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Article

Contrast-to-Noise Ratios to Evaluate the Detection of Glaucomatous Progression in the Superior and Inferior Hemiretina

Juleke E. A. Majoor[1], Koenraad A. Vermeer[2], and Hans G. Lemij[3]

[1] Rotterdam Ophthalmic Institute, The Rotterdam Eye Hospital, Rotterdam, The Netherlands
[2] Novo Research Consultancy, Voorburg, The Netherlands
[3] Glaucoma Service, The Rotterdam Eye Hospital, Rotterdam, The Netherlands

Correspondence: Juleke E. A. Majoor, The Rotterdam Eye Hospital, Rotterdam Ophthalmic Institute (R.O.I.), Schiedamse Vest 160d 3011 BH Rotterdam, The Netherlands.
e-mail: j.majoor2@oogziekenhuis.nl

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Purpose: To determine the sensitivity of optical coherence tomography (OCT) and standard automated perimetry (SAP) for detecting glaucomatous progression in the superior and inferior hemiretina.

Methods: We calculated contrast-to-noise ratios (CNRs) for OCT retinal nerve fiber layer (RNFL) thickness of hemiretinas and for SAP mean total deviation (MTD) of the corresponding hemifields from longitudinal data (205 eyes, 125 participants). The glaucoma stage for each hemiretina was based on the corresponding hemifield's MTD. Contrast was defined as the difference of the parameter between two consecutive glaucoma stages, whereas noise was the measurement variability of the parameter in those stages. The higher the CNR of a parameter, the more sensitive it is to detecting progression in the transition between successive stages.

Results: There were no statistically significant differences for the RNFL CNR and MTD CNR between superior and inferior hemiretinas. As the glaucoma stage of the opposite hemiretina worsened, the MTD CNR in the transition from moderate to advanced glaucoma significantly increased. The RNFL CNR in the transition from mild to moderate glaucoma significantly decreased in case of advanced glaucoma in the opposite hemiretina.

Conclusions: Similar to full retinas, detecting conversion to glaucoma in hemiretinas is more sensitive with OCT than SAP, whereas with more advanced disease, SAP is more sensitive for detecting progression. More importantly, the sensitivity for detecting progression in one hemiretina with either technique depends on the glaucoma severity in the opposite hemiretina.

Translational Relevance: Monitoring glaucomatous progression with either OCT or SAP partly depends on the glaucoma severity in the opposite hemiretina.

Introduction

Glaucoma is a leading cause of irreversible blindness in the world and requires lifelong follow-up.[1,2] If the disease progresses significantly, therapy should be intensified. Glaucomatous progression can be detected by structural and functional tests. Structural testing most commonly involves measuring the thickness of the peripapillary retinal nerve fiber layer (RNFL) by means of optical coherence tomography (OCT).[3,4] Functional testing is typically performed by using standard automated perimetry (SAP) to measure the extent of any visual field loss. Because these two techniques measure different features of glaucoma, expressed in different units of measure, it has been difficult to compare these techniques in terms of their sensitivity to detect progression.

In a previous study, we used contrast-to-noise ratios (CNRs) to determine which technology, OCT or SAP, was more sensitive for detecting glaucomatous progression in the various stages of the disease.[5] The CNR was defined as the change in magnitude of a parameter between two consecutive glaucoma stages (contrast)

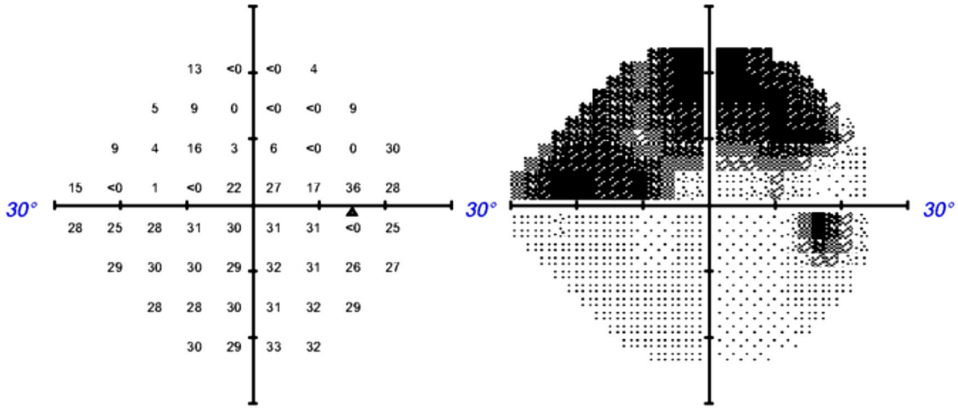

Figure 1. Example of a 24-2 HFA SITA-Standard visual field test result of a patient's right eye with moderate glaucoma (mean deviation = −10.22 dB).

divided by the measurement variability of that parameter in those stages (noise). Because the ratio is dimensionless, it enables a direct comparison between the different types of measurements (structural and functional) for their sensitivity to detect progression. The higher the CNR, the more levels between two stages can be distinguished reliably; hence, the more sensitive the parameter is to detecting progression from one stage to the next. Our study showed that OCT was more sensitive for detecting progression in early stages of the disease, whereas SAP was better at detecting progression in later stages, which was consistent with other studies that used different qualitative methods.[6–11] In that study, we only looked at averages of RNFL thickness and global visual field parameters (mean deviation and visual field index). However, glaucoma commonly involves local RNFL thinning and local visual field (VF) loss that respects the horizontal meridian and subsequently spreads in an arcuate pattern consistent with the orientation of the retinal nerve fiber bundles in either the superior or the inferior part of the retina.[12–16]

In a pilot study, we found that for eyes with a similar glaucoma severity, OCT was generally more sensitive for detecting progression in eyes with local glaucomatous damage than SAP, especially in the early stages of glaucoma, whereas SAP was generally more sensitive for detecting progression in eyes with generalized damage, even more so at later stages of glaucoma.[17] These results thereby indicated that localized damage affects the sensitivity of OCT and SAP for detecting progression in glaucoma differently from generalized damage. Furthermore, it has been found in various studies that the pattern of VF progression is often limited to a single hemifield.[18,19] Boden et al.[20] even found that eyes with early glaucoma rarely cross the horizontal midline. In addition, it has been shown that mild glaucoma is more frequently found in the inferior hemiretina corresponding to the superior hemifield.[15,21,22] These studies therefore indicate that a different pattern of progression and a different glaucoma stage between the superior and inferior hemiretina often exist. We therefore speculated that the approach for detecting progression may be different for the superior hemiretina than for the inferior hemiretina. For example, an eye with moderate glaucoma is best monitored with SAP and this may also apply to the more damaged superior hemiretina of this eye (Fig. 1). However, the healthier inferior hemiretina might perhaps be better monitored with OCT. Furthermore, in light of our former study that showed that the glaucoma stage affects the sensitivity of OCT and SAP for detecting progression,[5] we had reason to believe that, as the superior and inferior hemiretina are anatomically linked and often differ in their glaucoma severity, that the glaucoma stage of the opposite hemiretina might affect the sensitivity for detecting progression in a hemiretina as well. We therefore speculated that the approach for detecting progression in a hemiretina is likely also affected by the glaucoma stage of the opposite hemiretina. This has, to our knowledge, not been explored before, and any knowledge about any such relationship might assist in tailoring optimal progression detection to individual patients. We therefore aimed to determine the sensitivity of OCT for detecting progressive RNFL thinning and SAP for detecting progressive visual field loss in the superior and inferior hemiretina, and their dependency on the glaucoma severity of the opposite hemiretina. To that end, we used the CNR method.

