УДК 617.732-07: 617.7-007.681

Repeated Stratus OCT retinal nerve fiber layer thickness measurements

Ronit Nesher, MD[1, 2];
Michael D. Mimouni, MD[1];
Esther Epstein, MD[1];
Lilach Gorck[1];
Gary L. Trick, Ph.D.[3, 4]

[1]Department of Ophthalmology, Meir Medical Center, *Kfar Saba, Israel;*
[2]The Sackler Medical School, T*el-Aviv University, Israel*;
[3]Department of Ophthalmology, Henry Ford Hospital, *Detroit, Michigan;*
[4]Department of Anatomy and Cell Biology, Wayne State University School of Medicine, *Detroit, Michigan.*

Conflicts of Interest and Source of Funding: none declared.

Abstract

PURPOSE: Assessment of optic disc damage is an essential part of the ocular examination and differential diagnosis between the patient with ocular hypertension and pre-perimetric or perimetric glaucoma.

The Stratus optic coherent tomograph (Carl Zeiss Meditec, Inc, Dublin, Calif) is still one of the most used optic nerve imaging technology throughout the world. Therefore, the development of methodology that enhances the utility of optic disc measurements with the Stratus OCT remains a relevant and meaningful goal.

In an attempt to determine the optimal number of repeated measurements we investigated how the average of three sets of manually repeated measurements of retina nerve firer layer (RNFL) thickness would compare with a single set.

METHODS: A total of 73 individuals (136 eyes) aged 55.3±15.2 years with ocular hypertensive (OHT), pre-perimetric glaucoma or glaucoma were included in the final analysis. When the data was evaluated using a quadrant analysis we observed that 13.6% of the patients exhibited a clinically meaningful difference of 20% or more in the serial RNFL thickness measurements.

RESULTS: The difference ranged from 9.3 to 32.7 microns and in 10 of the 12 quadrants the averaged measurement exceeded the initial measurement. Most of the differences demonstrated in this study occurred in the horizontal meridian and are probably a result of instinctive saccadic eye movements. A difference in the vertical meridian (superior and/or inferior quadrants) which is the more relevant meridian for changes in glaucoma was seen in only 3 patients (4.1%).

CONCLUSIONS: One reliable RNFL measurement would be sufficient in most of these cases because in 95.9% of the cases the differences observed for the vertical meridian were less than 20%. Nevertheless, it is important to recognize that there can be more variability in the horizontal meridian and that in cases with visual loss encroaching on fixation serial measurements may be useful. At any rate, as with all ancillary tests, whenever a change is detected, it is wise to repeat the test to verify the results.

KEY WORDS: glaucoma, Stratus OCT, retina nerve firer layer.

Повторные измерения толщины слоя нервных волокон с помощью оптического когерентного томографа Stratus

Ронит Нешер, врач-офтальмолог[1, 2]; **Майкл Д. Мимуни**, врач-офтальмолог[1];
Эстер Эпштейн, врач-офтальмолог[1]; **Лилак Горк**[1]; **Гари Л. Трик**, к.м.н.[3, 4].

[1]Отделение офтальмологии, медицинский центр «Меир», *Кфар-Саба, Израиль;*
[2]Медицинская школа им. Саклера, Университет Тель-Авива, *Израиль;*
[3]Отделение офтальмологии, Больница Генри Форда, *Детройт, Мичиган*;
[4]Кафедра анатомии и биологии, медицинский факультет Университета Уэйна, *Детройт, Мичиган*.

Авторы не получали финансирование при проведении исследования и написании статьи.
Конфликт интересов: отсутствует.

Для контактов:
Ронит Нешер (Ronit Nesher), e-mail: nesher@inter.net.il

Резюме

ЦЕЛЬ. Оценка изменений в диске зрительного нерва является важной частью офтальмологического обследования и дифференциальной диагностики у пациентов с офтальмогипертензией и ранней и развитой стадиями глаукомы. Оптический когерентный томограф Stratus (Carl Zeiss Meditec, Inc, Dublin, Calif) до сих пор является одним из самых часто используемых приборов для визуализации зрительного нерва по всему миру. Поэтому разработка методологии, оптимизирующей оценку состояния диска зрительного нерва с помощью Stratus, остается важной и актуальной задачей. В попытке определить оптимальное количество последовательных измерений, мы сравнивали результаты одиночного измерения толщины слоя нервных волокон с усредненными результатами серии из трех последовательных измерений.

