

Correlation of Average RNFL Thickness Using the STRATUS OCT with the Perimetric Staging of Glaucoma

Sharah Mae G. Kaw, MD, Jose Ma. Martinez, MD, Joseph Anthony Tumbocon, MD, and Noel de Jesus Atienza, MD, MSc

International Eye Institute
St. Luke's Medical Center
Quezon City, Philippines

Correspondence: Sharah Mae G. Kaw, MD
St. Luke's Medical Center
Quezon City, Philippines
Email: sharahkaw@yahoo.com

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ABSTRACT

Objective: To determine the correlation between average peripapillary retinal nerve fiber layer (RNFL) thickness measured with time domain optical coherence tomography (TD-OCT) in normal and glaucoma eyes.

Methods: This was a cross-sectional study of 281 eyes randomly selected from a previous study. Assessment of glaucomatous damage was done by glaucoma specialists who based their diagnosis on the visual field tests and optic disc photos, independent of OCT results. Eyes were classified into the following groups: normal, mild, moderate, or severe glaucoma. Severity of glaucoma was based on visual field abnormalities following a modified Hodapp-Anderson-Parish criteria for staging. Average RNFL thickness of normal and glaucoma subgroups, as measured with STRATUS-OCT, were analyzed using single ANOVA test. Association between average RNFL thickness and severity of glaucomatous visual field loss was evaluated using the Pearson's correlation coefficient analysis.

Results: 183 eyes had no glaucoma; 27 had mild, 32 had moderate, and 39 had severe glaucoma. Mean average peripapillary RNFL thickness (μm) in the normal, mild, moderate, and severe glaucoma groups were $98.05(\pm 13.46)$, $76.27(\pm 11.79)$, $76.42(\pm 16.01)$, and $56.17(\pm 14.92)$ respectively. Significant differences were seen in the average RNFL thickness among the groups ($P < 0.05$), except in eyes with mild to moderate glaucoma. A moderately strong correlation of -0.57 ($P < 0.05$) was observed between average RNFL thickness and the stage of glaucoma.

Conclusion: TD-OCT showed moderately strong correlation between the average RNFL thickness and perimetric stages of glaucoma. Average RNFL thickness is a good parameter to discriminate normal from glaucoma eyes.

Keywords: Optical coherence tomography, Time-Domain OCT, Average peripapillary RNFL thickness, Glaucoma, Perimetry

The optical coherence tomography (OCT) is currently used to objectively assess the extent of structural damage in glaucoma at the level of the retinal nerve fiber layer (RNFL). It has been shown to produce highly specific and reproducible results by measuring the peripapillary RNFL thickness¹⁻⁵, and has proven to be useful as an adjunctive tool in the detection of glaucoma. It has strong ability to discriminate accurately between normal and glaucomatous eyes.⁶⁻¹⁰

Current staging of glaucoma is based on functional tests that determine reproducible visual field defects. The OCT/RNFL analysis has been shown to quantitatively discriminate normal from glaucomatous eye with some evidence showing its ability to discriminate between the different stages of glaucoma.^{6,7,10} However, there has not been enough data that specifically evaluated its relevance in the staging of glaucoma.

In this study, we evaluated the ability of the Stratus OCT (Carl Zeiss Meditec Inc., Dublin, CA, USA) to discriminate non-glaucomatous eyes from glaucomatous eyes in its various stages of functional damage using the average peripapillary RNFL thickness. Specifically, we compared the average RNFL thickness between patients with mild, moderate, and severe glaucomatous visual field loss based on the Hodapp-Anderson-Parish criteria and normal age-matched controls. We also determined the correlation between the visual field parameters mean defect (MD) and loss variance (LV) of the Octopus automated perimetry and the average peripapillary RNFL thickness as measured by the Stratus OCT. Lastly, we determined the level of RNFL percentage loss in mild, moderate, and severe glaucoma compared to normal eyes.