Methods

Data for this study was collected from the Rotterdam Glaucoma Imaging Study,[23] a prospective

longitudinal study of The Rotterdam Eye Hospital in which both eyes of glaucoma patients and healthy volunteers were regularly measured with various types of structural and functional measurement techniques that are often used in the management of glaucoma. Healthy subjects were included in this study if they had an intraocular pressure of 22 mm Hg or less, a normal appearance of the optic nerve head upon slit lamp examination as defined by a glaucoma specialist, and a normal visual field defined as a Glaucoma Hemifield test within normal limits and no abnormalities in the total or pattern deviation probability plots, which means a mean deviation and pattern standard deviation below the fifth percentile and decreased sensitivity scores with <1% probability at 1 test location or clusters of decreased sensitivity scores with <5% probability at two test locations on the total deviation plot. Glaucoma patients were included if their visual field defects were reproducible on at least one occasion and if at least two of the following findings were confirmed on the consecutive visual field: a pattern standard deviation (PSD) significant at the 5% probability level, a Glaucoma Hemifield test outside normal limits, and a cluster of 3 or more points below the 5% probability level or 1 individual point below the 1% probability level. Eyes were excluded from the study in the presence of coexistent ocular or systemic disorders known to potentially affect the visual field (e.g., diabetes mellitus), a history of intraocular surgery (except uncomplicated cataract surgery or glaucoma surgery), uncontrolled arterial hypertension and secondary glaucoma, except pigmentary. All participating eyes had a best corrected Snellen visual acuity of at least 20/40, a spherical equivalent refractive error between −10.0 D and 5.0 D and inconspicuous findings upon slit lamp examination, including open angles on gonioscopy. The study was approved by the Medical Ethics Committee of the Erasmus Medical Center and complies with the Helsinki Declaration. Written informed consent was obtained from all participants.

The five most recent eligible visits per eye were used for the current analysis. To be included in the analysis, a Spectralis OCT peripapillary circle scan (Spectralis OCT; Heidelberg Engineering GmbH, Heidelberg, Germany) and an HFA visual field examination (Humphrey Field Analyzer, II-i Series; Carl Zeiss Meditec Inc., Dublin, CA, USA) needed to have been performed on the same day. OCT circle scans consisted of a single B-scan (796 A-scans) centered on the optic nerve head (circle diameter 3.5 mm) that was averaged from 16 B-scans by the device's automatic real-time tracking. OCT scans with an image quality of less than 15 dB, incomplete scans or scans that were deemed unsuitable for analysis by the operator of the Glaucoma Imaging Study due to gross segmentation errors (see Fig. 2) were excluded. VF testing was performed with the 24-2 SITA Standard test algorithm. VFs had to have false positive or false negative values of less than 15% and fixation losses of less than 15% for inclusion in the analysis. In case of advanced or severe glaucoma VF damage, false negative values above 15% were accepted. The average RNFL thickness of each hemiretina was calculated from the OCT scan and the mean total deviation (MTD) of each corresponding hemifields was calculated from the VF (Fig. 3). A custom software program (MATLAB; MathWorks, Inc., Natick, MA, USA) computed the average RNFL thickness from the peripapillary scan for the superior hemiretina (0° to 180°) and the inferior hemiretina (180° to 360°). This MATLAB code used the segmentation of the inner limiting membrane and nerve fiber layer from Spectralis to get the boundaries of the retinal nerve fiber layer. Afterward, the thickness is computed for each individual A-scan and the mean across the two areas of interest is

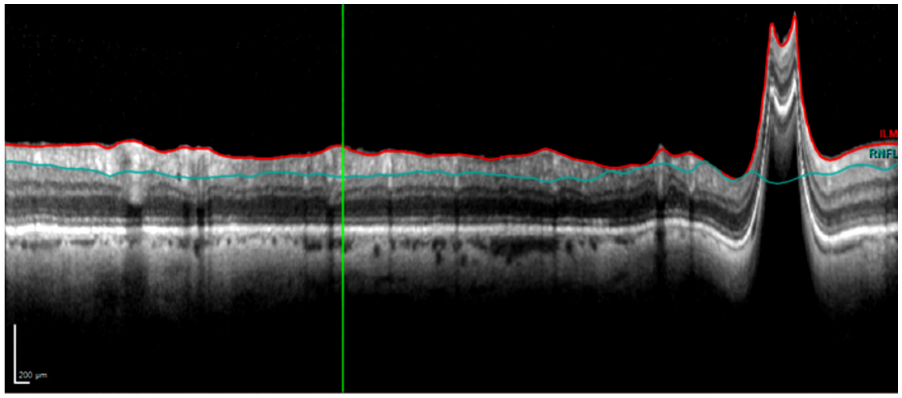

Figure 2. Example of an OCT circle scan that was excluded from this study because of a gross segmentation error.

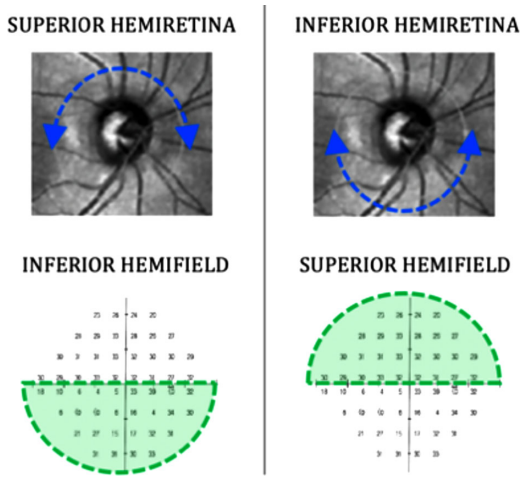

Figure 3. Hemiretina and corresponding hemifield.

taken. There is no registration considered other than potentially that of internal processing of the Spectralis device.