МЕТОДЫ. Всего в исследовании участвовало 73 пациента (136 глаз) в возрасте 55,3±15,2 года с офтальмогипертензией или диагностированной глаукомой. При анализе полученных данных по квадрантам поля зрения у 13,6% пациентов было обнаружено клинически значимое различие ≥20% в толщине слоя нервных волокон.

РЕЗУЛЬТАТЫ. Разница в измерениях составляла от 9,3 до 32,7 мкм, и в 10 из 12 квадрантов усредненный результат трех последовательных измерений превышал результат единичного измерения. В большинстве случав различие отмечалось в горизонтальном меридиане и, вероятно, являлось результатом естественных саккадных движений. Различие в результатах по более значимому для изменений поля зрения при глаукоме вертикальному меридиану (верхние и/или нижние квадранты) наблюдалось только у 3 (4,1%) пациентов.

ЗАКЛЮЧЕНИЕ. Поскольку в 95,9% случаев разница результатов по вертикальному меридиану не превышает 20%, можно сделать вывод, что в большинстве случаев достаточно одного достоверного измерения толщины слоя нервных волокон сетчатки. Тем не менее полезно помнить о большей вариабельности результатов по горизонтальному меридиану. Например, в случае со снижением зрения, затрудняющим фиксацию взгляда, может быть полезным проведение серии из нескольких исследований подряд. В любом случае при появлении изменений в результатах этого или других вспомогательных исследований наилучшей тактикой является повторение исследования для подтверждения результатов.

КЛЮЧЕВЫЕ СЛОВА: глаукома, оптический когерентный томограф Stratus, толщина слоя нервных волокон сетчатки.

Evaluating the optic disc is an essential part of the ocular examination in the glaucoma patient [1]. Moreover, the assessment of optic disc damage cannot be overemphasized as it is integral to the differential diagnosis between the patient with ocular hypertension and pre-perimetric or perimetric glaucoma [2].

While some clinicians advocate using optic disc photos together with optic nerve imaging for follow up of glaucoma patients, others feel that the latter may suffice [1, 3-4]. The most widely accepted optic nerve imaging technique is Spectral Domain Optical Coherence Tomography (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany) which provides an optical resolution of 7 micrometers axially and 14 micrometers laterally [5-6]. Alternative imaging techniques with resolution approaching that of the Spectralis are also available [7].

Given the limited resources available to many health care facilities, the cost of technological upgrades and the current global economic state, many ophthalmology clinics and practices are unable to afford the cost associated with upgrading optic nerve imaging technology [8-10]. Consequently, despite its lower optical axial resolution of 10 micrometers, the Stratus OCT (Carl Zeiss Meditec, Inc, Dublin, Calif) is still in use throughout the world [11]. For example, a PubMed search with the query for "Stratus and OCT and glaucoma" revealed 49 papers published in the last two years [12]. Therefore, the development of methodology that enhances the utility of optic disc measurements with the Stratus OCT remains a relevant and meaningful goal.

The variability and suboptimal alignment characteristics of Stratus OCT retinal nerve fiber layer (RNFL) measurements have been clearly described [13-17]. However, the optimal number of repeated measurements has not been determined. Several built-in scanning protocols have been demonstrated to effectively measure the RNFL thickness [18]. Currently, the "Fast RNFL thickness" protocol as programmed by the manufacturer is a single set comprised of three repeated measurements [11].

We investigated how the average of three sets of manually repeated measurements of RNFL thickness would compare with a single set.

Methods

All data for the study was collected and analyzed in accordance with the policies and procedures of the institutional review board of Meir Medical Center and the tenets set forth in the Declaration of Helsinki.

A prospective consecutive cohort design was used. All patients were examined in the glaucoma clinic of the Department of Ophthalmology of Meir Medical Center, a tertiary-care facility. All of the ocular hypertensive (OHT), pre-perimetric glaucoma or glaucoma patients that arrived between February 2005 and November 2006 were considered for inclusion. Only those with at least three scans with a signal strength above 6 were included.

