-up, whereas 22% progressed by OCT alone, 9% by VF mean deviation alone, and 3% by VF and OCT.

Conclusions: A greater likelihood of glaucomatous progression was identified by OCT vs automated perimetry. This might reflect OCT hypersensitivity or true damage identified by OCT before detection by conventional methods.


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Financial Disclosure: Drs Schuman and Fujimoto are inventors of optical coherence tomography. Drs Schuman and Fujimoto are inventors of optical coherence tomography. Drs Schuman and Fujimoto are inventors of optical coherence tomography.

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GLAUCOMA IS CHARACTERIZED by a combination of structural changes in the retina and optic nerve head (ONH) and functional perimetric damage. Previous studies have indicated that structural changes in patients with glaucoma, as detected by optic disc and/or nerve fiber layer assessment, precede functional changes detected by perimetry. In recent years, glaucoma imaging modalities were incorporated into the management of patients with glaucoma. These imaging modalities were designed to detect morphologic glaucomatous abnormalities, and they might improve the ability to detect longitudinal changes using quantitative measurements. Several cross-sectional studies have demonstrated the capability of these modalities to identify glaucomatous changes. Limited information, however, is available regarding their use for longitudinal glaucoma assessment.

Optical coherence tomography (OCT) is a high-resolution imaging device capable of obtaining reproducible retinal nerve fiber layer (RNFL) thickness measurements. This device has been shown to be a valuable tool for glaucoma assessment, and cross-sectional studies have shown that it allows differentiation between healthy individuals and patients with glaucoma. The purpose of this study is to longitudinally evaluate OCT circumpapillary RNFL measurements compared with standard clinical assessment and automated perimetry.

Methods: Data for this study were retrospectively collected from a prospective longitudinal study carried out in the glaucoma service at the New England Eye Center, Tufts–New England Medical Center, Tufts University School of Medicine, between July 1, 1994, and June 30, 2001. All individuals who attended the glaucoma service, who were willing to participate, and who qualified according to the criteria in the following paragraph were included in the study. Institutional review board and ethics committee approval from Tufts–New England Medical Center was obtained for the study, and all participants gave their approval to participate. This study followed the principles of the Declaration of Helsinki.

Patients were included in the study according to the following inclusion criteria: best-
corrected visual acuity of 20/60 or, better, refractive error of +3.00 to −6.00 diopters, and at least 5 reliable visual field (VF) tests and 5 good-quality OCT scans. The exclusion criteria consisted of a history of diabetes mellitus and signs of posterior pole pathologic abnormalities other than those attributed to glaucoma or substantial media opacity in which the fundus was not visible. Eyes that underwent cataract extraction or any other intraocular surgery during follow-up were excluded from the study.

STUDY PROTOCOL

All participants underwent a thorough baseline ophthalmic evaluation, including medical history, intraocular pressure measurement, undilated and dilated biomicroscopy, VF testing, and OCT scanning. Both eyes were included in the study if they were found to be eligible. All participants were scheduled for follow-up assessments every 6 months, unless additional visits were medically indicated. Each visit included a full ophthalmic evaluation, VF testing, and OCT scanning.

CLINICAL DIAGNOSIS

The study population included glaucoma suspects and patients with glaucoma. Suspected eyes were defined as those with no history of retinal pathologic abnormalities, laser therapy, or intraocular surgery. An intraocular pressure of 22 to 30 mm Hg or asymmetrical ONH cupping (difference in vertical cup-disc ratio >0.2 between eyes) or an abnormal-appearing ONH, all in the presence of normal VF test results, were also included in the definition. This group contained suspected eyes with different causes, such as ocular hypertension, increased cupping (vertical cup-disc ratio >0.6), asymmetrical cupping, and a family history of glaucoma. Glaucomatous eyes were defined as those with at least 1 of the following: (1) an abnormal-appearing VF defect, (2) intraocular pressure greater than 35 mm Hg despite a full VF in the presence of large ONH cupping, or (3) a nerve fiber layer defect on stereomicroscopy.

VISUAL FIELD TESTING

All patients underwent Humphrey full-threshold 24-2 achromatic perimetry or Swedish Interactive Thresholding Algorithm standard 24-2 perimetry. A reliable VF test was defined as having fewer than 30% false-negative or false-positive responses. Normal VF test results were defined as having no clusters of 3 or more adjacent points depressed more than 5 dB or 2 adjacent points depressed more than 10 dB in the pattern deviation plot. An abnormal VF test result was defined as a cluster of abnormal points as defined previously herein.