CNR-Calculation

A brief description of the CNR method is provided below; a more detailed description may be found elsewhere.[5] CNRs were calculated for both parameters: average RNFL thickness and MTD. The contrast was defined as the mean change in magnitude of the parameter for hemiretinas between two successive stages. The contrast thus represents the effective measuring range of the parameter for detecting progression in hemiretinas (i.e., the average measured difference between two successive stages). The noise was defined as the variability of the parameter in those stages. To assess this noise, we performed an analysis of residuals from linear regression of the average RNFL thickness data for each hemiretina from 5 subsequent OCT scans and of the MTD data for each hemifield from 5 subsequent HFA 24-2 tests. Under the assumption that progression occurs at a fixed rate, the residuals from these analyses represent the variability of the parameter.[24] The CNR is then defined as the change of the parameter between two stages divided by the average of the residuals in those stages. The higher the CNR, the more levels between two stages can reliably be distinguished, hence, the more sensitive the parameter is to detecting progression in a hemiretina from one stage to the next.

For this study, we performed two analyses. First, we analyzed the CNRs for the superior and inferior hemiretina separately to investigate the sensitivity of OCT and SAP for detecting glaucomatous progression in these parts. Second, we assessed if the CNRs of any hemiretina were affected by the severity of disease of the opposite hemiretina within the same eye.

Table 1. Glaucoma Stages for Hemifields and Corresponding Hemiretinas

	Criterion
Normal group	Healthy*
Mild glaucoma	MTD ≥ -6
Moderate glaucoma	$-6 >$ MTD ≥ -12
Advanced glaucoma	$-12 >$ MTD ≥ -18
Severe glaucoma	$-18 >$ MTD

*Hemifields within normal limits at baseline with the 24-2 SITA Standard HFA test.

The glaucoma stage for each hemiretina was based on the MTD of the corresponding hemifield and determined by the MTD value on the regression line halfway between the first and fifth HFA test. The mild, moderate and advanced glaucoma stage were defined based on the Hodapp-Parrish-Anderson criteria[25] (Table 1). To refine our first CNR analysis, advanced glaucoma was further divided into two stages; an advanced stage, defined as an MTD between ≤ -12 dB and > -18 dB, and a severe stage, defined as an MTD ≤ -18 dB. For our second CNR analysis, the normal group was excluded because there obviously were no differences in glaucoma severity between the two hemiretinas.

The total deviation in SAP is corrected for age by design. However, the average RNFL thickness from OCT is not. The median rate of RNFL thinning in our normal group was -0.14 µm/y, which is consistent with earlier reported thinning rates.[26,27] In case of any age differences between successive stages, the RNFL thickness data for hemiretinas in these stages was adjusted for this aging effect.

Statistics

Data were collected from the case report forms of the Glaucoma Imaging Study and analyzed with IBM SPSS Statistics Software (version 24; SPSS Inc., Chicago, IL, USA). Mean and standard deviations of the demographic characteristics and study parameters per group and glaucoma stage were evaluated. Kruskal Wallis H and one-way analysis of variance tests for continuous variables, and χ^2 test for categorical variables, were used for statistical analysis. A P value <0.05 was considered as statistically significant.

For comparison of the CNRs, a bootstrap sampling technique was used to determine 95% confidence intervals (CI) for the difference of the CNR between transitions, between the superior and inferior hemiretina, and between parameters (RNFL thickness and MTD). Values outside the 95% CI were considered as statis-

tically significant. The statistical software R (version 3.4.3, 2017-11-30) was used for the bootstrap analysis.

Results

Data from 205 eyes from 125 participants (54% women; 46% men) were included for the analysis. There were 82 healthy eyes and 123 glaucoma eyes. A total of 38 eyes from 27 glaucoma patients and 20 eyes from 13 healthy patients in the ongoing Glaucoma Imaging Study were excluded from analysis because of poor OCT or VF quality.

Superior Versus Inferior Hemiretina Analysis

Tables 2A and 2B show the descriptive statistics for the superior and inferior hemiretinas separately. Any glaucoma surgery that took place during follow-up, consisted of a single Baerveldt glaucoma drainage tube placement that was performed anytime between the first and fifth visit for the eyes under consideration (15 eyes in total). For both the superior and inferior hemiretinas, there were no statistically significant differences for the proportion of glaucoma surgical procedures performed between the various glaucoma stages. The normal group was statistically significantly younger than the mild glaucoma group for both the superior (median 58 vs. 67 in years, Dunn-Bonferroni test, $P < 0.05$) and the inferior pooled hemiretinas (median 58 vs. 68 in years, Dunn-Bonferroni test, $P < 0.05$). To correct for this age difference, 1.26 µm (1.33 µm) was subtracted from the estimated average RNFL thickness for normal superior (inferior) hemiretinas in the calculation of the contrast for the transition from normal to mild stage glaucoma. Tables 3A and 3B show the contrast, noise, and CNR values per parameter and per transition between the various stages of glaucoma.

Figure 4 shows the CNR values of the average RNFL thickness and MTD for the various transitions of the superior and inferior pooled hemiretinas. For both the superior and the inferior hemiretina, the RNFL CNR was highest in the transition from normal to mild glaucoma (10.6 and 10.9, respectively) and the MTD CNR was highest in the transition from advanced to severe glaucoma (5.9 and 5.5, respectively). There were no statistically significant differences for the RNFL CNR nor for the MTD CNR between the superior and inferior hemiretinas.

The RNFL CNR was statistically significantly higher than the MTD CNR in the transition from normal to mild glaucoma for both superior and inferior hemiretinas (3.3 vs. 10.6, 95% CI for the MTD vs. RNFL CNR difference [−9.2, −5.5], and 3.2 vs. 10.9, 95% CI for the MTD vs. RNFL CNR difference

Table 2A. Descriptive Statistics: Superior Versus Inferior Hemiretina Analysis—Superior Hemiretina

	Normal (n = 82)	Mild (n = 51)	Moderate (n = 31)	Advanced (n = 21)	Severe (n = 20)	*P* Value
Women (%), mean (95% CI)	57 (46.5, 67.4)	57 (43.3, 69.5)	36 (21.1, 53.2)	52 (32.4, 71.6)	60 (38.6, 78.1)	0.57*
Surgery (%), mean (95% CI)	NA	7.8 (2.2, 18.9)	19.4 (7.5, 37.5)	14.3 (3.0, 36.3)	10.0 (1.2, 31.7)	0.46*
Age (y), median (IQR)	58 (47, 67)	67 (63, 73)	65 (56, 74)	71 (61, 75)	72 (62, 76)	< .001†
Follow-up time (mo), median (IQR)	73.0 (61.5, 78.0)	44.0 (41.0, 49.0)	48.0 (42.0, 67.0)	45.0 (42.0, 49.0)	48.0 (42.3, 67.8)	< .001†
RNFL (µm), median (IQR)	94.2 (86.6, 101.7)	68.4 (59.7, 78.4)	57.5 (48.0, 65.0)	52.8 (46.7, 59.7)	44.4 (37.6, 53.3)	< .001†
MTD (dB), median (IQR)	0.19 (−0.58, 0.81)	−2.9 (−4.8, −1.3)	−8.2 (−10.0, −6.6)	−15.1 (−16.6, −13.6)	−22.5 (−27.1, −19.4)	< .001†

Surgery is the proportion of glaucoma surgical procedures performed anytime between the first and fifth visit. Follow-up time is expressed in months between the first and fifth visit.