All of the measurements were performed following dilation of pupils. The measurements were performed by a single examiner (R.N.). The "Fast RNFL thickness" protocol was applied for each measurement. In this

Table 1

Segmental Analysis of retinal nerve fiber layer thickness in both eyes

	Total	Scan 1	Scan 2-4	p*
Superior	OD	107.1 (27.3)	107.6 (26.2)	NS
	OS	112.5 (19.2)	112.5 (20.0)	NS
Temporal	OD	66.3 (13.5)	67.0 (13.6)	NS
	OS	67.9 (15.0)	67.9 (13.5)	NS
Inferior	OD	120.2 (24.6)	119.3 (24.4)	NS
	OS	117.5 (24.5)	117.6 (23.0)	NS
Nasal	OD	75.5 (19.5)	74.7 (17.4)	NS
	OS	72.8 (18.1)	72.9 (18.0)	NS

* — applying the paired t-test, p was not significant also when applying repeated measures ANOVA to compare each of the 4 scans individually.

Table 2

Patient Characteristics in both groups

	Total	Group with Variability ‹ 20% (Group A)	Group with Variability › 20% (Group B)	Significance
No. of Patients	73	63	10	
No. of Eyes	136	125	11	
Age+SD	55.3±15.2	54.7±15	58.7±17.8	*P=0.456
Gender (male; female)	36; 37	29; 34	3; 7	**P=0.19

* — applying the paired t-test; ** — applying the Fisher test.

protocol, each individual measurement consists of a set of three circle scans of a 3.4 mm diameter combined into one scan. For each patient an initial measurement was performed using this procedure. All patients then underwent a minimum of 3 repeated individual measurements (range 3 to 7) using the same procedure on the same day. Only patients with three or more reliable measurements (signal strength > 6) were included. Measurements flagged as "low confidence analysis" were excluded. In each eye three measurements with the best apparent overlap on serial analysis were evaluated. A comparison between the first individual measurement and the mean of three overlapping individual measurements was performed. A segmental analysis of each of the four quadrants was performed.

The Student t-test was used to compare the initial measurement to the repeated measurements. A repeated measures ANOVA was used to compare the four measurements.

Results

A total of 73 individuals and 136 eyes were included in the final analysis. There was an even distribution between males (n=36) and females (n=37) with an average age of 55.3 ± 15.2 years. The thickness measurements of the RNFL were analyzed separately for both eyes *(table 1)*. There was no statistically significant difference in the RNFL thickness between the first measurement and the mean of three repeated measurements in any quadrant of either eye.

For further comparison, a 20% difference in RNFL thickness between the initial measurement and the averaged measurement was arbitrarily chosen to represent a clinically meaningful difference and used as a cut-off value. Using this cut-off value the data for each quadrant from each individual patient was analyzed. Using this criteria a clinically meaningful difference was detected in one quadrant of one eye in 8 patients (i.e. 8 quadrants in all), in one quadrant

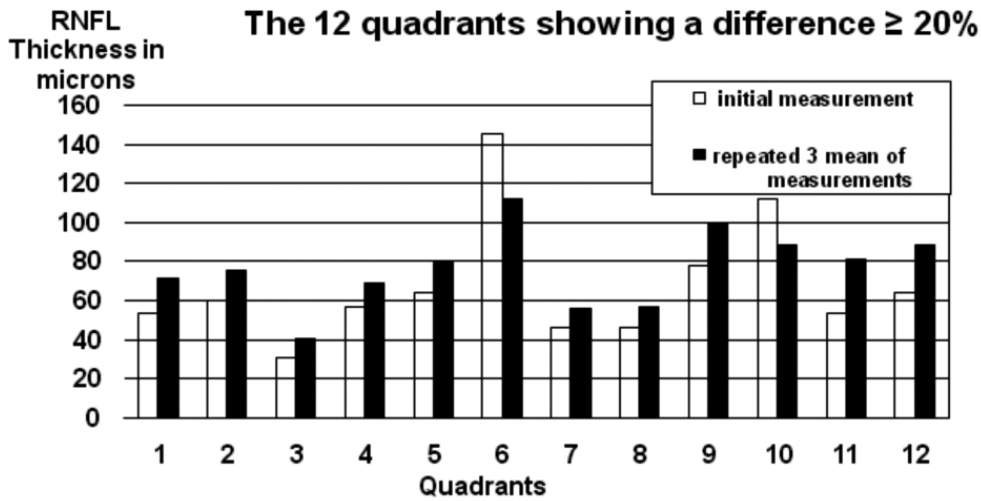

Figure 1: A comparison of the RNFL thickness values (in microns) determined by the initial measurement or the mean of 3 repeated measurements. The data shown come from the 12 quadrants in which the difference between the two measurement techniques resulted in a difference of 20% or more. Eight patients had such a difference in one quadrant in a single eye while there was one patient with such difference in both eyes. In addition, one patient exhibited a difference in two quadrants (nasal and temporal) in the same eye

