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# Comparison between time-domain and spectral-domain OCT in the detection of retinal nerve fiber layer defects in glaucoma patients

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## 时域 OCT 和频域 OCT 检测青光眼患者视网膜神经纤维层缺损敏感性的比较

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摘要

**目的**:使用设备内置标准数据库,比较时域光学相干断层扫描仪(Stratus OCT)和频域光学相干断层扫描仪(Spectralis OCT)检测青光眼患者视网膜神经纤维层(RNFL)缺损的敏感性。

**方法**:该研究包括 35 例 52 眼开角型青光眼患者。已明确 RNFL 缺损的 69 例半视网膜(每一例 OCT 检查结果再次分为上方 1/2 和下方 1/2)使用 Stratus OCT 的快速扫描和 Spectralis OCT 的环形扫描进行检测。使用设备内置数据库以 RNFL 厚度属于最低的 5% 人群或 1% 人群分别评估,以比较两种设备的诊断敏感性。

**结果**:在 5% 和 1% 两个水平上,Spectralis OCT 在每一象限中均比 Stratus OCT 更多的检测到 RNFL 缺损(5%:79.7% *vs* 63.8%, $P$=0.01;1%:56.5% *vs* 40.6%, $P$=0.01)。以 1% 异常水平,Spectralis OCT 的标准扇形区域检测敏感性显著高于 Stratus OCT 的时钟数字区域(68.1% *vs* 39.1%, $P$ <0.01)。

**结论**:使用设备内置数据库检测青光眼患者 RNFL 缺损时,Spectralis OCT 各项参数的敏感性较 Stratus OCT 高。

**关键词**:青光眼;光学相干断层扫描;视网膜神经纤维层厚度;敏感性;标准数据库

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## Abstract

• AIM: To compare the use of the instruments' built-in normative databases, the sensitivities of time-domain optical coherence tomography (Stratus OCT) and spectral-domain OCT (Spectralis OCT) in the detection of retinal nerve fiber layer (RNFL) defects in patients with glaucoma.

• METHODS: Fifty-two eyes of 35 patients with open angle glaucoma were included. A total of 69 hemiretinas with photographically identified RFNL defects were analyzed using the fast RNFL scan of Stratus OCT and the circle scan in Spectralis OCT. The OCT parameters were evaluated at 5% and 1% abnormality levels using the instruments' built-in normative databases. The diagnostic sensitivity of each parameter was compared between the two devices.

• RESULTS: The Spectralis OCT detected RNFL defects within each quadrant more frequently than the Stratus OCT at both the 5% (79.7% *vs* 63.8%, $P$=0.01) and 1% (56.5% *vs* 40.6%, $P$ = 0.01) abnormality levels. At the 1% abnormality level, the sensitivity was significantly higher in the standard sector of Spectralis OCT than in the clock-hour sector of the Stratus OCT (68.1% *vs* 39.1%, $P$<0.01).

• CONCLUSIONS: Using the instruments' built-in normative databases, the diagnostic sensitivity of the Spectralis OCT parameters was higher than that of the Stratus OCT parameters for detecting glaucomatous RNFL defects.

• KEYWORDS: glaucoma; optical coherence tomography; retinal nerve fiber layer defect; sensitivity; normative database

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## INTRODUCTION

Glaucoma is a progressive neurodegenerative disease characterized by ganglion cell loss, optic nerve damage, and visual field (VF) defects. Retinal ganglion cell death indicates glaucomatous optic neuropathy, ganglion cell axons slowly deteriorate, leading to retinal nerve fiber layer (RNFL) thinning, narrowing of the neuroretinal rim, and a characteristic glaucomatous cupping at the optic disc. Therefore, color and red-free fundus photography is essential to diagnosing and monitoring glaucoma[1]. In recent years, imaging devices have become more common in the detection and monitoring of glaucoma, as they provide quantitative measurement of structural glaucomatous damage. In particular, optical coherence tomography (OCT), which provides high-resolution measurements of optic disc morphology and RNFL thickness, is widely used to detect glaucomatous damage and progression[2-4].