*χ^2 test.

†Kruskal-Wallis H test.

Table 2B. Descriptive Statistics: Superior Versus Inferior Hemiretina Analysis— Inferior Hemiretina

	Normal (n = 82)	Mild (n = 46)	Moderate (n = 32)	Advanced (n = 14)	Severe (n = 31)	*P* Value
Women (%), mean (95% CI)	57 (46.5, 67.4)	44 (30.3, 57.8)	66 (48.2, 79.6)	50 (26.9, 73.1)	48 (32.0, 65.1)	0.62*
Surgery (%), mean (95% CI)	NA	10.9 (3.6, 23.6)	9.4 (2.0, 25.0)	21.4 (4.7, 50.8)	12.9 (3.6, 0.30)	0.70*
Age (y), median (IQR)	58 (47, 67)	68 (61, 75)	72 (64, 75)	69 (61, 76)	66 (54, 73)	<0.001†
Follow-up time (mo), median (IQR)	73.0 (61.5, 78.0)	45.5 (42.0, 52.3)	44.5 (35.3, 54.3)	48.0 (42.0, 68.5)	48.0 (42.0, 57.0)	<0.001†
RNFL (µm), median (IQR)	91.1 (84.4, 98.0)	62.2 (55.6, 70.8)	55.9 (49.1, 62.6)	48.6 (41.9, 53.5)	41.0 (36.7, 47.8)	<0.001†
MTD (dB), median (IQR)	0.23 (−0.72, 1.04)	−2.7 (−4.6, −1.4)	−8.3 (−10.6, −6.6)	−16.2 (−18.1, −14.0)	−25.5 (−27.8, −22.9)	<0.001†

Surgery is the proportion of glaucoma surgical procedures performed anytime between the first and fifth visit. Follow-up time is expressed in months between the first and fifth visit.

*χ^2 test.

†Kruskal-Wallis H test.

Table 3A. Contrast, Noise, and CNR Values: Superior Versus Inferior Hemiretina Analysis—RNFL

	Contrast (µm)		Noise (µm)		CNR	
Transition	Superior	Inferior	Superior	Inferior	Superior	Inferior
Normal to mild (95% CI*)	26.2 (22.0, 30.0)	28.6 (24.7, 32.5)	2.5 (2.1, 2.8)	2.6 (2.0, 3.4)	10.6 (8.8, 12.8)	10.9 (8.0, 15.0)
Mild to moderate (95% CI)	11.3 (6.6, 16.3)	5.8 (1.11, 10.3)	2.8 (2.3, 3.3)	3.2 (2.3, 4.1)	4.1 (2.3, 6.4)	1.8 (0.3, 3.6)
Moderate to advanced (95% CI)	3.6 (0.2, 8.6)	8.3 (3.6, 13.0)	2.6 (2.0, 3.1)	3.3 (2.4, 4.3)	1.4 (0.1, 3.3)	2.5 (1.2, 4.2)
Advanced to severe (95% CI)	7.0 (0.7, 13.0)	6.1 (2.5, 10.1)	2.8 (2.1, 3.4)	3.3 (2.5, 4.1)	2.5 (0.3, 4.8)	1.9 (0.7, 3.6)

*95% confidence interval after bootstrap sampling.

Table 3B. Contrast, Noise, and CNR Values: Superior Versus Inferior Hemiretina Analysis—MTD

	Contrast (dB)		Noise (dB)		CNR	
Transition	Superior	Inferior	Superior	Inferior	Superior	Inferior
Normal to mild (95% CI*)	3.2 (2.6, 3.7)	3.0 (2.4, 3.5)	1.0 (0.8, 1.1)	0.9 (0.8, 1.0)	3.3 (2.7, 4.1)	3.2 (2.5, 4.0)
Mild to moderate (95% CI)	5.3 (4.6, 6.2)	5.9 (5.1, 6.7)	1.3 (1.1, 1.5)	1.3 (1.1, 1.5)	4.1 (3.3, 5.1)	4.4 (3.7, 5.3)
Moderate to advanced (95% CI)	6.5 (5.6, 7.3)	6.8 (5.6, 7.9)	1.4 (1.2, 1.6)	1.9 (1.5, 2.2)	4.5 (3.7, 5.5)	3.7 (2.8, 4.8)
Advanced to severe (95% CI)	8.1 (6.2, 9.8)	9.4 (7.9, 10.9)	1.4 (1.1, 1.6)	1.7 (1.3, 2.1)	5.9 (4.3, 7.9)	5.5 (4.4, 7.5)

*95% confidence interval after bootstrap sampling.

[−11.6, −4.3], respectively). The MTD CNR was statistically significantly higher than the RNFL CNR for superior hemiretinas in the transition from moderate to advanced and advanced to severe glaucoma (4.5 vs. 1.4, 95% CI for the MTD vs. RNFL CNR difference [1.3, −5.5], and 5.9 vs. 2.5, 95% CI for the MTD vs. RNFL CNR difference [1.3, 5.7], respectively) and for inferior hemiretinas in the transition from mild to moderate and advanced to severe glaucoma (4.4 vs. 1.8, 95% CI for the MTD vs. RNFL CNR difference [1.1,4.0], and 5.5 vs. 1.9, 95% CI for the MTD vs. RNFL CNR difference [1.8,5.7], respectively).

Effect of the Severity of the Opposite Hemiretina

With this analysis, we evaluated how the CNR of a hemiretina was affected by the severity of disease of the opposite hemiretina within the same eye. Table 4 shows the descriptive statistics per hemiretina for the various glaucomatous stages combined with the stages for the opposite hemiretina in the same eye. Because the subgroups for hemiretinas with severe glaucoma were too small for this analysis, these hemiretinas were pooled with the advanced glaucoma hemiretinas and defined as advanced glaucoma with an MTD $<$ −18 dB. The proportion of glaucoma surgical procedures performed during follow-up differed statistically significantly between the various glaucoma groups (χ^2 test, $P < 0.05$) (Table 4). There were no statistically significant differences in age between the various pooled hemiretinas. Therefore no age corrections were performed. Tables 5A and 5B show the contrast, noise, and CNR values per hemiretina for the various stage-transitions, stratified by the stages for the opposite hemiretina in the same eye.