Two glaucoma experts (G.W. and J.S.S.) independently assessed the VF test results to determine progression between consecutive visits and between the first and last visits. The graders were masked to each other and to any clinical information. Printouts of the VF were organized in chronological order, with masking of the patient identification and age and the test date. The graders had access to the entire set of VFs for each eye before making their assessment, and they were asked to determine VF deterioration between consecutive visits. Consensus between the graders was required in cases of disagreement.

Eyes were defined for the analysis as VF progressors by subjective assessment when both graders or the consensus agreement labeled reproducible deterioration in 2 of 3 consecutive follow-up VFs. All other eyes were classified as VF nonprogressors. Eyes were defined as VF progressors by mean deviation (MD) when VF-MD decreased by 2 dB from the baseline value in 2 of 3 consecutive follow-up visits. A third method of VF assess-

OPTICAL COHERENCE TOMOGRAPHY

Optical coherence tomography is the optical equivalent of B-scan ultrasound, in which the delay of the backscattered light from the various components of the scanned tissue enables differentiation of various tissue layers. Detailed descriptions of OCT have been published previously.27-30 Optical coherence tomography has been shown to obtain accurate and reproducible RNFL and retinal thickness measurements.26-28

All OCT scans in this study were performed using a prototype device with a reported resolution of 10 µm.26 This device acquired 100 circumpapillary measuring points in approximately 2.5 seconds. Measurements of RNFL thickness acquired by this device have been shown to highly correlate with those obtained by a commercially available OCT device (H. M. Pakter, J.S.S., E.H., et al, unpublished data, 2001).

All patients underwent pupillary dilation with 1% tropicamide and 2.5% phenylephrine hydrochloride before recording OCT images. Each patient had 3 circular scans centered on the optic disc, with a diameter of 3.4 mm. Poor-quality scans were defined as those with a signal-noise ratio less than 40 or the presence of overt misalignment of the surface detection algorithm of at least 15 consecutive pixels or 20 additive pixels.

Variables used for the analysis were mean peripapillary RNFL thickness (OCT-mean) and 2 new variables that were computed for this study: OCT-MD (the mean difference between each of the 100 measuring points and age-adjusted normative values as determined in a previous study [H. M. Pakter, J.S.S., E.H., et al, unpublished data, 2001]) and OCT-PSD (the SD of the difference between the measured value and the age-adjusted normative value). The normative database consisted of 127 eyes of healthy individuals (mean±SD age, 47.0±17.4 years, with 25% of the individuals aged >38 years) that were scanned using the prototype device. Confirmed OCT progression was defined as thinning of the mean RNFL of at least 20 µm (based on 2× the reproducibility error of the device26) from the baseline measurement in 2 of 3 consecutive follow-up OCT scans.

STATISTICAL ANALYSIS

The data were analyzed using a statistical software program (SAS; SAS Institute Inc, Cary, NC). The mixed procedure in SAS was used to correct for the correlation between measurements from the same patient. Pearson correlations were calculated between VF results and OCT measurements for tests conducted within 6 months of each other. Linear regression was used to determine the slope of change for VF and OCT measurements for each eye across time. The group mean slope was used for each variable as defined according to the AGIS criteria as a reproducible increase by 4 points from the baseline level in 3 consecutive follow-up visits.36 Variables used for the analysis were VF-MD, pattern standard deviation (VF-PSD), subjective assessment of the VF, and AGIS scoring. For eyes that were tested by the full-threshold and Swedish Interactive Thresholding Algorithm protocols during follow-up, the global VF indices were treated as a continuum. Switching from full-threshold to Swedish Interactive Thresholding Algorithm standard perimetry has been found to affect the threshold sensitivity level. However, previous studies7,38 could not find a significant effect on VF-MD, and, therefore, this variable was used for the statistical analysis.
RESULTS

Fifty-five glaucoma eyes (32 patients) and 9 glaucoma suspect eyes (5 patients) qualified for the study. The characteristics of the study population are summarized in Table 1. During median follow-up of 4.7 years, the participants had a median of 5 qualified OCT scans (range, 5-11 in the glaucoma group and 5-15 in the glaucoma suspects group). A median of 6 qualified VF tests (range, 5-11 in the glaucoma group and 5-9 in the glaucoma suspects group) were performed within a median of 4.2 years of follow-up. Most OCT scans and VF tests (95%) were conducted within 6 months of each other (Figure 1).

