

Longitudinal Analysis of Progression in Glaucoma Using Spectral-Domain Optical Coherence Tomography

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PURPOSE. To compare the longitudinal loss of RNFL thickness measurements by SD-OCT in healthy individuals and glaucoma patients with or without progression concerning optic disc morphology.

METHODS. A total of 62 eyes, comprising 38 glaucomatous eyes with open angle glaucoma and 24 healthy controls, were included in the study (Erlangen Glaucoma Registry, NTC00494923). All patients were investigated annually over a period of 3 years by Spectralis SD-OCT measuring peripapillary RNFL thickness. By masked comparative analysis of photographs, the eyes were classified into nonprogressive and progressive glaucoma cases. Longitudinal loss of RNFL thickness was compared with morphological changes of optic disc morphology.

RESULTS. Mixed model analysis of annual OCT scans revealed an estimated annual decrease of the RNFL thickness by 2.12 μm in glaucoma eyes with progression, whereas glaucoma eyes without progression in optic disc morphology lost 1.18 μm per year in RNFL thickness ($P = 0.002$). The rate of change in healthy eyes was 0.60 μm and thereby also significantly lower than in glaucoma eyes with progression ($P < 0.001$). The intrasession variability of three successive measurements without head repositioning was $1.5 \pm 0.7 \mu\text{m}$. The loss of mean RNFL thickness exceeded the intrasession variability in 60% of nonprogressive eyes, and in 85% of progressive eyes after 3 years.

CONCLUSIONS. Longitudinal measurements of RNFL thickness using SD-OCT show a more pronounced reduction of RNFL thickness in patients with progression compared with patients without progression in glaucomatous optic disc changes. (ClinicalTrials.gov number, NTC00494923.)

Keywords: optical coherence tomography, glaucoma, progression, optic disc morphology

Progressive glaucomatous optic disc atrophy is characterized by optic disc changes, including enlargement of the optic disc cup and loss of the neuroretinal rim. Morphologic changes may precede loss of function as found by visual field testing.¹ Optical coherence tomography (OCT) was introduced approximately 20 years ago and has achieved an important role in clinical diagnostics.^{2–4} The measurement of peripapillary retinal nerve fiber layer (RNFL) thickness can be used to detect glaucoma. Spectral domain (SD) OCT allows a better axial resolution and shorter acquisition time than time-domain (TD) OCT.^{5–7} A more precise segmentation of retinal layers may help to improve detection of slight changes in RNFL thickness. Focal defects in the RNFL are correlated with visual field changes.⁸ Detection of local RNFL defects is more likely using SD-OCT with eye tracking and averaging due to improved signal-to-noise ratio compared with TD-OCT.⁹

If glaucoma has been diagnosed, it is necessary to identify glaucoma progression in order to intensify the treatment before nerve fiber loss proceeds. In advanced glaucoma, progression can be detected by deterioration in visual field testing and visual acuity. Different diagnostic tools have been developed to detect slight progression in morphology, as morphological

changes frequently precede functional deficits found by visual field testing.¹

Few data exist about the long-term course of OCT measurements and its relevance for detection of glaucoma progression. Wollstein et al.¹⁰ found a loss of average RNFL thickness of 11.7 μm within 4.7 years in glaucoma patients using TD-OCT. To assess whether a decrease in RNFL thickness is due to a true loss of nerve fibers caused by glaucoma or due to the variability of the technique, the intra- and intersession variability have to be calculated first.

The purpose of this study was the longitudinal evaluation of RNFL thickness measured by SD-OCT in three groups with a trend- and event-based approach: healthy subjects, glaucoma without progression, and glaucoma with progression in optic disc morphology within a period of 3 years.

METHODS

Study Design

All study subjects were members of the Erlangen Glaucoma Registry (1460 participants in total, www.clinicaltrials.gov: ID: NTC00494923), which is a longitudinal study founded in 1991.

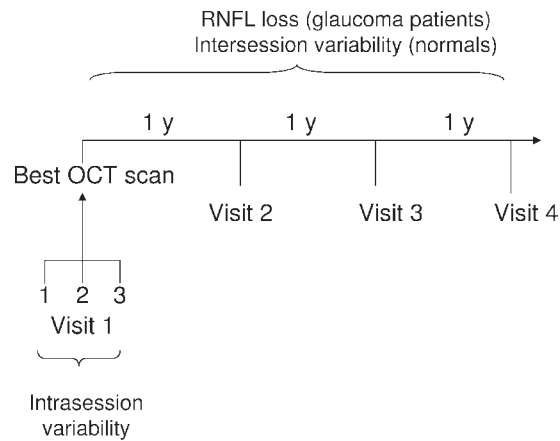


FIGURE 1. Study design: OCT scans were taken three times at each visit. The OCT scan with the best quality was taken for longitudinal analysis. To obtain the intrasession variability, the SD of the three measurements at visit 1 was calculated. The interval between each visit was 1 year.