Figure 5 shows the CNR values of the average RNFL thickness and MTD per hemiretina for the various glaucomatous stages combined with the stages of the opposite hemiretina in the same eye. The MTD CNR for the hemiretinas under consideration in the transition from moderate to advanced glaucoma was statistically significantly higher than the RNFL CNR for all glaucoma stages of the opposite hemiretina and showed a statistically significant increase as the glaucoma stage of the opposite hemiretina worsened (6.1 to 9.5, 95% CI for the CNR difference [−6.4, −0.5]). The CNR for the transition from mild to moderate glaucoma was independent of the glaucoma stage of the opposite hemiretina, except for the RNFL CNR in case of opposite hemiretinas with advanced glaucoma which was statistically significantly lower than the RNFL CNR for opposite hemiretina with moderate glaucoma (1.3 vs. 7.0, 95% CI for the CNR difference [0.4, 10.8]). Furthermore, only for opposite hemiretinas with advanced glaucoma in this transition did the RNFL CNR differed statistically significantly from the MTD CNR (1.3 vs. 4.1, 95% CI for the CNR difference [0.8, 4.4]).

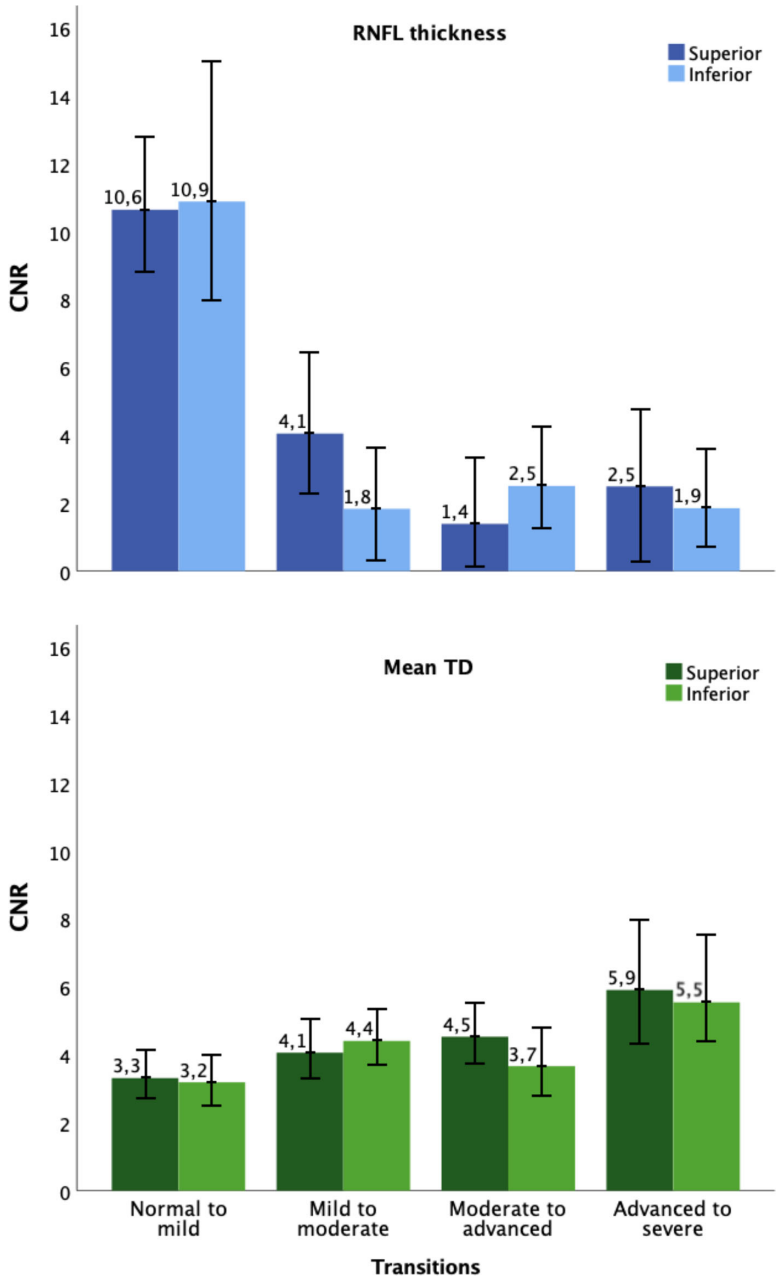

Figure 4. CNRs of the average RNFL thickness (*blue bars*) and MTD (*green bars*) for the superior (*dark color bars*) and inferior hemiretina (*light color bars*). The *whiskers* indicate the upper and lower limit of the 95% confidence interval after bootstrap sampling.

Discussion

The current study confirms previous results[5–11] and showed that, for hemiretinas, the detection of conversion to glaucoma by OCT RNFL thickness is more sensitive than by SAP, whereas with more advanced disease, SAP is more sensitive than RNFL thickness for detecting progression. Furthermore, we have currently found that for SAP the sensitivity for detecting progression in one hemiretina depends on the severity of disease in the opposite hemiretina.

An important finding from this study is that the MTD CNR for detecting progression from moderate to advanced glaucoma in hemiretinas significantly increased as the glaucoma stage of the opposite hemiretina worsened. This increase of the MTD CNR resulted from a statistically significantly decrease of