The recent introduction of spectral-domain (SD)-OCT (also known as Fourier-domain OCT) offers significant advantages over time-domain (TD)-OCT. For instance, SD-OCT collects much more data in the same amount of time, minimizes motion artifacts, and has higher axial resolution[5-7]. In addition, in both normal and glaucomatous eyes, SD-OCT demonstrates higher intra- and inter-visit RNFL thickness reproducibility than TD-OCT[8-11].

However, while SD-OCT is the more advanced commercially available technology, TD-OCT is still widely used, especially in local ophthalmologic clinics. Although several studies have compared diagnostic capability between SD-OCT and TD-OCT, it remains unclear whether SD-OCT is superior to TD-OCT in detecting glaucomatous RNFL damage. Furthermore, some reports have claimed that SD-OCT has no statistically significant advantage over TD-OCT[8,12-16]. Therefore, it is still necessary to compare diagnostic sensitivity between SD-OCT and TD-OCT.

Notably, most previous studies have compared diagnostic performance among various OCT devices using the area under the receiver operating characteristic curves (AUROC), which requires a normal control and a cut-off value. However, the optimal cut-off values, which are based on comparisons to healthy controls, may not be applicable clinically. The cut-off values provided by area under the curve (AUC) studies may not be useful to practicing clinicians because these values are not fixed within each parameter. All commercially available OCT devices employ built-in normative databases that highlight abnormal RNFL thickness[17-18]. In their usual practice, clinicians use the data derived from these databases to determine whether the targeted RNFL area is statistically likely to be abnormal[19]. Therefore, a study of the built-in normative databases seems necessary.

In the present cross-sectional study, we compared TD-OCT (Stratus) with SD-OCT (Spectralis) in terms of its sensitivity for detecting circumpapillary (cp) RNFL defects in glaucoma patients. To do so, we used their built-in normative databases. To our knowledge, among studies comparing the diagnostic performance of SD-OCT and TD-OCT, there is little evidence regarding the Spectralis OCT, which was used in the present study. Our assessment of OCT sensitivity was based on correlated superior-inferior RNFL defect locations identified on red-free fundus photographs. The cpRNFL defect locations were divided into two hemi retinas (superior and inferior) and the OCT sensitivity was analyzed in each.

## SUBJECTS AND METHODS

The present study was approved by the Kangdong Sacred Heart Hospital Institutional Review Board. All procedures adhered to the tenets of the Declaration of Helsinki, and all subjects provided informed consent.

From among patients who had routinely visited the Kangdong Sacred Heart Hospital glaucoma clinic between June and July 2012, we recruited consecutive patients who had undergone color and red-free fundus photography, two types of OCT examination, and visual field (VF) testing. Patients with clearly visible RNFL defects on red-free fundus photography were eligible for inclusion in the study. The patients underwent a comprehensive ophthalmological examination, including best corrected visual acuity measurement, intraocular pressure measurement by Goldmann applanation tonometry, central corneal thickness measurement, slit-lamp biomicroscopy, gonioscopy, stereoscopic optic disc examination after pupil dilation, red-free RNFL photography (Topcon TRC-50DX, Topcon, Tokyo, Japan), and standard automated perimetry using the 24-2 Swedish interactive threshold algorithm (SITA) standard strategy (Humphrey Field Analyzer II; Carl Zeiss Meditec Inc., USA). The cpRNFL scans using either the Stratus OCT or the Spectralis OCT were completed within a 3-month period.

Two observers (Chung JK and Yoo YC) who were blinded to the eyes' clinical information determined cpRNFL abnormalities in the superior and inferior hemiretinas. Only eyes diagnosed by both observers as having localized or diffuse RNFL defects were included in the present study. Hemiretinal RNFL defects were analyzed separately in each eye. All enrolled eyes had cpRNFL defects visible on red-free fundus photography, as well as a characteristic glaucomatous optic disc or VF loss. Glaucomatous optic neuropathy was defined as the presence of increased cupping [vertical cup-disc (C/D) ratio > 0.6], a difference in vertical C/D ratio of > 0.2 between eyes, diffuse or focal neural rim thinning, or optic disc hemorrhage. Glaucomatous VF defect was defined as a cluster of three points with probabilities <5%, including at least one point with a probability <1%, on the pattern deviation map of the corresponding hemifield. Subjects were excluded if they had a best corrected visual acuity less than 20/40 (Snellen equivalent), a spherical refractive error outside a -6.0 to +3.0 diopter range, evidence of vitreoretinal disease, any ophthalmic or neurologic disease known to affect RNFL thickness or visual sensitivity, red-free photographs of inadequate quality, low signal-strength OCT scans, or unreliable VF results (a fixation loss rate greater than 20% or a false-positive rate greater than 15%).