The mean ± SD VF-MD for the glaucoma suspects group was −0.7±2.1 dB at baseline and −1.1±1.7 dB at the last visit (P=.04). The mean ± SD VF-MD for the glaucoma group was −4.1±4.8 dB at baseline and −4.1±5.4 dB at the last visit (P=.67) (Table 2). No statistically significant difference was found between initial and final VF-PSD and AGIS scoring in either group. For OCT-mean, the mean ± SD measure in the glaucoma suspects group was 115.7±36.2 µm at baseline and 111.3±23.0 µm at the last visit (P=.02). In the glaucoma group, the initial mean ± SD OCT-mean was 94.0±21.9 µm, and the final value was 82.3±25.3 µm (P<.001). For OCT-MD and OCT-PSD, the differences between the first and last values were statistically significant only in the glaucoma group (Table 2). Cross-sectional correlations between OCT measures and global VF indices of tests conducted within 6 months of each other were moderate to good at each visit (Table 3).

Kaplan-Meier survival curves were used for evaluating time to progression. Overall, there was a greater likelihood of a repeatable OCT-mean RNFL decrease of 20 µm compared with a VF-MD decrease of 2 dB (P=.12) (Figure 2). Allogether, 22 of 64 eyes were found to progress when applying the repeatable VF-MD decrease of 2 dB and repeatable OCT decrease of 20 µm criteria. Fourteen eyes (22%) progressed by OCT only, 6 (9%) by VF only, and 2 (3%) by both methods. In setting the cutoff value for VF-MD, we tried to simulate clinical criteria for progression. Defining VF-MD progression as a repeatable decline of 1 dB yielded a higher number of VF progressors (12 eyes by OCT only, 15 by VF only, and 4 by both methods), whereas setting the level at 4 dB reduced the number of VF progressors (16 eyes by OCT only, 1 by VF only, and none by both methods) (Figure 3). Using the AGIS criteria, none of the participating eyes deteriorated during follow-up.

Eleven eyes had an increase in RNFL thickness of at least 20 µm from the baseline measurement in 1 visit. Only 4 eyes had reproducible RNFL thickening of at least 20 µm in 2 of 3 consecutive visits. The K-M curves using OCT-mean did not differ significantly in glaucoma suspects vs patients with glaucoma (P=.72). Similar results were found for K-M curves of OCT-mean stratified by subjective VF assessment (P=.40).

Comparing OCT-mean and VF-MD for patients defined as progressors or nonprogressors by the subjective assessment of VF, we found a greater likelihood for progression by OCT-mean compared with VF-MD in the VF nonprogressor group (P=.01) (Figure 4A). In VF progressors, the curves overlapped and the difference was not significant (P=.31) (Figure 4B).

Linear regression analysis was used as an additional method to assess progression. The mean ± SD linear regression slope for VF-MD in the glaucoma suspects group was −0.12±0.45 dB per year and for the glaucoma group was 0.04±0.54 dB per year (P=.78). The mean ± SD VF-PSD mean linear regression slope was −0.07±0.16 dB per year in the glaucoma suspects group and −0.04±0.36 dB per year in the glaucoma group (P=.77). No significant differences were found for OCT regression slopes between glaucoma suspects and glaucomatous eyes for mean ± SD OCT-mean (−2.56±5.76 µm per year and −2.21±4.12 µm per year, respectively; P=.88), OCT-MD (−2.10±5.75 µm per year and −1.77±4.12 µm per year; P=.87), and OCT-PSD (−0.72±1.73 µm per year and 0.57±1.85 µm per year; P=.06). Stratifying the group based on the subjective assessment of VF into VF progressors and VF nonprogressors, we found a significant difference only for VF-PSD (Table 4).

To determine the possibility of identifying changes using sectoral analysis, we reanalyzed the data after grouping the OCT data into 4 quadrants: superior, temporal, inferior, and nasal. The slope for each quadrant was calculated for each variable after subdividing the group to

Table 1. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Glaucoma Suspects</th>
<th>Glaucoma Group</th>
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<tbody>
<tr>
<td>Eyes/patients, No.</td>
<td>9/5</td>
<td>55/32</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>50.9 (15.1)</td>
<td>66.6 (14.4)</td>
</tr>
<tr>
<td>Sex, M/F, No.</td>
<td>2/3</td>
<td>12/20</td>
</tr>
<tr>
<td>Ethnicity, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eastern Asian</td>
<td>0</td>
<td>2 (6)</td>
</tr>
<tr>
<td>African American</td>
<td>0</td>
<td>7 (22)</td>
</tr>
<tr>
<td>White</td>
<td>5 (100)</td>
<td>23 (72)</td>
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Figure 1. Difference in time between visual field testing and optical coherence tomography scanning.