METHODOLOGY

Data from the “Diagnostic Accuracy of Optical Coherence Tomography in Assessing Glaucoma among Filipinos” study were reviewed. This was a cross-sectional study of Filipino patients with varying degrees of glaucoma and normal controls who were recruited from September 2008 to October 2010 at the St. Luke’s International Eye Institute with a diagnosis of glaucoma suspect.¹¹ All subjects underwent three diagnostic examinations, composed of the standard automated perimetry (Octopus TOP and Humphrey Field Analyzer SITA-Standard), optical coherence tomography (STRATUS OCT, Carl Zeiss Meditec,

Dublin, CA) using the fast optic disc and fast RNFL protocols, and optic nerve head photography (Zeiss fundus camera and VISUPAC system). Only those with acceptable perimetry results and OCT scans were included. Acceptable perimetry result was defined as those with <20% fixation losses, false positive, and false negative responses. Acceptable OCT scan was defined as those with signal-to-noise ratio of >35 dB or a signal strength of 6/10 and above, and a well-centered circular scan around the disc.

Normal and glaucoma eyes were assessed independently by 2 glaucoma specialists. Diagnosis was based on the optic nerve head photographs, visual field tests, and the clinical data. Both readers were blinded by the OCT-RNFL results. Subjects were labeled as glaucomatous with the presence of any of the following features: 1) Optic disc cupping to the disc margin and associated enlargement of the peripapillary atrophy with or without detectable abnormalities on perimetry; 2) Glaucomatous abnormalities of the optic nerve head with pertinent characteristics, such as notching, disc asymmetry of more than 0.2 between the two eyes, focal or diffuse atrophy of the RNFL, vertical cup/disc ratio more than 0.6; and 3) An abnormal visual field on standard automated perimetry characteristic of glaucoma with a minimum criteria of: a cluster of three or more non-edge points in a location typical for glaucoma, all of which were depressed on pattern deviation plot at $p < .05$ level and one of which was depressed at $p < .01$ level. Glaucomatous eyes were further classified as having mild, moderate, or severe glaucoma based on a modified Hodapp-Anderson-Parish classification for Octopus perimetry (Appendix A).

In this study, normal and subjects with established perimetric glaucoma that were in the age range of 40-80 years were included. The age distribution of groups of glaucoma patients was determined for age-matching. Normal controls were randomly selected using the “fishbowl” method to match the age distribution of the glaucoma groups.

Statistical Analysis

Statistical differences between the average RNFL thickness in the normal and the different glaucoma subgroups were analyzed using the one-way ANOVA test. The Bootstrap estimation method was used for multiple comparisons to determine which subgroups were significantly different from each other. The

relationship between the average peripapillary RNFL thickness and the various stages of glaucoma as determined by the global indices (MD and LV) was analyzed using the Pearson's correlation coefficient. A value of $p < 0.05$ was considered statistically significant for both analyses.

RESULTS

Out of the 486 eyes of glaucoma suspects from the original source study, a total of 281 eyes were included for this study. 183 eyes were found to be normal while 98 were diagnosed with glaucoma. Of the 98 glaucoma eyes, 27 were classified as mild, 32 moderate, and 39 severe. The mean age of the normal and glaucoma subgroups were not statistically different ($p > 0.05$) from each other. There was, however, a significant difference of the sex distribution within the groups, showing a higher predilection for females ($p < 0.05$) (Table 1).

The mean average peripapillary RNFL thickness in the normal was 98.05 (± 13.46) and in the glaucoma 76.27 (± 11.79), 76.42 (± 16.01), and 56.17 (± 14.92) for the mild, moderate, and severe subgroups respectively (Figure 1). Significant differences were present between the normal and all the glaucoma subgroups, and between severe and all the subgroups. There was no significant difference between the mild and moderate groups (Table 2).

Table 1. Demographic Characteristics of the Normal and Glaucoma Subgroups.

	Normal (n= 183)	Mild (n=27)	Moderate (n=32)	Severe (n=39)	ρ -value
Mean Age (years) (\pm SD)	62.5 (7.7)	63.0 (7.0)	60.9(7.6)	63.5 (8.2)	$>0.05^*$
Age Range (years)	43-80	43-71	43-76	48-78	
Sex					
Male (%)	28.4(%)	37.0(%)	50.0(%)	53.9(%)	$<0.05^*$
Female (%)	71.6(%)	63.0(%)	50.0(%)	46.1(%)	$<0.05^*$

* one-way ANOVA

Table 2. Multiple Comparisons of the Average RNFL Thickness Between Normal and Glaucoma Subgroups.