**Optical Coherence Tomography** Following pupil dilation, the cpRNFL thickness was measured using both the Stratus OCT (Carl Zeiss Meditec, Dublin, CA, USA) and the Spectralis OCT (Heidelberg Engineering, Dossenheim, Germany). In the case of the Stratus OCT (software version 4.0), the fast RNFL thickness protocol was used, which measures 256 test points along a 3.4 mm-diameter circle surrounding the optic disc. Scan images were excluded due to poor image quality if they showed inappropriate centering of the circular ring around the optic disc, or a signal strength

<6. In the case of Spectralis OCT (software version 4.0), a scan diameter of approximately 3.46 mm was manually positioned at the center of the optic disc. Sixteen high-resolution scans (1,536 A-scans) were acquired along the scan circle and averaged automatically by the software. The RNFL boundaries were automatically delineated underneath the cp circle by software algorithms.

The measured RNFL thicknesses were averaged to yield global and sector means [Stratus OCT parameters: four quadrants and 12 clock-hour sectors; Spectralis OCT parameters: four quadrants and six sectors—standard temporal, superotemporal (ST), superonasal (SN), nasal, inferonasal (IN), and inferotemporal (IT)]. The software of both instruments automatically compares the mean of each parameter to an built-in, age-matched normative database to provide classification results. The result is a color-coded map in which sectors with mean thickness within the 95% confidence interval (*CI*) values are green; sectors with mean thickness between the 95% and 99% *CI* are yellow, indicating borderline results; sectors with a mean thickness outside the 99% *CI* are in red, indicating that they are outside normal limits.

The photographically identified cpRNFL defect was located in either the superior or the inferior hemiretina, and its correlation with OCT parameters was assessed. To determine the quadrant sector parameters using both OCT instruments, the superior quadrant sector was evaluated for RNFL defects in the superior hemiretina, and the inferior quadrant sector was evaluated for defects in the inferior hemiretina. In the 12 clock-hour sectors of the Stratus OCT, superior RNFL defects were evaluated in the 10, 11, and 12 clock-hour sectors (right eye orientation); the inferior RNFL defects were evaluated in the 6, 7, and 8 clock-hour sectors (right eye orientation). In the six standard sectors of the Spectralis OCT, superior RNFL defects were evaluated in the ST sector, and inferior defects were assessed in the IT sector. The OCT sensitivity was calculated using a criterion of more than one sector abnormality in the cpRNFL thickness analysis.

**Visual Field Sensitivity** To calculate the average VF sensitivity (VFS) in each hemifield, the dB scale at each point, other than two points at the blind spot, was converted to an unlogged 1/L scale, where "L" is the luminance measured in lamberts. The differential light sensitivity (DLS) at each tested point can be expressed using the following formula: $DLS\ (dB) = 10 \times \log_{10}(1/L)$. Thus, the dB reading was divided by 10 to give the non-logarithmic 1/L value at each point; the anti-logarithm was then derived. The non-logarithmic values were averaged, and the means were converted back to the dB scale. The superior VFS relative to the inferior RNFL thickness was calculated from the 26 superior hemifield test points, and the inferior VFS relative to the superior RNFL thickness was calculated from 26 inferior hemifield test points.

**Statistical Analysis** All statistical analyses were performed using the SPSS statistics 19.0 doctor's pack (SPSS Inc., Chicago, IL, USA). *P* values less than 0.05 were considered statistically significant. The McNemar test was used to compare the Stratus OCT with the Spectralis OCT in terms of the sensitivity for detecting a hemiretinal cpRNFL defect that had been identified on red-free fundus photographs. The VFS was designated as the dependent variable, and the OCT parameters as the independent variable. The correlation between VFS and the RNFL defect diagnostic sensitivity on OCT was assessed using binary logistic regression analysis.