Its primary aim is research on established and newly implemented diagnostic tools as visual field testing, scanning laser polarimetry (GDx), Heidelberg Retina Tomography, and OCT. The Erlangen Glaucoma Registry study was approved by the local ethics committee. The study complied with the tenets of the Declaration of Helsinki and informed consent was obtained from all participants. The main purpose of the Erlangen Glaucoma Registry is the performance of diagnostic studies in a longitudinal setting. The patients participate in annual visits with a thorough ophthalmological examination including visual acuity, applanatory tonometry, slit lamp examination, funduscopy, standard automated perimetry, optic disc photography, and techniques that have been introduced into glaucoma diagnostics during the past 20 years (e.g., SD-OCT). Pharmacological studies or studies about surgical interventions are not performed in this study population. All glaucoma patients are treated according to current glaucoma treatment guidelines (European Glaucoma Society).

Clinical Data

A total of 116 eyes of 58 patients have been examined in at least four SD-OCT measurements in annual intervals since November 2007. Thereby, a 3- to 4-year follow-up in SD-OCT-assessed RNFL changes could be evaluated up to now (Fig. 1). Only one eye per patient was taken into account. If glaucoma was unilateral, the glaucomatous eye was chosen for the study. If both eyes were affected, the eye with the better OCT image quality was included. After elimination of patients who fulfilled the exclusion criteria, 38 eyes of 38 glaucoma patients remained for analysis of long-term changes in glaucoma. Inclusion criteria in our study were primary or secondary open-angle glaucoma, and at least four successive annual OCT scans. Exclusion criteria were ocular hypertension, other optic nerve neuropathies causing optic nerve atrophy, and angle-closure glaucoma. The diagnosis of glaucoma was made if one or more of the following morphological criteria were present: thinning or notching of the neuroretinal rim, loss of the peripapillary RNFL, unfulfilled Inferior-Superior-Nasal-Temporal (ISNT) rule.¹¹ Pathologic visual field test results associated with a pathologic optic disc configuration confirmed the diagnosis, but were not necessary for the inclusion into the study.

All subjects had a visual acuity of at least 20/40 at the beginning of the study, no myopic refractive error more than -8 diopters (D), no hyperopic refractive error more than +4 D,

and no systemic disorders that might influence the retina. In case of retinal changes and errors in scan acquisition, which can influence segmentation of the RNFL, eyes were excluded from our study. These changes comprised macular pucker ($n = 5$), schisislike remodeling of the inner retinal layers ($n = 5$), choroidal folds due to intraocular hypotony after filtering surgery ($n = 4$), insufficient fixation due to advanced visual field loss ($n = 3$), incorrect positioning of the scanning circle ($n = 1$), and peripapillary small detachments of RPE layer ($n = 1$).

For the assessment of intersession variability, healthy participants were included. These participants were recruited from healthy volunteers and hospital staff and were enrolled in the Erlangen Glaucoma Registry. They performed the same diagnostic program as the glaucoma patients in a longitudinal setting. For inclusion into this study, healthy subjects had to meet the following criteria: completely normal findings in slit-lamp inspection, IOP lower than 21 mm Hg, normal optic disc, best-corrected visual acuity of 20/25 or better, and normal and reliable visual field. A normal optic disc was defined by following criteria: fulfillment of the ISNT rule according to Jonas et al.,¹¹ good visibility of the peripapillary RNFL (in red-free light), absence of optic disc hemorrhages, no enlargement of the optic disc cup in relation to the optic disc size, and absence of neuroretinal rim notching or thinning.

A total of 62 eyes were included and classified into three groups: (1) healthy control eyes ($n = 24$), (2) glaucoma eyes without progression ($n = 25$), and (3) glaucoma eyes with progression ($n = 13$). Patient characteristics are listed in Table 1. Optic disc photographs were the basis for dividing the patients into nonprogressors and progressors. Visual field tests were performed (Table 1), but visual field data were not used for correlation analyses in this study. All included patients were experienced in perimetric tests and had multiple tests before this study. The accepted rate was 12% for false-positive or false-negative answers, respectively.

Optic Disc Photographs

Optic disc photographs were taken at each visit using the Canon CF 1 fundus camera (Canon Inc., Tokyo, Japan) and used to determine progression. Applying the two-dimensional method described by Jonas et al.¹¹ and by Laemmer et al.,¹² the criteria for progression were an increased loss of the neuroretinal rim, new occurrence of a notch with kinking of small vessels at the neuroretinal rim, or new appearance of retinal nerve fiber layer defects.