Dependent Variable	(I) Stage of Glaucoma	(J) Stage of Glaucoma	Mean Difference (I-J)	95% Confidence Interval	
				Lower	Upper
Average RNFL Thickness	Normal	Mild	21.78	17.29	26.45
		Moderate	21.63	15.72	27.55
		Severe	41.88	36.51	46.51
	Mild	Normal	-21.78	-26.45	-17.29
		Moderate	-0.15	-7.64	7.01
		Severe	20.10	13.77	26.66
	Moderate	Normal	-21.63	-27.55	-15.72
		Mild	0.15	-7.01	7.64
		Severe	20.25	13.04	27.31
	Severe	Normal	-41.88	-46.51	-36.51
		Mild	-20.10	-26.66	-13.77
		Moderate	-20.25	-27.31	-13.04

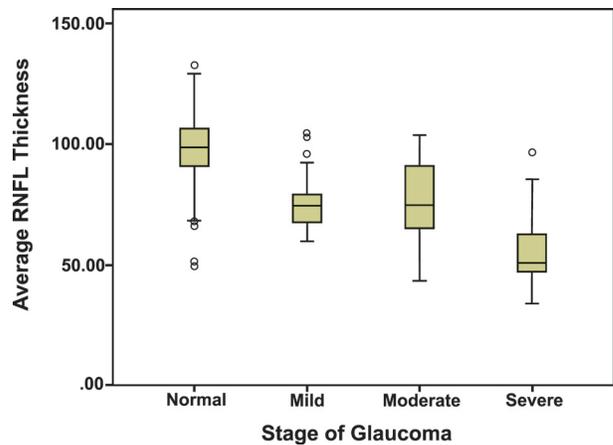


Figure 1. Distribution of the average RNFL thickness (um) in normal and the different glaucoma subgroups (mild, moderate, severe).

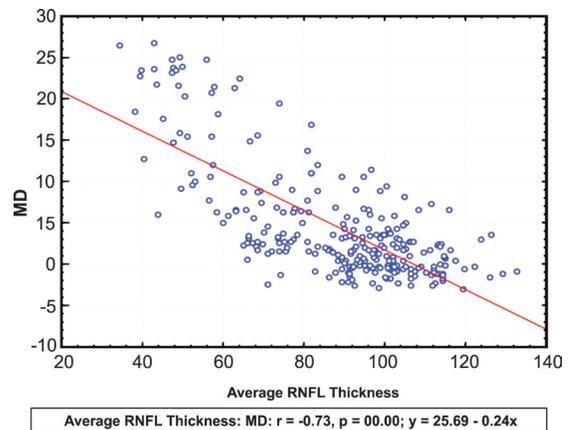


Figure 2. Scatterplot of the mean defect (MD) and the average RNFL thickness (um) in normal and glaucoma subgroups.

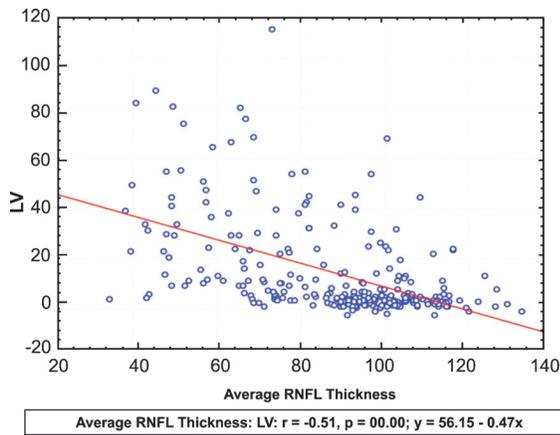


Figure 3. Scatterplot of the loss variance (LV) and the average RNFL thickness (um) in normal and glaucoma subgroups.

Correlation analyses determining the relationship between average RNFL thickness and the different perimetric stages of glaucoma using the MD and LV indices showed significant inverse correlation for all variables (Table 3). The highest correlation was found between the average RNFL thickness and MD ($r=0.73$). Scatterplot of the MD and LV values against RNFL thickness showed negative correlation (Fig. 2 and 3).

Table 3. Pearson's Correlation Coefficient of Mean Defect (MD) and Loss Variance (LV) with Average RNFL Thickness.