Table 4. Descriptive Statistics: Opposite Hemiretina Analysis

	Glaucoma Stage Considered Hemiretina									
	Mild			Moderate			Advanced			
Glaucoma Stage Opposite Hemiretina	Mild (n = 46)	Moderate (n = 30)	Advanced (n = 21)	Mild (n = 30)	Moderate (n = 6)	Advanced (n = 27)	Mild (n = 21)	Moderate (n = 27)	Advanced (n = 38)	*P* Value
Women (%), mean (95% CI)	52 (38.2, 65.9)	57 (39.2, 72.6)	38 (20.8, 59.2)	57 (39.2, 72.6)	33 (9.6, 70.3)	48 (30.8, 65.9)	38 (20.8, 59.2)	48 (30.8, 65.9)	63 (47.3, 76.6)	0.56*
Surgery (%), mean (95% CI)	4.3 (0.5, 14.8)	6.7 (0.8, 22.1)	23.8 (8.2, 47.2)	6.7 (0.8, 22.1)	33.3 (4.3, 77.7)	18.5 (6.3, 38.1)	23.8 (8.2, 47.2)	18.5 (6.3, 38.1)	5.3 (0.6, 17.7)	0.04*
Superior hemiretina (%), mean (95% CI)	50 (30.8, 69.2)	60 (36.7, 80.9)	48 (17.0, 78.9)	40 (19.1,63.3)	50 (1.0, 99.0)	59 (33.1, 83.1)	52 (21.1, 83.0)	41 (16.9, 66.9)	50 (30.8, 69.2)	0.83*
Age (y), median (IQR), mean (95% CI)	67 (64, 77)	66 (60, 73)	71 (62, 75)	66 (60, 73)	74 (63, 75)	68 (62, 74)	71 (62, 75)	68 (62, 74)	68 (54, 75)	0.346†
Follow-up time (mo), median (IQR), mean (95% CI)	45.0 (42.0, 48.0)	45.5 (41.8, 56.0)	48.0 (42.5, 57.0)	45.5 (41.8, 56.0)	63.0 (48.0, 77.0)	45.0 (41.0, 62.0)	48.0 (42.5, 57.0)	45.0 (41.0, 62.0)	48.0 (44.0, 54.0)	0.429†
OCT circle scan quality (dB), median (IQR)	28.0 (26.0,30.0)	27.5 (25.0,30.0)	27.3 (25.0,30.0)	27.5 (25,30)	27.4 (25.0,30.0)	28.0 (26.0,30.0)	27.3 (25.0,30.0)	28.1 (26.0,30.0)	27.4 (25.0,29.0)	0.678†
RNFL (μm), median (IQR)	63.6 (56.3, 73.0)	69.2 (60.2, 77.1)	66.1 (57.2, 71.7)	55.2 (49.0, 59.7)	55.2 (46.1, 63.2)	61.9 (49.4, 69.5)	45.5 (39.3, 50.1)	46.0 (40.5, 55.9)	47.6 (40.4, 52.3)	<0.001†
MTD (dB), median (IQR)	−2.6 (−4.7, −1.2)	−2.6 (−4.0, −1.3)	−3.9 (−5.0, −2.0)	−8.3 (−10.4, −6.8)	−9.0 (−10.9, −7.3)	−7.8 (−10.0, −6.4)	−19.4 (−24.9, −15.6)	−20.4 (−25.5, −17.1)	−19.6 (−26.8, −15.5)	<0.001†

Surgery is the proportion of glaucoma surgical procedures performed anytime between the first and fifth visit. Follow-up time is the time in months between the first and fifth visit. RNFL is the average RNFL thickness of the OCT hemiretina. MTD is the Mean Total deviation of the hemifield.

*χ^2 test.

†One-way analysis of variance.

Table 5A. Contrast, Noise, and CNR Values: RNFL

	Glaucoma Stage Opposite Hemiretina								
	Contrast (μm)			Noise (μm)			CNR		
Transition	Mild	Moderate	Advanced	Mild	Moderate	Advanced	Mild	Moderate	Advanced
Mild to moderate (95% CI*)	9.2 (4.8, 13.6)	15.0 (5.7, 24.3)	5.0 (0.3, 12.2)	2.7 (1.9, 3.6)	2.2 (1.6, 2.6)	3.7 (2.7, 4.9)	3.4 (1.5, 6.4)	7.0 (2.5, 12.6)	1.3 (0.1, 3.5)
Moderate to advanced (95% CI)	8.7 (4.1, 13.1)	6.3 (0.4, 15.1)	12.8 (7.2, 17.7)	2.8 (2.1, 3.7)	2.6 (2.0, 3.2)	3.1 (2.6, 3.7)	3.1 (1.5, 4.9)	2.4 (0.2, 6.0)	4.1 (2.4, 5.9)

Contrast, noise, and CNR values of the average RNFL thickness for the various transitions of the hemiretina under consideration (first column) and the various glaucoma stages of the opposite hemiretina (second row).

*95% confidence interval after bootstrap sampling.

Table 5B. Contrast, Noise and CNR Values: MTD

	Glaucoma Stage Opposite Hemiretina								
	Contrast (dB)			Noise (dB)			CNR		
Transition	Mild	Moderate	Advanced	Mild	Moderate	Advanced	Mild	Moderate	Advanced
Mild to moderate (95% CI)	5.8 (5.0, 6.6)	6.4 (5.1, 7.7)	4.9 (3.8, 5.9)	1.3 (1.2, 1.5)	1.4 (1.1, 1.7)	1.2 (1.0, 1.4)	4.3 (2.6, 4.1)	4.5 (3.6, 5.6)	4.1 (3.1, 5.2)
Moderate to advanced (95% CI)	10.9 (8.8, 13.1)	11.6 (9.5, 13.9)	12.4 (10.4, 14.5)	1.8 (1.5, 2.1)	1.4 (1.1, 1.7)	1.3 (1.1, 1.5)	6.1 (4.5, 8.2)	8.1 (5.9, 11.5)	9.5 (7.5, 12.1)

Contrast, noise, and CNR values of the mean TD for the various transitions of the hemiretina under consideration (first column) and the various glaucoma stages of the opposite hemiretina (second row).

*95% confidence interval after bootstrap sampling.

the MTD noise. To our knowledge, this has not been described nor explored before. We believe that this interdependence deserves further study.

Another finding from this study is that the sensitivity of the RNFL thickness for detecting progression from mild to moderate glaucoma in hemiretinas significantly decreased in case of advanced glaucoma in the opposite hemiretina. Although we found a statistically significant difference in this transition between opposite hemiretinas with moderate glaucoma and opposite hemiretinas with advanced glaucoma, it is debatable whether this difference is not merely based on chance, especially considering the wide confidence intervals. Further studies are therefore warranted to better understand the effect of the glaucoma stage of the opposite hemiretina to the sensitivity of the RNFL