To assess changes in optic disc morphology indicating progression, the first and the last photograph of the optic disc from the same eye were shown in random order.¹² Two experienced examiners had to confirm progression in optic disc morphology independently from each other. If the examiners disagreed on the assessment of progression according to optic disc morphology, they discussed these cases. If they were of different opinions despite that, a third clinical glaucoma expert was consulted. Progression in optic disc morphology was determined comparing the optic disc photographs at visits 1 and 4.

SD-OCT

Peripapillary RNFL thickness was measured using spectral-domain OCT (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany). In order to test the reliability of the OCT instrument and thereby the validity of our data, we first performed a calibration testing using a sheet of scale paper, which was adjusted in front of the OCT instrument instead of an eye (Supplementary Fig. S1). The first scan was taken in 2007, when we first applied the SD-OCT device in our clinic.

TABLE 1. Patient Characteristics

Parameter	Healthy Controls	Glaucoma Without Progression	Glaucoma With Progression	P Value
Eyes, <i>n</i>	24	25	13	
Mean age, y	57.3 ± 12.3	58.0 ± 12.5	59.9 ± 9.3	ns
Male/female	9/15	13/12	5/8	ns
Eye side, right/left	13/11	12/13	4/9	ns
Mean defect (30° visual field) in dB at visit 1	-0.2 ± 0.7*	4.6 ± 7.2	2.8 ± 5.3	ns
Median of mean defect				
Visit 1	-0.7	1.6	0.7	
Visit 2	-0.3	2.2	2.2	
Visit 3	0.3	2.8	4.2	
Visit 4	0.5	3.5	4.2	

The group of healthy controls, glaucoma patients without progression, and glaucoma patients with progression showed a similar distribution regarding age, sex, and eye side ($P > 0.05$, Mann-Whitney U test, χ^2 test). Mean defect in 30° visual field test was significantly ($*P < 0.05$) lower in healthy control eyes compared with the mean defect in glaucoma patients with or without progression. There was no significant difference between mean defect in glaucoma patients with and without progression.

ns, nonsignificant.

The thickness of the sheet was 63 μm at the first measurement in 2007 (Supplementary Fig. S2), and $62 \pm 0.7 \mu\text{m}$ at the last measurement in 2012 (Supplementary Fig. S3). Thereby, the drift of precision is very low over time. Infrared reflection images ($\lambda = 820 \text{ nm}$) and OCT B-scans ($\lambda = 870 \text{ nm}$, 40,000 A-scans/s) of the dual-laser scanning systems of Spectralis OCT were acquired simultaneously; 3.4-mm-wide circular scans were taken (768 A-scans) around the optic disc and averaged automatically. Eye movements were compensated by the use of an eye-tracking system (ART/Automatic Real-Time function) (PASW 18.0; IBM, Armonk, NY). The variability of the measurement due to different positioning and tilting of the head at different visits were reduced by fovea-to-disc-alignment. Segmentation of the upper and lower border of the RNFL was performed by the software of Spectralis OCT. All calculated segmentations were controlled and corrected manually by an experienced examiner if the scan quality itself was good but the automatic segmentation was wrong. The errors in segmentation were mainly a wrong identification of the posterior vitreous membrane instead of the internal limiting membrane for the inner boundary of the RNFL in cases with posterior vitreous detachment. Furthermore, shadowing of the RNFL layer by large retinal vessels made the automatic identification of the RNFL difficult. The circular “band” of RNFL thickness was divided into 12 sectors by averaging the values of 64 measured A-scans. Sector 1 starts at 12 o'clock and continues circumpapillary via the nasal, inferior, and temporal sides.

At each visit, the peripapillary RNFL thickness was scanned three times successively without head repositioning. In order to exclude an effect of the head positioning we performed a prestudy. First, we had measured the RNFL thickness in 30 eyes of 16 patients three times successively without head repositioning. Afterward, we had performed another three measurements with head repositioning after each scan. We found no significant difference in the variability of the RNFL thickness between these groups ($1.5 \pm 1.9 \mu\text{m}$ vs. $1.0 \pm 0.9 \mu\text{m}$, $P = 0.85$, Mann-Whitney U test). The B-scan with the best quality at the first visit was chosen as reference and every following OCT scan was aligned to this position using the follow-up modus of the instrument (Spectralis HRA+OCT; Heidelberg Engineering). Intrasession variability was assessed by calculating the mean and coefficient of variation (COV) of three successive scans within the first session.