**Table 1 Demographic characteristics of subjects**

| Parameters | Values |
|---|---|
| Age (y) | 59.71±12.36 |
| Female | 10 (28.6%) |
| IOP (mmHg) | 16.90±5.26 |
| SE (diopters) | -0.82±1.70 |
| CCT (μm) | 529.63±34.49 |
| CD ratio | 0.67±0.15 |
| MD (dB) | -3.76±6.62 |
| Average RNFL thickness (μm) (Stratus OCT) | 79.92±15.29 |
| Average RNFL thickness (μm) (Spectralis OCT) | 72.85±14.97 |

IOP: Intraocular pressure; SE: Spherical equivalent; CCT: Central corneal thickness; CD: Cup to disc; MD: Mean deviation; OCT: Optical coherence tomography.

**Table 2 Descriptive data of the analyzed hemiretinas**

| Parameters | Number of hemiretinas with an RNFL defect |
|---|---|
| Superior (%) | 27 (39.1) |
| Inferior (%) | 42 (60.9) |
| Pattern of identified RNFL defects on a hemiretina | |
| Localized, wedge-shaped (%) | 41 (59.4) |
| Diffuse thinning (%) | 23 (33.3) |
| Combined (%) | 5 (7.2) |
| Average visual field sensitivity in hemiretina (dB) | -2.91±5.68 |

RNFL: Retinal nerve fiber layer.

## RESULTS

During the enrollment period, 65 eyes of 44 patients were deemed eligible. A total of 13 eyes of 9 patients were excluded due to unsatisfactory red-free RNFL photograph quality, low OCT signal strength, or unreliable VF tests. Ultimately, 52 eyes of 35 patients were considered for statistical analysis. Their characteristics and VF indices are summarized in Table 1.

Of the 52 eyes, 35 had at least one RNFL defect on either hemiretina, and 17 had at least one RNFL defect on both the superior and inferior hemiretinas. In total, 69 hemiretinas with a cpRNFL defect were analyzed, and their descriptive data are provided in Table 2.

Table 3 summarizes the Stratus OCT and Spectralis OCT

**Table 3　OCT sensitivities for detecting circumpapillary RNFL defects (69 hemiretinas from 52 eyes)**

| OCT parameters | Sensitivity (%) | | $P^a$ |
|---|---|---|---|
| | Spectralis OCT | Stratus OCT | |
| Quadrant sector | | | |
| Abnormality at 5% level | 79.7 | 63.8 | 0.01 |
| Abnormality at 1% level | 56.5 | 40.6 | 0.01 |
| Standard/Clock-hour sector | | | |
| Abnormality at 5% level | 82.6 | 72.5 | 0.09 |
| Abnormality at 1% level | 68.1 | 39.1 | <0.01 |

[a]McNemar test; OCT: Optical coherence tomography; RNFL: Retinal nerve fiber layer.

**Table 4　Relationship between the detection rate of OCT parameters and the average visual field sensitivities**

| Parameters | Spectralis OCT | | | Stratus OCT | | |
|---|---|---|---|---|---|---|
| | *OR* | 95% *CI* | $P^a$ | *OR* | 95% *CI* | $P^a$ |
| ≥1 Quadrant | | | | | | |
| Abnormality at 5% level | 0.85 | 0.67-1.09 | 0.20 | 0.83 | 0.68-1.01 | 0.07 |
| Abnormality at 1% level | 0.66 | 0.49-0.90 | 0.01 | 0.86 | 0.76-0.99 | 0.03 |
| ≥1 Clock-hour/standard sector | | | | | | |
| Abnormality at 5% level | 0.60 | 0.37-0.97 | 0.04 | 0.82 | 0.64-1.04 | 0.10 |
| Abnormality at 1% level | 0.53 | 0.35-0.82 | <0.01 | 0.81 | 0.69-0.96 | 0.01 |

[a]McNemar test; OCT: Optical coherence tomography; *OR*: Odds ratio; *CI*: Confidence interval.

diagnostic sensitivities for detecting cpRNFL defects. The sensitivity of the Spectralis OCT was higher than that of the Stratus OCT in all parameters, regardless of abnormality level (5% or 1%). Furthermore, based on the quadrant sectors, the sensitivity of the Spectralis OCT was significantly higher than that of the Stratus OCT (79.7% *vs* 63.8% at 5% abnormality; 56.5% *vs* 40.6% at 1% abnormality; $P=0.01$, McNemar test). A similar outcome was observed when the sensitivity was compared between the standard sector Spectralis OCT and the clock-hour sector Stratus OCT parameters (68.1% *vs* 39.1% at 1% abnormality level; $P<0.01$, McNemar test). However, the difference was marginally significant at a 5% abnormality level (82.6% *vs* 72.5%; $P=0.09$, McNemar test).