Figure 2. Kaplan-Meier survival curves were used for evaluating time to progression. Overall, there was a greater likelihood of a repeatable OCT-mean RNFL decrease of 20 µm compared with a VF-MD decrease of 2 dB (P=.12) (Figure 2). Allogether, 22 of 64 eyes were found to progress when applying the repeatable VF-MD decrease of 2 dB and repeatable OCT decrease of 20 µm criteria. Fourteen eyes (22%) progressed by OCT only, 6 (9%) by VF only, and 2 (3%) by both methods. In setting the cutoff value for VF-MD, we tried to simulate clinical criteria for progression. Defining VF-MD progression as a repeatable decline of 1 dB yielded a higher number of VF progressors (12 eyes by OCT only, 15 by VF only, and 4 by both methods), whereas setting the level at 4 dB reduced the number of VF progressors (16 eyes by OCT only, 1 by VF only, and none by both methods) (Figure 3). Using the AGIS criteria, none of the participating eyes deteriorated during follow-up.

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progressors and nonprogressors based on subjective assessment of VF. No significant differences were found between the mean slopes of progressors and nonprogressors for any sector.

This study evaluated longitudinal morphologic RNFL changes as determined by OCT and compared these changes with clinical status and functional glaucoma testing. The results of this study indicate that the rate of RNFL thinning as determined by OCT exceeded the rate of func-

<table>
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<tr>
<th>Table 2. Baseline and Last Visit VF and OCT Results*</th>
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<tbody>
<tr>
<td>VF-MD, dB</td>
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<tr>
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<tr>
<td>Glaucoma suspects (n = 9)</td>
</tr>
<tr>
<td>Baseline</td>
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<tr>
<td>Last visit</td>
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<tr>
<td>P value</td>
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<tr>
<td>Glaucoma (n = 55)</td>
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<tr>
<td>Baseline</td>
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<tr>
<td>Last visit</td>
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<tr>
<td>P value</td>
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</tbody>
</table>

Abbreviations: AGIS, Advanced Glaucoma Intervention Study; OCT, optical coherence tomography; MD, mean deviation; PSD, pattern standard deviation; VF, visual field.

*Data are given as mean (SD).

<table>
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<tr>
<th>Table 3. Cross-sectional Pearson Correlation Between OCT Measures and VF Indices for Each Visit</th>
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<td></td>
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<tr>
<td>Visit 1 (n = 64)</td>
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<tr>
<td>VF-MD</td>
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<tr>
<td>VF-PSD</td>
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<tr>
<td>Visit 2 (n = 64)</td>
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<tr>
<td>VF-MD</td>
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<tr>
<td>VF-PSD</td>
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<tr>
<td>Visit 3 (n = 62)</td>
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<tr>
<td>VF-MD</td>
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<tr>
<td>VF-PSD</td>
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<tr>
<td>Visit 4 (n = 57)</td>
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<tr>
<td>VF-MD</td>
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<tr>
<td>VF-PSD</td>
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Abbreviations: OCT, optical coherence tomography; MD, mean deviation; PSD, pattern standard deviation; VF, visual field.
criterion of VF-MD of 4 dB, very few subjectively stable and localized changes in detecting progression. Using a subjective assessment, which takes into account global variable, are not expected to be more sensitive than Moreover, the objective criteria, which are based on a progressors by the objective global criteria at this level. Many eyes subjectively identified as stable were called the sensitivity increased but the specificity decreased. (Figure 3). When we liberalized the cutoff value to 1 dB, progressors and nonprogressors based on subjective VF as criteria for progression. We stratified the eyes into pro-

When grouping the participating eyes by subjective assessment of VF, K-M analysis showed a significantly greater likelihood of progression by OCT than by VF for those who were classified as VF nonprogressors, and there were overlapping curves in the VF progressor group. The findings from the present study for subjective assessment of VF are biased in favor of VF-MD results because the graders were not masked to the global indices results in the VF printouts. The higher rate of RNFL loss in the nonprogressor group might reflect hypersensitivity of the OCT, or it might reflect true structural changes preceding the appearance of functional changes. This latter explanation is in agreement with previous studies, in which a curvilinear relationship was found between functional and structural changes. One would expect a much larger change to be required initially to manifest a detectable functional change than a structural change (Figure 5). In the midportion of the disease, functional change has a greater slope than structural change, but late in the disease, structural change is again more acute. However, a recent study suggested that there is a linear structural and functional relation-