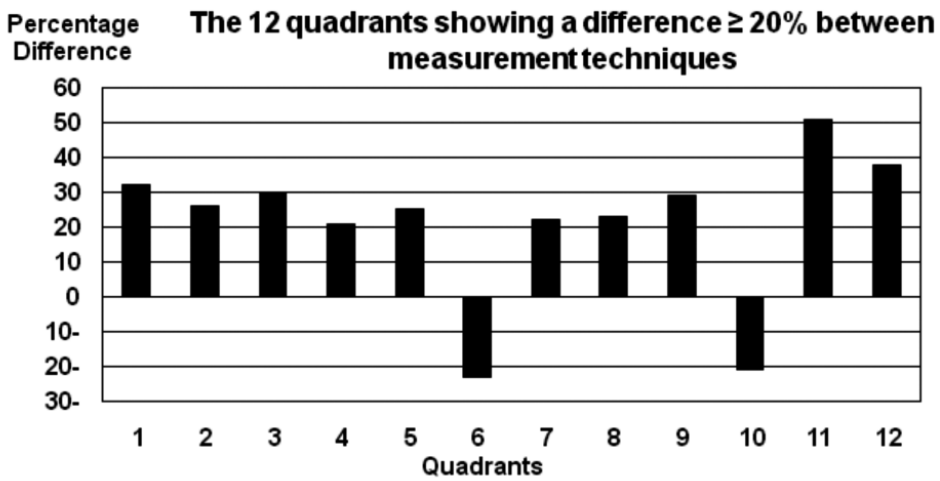

Figure 2: The percent difference in RNFL thickness comparing the average RNFL thickness from three measurements to the first measurement. The data shown come from the 12 quadrants in which the difference between the two measurement techniques resulted in a difference of 20% or more. Eight patients had such a difference in one quadrant in a single eye while there was one patient with such difference in both eyes. In addition, one patient exhibited a difference in two quadrants (nasal and temporal) in the same eye

in both eyes in one patient (i.e. 2 quadrants in all) and in two quadrants in one eye of one patient (i.e. 2 quadrants in all). Consequently, there was a total of 12 quadrants (8+2+2 = 12) in which the difference between the initial measurement and the averaged measurement was at least 20%. Therefore, clinically meaningful differences were observed in 13.6% of patients (10/73) or 8.1% of eyes (11/136).

Mean retinal nerve fiber layer (RNFL) thickness in microns (SD) in the four quadrants of the both eyes. This is the comparison of the initial Stratus OCT mesurment (”Scan 1”) with the mean of the following three repeated measurments (”Scan 2-4”).

The demographic characteristics of the group in which a clinically meaningful difference was detected in at least one quadrant are presented in *table 2*. This group did not differ in age or gender from the group of individuals who did not exhibit a clinically meaningful difference in any quadrant. *Figure 1* compares the RNFL thickness values determined from the initial measurement and determined from the averaged measurements for each of the quadrants in which a clinically meaningful difference was detected. The difference ranged from 9.3 to 32.7 microns and in 10 of the 12 quadrants the averaged measurement exceeded the initial measurement. In *figure 2*, these same data are

presented as the percentile difference between the initial and the averaged RNFL thickness values. In general the differences were between 21 and 30%, however, differences exceeding 30% were noted and in one case the difference exceeded 50%.

As illustrated in *figure 3*, in 8 of these 11 eyes the observed difference was in the horizontal meridian (i.e. either nasal or temporal). In one of these 8 eyes a difference was noted in both the nasal and the temporal quadrants. The other 3 patients showed a difference in either the superior or inferior meridian (i.e. vertical).

Discussion

Currently many RNFL thickness measurements are performed with the Spectral OCT providing both better resolution and repeatability between serial examinations [19]. The repeatability is a result of the Spectral OCT's software as the software's default configuration enables repeated measurements at the same location [6]. The Stratus OCT lacks an inherent feature to assure that serial measurements are consistently obtained from the same location. Whether this contributes to the finding that RNFL thickness measurement made with the Stratus OCT exhibits greater variance in glaucoma eyes than in normal is unclear [13, 20]. Despite this deficiency, the Stratus OCT can still provide clinically valuable information and continues to be used in many clinics.