The diagnostic sensitivity of the Spectralis and Stratus OCT parameters tended to decrease as the VFS increased on logistic regression analysis (Table 4). At a 1% abnormality level, the VFS was significantly correlated with the diagnostic sensitivity of all OCT parameters. However, at the 5% abnormality level, only the standard sector Spectralis OCT parameter was significantly associated with VFS; there were no significant association in of the other Spectralis OCT or Stratus OCT parameters at a 5% abnormality level.

**DISCUSSION**

In the current study, Spectralis OCT (SD-OCT) had higher sensitivity for detecting photographic RNFL defects than Stratus OCT (TD-OCT) using the devices' built-in normative databases. Furthermore, both instruments showed improved diagnostic sensitivity for cpRNFL thinning in hemiretinas with more severe functional glaucomatous damage.

At present, several SD-OCT instruments are clinically available, including the Cirrus HD-OCT (Carl Zeiss Meditec), Spectralis OCT (Heidelberg) and RTVue-100 (Optovue). The advantages of these newer OCTs have been well documented, but there is currently no convincing evidence that the sector parameters of SD-OCT outperform those of TD-OCT in glaucoma diagnosis[5-11]. In addition, the diagnostic performance of the Spectralis OCT has been less studied than that of other SD-OCT devices, such as the Cirrus HD-OCT, and it is still unclear whether the Spectralis OCT is superior to the Stratus OCT. Recent studies have reported that RNFL measurements taken using the Spectralis, RTVue, and Cirrus have excellent correlation with those taken using the Stratus as well as good reproducibility. However, RNFL values differ significantly between instruments, and it may be necessary to analyze diagnostic sensitivity using the built-in normative databases of each machine[20-23].

When detecting abnormally thinned cpRNFL at the sites of RNFL defects identified on red-free fundus photographs, both the Stratus and Spectralis OCTs showed moderate sensitivity using their built-in normative databases. Regardless of the chosen abnormality level (5% or 1%), the Spectralis OCT had a higher sensitivity than the Stratus OCT overall. The difference between the two devices was statistically significant when quadrants were compared. However, when the clock-hour parameters of the Stratus OCT were compared with the standard sector parameters of the Spectralis OCT, the difference was only significant at a 1% abnormality level. These results are consistent with previous studies reporting that the Spectralis OCT has higher diagnostic sensitivity than the Stratus OCT when both instruments used their built-in normative database to detect abnormally thinned RNFL[7,24]. The same studies speculated that the Stratus OCT has lower diagnostic ability because the single scan system generates less accurate cpRNFL boundaries. In contrast, the Spectralis OCT can acquire 40,000 A-scans per second using an active eye-tracking system, and multiple B-scans can be acquired at an identical location. Moreover, the reduced speckle noise dramatically improves boundary clarity between the inner retinal layers[25]. The axial resolution of Spectralis OCT is almost twice (5 - 7 μm) that of Stratus OCT (approximately 10 μm), and the Spectralis OCT may have better automatic RNFL segmentation, leading to its higher diagnostic ability[7].

One previous study proposed that TD-OCT and SD-OCT have similar diagnostic abilities because of limitations in the conventional circumpapillary method[6]. The authors reported that RNFL thickness and significance maps were better than cpRNFL thickness measurement at distinguishing eyes with localized RNFL defects from healthy eyes. However, other studies have shown that such results may vary depending on the type of SD-OCT and regardless of the analysis method used. Briefly, there was no significant difference in diagnostic sensitivity between the Cirrus OCT and TD-OCT, but there was between the Spectralis OCT and TD-OCT[7,14], even though both studies used the conventional circumpapillary method. We assume that these differences are due to the speckle noise reduction algorithm of the Spectralis OCT.

