

Parameters of ocular fundus on spectral-domain optical coherence tomography for glaucoma diagnosis

Yu-Lin Tao^{1,2}, Li-Ming Tao², Zheng-Xuan Jiang², He-Ting Liu², Kun Liang², Mo-Han Li², Xuan-Sheng Zhu², Yan-Lin Ren², Bing-Jie Cui^{2,3}

¹Department of Ophthalmology, the First People's Hospital of Jiujiang City, Jiujiang 332000, Jiangxi Province, China

²Department of Ophthalmology, the Second Affiliated Hospital of Anhui Medical University, Hefei 230000, Anhui Province, China

³Department of Ophthalmology, the Fuyang Affiliated Hospital of Anhui Medical University, Fuyang 236000, Anhui Province, China

Correspondence to: Li-Ming Tao. Department of Ophthalmology, the Second Affiliated Hospital of Anhui Medical University, Hefei 230000, Anhui Province, China. Lmtao9@163.com

Received: 2016-07-22 Accepted: 2017-02-06

Abstract

• In this review, we summarize the progression of several parameters assessed by spectral-domain optical coherence tomography (SD-OCT) in recent years for the detection of glaucoma. Monitoring the progression of defects in the retinal nerve fiber layer (RNFL) thickness is essential. Imaging and analysis of retinal ganglion cells (RGCs) and inner plexiform layer (IPL), respectively, have been of great importance. Optic nerve head (ONH) topography obtained from 3D SD-OCT images is another crucial step. Other important assessments involve locating the Bruch's membrane opening (BMO), estimating the optic disc size and rim area, and measuring the lamina cribrosa displacement. Still other parameters found in the past three years for glaucoma diagnosis comprise central retinal artery resistive index, optic disc perfusion in optical coherence tomography angiography (OCTA) study, peripapillary choroidal thickness, and choroidal area in SD-OCT. Recently, several more ocular fundus parameters have been found, and compared with the earlier parameters to judge the accuracy of diagnosis. While a few of these parameters have been widely used in clinical practice, a fair number are still in the experimental stage.

• **KEYWORDS:** glaucoma progression; retinal nerve fiber layer; ganglion cells; macular thickness; optic nerve head; lamina cribrosa; optical coherence tomography

DOI:10.18240/ijo.2017.06.23

Tao YL, Tao LM, Jiang ZX, Liu HT, Liang K, Li MH, Zhu XS, Ren YL, Cui BJ. Parameters of ocular fundus on spectral-domain optical coherence tomography for glaucoma diagnosis. *Int J Ophthalmol* 2017;10(6):982-991

INTRODUCTION

Glaucoma is a group of optic neuropathies that is characterized by progressive degeneration of retinal ganglion cells (RGCs), slow atrophy and thinning of the retinal nerve fiber layer (RNFL), irreversible morphological changes to the optic nerve head (ONH) that contains the narrowing of disc rim area (RA), and expansion of the optic cup^[1-2]. Loss and shrinkage of the visual field is another characteristic of glaucoma caused by the degeneration of these nerves, which can eventually lead to blindness and a decline in the quality of life without early and adequate treatment^[1]. There are more than 70 million people threatened by glaucoma worldwide with approximately 10% being blind in both eyes^[3], making it one of the predominant reasons of blindness in the world. Glaucoma, especially primary open angle glaucoma (POAG), usually involves both eyes, occurs insidiously, and progresses slowly, and is often only detected at an advanced stage where visual function has already been seriously compromised; this is because patients with POAG rarely show early-stage symptoms. Mid- or late-stage glaucoma has poor prognosis despite related treatment, because these patients have a relatively shrunk visual field and depressed atrophy of the optic disc.

Several studies have found that visual field loss in many patients is only detected when a substantial number of RGCs have been lost and a vast amount of RNFL has thinned^[4-8]. Besides, *in vivo* research in experimental glaucoma (EG) involving a nonhuman primate (NHP) model of EG has also shown that RNFL impedance and RGC function exhibit progressive loss from baseline before any loss of retinal nerve fiber layer thickness (RNFLT) or orbital optic nerve axons occurs^[9], prior to the loss of visual field. With regard to *in vivo* measurement, it might serve as potential biomarkers of early-stage glaucomatous damage preceding axon loss and RGC death^[9]. Therefore, it is essential to measure and estimate the

parameters of ocular fundus from spectral-domain optical coherence tomography (SD-OCT) and apply these findings to the monitoring and detection of progression of primary glaucoma.