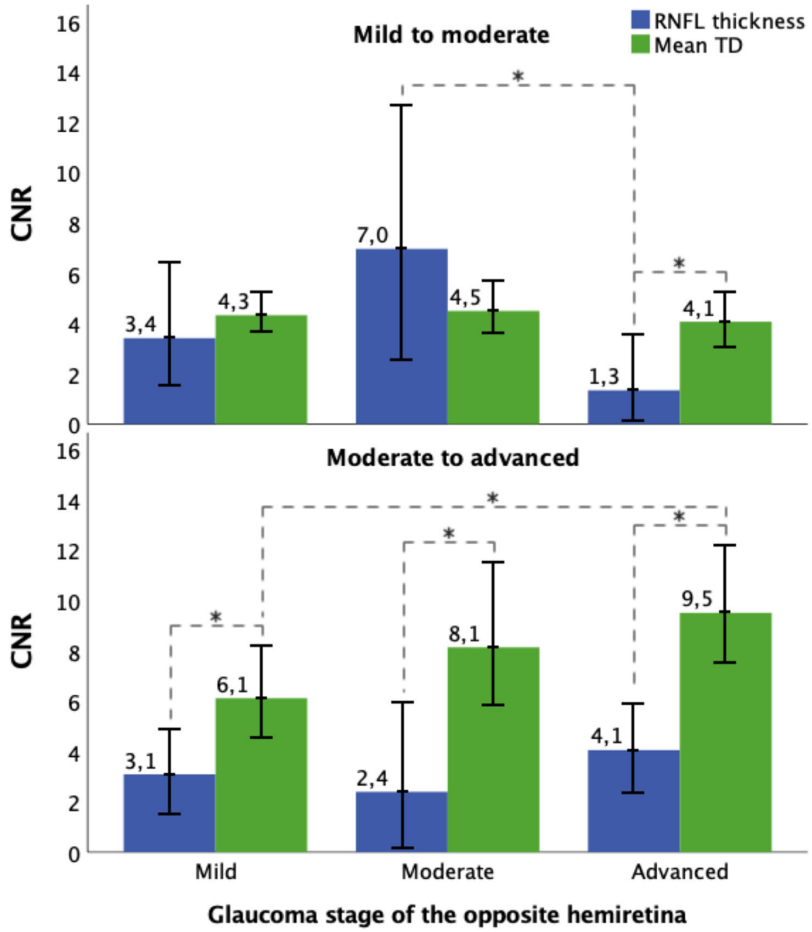

Figure 5. CNRs of the average RNFL thickness (*blue bars*) and MTD (*green bars*) for the transition from mild to moderate (*upper panel*) and from moderate to advanced glaucoma (*lower panel*) of the hemiretina under consideration. The x-axis indicates the glaucoma stages of the opposite hemiretina. The *whiskers* indicate the upper and lower limit of the 95% confidence interval after bootstrap sampling. The *asterisk brackets* show the statistically significant differences between the CNRs based on the 95% confidence intervals ($P < 0.05$).

thickness for detecting progression in hemiretinas. In addition, we also wondered whether the decrease of the RNFL CNR in the transition of mild to moderate glaucoma from opposite hemiretinas with moderate glaucoma to opposite hemiretinas with advanced glaucoma (from 7.0 to 1.3; Fig. 5) could have also partly resulted from small segmentation errors, considering the increase of the RNFL noise between these groups (from 2.2 to 3.7; Tables 5A, 5B). Indeed, when we looked more closely at the OCT peripapillary scans of this set of eyes, we found many segmentation errors that originated from the opposite hemiretinas with advanced glaucoma. The RNFL segmentation of the considered hemiretina partly depends on the segmentation of the opposite hemiretina: the segmentation of the peripapillary, circularly scanned RNFL is continuous and segmentation errors can therefore propagate into the temporal and nasal part of the other hemiretina, thereby causing the variability of the RNFL thickness to increase and therefore its CNR to decrease. Figure 6 provides an example of such a segmentation error in the superior hemiretina with mild glaucoma that originates from the inferior hemiretina with advanced glaucoma. Previous literature has shown that segmentation errors are associated with advanced glaucoma and that this failure of RNFL segmentation often results in erroneous RNFL thickness results that may vary between visits.[28–31] However, to date it has not yet been described that the segmentation errors of a hemiretina with advanced glaucoma can also affect the segmentation of the less affected hemiretina of the same eye. We therefore think that one should beware of segmentation errors that may propagate from some parts of the retina into adjacent parts, which may then affect clinical judgement.

This study could provide insight into the interpretation of discrepancies between OCT and SAP in terms

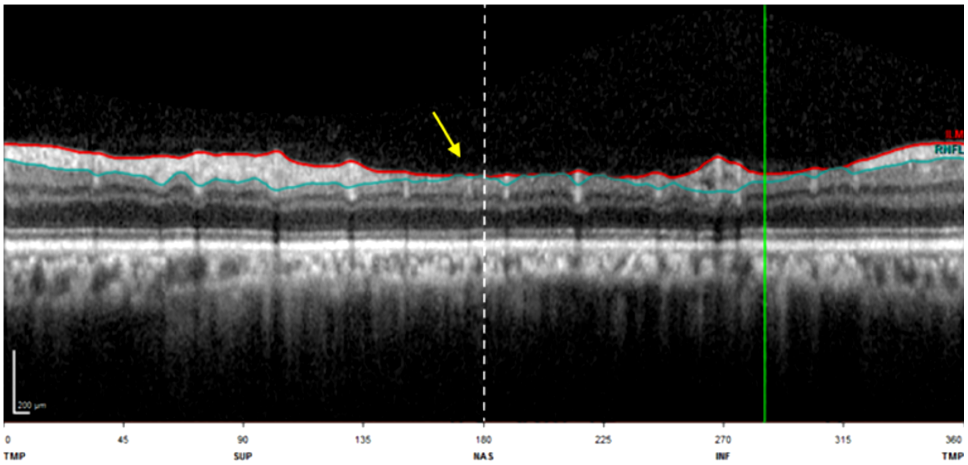

Figure 6. Example of a segmentation error (*yellow arrow*) in the superior hemiretina that corresponds to an inferior hemifield with mild glaucoma (MTD-3.1). This segmentation error originates from the segmentation errors in the inferior hemiretina that corresponds to the superior hemifield with advanced glaucoma (MTD-24.3).

of their detection of progression in glaucoma. For example, if an eye shows thinning of the RNFL thickness with the OCT in a previously healthy hemiretina, such that it is suspected of glaucomatous thinning, whereas the visual field of the corresponding hemifield shows no deterioration with SAP, we recommend to rely more on the OCT changes than on the stable SAP findings for detecting the conversion to glaucoma. With increasing glaucoma severity, the sensitivity of SAP for detecting progression in both hemiretinas increases, even if the better hemiretina has only mild glaucoma. In case of any discrepancies between SAP and OCT thickness findings, in these later stages of glaucoma, we would recommend to rely on SAP instead of on OCT for detecting progression. In case of mild glaucoma in the worse hemiretina, OCT and SAP are equally sensitive for detecting progression in both hemiretinas. However, care should be taken with the generalizability of these results, as OCT technology is still under development. Improved OCT technology may therefore produce lower noise because of better image registration, consequently resulting in a greater CNR.