<table>
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<tr>
<th></th>
<th>VF Nonprogressors (n = 39)</th>
<th>VF Progressors (n = 25)</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>VF-MD, dB per year</td>
<td>0.07 (0.45)</td>
<td>-0.05 (0.64)</td>
<td>.58</td>
</tr>
<tr>
<td>VF-PSD, dB per year</td>
<td>-0.13 (0.33)</td>
<td>0.08 (0.33)</td>
<td>.006</td>
</tr>
<tr>
<td>OCT-mean, µm per year</td>
<td>-2.14 (4.38)</td>
<td>-2.44 (4.34)</td>
<td>.57</td>
</tr>
<tr>
<td>OCT-PSD, µm per year</td>
<td>-1.70 (4.38)</td>
<td>-2.00 (4.34)</td>
<td>.66</td>
</tr>
<tr>
<td>OCT-MD, µm per year</td>
<td>0.17 (1.97)</td>
<td>0.71 (1.68)</td>
<td>.25</td>
</tr>
</tbody>
</table>

Abbreviations: OCT, optical coherence tomography; MD, mean deviation; PSD, pattern standard deviation; VF, visual field.

*Data are given as mean (SD).
ship and attributed the curvilinear relationship described previously herein to the logarithmic scaling of VF. Further studies are warranted to investigate this relationship.

To obtain longitudinal data, the study was conducted using data collected from our prototype OCT device. Although this device differs from current commercially available devices in that it has a longer scan time (2.5 seconds) and fewer points per scan (100 A-scans), a previous study showed high correlation between measurements obtained by the prototype device and the commercial OCT 2000 (H. M. Pakter, J.S.S., E.H., et al, unpublished data, 2001). Taking into account that OCT devices use the same physical principals and the high correlation between measurements obtained by prototype and OCT 2000 devices, we believe that the data in this study are relevant to the currently available commercial device. The reproducibility of RNFL measurements with the currently available commercial OCT (StratusOCT; Carl Zeiss Meditec Inc, Dublin, Calif) is approximately 2.5 μm compared with the approximately 10 μm of the prototype device used in this study. The improved reproducibility of the StratusOCT might improve the ability to detect longitudinal structural changes to a greater degree than found in this study. This warrants further investigation.

Cross-sectional correlation between OCT measures and global VF indices was found to be moderate to good throughout follow-up (Table 3). This finding is in agreement with previous studies that found good cross-sectional correlation between OCT and VF findings. Linear regression analysis has been used in previous studies to evaluate longitudinal VF changes. However, owing to the large intervisit VF fluctuation, it has been recommended to obtain many VF tests across a long follow-up period. Thus, we required at least 5 VF tests as an inclusion criterion for this study. Most participants in the study were familiar with VF testing at the initial study visit. No perimetry learning effect was noted for the remaining participants.

The difference between the likelihood of progression of VF and OCT measures as defined by the linear regression slope stratified by baseline clinical diagnosis was found to be nonsignificant. The difference between the likelihood of progression for eyes that were classified as VF progressors and nonprogressors was found to be nonsignificant except for VF-PSD (Table 4). The subjective assessment of the VF was not masked to the global VF indices, and, thus, the results may be biased in favor of VF-related variables. We cannot explain the similarity of these VF-MD curves. Sectoral analysis of OCT results did not yield differences in the likelihood of progression between groups as determined by subjective assessment of VF.

Based on our results, the usefulness of linear regression for the detection of longitudinal glaucomatous changes with OCT is questionable. It is possible that glaucoma progression occurs in a nonlinear manner and that regression is not the most suitable technique for progression detection. The use of OCT-MD and OCT-PSD did not improve the ability to detect change.

In summary, this study longitudinally evaluated OCT peripapillary RNFL measurements and compared these with functional measures as determined by VF and with clinical status. There was a greater likelihood of glaucomatous progression as measured by OCT compared with VF. These findings suggest that OCT may be a more sensitive indicator than automated perimetry for glaucomatous progression; however, we cannot rule out the possibility that some of the progression identified by OCT represented type I error. Because there is no gold standard measure of glaucomatous progression, further study of larger populations across longer periods will be required to definitively answer this question.

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REFERENCES


**Correction**

Error in Figure. In the Clinical Sciences article by Wollstein et al titled “Optical Coherence Tomography Longitudinal Evaluation of Retinal Nerve Fiber Layer Thickness in Glaucoma,” published in the April issue of the ARCHIVES (2005; 123:464-470), an error occurred in the key to Figure 2. The correct figure and key are reproduced below. The journal regrets the error.

![Figure 2](https://www.archophthalmol.com)