With the rapid development of resolution and scanning speed on OCT imaging and its advantages of non-contact, good repeatability, and quick imaging, OCT has been widely used in the field of ophthalmology, ranging from time-domain OCT (TD-OCT) to SD-OCT^[10-14]. Different parameters in structural measurements for early glaucoma diagnosis obtained with SD-OCT have emerged in several research articles and been published to evaluate their accuracy^[15-18]. This paper critically reviews and evaluates relevant research of these parameters obtained from SD-OCT for the diagnosis of primary glaucoma. We also review issues related to what types of SD-OCT can provide optimal results in the potential ability for diagnosing glaucoma, how to evaluate the parameters in glaucoma diagnosis, and how these results from SD-OCT could be applied to clinical practice.

TYPES OF SPECTRAL-DOMAIN OPTICAL COHERENCE TOMOGRAPHY FOR GLAUCOMA DIAGNOSIS

Although currently, some other inspection equipment that contains scanning laser polarimetry (SLP) and confocal scanning laser ophthalmoscopy (CSLO) has been used to detect RNFL thickness clinically^[10,19], the most widely used tool for glaucoma diagnosis in clinical practice is SD-OCT, which can obtain high-resolution images of RNFL, optic disc parameters, and macular ganglion cell complex (mGCC) thickness data^[12-13,20-24]. Since its introduction in 1991 by Huang *et al*^[25], OCT has rapidly emerged and become widespread in its use as a useful tool in ophthalmology worldwide.

In the past two decades, TD-OCT was clinically applied to obtain images of ocular fundus parameters. TD-OCT can also provide the RNFL, retinal ganglion cell layer thickness (RGCLT), and ONH parameters to differentiate glaucomatous eyes from people alive and to detect changes over time^[14,26-29]. However, owing to its limited suboptimal axial resolution (10 μm) and scan speed (100-400 A-scan/s), acquisition times with TD-OCT are much longer than SD-OCT. Therefore, its popularity in hospitals to detect glaucoma progression has declined. Nowadays, most commercially available instruments provide a quicker scan speed (26 000-53 000 A-scan/s) and a wider axial resolution of about 5 μm ; hence, aptly named SD-OCT. We can acquire much clearer and more comprehensible images from SD-OCT that leads to much improved reproducibility and accuracy to differentiate glaucomatous eyes from healthy eyes^[18,30].

Our online search of published articles showed that seven types of SD-OCT have been widely popularized to diagnose glaucoma clinically; these include RTVue SD-OCT, Cirrus HD-OCT, Spectralis OCT, Topcon 3D OCT, RS-3000 OCT, swept-

source OCT (SS-OCT), and Envisu C-Class SDOIS, with the first four types being more popular than the others^[21,24,29,31-43]. Some of these are still in the experimental stage and not widely used in clinical, *e.g.* Envisu C-Class SDOIS. Each type offers a special function and has its own advantages: RTVue SD-OCT is useful for RNFL change analysis and ganglion cell complex (GCC) progression analysis; Cirrus HD-OCT, for guided progression analysis (GPA) of RNFL and ONH measurements; Spectralis OCT, for the RNFL change report with fovea-to-disc alignment (FoDi); Topcon 3D OCT, for RNFL trend analysis; RS-3000 OCT, for the detection of changes in RNFL and complex thicknesses about structures comprising the nerve fiber layer (NFL), ganglion cell layer (GCL), and inner plexiform layer (IPL) and for its multifunctional follow-up; and swept-source OCT, for the detection of axonal damage on the lamina cribrosa (LC), *in vivo* glaucoma, and evaluation of its ability to qualify lamina cribrosa thickness (LCT)^[35]. The function and current reports of Envisu C-Class SDOIS are not available.