Statistical Analysis

Statistical analysis was performed using PASW 18.0 for Windows (IBM) and the R System for Statistical Computing, version 2.15.2 (provided in the public domain, <http://www.r-project.org>). Results are demonstrated as mean and SD or frequency and percentage if appropriate for all subgroups. Comparisons between groups and variables were performed using t -test or Mann-Whitney U test for quantitative variables and the χ^2 test for qualitative variables. Linear mixed model analysis¹³ was used to analyze the rate of change in mean RNFL thickness during follow-up. The overall time trend and the mean differences among the groups (healthy, glaucoma without progression, and glaucoma with progression) were modeled as fixed effects. Individual distributions of the intercepts of the patients were modeled as normally distributed random effects. In addition, a fixed interaction term between the time trend and the groups was included in the linear mixed model. This strategy resulted in individual trend

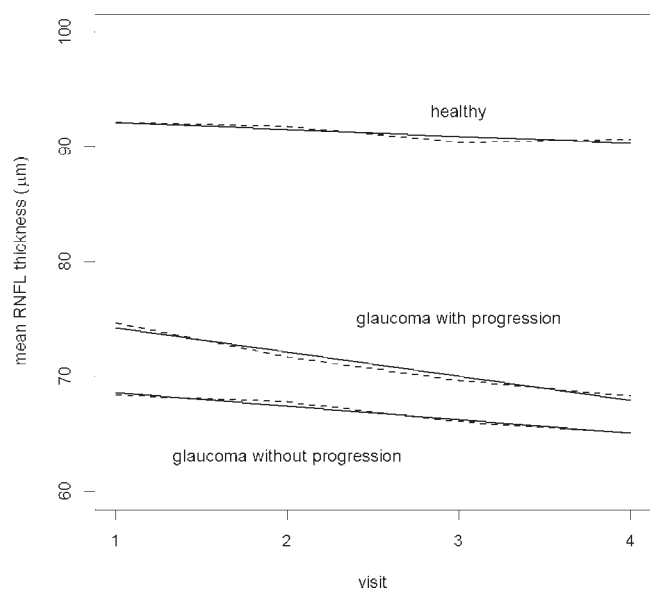


FIGURE 2. Progression of mean RNFL thickness values in the three groups (solid lines: mean values estimated from linear mixed model; dashed lines: mean values calculated from the measurement data).

TABLE 2. Mean RNFL Thickness Values for Each Diagnosis Group and Visit (Estimated From Linear Mixed Model)

	Visit 1	Visit 2	Visit 3	Visit 4	Estimated Rate of Change in $\mu\text{m}/\text{y}$, β_i
Healthy	92.12	91.52	90.91	90.31	-0.60
Glaucoma without progression	68.54	67.37	66.20	65.02	-1.18
Glaucoma with progression	74.23	72.11	70.00	67.88	-2.12

lines for each of the three groups (Fig. 2). By definition of the model, group-specific rates of change in mean RNFL thickness could be quantified by the estimated slopes of the trend lines. In the following, the slopes are denoted by β_i , $i = 1, 2, 3$. To investigate whether the rates of change in mean RNFL thickness differed among the groups, differences between the group-specific rates were tested against zero. This was done by using general linear hypothesis tests.¹⁴ The method by Bretz et al.¹⁴ automatically adjusted P values for multiple comparisons. A significance level of $\alpha = 0.05$ was used for all statistical hypothesis tests.

RESULTS

Patient characteristics of the three groups (healthy eyes, glaucoma eyes without and with progression) are listed in Table 1.

The mean RNFL thickness at study beginning did not show a significant difference in glaucoma without progression (68.4

$\pm 14.1 \mu\text{m}$) versus glaucoma with progression ($74.7 \pm 14.4 \mu\text{m}$, $P > 0.4$), whereas the mean RNFL thickness was significantly higher in healthy control eyes compared with glaucoma eyes ($92.1 \pm 7.4 \mu\text{m}$, $P < 0.001$ for all visits).

Using the linear mixed model analysis described by Verbeke and Molenberghs,¹³ estimated rates of change were largest in absolute value for glaucoma patients with progression ($\beta_3 = -2.12 \mu\text{m}$ per year) and smallest for healthy patients ($\beta_1 = -0.60 \mu\text{m}$ per year, Table 2, Fig. 2). The rates of change in mean RNFL thickness differed significantly between glaucoma patients with ($\beta_3 = -2.12 \mu\text{m}$ per year) and without progression ($\beta_2 = -1.18 \mu\text{m}$ per year, $P = 0.002$) and also between healthy patients and glaucoma patients with progression ($P < 0.001$). The distribution of the measured values and of the estimated rates of mean RNFL thickness change after three years is visualized in Figures 3 and 4, respectively.