Disease severity has a significant effect on the diagnostic performance of OCT[6,26]. This may explain the difference in OCT sensitivity measurements between the present and previous studies. The mean deviation of the each subject in the present study was -3.76dB (present study). In past studies, the corresponding values have been -8.5 dB and -0.17 dB[7,24]. The mean sensitivity in the present study was 56.5%-79.7%, whereas that in previous studies was 66.2% - 83.1% and 5.4%-45.9%, respectively. In addition, recent studies have reported that the angular width of RNFL defects is related to the detection sensitivity of RNFL defects[6-7]. In the current study, we analyzed both localized RNFL defects and diffuse RNFL thinning. For this reason, it may not be possible to draw direct comparisons with previous studies.

The present study demonstrated significant negative correlation between VFS and the diagnostic sensitivity of OCT parameters. That is, as the hemiretinal VFS increased, the rate of RNFL defect detection using the OCT parameters decreased. Both OCT devices showed a statistically significant correlation in this regard based on all of the tested parameters at a 1% abnormality level. However, at the 5% abnormality level, statistically significant correlation was only observed using the standard sector parameter of the Spectralis OCT. These findings are consistent with the stronger structure-function relationship in patients with more advanced glaucoma[27]. However, even though the parameters of the Spectralis OCT had a higher odds ratio than those of the Stratus OCT, we cannot conclude that the relationship between the VFS and OCT sensitivity was stronger in the Spectralis OCT than in the Stratus OCT. That is, a cautious interpretation is warranted, because the strength of the structure-function relationship may vary depending on the specific retinal and VF areas—the 95% *CI* considerably overlaps across all parameters, regardless of the designated abnormality level.

The present study had several limitations. Firstly, it had no control group and analyzed diagnostic sensitivity using a built-in normative database rather than AUROC. In this way, it differed from most previous studies. Comparing the AUROCs of the disease and control groups is a standard method for analyzing diagnostic ability. However, we wished to focus on how to use the OCT in practice, and most clinicians use the built-in normative database as a control to identify abnormal findings in OCT. Thus, we believe that our method of analysis will provide practical information to clinicians.

Furthermore, the circumpapillary locations of the abnormal OCT sectors assessed in the average RNFL thickness analysis may have differed somewhat from those of the cpRNFL defects identified on red-free fundus photographs.

Diffuse RNFL thinning may be more difficult to detect than the clearly visible localized RNFL defects presented on red-free fundus photographs. To compensate for this, we only included eyes that had been deemed eligible by two observers. Previous studies have only analyzed localized RNFL defects, but glaucomatous RNFL loss often also manifests as diffuse thinning[7,24].

There may have been enrollment bias in the present study, because some subjects had glaucomatous RNFL defects in both the superior and inferior hemiretinas, and four hemiretinas were thus evaluated in these particular patients.

Ideally, the OCT examinations would be performed on the same day using both instruments. However, in the present study, the relatively long duration between the two procedures was unavoidable, because the subjects were recruited retrospectively. Finally, our lack of specificity analysis and small patient population were also relevant study limitations.

Notwithstanding these limitations, our study had distinctive features not found in previous studies. We used built-in normative databases to compare diagnostic sensitivity between OCT devices, whereas most previous studies have used AUROC, which requires a normal control and provides a cut-off value that may be unnecessary and overly complicated for most clinicians. Moreover, since most glaucomatous RNFL defects arise in a particular area (*e. g.* superior temporal or inferior temporal sector), statistical methods comparing this focal sector with normative databases may be more clinically appropriate.

In summary, the present study used clinically available age-matched normative databases to compare diagnostic ability between two OCT devices without a normal control group. The sensitivities of the corresponding Spectralis and Stratus OCT parameters were evaluated at the locations of the cpRNFL defects. The OCT parameters of both devices were moderately sensitive for detecting glaucomatous RNFL defects when using their built-in normative databases. The parameters of the Spectralis OCT were better than those of the Stratus OCT at discriminating the RNFL defect, regardless of the defect pattern. The sensitivities of both the Spectralis OCT and Stratus OCT correlated well with the VFS in the areas corresponding to the RNFL defects. Furthermore, both OCT parameters showed improved diagnostic sensitivity for cpRNFL thinning in hemiretinas with more severe functional glaucomatous damage.

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