Several studies have shown and compared some types of SD-OCT with respect to diagnostic accuracy in glaucoma. Akashi *et al*^[32] who studied glaucomatous eyes, normal eyes with high myopia, and normal eyes by using RTVue, Cirrus, and 3D OCT, concluded that the average circumpapillary retinal nerve fiber layer (cpRNFL) and GCC thicknesses displayed similar efficacies in the diagnosis of glaucoma with high myopia. RTVue OCT exhibited the best diagnostic potential when the position was spotted in nasal cpRNFL, whereas when spotted in the macular retinal nerve fiber layer (mRNFL), 3D OCT showed better diagnostic potential than Cirrus OCT. Both cpRNFL and GCC measurements obtained from each instrument showed good performance in detecting highly myopic glaucoma. The same research team published another dissertation with the same instruments and showed that the abilities for the parameters of GCL/IPL and mRNFL gained from Cirrus and 3D OCT was different^[33]. Other groups have also reviewed the usage of SD-OCT to detect glaucoma progression and analyzed reproducibility and accuracy of different types of SD-OCT performed on different parameters of ocular fundus in glaucoma patients^[44]. Thus, it is critical to maintain tight surveillance on the progression of early-stage glaucoma and correctly diagnose with SD-OCT in order to prevent or delay vision loss in these patients.

DETECTION OF RETINAL NERVE FIBER LAYER THICKNESS IN GLAUCOMA DIAGNOSIS

With the enhancement of OCT resolution and SD-OCT imaging, the hierarchy of retinal structures and tissues can be meticulously visualized, including any pathology. The structures can be distinguished clearly including NFL, GCL, IPL, and mGCC. After calculating the thickness of each layer, the difference between glaucomatous and healthy eyes can

be evaluated and the above four parameters were seen to be significantly lower in glaucomatous eyes than healthy eyes^[16,21,24,26,33,38,45-49]. Despite the thinning of the above-mentioned four parameters and the change of ONH seen on SD-OCT, RNFL has wider applications in the detection of glaucomatous degeneration than the other parameters. Actually, the first and most common parameter analyzed by OCT is average cpRNFLT to follow the progression of glaucoma^[50]. Detection of RNFL thickness has been accurate with respect to each quadrant and each hour circled around the peripapillary in recent years. Before obtaining the optimal diagnostic parameters using which the thickness differentiation between glaucoma and healthy eyes can be compared, they calculated the specificity and sensitivity for glaucoma diagnostic parameters and analyzed and compared their area under the receiver operating characteristic curves (AUC)^[51-55]. Many research studies estimate that repeatability changes with different parameters of quadrants and hours. Vazirani *et al*^[51] measured 40 normal and 40 glaucomatous eyes (including 14 cases with advanced glaucoma) and reported that the average RNFLT shows the best reproducibility for longitudinal follow-up in all quadrants and the parameter of temporal quadrant yields minimum repeatability. Mansoori *et al*^[52] showed that inferior RNFL is the thickest quadrants after studying 95 normal eyes and 83 glaucoma eyes in patients aged >40y. All the parameters in normal and glaucomatous eyes showed statistically significant differences except for the temporal quadrant and at the 10 o'clock position. Especially for the temporal side, the test results showed the same results in the two groups, reflecting that the temporal side exhibits a low specificity in identifying patients with early glaucoma in the healthy population. They concluded that superior quadrant and mean RNFLT parameters of cpRNFLT have the maximum diagnostic potential for primary glaucoma. Nouri-Mahdavi *et al*^[56] and Leite *et al*^[42] obtained the same results by using the OCT2000 and Spectralis OCT, respectively, that proved superior and average RNFLT have the largest AROC and are regarded as the best parameters to distinguish between normal and glaucomatous eyes. Park *et al*^[55] compared the diagnostic ability between Stratus OCT and Cirrus HD-OCT and concluded that the Cirrus HD-OCT showed stronger diagnostic capability than Stratus OCT, which is related to the result of detection technology improvement, a higher resolution of Cirrus HD-OCT, and more accurate database standards. Previous studies confirmed the superior quadrant^[28,52], inferior quadrant^[28,55], and average RNFLT^[51-52,55] to be the most valuable parameters in differentiating between normal and early glaucomatous eyes. Through these measurements, we can explain the degeneration of visual field associated with glaucoma that usually first occurs in the superior area, which is in accordance with the initial damage that occurred in the