OCT analysis of RNFL thickness showed a positive slope (i.e., increase of RNFL thickness) in three eyes of the healthy control eyes, and in two eyes of the nonprogressive glaucoma

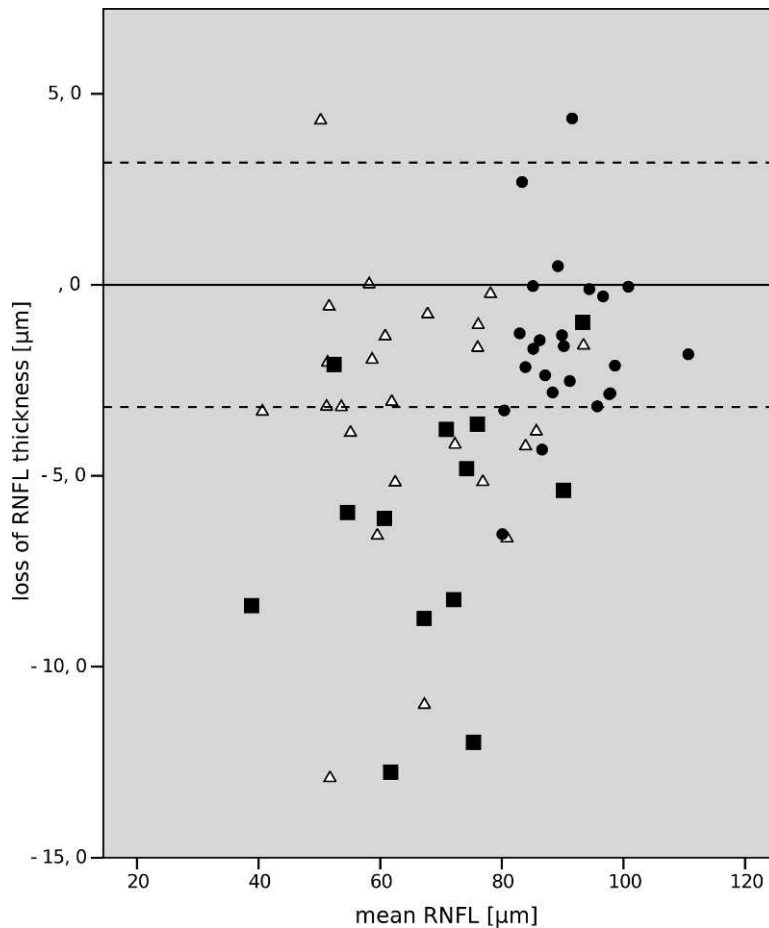


FIGURE 3. The Bland-Altman plot shows the RNFL loss in micrometers within 3 years compared with the mean RNFL thickness in healthy control eyes (circles), glaucoma eyes without progression (triangles), and glaucoma eyes with progression (squares) (horizontal line: 95% confidence interval for intrasession variability in glaucoma patients).

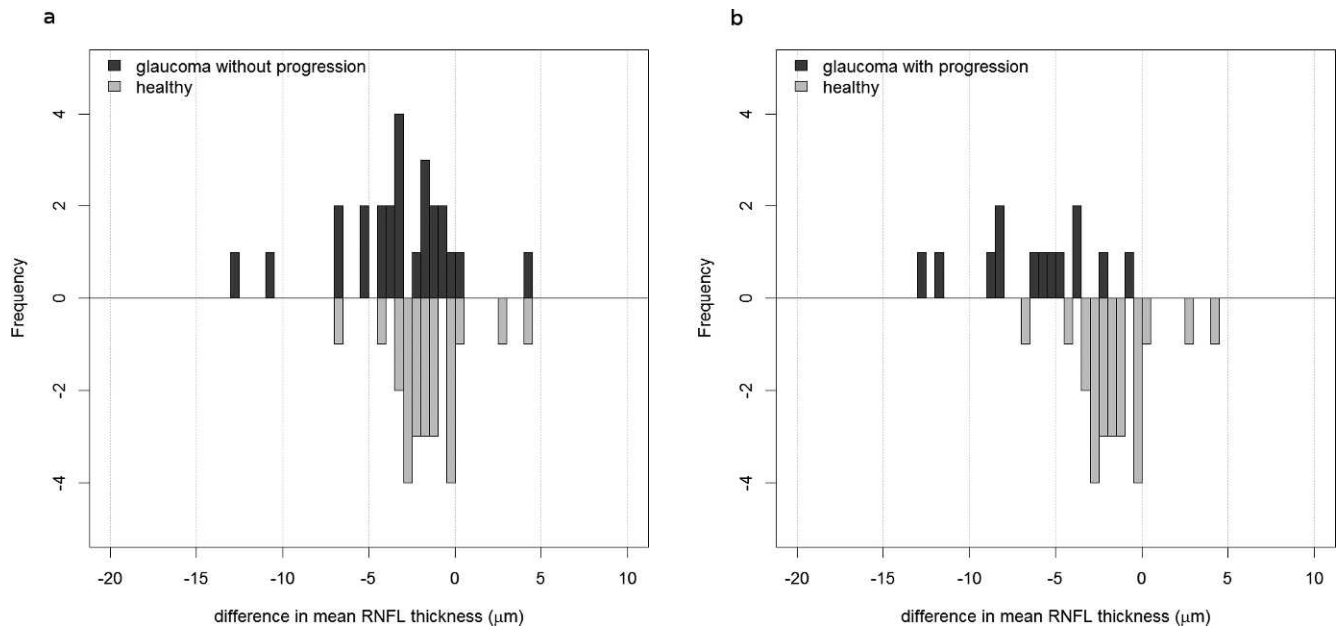


FIGURE 4. Distribution of rates of mean RNFL thickness change in glaucoma patients (*dark bars*) with and without morphologic optic disc changes during follow-up of 3 years compared with the healthy control group (*light bars*). (a) Glaucoma eyes without progression versus healthy eyes. (b) Glaucoma eyes with progression versus healthy eyes.

group. In the group of progressive glaucoma cases, no eye showed a positive slope within three years.