In this study, we performed serial measurement of RNFL thickness on 136 eyes of 73 patients with OHT, pre-perimetric glaucoma or glaucoma. When the data were evaluated using a quadrant analysis we observed that 13.6% of the patients exhibited a difference of 20% or more in the serial RNFL thickness measurements. We also observed that this difference occurred most frequently in measurements made in the horizontal meridian. A similar finding of increased variability in the horizontal meridian was demonstrated in a smaller group of glaucoma patients by Schuman et al [13]. We believe this finding is likely to be the result of increased horizontal saccades, a finding that has been established by others [21, 22]. The effect of eye movements on the repeatability of RNFL thickness measurements has been acknowledged, and recently several solutions have been proposed [14, 19].

An intriguing additional finding of this study is that in 10 of the 12 quadrants in which a difference was demonstrated, the averaged RNFL thickness of the repeated measurements was greater than RNFL thickness obtained from the initial, single measurement. Assuming the accuracy of the initial measurements this finding would suggest that serial measurements with the Status OCT tend to over-estimate RNFL thickness, perhaps due to unstable fixation. We currently have no way to decide which of the two methods is more accurate. However, it should be noted that in longitudinal comparison choosing between the two

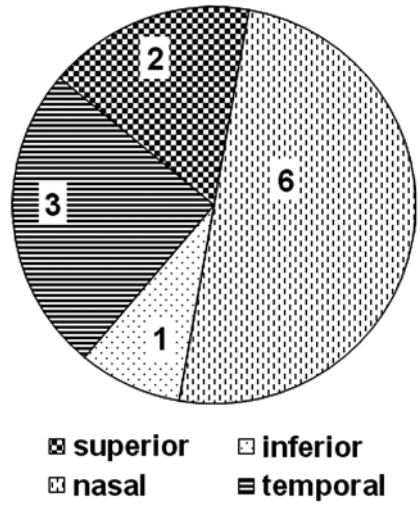

Figure 3: A representation of the frequency for which differences in RNFL thickness of at least 20% between the initial and the averaged measurements fell within each quadrant. The data shown come from the 12 quadrants in which the difference between the two measurement techniques resulted in a difference of 20% or more. Eight patients had such a difference in one quadrant in a single eye while there was one patient with such difference in both eyes. In addition, one patient exhibited a difference in two quadrants (nasal and temporal) in the same eye

options could lead to two very different interpretations. If indeed repeated measurements cause an overestimation of RNFL thickness, then it could cause the clinician to overlook progression of disease. On the other hand, if repeated measurements are more accurate than performing just one set, then obtaining only one set of measurements may result in an under-estimation of RNFL thickness resulting in an over-diagnosis of progression.

At any rate, this observation was seen in a small group of patients (13.6%), and mostly in the horizontal meridian which is less relevant for changes in glaucoma. A difference in the vertical meridian (superior and/or inferior quadrants) which is the more relevant meridian for changes in glaucoma was seen in only 3 patients (4.1%). Thus, a single set of RNFL measurement may be sufficient in most cases (95.9%).

This study has several limitations. First, we were unable to compare the Stratus measurements to those made with the Spectralis on the same patients. Given the higher resolution of the Spectralis this might have given us a better idea of which measurement technique was more accurate. Second, all measurements in each patient were performed on the same day. Thus, fatigue may have played a role in the frequency of eye movements and thus on the variability of the results.

In summary, repeated RNFL measurements with the Stratus OCT may show a difference in a small fraction (13.6%) of patients. Most of the differences

demonstrated in this study occurred in the horizontal meridian and are probably a result of instinctive saccadic eye movements. In patients known or suspected to have glaucoma, RNFL thickness in the superior or inferior quadrants is of greatest interest. Consequently, one reliable RNFL measurement would be sufficient in most of these cases because in 95.9% of the cases the differences observed for the vertical meridian were less than 20%. Nevertheless, it is important to recognize that there can be more variability in the horizontal meridian and that in cases with visual loss encroaching on fixation serial measurements may be useful. At any rate, as with all ancillary tests, whenever a change is detected, it is wise to repeat the test to verify the results.