It has been generally held that the RNFL thickness is not suitable for detecting progression in later stages of glaucoma.[7–9] Hood and colleagues suggested, however, that some of these eyes with advanced glaucoma may still have 24-2 or 10-2 VF locations with a total deviation value better than −8 dB corresponding to a preserved circumpapillary RNFL (cpRNFL) region that may be well monitored with OCT.[13,15,32] As the current study looked at averages of RNLF thickness of hemiretinas, which could well be too large of a cpRNFL area to detect small RNFL thickness changes, a more local approach such as that of Hood and coworkers[15,32] might possibly provide a greater sensitivity of the OCT for detecting progression in eyes with moderate and advanced glaucoma. Investigating the CNR in these preserved cpRNFL areas could help in determining the best approach for monitoring progression in later stages of glaucoma.

A limitation of our study was that the staging of glaucoma was based on the MTD from SAP. As the MTD was one of the investigated parameters in this study, this may have led to a selection bias. However, we do not expect that the trend of the parameters (RNLF thickness becomes overall less sensitive compared to MTD as the glaucoma worsens and the functional parameters become more sensitive as the glaucoma worsens) will change when using an RNFL based staging system. In addition, the CNR results of the severe or even advanced stage could not be properly viewed when using an RNFL staging system, since the RNFL reaches its floor in these stages. For these reasons, we used the more familiar and clinically used functional staging system. In addition, the calculation of the average RNFL thickness for hemiretinas was determined without a normalization of all OCT images to the fovea-disc orientation. As a result of these factors, the calculated average RNFL thickness for hemiretinas could have a wider distribution and greater variability than if the RNFL thickness was used to define the stages or if a fovea-to-disc-alignment was used. However, we expect that these factors had a negligible impact on the CNR outcomes, as the RNFL contrasts were based on the averages in each stage

Table 6. Contrast, Noise, and CNR Values of the Total Group Versus The Group Without Eyes That Underwent Surgery

	Glaucoma Stage of the Opposite Hemiretina		
	RNFL		
Transition From Mild to Moderate Glaucoma*	Moderate	Advanced	MTD, Advanced
Contrast (95% CI)			
Total group	15.0 (5.7, 24.3)	5.0 (0.3, 12.2)	4.9 (3.8, 5.9)
Group without eyes that underwent surgery	17.8 (6.9, 28.7)	6.2 (0.4, 14.3)	5.2 (4.1, 6.4)
Noise (95% CI)			
Total group	2.2 (1.6, 2.6)	3.7 (2.7, 4.9)	1.2 (1.0, 1.4)
Group without eyes that underwent surgery	1.9 (1.4, 2.4)	2.5 (1.8, 3.3)	1.2 (1.0, 1.4)
CNR (95% CI)			
Total group	7.0 (2.5, 12.6)	1.3 (0.1, 3.5)	4.1 (3.1, 5.2)
Group without eyes that underwent surgery	9.2 (3.6, 16.4)	2.4 (0.2, 6.1)	4.4 (3.3, 6.0)

*Transition of the hemiretina under consideration.

which are not affected by a symmetrical broadening of the RNFL distribution. In addition, the RNFL noise was based on a regression model applied to individual hemiretinas and the resulting variability was similar for successive stages.

We found that the proportion of glaucoma surgical procedures performed during follow-up statistically significantly differed between the various glaucoma stages of the considered and opposite hemiretina (Table 4). We therefore repeated the CNR analysis in question, this time excluding the eyes that underwent surgery. We found that the CNR results of the group without eyes that underwent surgery were similar to the CNR results of the total group, except that no statistically significant differences were found in the transition from mild to moderate glaucoma for the RNFL CNR between opposite hemiretinas with moderate glaucoma versus opposite hemiretinas with advanced glaucoma (9.2 vs. 2.4, 95% CI for the CNR difference [−0.5, 14,2]), and for opposite hemiretinas with advanced glaucoma between the MTD CNR versus the RNFL CNR (4.4 vs. 2.4, 95% CI for the CNR difference [−1.1, 4.9]). For these particular CNR results, excluding eyes that underwent glaucoma surgery resulted in a higher contrast for both the RNFL and MTD, a lower noise for the RNFL and equal noise for the MTD, consequently resulting in higher CNR results of the group without eyes that underwent surgery compared to the CNR results of the total group (Table 6).

However, the CNR differences were still quite similar, whereas the 95% CI for the CNR differences were all broader for the CNR differences of the group without eyes that underwent surgery compared to the CNR differences of the total group (Table 7). We therefore expect that the observed changes in statistical significance after excluding eyes that underwent glaucoma surgery are mostly due to the smaller sample size and the consequently lower statistical power.

Perhaps glaucoma surgery affects the residuals for the RNFL thickness from linear regression over time differently than for the MTD, especially since the noise results of the total group for the RNFL were higher compared to the noise results of the group without eyes that underwent surgery, whereas the noise results

Table 7. CNR Differences for the Transition From Mild to Moderate Glaucoma of the Total Group Versus the Group Without Eyes That Underwent Surgery

Opposite Hemiretinas	CNR vs. CNR	CNR Difference (95% CI)
RNFL CNR for moderate versus RNFL CNR for advanced glaucoma		
Total group	7.0 vs. 1.3	5.7 (0.4, 10.8)
Group without eyes that underwent surgery	9.2 vs. 2.4	6.8 (−0.5, 14.2)
MTD CNR versus RNFL CNR for advanced glaucoma		
Total group	4.1 vs. 1.3	2.8 (0.8, 4.4)
Group without eyes that underwent surgery	4.4 vs. 2.4	2.0 (−1.1, 4.9)

of both groups for the MTD were the same. Several studies have reported that the RNFL was thicker after IOP-lowering than before treatment.[33–35] The lower contrast and higher noise for the RNFL could therefore be explained by the thicker RNFL thickness after surgery, as this decreases the slope of the regression line (thereby reducing the contrast with the less severe glaucoma category) and increases the residuals (because the sudden change in thickness reduces the goodness-of-fit). Because, to the best of our knowledge, a similar effect of surgery on functional measurements has not been described, this could have affected the CNR outcomes and CNR differences between these different types of measurements. More studies with larger samples of non-surgical eyes are therefore warranted to support our CNR results of the hemiretinas in the transition from mild to moderate glaucoma with either advanced or moderate glaucoma in the opposite hemiretina.

In conclusion, this study showed that, for both the superior and the inferior hemiretina, the detection of conversion to glaucoma by OCT RNFL thickness is more sensitive than with SAP, whereas SAP is more sensitive than OCT RNFL thickness for detecting progression once a moderate glaucoma stage has been reached. Furthermore, we found that the sensitivity of SAP significantly increased as the glaucoma stage of the opposite hemiretina worsened. Clinical recommendations will strongly depend on the local situation.

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