Mean RNFL thickness revealed an intrasession variability of $1.5 \pm 0.7 \mu\text{m}$ (COV $2.5\% \pm 1.1\%$) in three consecutive measurements regarding all 38 glaucoma patients (95% confidence interval: $3.2 \mu\text{m}$). In healthy subjects, we found a comparable intrasession variability of $2.0 \pm 1.7 \mu\text{m}$ (COV $2.3\% \pm 1.9\%$) (Table 3). There was no significant difference in the intrasession variability between progressive ($1.4 \pm 0.6 \mu\text{m}$, COV $2.2\% \pm 1.8\%$) and nonprogressive eyes ($1.6 \pm 0.7 \mu\text{m}$, COV $2.7\% \pm 1.2\%$, $P = 0.100$, Mann-Whitney U test, Table 3).

The intrasession variability patients ranged in different sectors from $1.1 \pm 0.8 \mu\text{m}$ (sector 10, COV $1.8\% \pm 1.3\%$) to $2.2 \pm 1.8 \mu\text{m}$ (sector 12, COV $2.5\% \pm 2.4\%$) in respect to all 38 glaucoma eyes. Regarding different sectors, we found no significant differences in COV values in progressive compared

with nonprogressive glaucoma eyes apart from sector 1 (Table 3).

Further, an event-based analysis was performed on the basis of an intrasession variability of $1.5 \mu\text{m}$. The 2-fold SD of the intrasession variability was exceeded by 54%, 69%, and 85% of the patients with optic disc progression within 1, 2, and 3 years, respectively. In patients without optic disc progression, the intrasession variability was exceeded by 20%, 40%, and 60% within 1, 2, and 3 years, respectively.

DISCUSSION

In glaucoma, detection of progression is crucial for prognosis, because morphologic changes in adults are incurable. Reduction of the IOP is the main therapeutic strategy to avoid progression of the disease.

TABLE 3. Intrasession Variability and COV in Different Sectors in Glaucoma Patients in Three Consecutive Measurements at the Same Date ($t = 0$)

	Healthy Control Eyes, <i>n</i> = 24	All Glaucoma Patients, <i>n</i> = 38	Without Progression, <i>n</i> = 25	With Progression, <i>n</i> = 13
Mean variability \pm SD, μm	2.0 ± 1.7	1.5 ± 0.7	1.6 ± 0.7	1.4 ± 0.6
Mean COV, %	2.3 ± 1.9	2.5 ± 1.1	2.7 ± 1.2	2.2 ± 0.8
COV sector 1, %	2.3 ± 2.6	2.5 ± 3.3	3.0 ± 3.6	$1.7 \pm 2.5^*$
COV sector 2, %	2.3 ± 2.3	2.3 ± 1.5	2.3 ± 1.6	2.2 ± 1.3
COV sector 3, %	2.7 ± 2.8	2.8 ± 2.0	2.7 ± 2.0	2.9 ± 1.9
COV sector 4, %	2.2 ± 2.3	2.9 ± 3.2	2.7 ± 2.0	3.2 ± 4.9
COV sector 5, %	2.3 ± 2.0	1.8 ± 1.2	1.8 ± 1.1	1.8 ± 1.3
COV sector 6, %	2.8 ± 2.9	1.8 ± 1.3	2.1 ± 1.4	1.4 ± 1.0
COV sector 7, %	1.4 ± 1.9	2.1 ± 1.3	2.1 ± 1.5	2.0 ± 1.0
COV sector 8, %	2.3 ± 2.1	2.9 ± 2.6	2.8 ± 2.8	3.0 ± 2.1
COV sector 9, %	3.4 ± 3.4	3.3 ± 2.9	3.7 ± 3.3	2.6 ± 2.0
COV sector 10, %	2.2 ± 1.9	1.8 ± 1.3	1.8 ± 1.5	1.8 ± 1.1
COV sector 11, %	1.6 ± 1.3	3.4 ± 4.2	4.1 ± 4.9	2.0 ± 1.2
COV sector 12, %	1.7 ± 1.7	2.5 ± 2.4	3.0 ± 2.7	1.7 ± 1.3

Apart from sector 1, there was no significant difference in the COV of glaucoma eyes with progression compared with nonprogressive eyes (Mann-Whitney U test).