References

1. Hitchings R.A., Wheeler C.A. The optic disc in glaucoma. IV: Optic disc evaluation in the ocular hypertensive patient. *Br J Ophthalmol* 1980; 64(4):232–239.
2. Cvenkel B., Kontestabile A.S. Correlation between nerve fibre layer thickness measured with spectral domain OCT and visual field in patients with different stages of glaucoma. *Graefes Arch Clin Exp Ophthalmol* 2011; 249(4):575–584.
3. Greaney M.J., Hoffman D.C., Garway-Heath D.F., Nakla M., Coleman A.L., Caprioli J. Comparison of optic nerve imaging methods to distinguish normal eyes from those with glaucoma. *Invest Ophthalmol Vis Sci* 2002; 43(1):140–145.
4. Mardin C.Y., Jünemann A.G. The diagnostic value of optic nerve imaging in early glaucoma. *Curr Opin Ophthalmol* 2001; 12(2):100–104.
5. Adhi M., Duker J.S. Optical coherence tomography-current and future applications. *Curr Opin Ophthalmol* 2013; 24(3): 213–221.
6. Heidelberg Engineering GmbH 2007. Spectralis hardware operating manual Version 001. Heidelberg, Germany. 2007; 22.
7. Medeiros F.A., Zangwill L.M., Bowd C., Weinreb R.N. Comparison of the GDx VCC scanning laser polarimeter, HRT II confocal scanning laser ophthalmoscope, and stratus OCT optical coherence tomograph for the detection of glaucoma. *Arch Ophthalmol* 2004; 122(6):827–837.
8. Shani S., Siebzehner M.I., Luxenburg O., Shemer J. Setting priorities for the adoption of health technologies on a national level – the Israeli experience. *Health Policy* 2000; 54(3): 169–185.
9. Woertman W.H., Van De Wetering G., Adang E.M. Cost-effectiveness on a local level: whether and when to adopt a new technology. Med Decis Making 2013 Aug 5.
10. Greenberg D., Peterburg Y., Vekstein D., Pliskin J.S. Decisions to adopt new technologies at the hospital level: insights from Israeli medical centers. *Int J Technol Assess Health Care* 2005; 21(2):219–227.
11. Carl Zeiss Meditec AG. Stratus OCT User Manual English. Jena, Germany. 2007;171.
12. Pubmed. http://www.pubmed.gov. Accessed on 16.09.2013.
13. Schuman J.S., Pedut-Kloizman T., Hertzmark E., et al. Reproducibility of nerve fiber layer thickness measurements using optical coherence tomography. *Ophthalmology* 1996; 103(11):1889–1898.
14. Zhu H., Crabb D.P., Schlottmann P.G., Wollstein G., Garway-Heath D.F. Aligning scan acquisition circles in optical coherence tomography images of the retinal nerve fibre layer. *IEEE Trans Med Imaging* 2011; 30(6):1228–1238.
15. Gabriele M.L., Ishikawa H., Wollstein G., et al. Optical coherence tomography scan circle location and mean retinal nerve fiber layer measurement variability. *Invest Ophthalmol Vis Sci* 2008; 49(6):2315–2321.
16. Vizzeri G., Bowd C., Medeiros F.A., Weinreb R.N., Zangwill L.M. Effect of improper scan alignment on retinal nerve fiber layer thickness measurements using stratus optical coherence tomograph. *J Glaucoma* 2008; 17(5):341–349.
17. Vizzeri G., Bowd C., Medeiros F.A., Weinreb R.N., Zangwill L.M. Effect of signal strength and improper alignment on the variability of stratus optical coherence tomography retinal nerve fiber layer thickness measurements. *Am J Ophthalmol* 2009; 148(2):249–255.
18. Carpineto P., Ciancaglini M., Aharrh-Gnama A., Cirone D., Mastropasqua L. Custom measurement of retinal nerve fiber layer thickness using STRATUS OCT in normal eyes. *Eur J Ophthalmol* 2005; 15(3):360–366.
19. Kim J.S., Ishikawa H., Gabriele M.L., et al. Retinal nerve fiber layer thickness measurement comparability between time domain optical coherence tomography (OCT) and spectral domain OCT. *Invest Ophthalmol Vis Sci* 2010; 51(2):896–902.
20. Blumenthal E.Z., Williams J.M., Weinreb R.N., Girkin C.A., Berry C.C., Zangwill L.M. Reproducibility of nerve fiber layer thickness measurements by use of optical coherence tomography. *Ophthalmology* 2000; 107(12):2278–2282.
21. Martinez-Conde S., Macknik S.L., Hubel D.H. The role of fixational eye movements in visual perception. *Nat Rev Neurosci* 2004; 5(3):229–240.
22. Heijl A., Patella V.M., Bengtsson B. Effective Perimetry – The field analyzer primer 4th edition. Dublin, CA, USA. 2012; 26.

Поступила 20.02.2014