Variables	Correlation Coefficient (r)	R ²	p-value
Average RNFL thickness vs. stages of glaucoma	-0.57	32.53%	<0.05
MD vs. average RNFL thickness	-0.73	53.44%	<0.05
LV vs. average RNFL thickness	-0.51	26.42%	<0.05

*significant correlation defined as $r>0.5$ with $p<0.05$

Table 4. Percentage RNFL Thinning in the Different Glaucoma Subgroups.

Stage	Average RNFL Thickness	% RNFL Thinning
Normal	98.05	0%
Mild	76.27	22.21%
Moderate	76.42	22.06%
Severe	56.17	42.72%

The percentage RNFL loss was also computed for the different glaucoma subgroups when compared to the normal average RNFL thickness. There was a decrease by 22% from the normal in the mild and moderate subgroups, and by 43% in the severe group (Table 4).

DISCUSSION

The results from this cross-sectional study showed that OCT clearly delineated normal from glaucoma patients with mild-moderate functional damage and those with severe functional damage in terms of average RNFL thickness. This was similar to the findings by Galvao.¹² and Chen.¹³, who compared average RNFL thickness and visual field loss among various glaucoma subgroups using the scanning laser polarimetry (GDx). This same linear relationship was replicated across two different imaging technologies measuring the RNFL. The discriminatory ability seemed to decrease in the early stages of glaucoma, perhaps due to neural redundancy.

Global visual field indices have been used extensively to monitor glaucoma status over time. We found strong negative linear correlation between average peripapillary RNFL thickness and MD ($r=0.73$) and LV ($r=0.51$) on Octopus perimetry (Figures 2 and 3) in the normal and all the glaucoma subgroups. A more modest correlation was found by Taliantzis¹⁴ who reported correlations with MD ($r=0.58$) and LV ($r=0.53$) among pre-perimetric and chronic open angle glaucoma eyes.

We were able to detect approximately 22% RNFL thinning in the mild and moderate groups and 43% in the severe glaucoma group (Table 4). Sihota noted very similar estimates at 25% for early glaucoma and 48% for severe glaucoma.¹⁵ There was decreased ability to distinguish between early and moderate glaucoma.

Despite limitations in the cross-sectional design and unequal sample sizes among the groups, our study compared favorably with the results of other studies looking into structural and functional status across the glaucoma disease continuum. Thus, OCT RNFL thickness may be used as an adjunct to visual field determination in monitoring glaucoma progression. It can also be a primary measure of glaucoma status in patients who are unable to perform functional tests reliably.

Detecting glaucoma changes over time is best evaluated by longitudinal studies. Wollstein followed OCT RNFL thickness in open angle glaucoma patients over a 4 year period and found that the OCT was even more sensitive to change compared to visual field analysis.¹⁶ It is not clear how much change was clinically significant to move from one stage of glaucoma to another. It is hoped that the percentage RNFL thinning estimates in our study can guide clinicians, as well as, developers of progression analysis software in setting minimum change limits for defining progression.

In conclusion, the average peripapillary RNFL thickness measured by the Stratus OCT is a useful parameter to discriminate between normal, and early to severe glaucoma eyes. Further prospective studies can be done to investigate the ability of the OCT to detect temporal progression of glaucoma using the baseline findings obtained from this study.

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APPENDIX

Modified Hodapp-Anderson-Parish Criteria for Staging of Glaucomatous Visual Field Loss in Octopus Automated Perimetry

Mild glaucoma (1)	Mean defect (MD) no worse than 6 dB with 25% of points depressed below the 5% level and 15% of points depressed below the 1% level, with no point within central 5° with sensitivity 15 dB
Moderate glaucoma (2)	MD worse than 6 dB but no worse than 12 dB with 50% of points depressed below the 5% level and 25% of points depressed below the 1% level, with no point within central 5° with sensitivity 0 dB, and only 1 hemifield containing a point with sensitivity 15 dB within 5° of fixation
Severe glaucoma (3)	MD worse than 12 dB on pattern deviation plot with 50% of points depressed below the 5% level or 25% of points depressed below the 1% level, with presence of any point within central 5° with sensitivity 0 dB, having both hemifields containing point(s) with sensitivity 15 dB within 5° of fixation