* $P < 0.05$.

Our trend-based analysis revealed a rate of progression of $-2.12 \mu\text{m}$ per year in patients with progressive optic disc changes, which was significantly higher than in nonprogressors or healthy eyes. Even in the group of nonprogressors, the rate of progression was nearly twice as high as in the healthy control group. To assess a change in RNFL thickness over a period of time, the variability of the method is crucial. The intersession variability of OCT measurements depends on the OCT instrument that is used. In a comparative study with six different TD- and SD-OCT instruments, the COV in measurements of the central retinal thickness in healthy patients was 0.46% using Spectralis OCT.¹⁵

In our study, the intrasession variability in RNFL thickness measurements was $1.5 \pm 0.7 \mu\text{m}$ (COV = $2.5\% \pm 1.1\%$) in three successive OCT scans. The variability of OCT measurements can be influenced by different factors: technical differences, such as the method of scan acquisition, segmentation, eye tracking, and signal quality, as well as patient-specific factors, such as corneal dryness, or opacity of the optic media can have a high influence on the variability of OCT measurements.

Regarding the intrasession variability of RNFL thickness measurements in SD-OCT, Mansoori et al.¹⁶ detected a COV between 1.2% and 5.1% in normal eyes and between 1.3% and 3.6% in glaucomatous eyes. In contrast to this study, they did not perform the scans successively, but after 1 hour of rest. Wu et al.¹⁷ reported results on intrasession variability in healthy and glaucoma patients showing a sector-depending variability (COV) between 1.45% and 2.59% in normal eyes, and between 1.74% and 3.22% in glaucomatous eyes using SD-OCT.

Intrasession variability in SD-OCT can be minimized to values between 1.3% and 3.5% using the eye tracker and retest function of this device,¹⁸ which we applied in this study as well. If progression of glaucoma is intended to be detected by OCT, the loss of RNFL thickness must exceed the variability of the method. We expected a lower intrasession variability compared with the intersession variability within 3 years, because the eye position and the adjustment of the camera (e.g., focus) were not changed in the three successive scans at the baseline visit. However, the intrasession variability we found in healthy individuals ($2.0 \mu\text{m}$) was in the same range as the intersession variability of $1.5 \mu\text{m}$ within 3 years.

In SD-OCT, the published results of test-retest variability of the average RNFL thickness vary between $2.96 \mu\text{m}$ ¹⁶ and $10.00 \mu\text{m}$ ¹⁹ in glaucoma patients. To analyze the intersession variability, we compared the RNFL loss in glaucoma patients with RNFL changes in healthy subjects. We found a mean RNFL loss of $1.5 \pm 2.2 \mu\text{m}$ within 3 years in healthy control subjects (e.g., a decrease of 0.54% per year). The change of RNFL thickness within 3 years includes a physiologic loss of RNFL thickness and the variability of the method. Bendschneider et al.²⁰ reported a decrease in mean RNFL thickness by $1.90 \mu\text{m}$ per decade, which is similar to the mean annual loss reported by Budenz et al.,²¹ Parikh et al.,²² and Feuer et al.²³ However, these studies used a different approach for the acquisition of the aging rate. In contrast to longitudinal follow-up measurements, they compared the RNFL thickness of patients in different age groups and calculated the aging rate by linear regression.

A decrease in nerve fibers in healthy eyes can be detected by other methods, too. The mean neuroretinal rim measured by digital planimetry decreased by 0.36% per year in healthy participants,¹² although calculations of aging rates between different morphometric techniques cannot be compared due to differences in the measurement variability of the method.

The intersession variability in healthy eyes exceeded the expectable loss due to age-related changes slightly, but was comparable to the intersession variability reported by Mansoori et al.¹⁶ Using SD-OCT they found a test-retest variability of

$1.4 \mu\text{m}$ in healthy subjects. Regarding the intersession variability in different sectors, Mansoori et al.¹⁶ measured sector-related COV values up to 9.56%. We found a lower variability with sector-dependent COV values between 1.4% and 3.4% in healthy subjects (Table 3). The improvement in our results lies probably in the eye-tracking system and fovea-to-disc alignment we used, which compensates rotations in the head positioning.

Only a few reports have been published about the value of OCT for detection of progression in glaucoma. Wollstein et al.¹⁰ defined progression in OCT as a loss of more than $20 \mu\text{m}$ within a follow-up time of 4.7 years. However, they used a prototype version of OCT with a resolution of $10 \mu\text{m}$, which cannot be compared to SD-OCT instruments. A simultaneous progression of glaucoma in OCT and visual field testing was found in only 3% of their study group. In an experimental study with laser-induced glaucoma in Rhesus monkeys, longitudinal progression has been investigated using Spectralis OCT.²⁴ A loss of RNFL thickness of 23% had been detected in their glaucoma group.