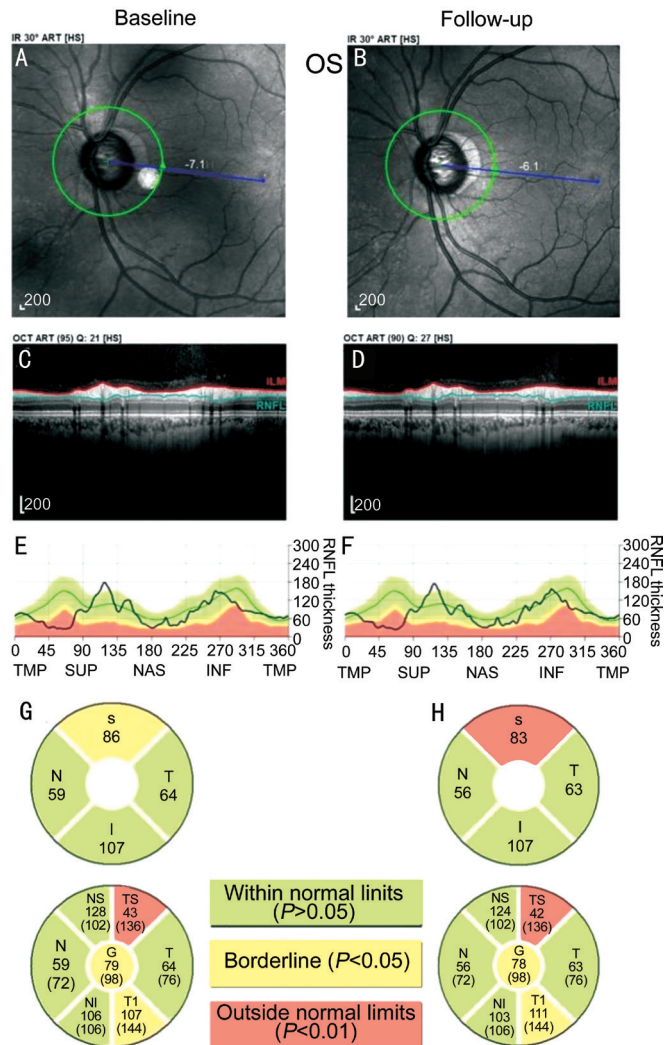


Figure 1 RNFL measurement and analysis printed out of the Spectralis OCT in the same patient with glaucoma We detected it on December 12, 2014 and April 17, 2015, respectively. The images show the progression and degeneration in ONH (A, B), cpRNFLT images (C, D), thickness graph (E, F), and changes of every quadrant of RNFL (G, H). In the two spots of detection period, apparent advancements of RNFL can be seen in the section of superior and global parameters. Superior RNFLT has exceeded normal limits ($P<0.01$) and is temporal-inferior to borderline ($P<0.05$), while the other quadrants are still within normal limits ($P>0.05$). Given a longer follow-up without any intervention in this patient, the progression would be deeper and more severe, thereby requiring more thorough inspection and management.

inferior quadrant of cpRNFLT (Figure 1). Because of different damage scope of visual field on the glaucomatous involved into studies, the diagnostic capabilities are different among different quadrants. For example, Mansoori *et al*^[52] included more patients with visual field damage and more degeneration in the superior RNFL than the inferior. Visual function worsens with glaucoma progression. Diagnostic capabilities of most OCT on measuring RNFLT parameters have improved (although there was no significant increase), as there is more RNFL damage in the early stage of glaucoma than in those

who have not yet progressed to the period of visual field defects.