Progression analysis using the SD-OCT technique in humans was performed using Cirrus OCT (Carl Zeiss Meditec, Jena, Germany) in a recent event-based study by Leung et al.²⁵ Event-based analyses are even more difficult to compare than trend-based analyses because they are more dependent on the inclusion criteria of the study group and the definition of the event. In our study, the event was defined by the 2-fold SD of the intrasession variability. The event criterion was fulfilled by 85% of the progressors and 60% of the nonprogressors within 3 years.

In contrast to the event-based approaches by Wollstein et al.,¹⁰ defining progression as a loss of $20 \mu\text{m}$, Leung et al.²⁶ performed a trend-based approach using a software tool in Stratus OCT (Carl Zeiss Meditec), the so-called "guided progression analysis (GPA)." They found rates of progression between 1.2 and $15.4 \mu\text{m}$ per year in glaucoma eyes, with a median loss of $3.3 \mu\text{m}$ per year. The agreement of progression detection in visual field testing and Stratus OCT was very poor. They did not have a healthy control group.

Lee et al.²⁷ performed a trend-based analysis using the Stratus OCT (Carl Zeiss Meditec). Progression of glaucoma was defined on the basis of optic disc photographs, as in our study. They found a rate of progression of $-1.58 \mu\text{m}$ per year in progressors and of $-0.34 \mu\text{m}$ per year in nonprogressors. However, the study was performed using time-domain OCT technique, which cannot be compared directly to SD-OCT. They did not relate their data to healthy eyes and did not perform an analysis of the intersession variability of OCT measurements. Compared with Lee et al.,²⁷ the rate of change found by Medeiros et al.²⁸ in their trend-based analysis was lower with a rate of change of $-0.72 \mu\text{m}$ per year in progressors.

We found an estimated rate of progression of $-2.1 \mu\text{m}$ per year in patients with progression in optic disc morphology. The differences in the rate of change that were found in our study compared with the studies mentioned above can have different reasons: different OCT technique (TD-OCT versus SD-OCT), or different study population and stage of glaucoma: none of these studies distinguished between early and advanced glaucoma, which have possibly a different rate of change. The rate of progression might be of use in order to decide whether it is necessary to intensify the treatment in patients where visual field testing cannot be used as a method to detect progression either due to preperimetric glaucoma or due to low compliance at visual field testing. A limitation of this rate of progression is that a focal loss in RNFL thickness has only a small effect on the mean RNFL thickness, whereas it can cause remarkable damage in the visual field. Such kind of progression could be overlooked if the question about

progression is answered by regarding the rate of progression in average RNFL thickness alone.

Regarding single sectors, the rate of detection of progression in glaucoma was higher. The difference in RNFL loss between progressive glaucoma eyes and nonprogressive eyes was maximal in sector 7 (inferior to optic disc). Interestingly, Tornow et al.²⁹ found a reduced choroidal thickness in the same sector. In Stratus OCT (Carl Zeiss Meditec), the discrimination between glaucomatous and healthy eyes is easiest in the inferior quadrant.³⁰

When analyzing our statistical results, we have taken the clinical plausibility of the results into account. However, it has to be mentioned that the multitude of statistical comparisons in this study can create illusive false-positive significant results.

The decrease of RNFL thickness in patients without progression in optic disc morphology indicates that the measurement of RNFL loss by OCT might be more sensitive than optic disc assessment. Eyes that had been assessed as stable in optic disc morphology could in fact be undergoing a slow progression. Regular visits with critical adjustment of IOP lead to a reduction of RNFL thickness of only $4.8 \pm 3.8 \mu\text{m}$ within 3 years (all glaucoma patients). The result can be explained by the intensive antiglaucomatous treatment. The natural course of untreated glaucoma is assumed to be faster with a higher loss of RNFL thickness. Another reason might be the relatively short follow-up time of 3 years compared with the slowly progressive character of open-angle glaucoma. Therefore, the long-term outcome of patients with a slight progression in OCT could not be determined. Long-term studies are required to analyze whether early detection of progression in RNFL thickness measured by OCT is followed by progression in visual field testing.

The loss of mean RNFL thickness in nonprogressive patients might be explained by a higher sensitivity of SD-OCT compared with optic disc assessment on photographs. Alternatively, this finding could indicate a false-positive measurement due to the technical variability of the technique. This question can be solved only by longer observation of these patients. If they show unambiguous signs of progression at the following visits (e.g., clear thinning of the neuroretinal rim, formation of a notch, or conversion from preperimetric to perimetric glaucoma), the theory of a higher sensitivity of OCT measurements is in favor.

In conclusion, this study revealed that SD-OCT is capable of detecting a loss in the nerve fiber thickness in glaucoma patients in a longitudinal setting. Glaucoma patients with progression in optic disc morphology show a higher decline in RNFL thickness than patients without progression within a follow-up time of 3 years.

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