Several scholars^[57] have conducted Meta-analysis about 17 parameters of cpRNFL (including the location about the thickness of average, superior, inferior, nasal, and temporal quadrants of RNFL, and 12 total hour from 1 to 12). The subjects involved in this study were included by a random-effects model, and the diagnostic performance was evaluated with the area under the AUC. They also considered a number of important factors related to the consequence in the Meta-regression analysis: 1) severity of glaucoma (divided into five stages); 2) types of glaucoma (four types); and 3) ethnicity (four categories). The result obtained was in accordance with the diagnostic capability of all parameters followed in descending order as follows: average RNFLT>inferior>superior>7 o'clock>6 o'clock>11 o'clock>12 o'clock>1 o'clock>5 o'clock>nasal>temporal>2 o'clock>10 o'clock>8 o'clock>9 o'clock>4 o'clock>3 o'clock. After excluding the influence of the factors mentioned above, the average RNFLT showed the highest diagnostic accuracy. The diagnostic accuracy is significantly lower in Asian populations than in the other two categories. Only in this way, we can demonstrate which parameter has the best diagnostic potential in differentiating glaucomatous from normal eyes.

DETECTION OF RETINAL GANGLION CELL COMPLEX LAYER THICKNESS IN GLAUCOMA DIAGNOSIS

Composition and Fundamental Functions of Ganglion Cell Complex NFL is mainly composed of ganglion cell axons, efferent fibers, Müller cells, glial cells, and retinal blood vessels. GCL is mainly composed of the cell bodies of ganglion cells, Müller cells, glial cells, and the branch of retinal vessels. IPL is the main connection between the first and the second neurons of the retinal neurons in the brain, comprising the inner nuclear layer (INL) and enormous projections of ganglion cells. IPL is the synaptic site of bipolar cells, amacrine cells, and ganglion cells. These three structures together constitute the GCC^[58]. Human retina contains approximately 1.5 million RGCs, which is not limited to only one layer of the 10 retinal layer structures^[11]. Although NFL and IPL are widely distributed on the inside of the retina, GCC has the largest thickness in the macula except for parts of the area around the optic disc, which plays an important role in retinal photoreceptors and the conduction of visual signaling, as the densest area of the RGC is distributed in the macular area and shows a multi-layered structure^[11,49]. RNFL measurement is susceptible to retinal vascular, peripapillary atrophy arc and other physiological factors, as blood vessels are rich around the optic disc. Measurement results obtained in the macular area, which is the physiological a vascular zone, have the least interference from external factors. Therefore, GCC thickness measurement to identify and differentiate

healthy from primary glaucoma patients has a comparative advantage when compared to the detection of RNFL.

Role and Value in Detecting Ganglion Cell Complex Thickness for Primary Glaucoma Diagnosis Studies have confirmed the emergence of RGC apoptosis in GCL in glaucoma patients, and with the progression of the disease, the number of apoptosis of RGCs increased and the thickness of RGC decreased. SD-OCT can clearly display the internal structure and can calculate the thickness variation accurately, thus playing an important role in the diagnosis of glaucoma^[4,8,31,45,49,53,59-62]. Sung *et al*^[63] examined 98 patients with advanced glaucoma (mean deviation of visual field, -14.3 ± 5.5 dB) with SD-OCT, and followed-up for about 2.2y. Finally, they confirmed significant changes that occurred in the average thickness of the macula (about the scale of 6×6 -mm² covered with 128 scan lines). On the other hand, such significant changes in average cpRNFLT could not be found between advanced glaucoma and the non-progression group. However, their next study included 162 cases involving early and mid-term stages of glaucoma (defined MD of visual field of the two groups, -4.30 and -9.84 dB respectively), and the same follow-up period. Eventually, they found significant changes that appeared in average cpRNFLT and macular thickness (MT) between the two groups^[64]. These results indicate the potential ability of MT detection and the limitation of RNFLT measurement in monitoring the progression of advanced glaucoma. It is worth noticing that optic nerve damage in glaucoma may not involve the peripheral retina. In addition, it has been confirmed that measurement of macular nerve fibers, ganglion cells, and the thickness of the IPL can be applied in the detection of glaucoma progression (Figures 2 and 3)^[65].

Recent studies have confirmed that the loss of ganglion cells mainly contribute to decrease in MT, especially due to the thinning of the GCC and INL^[58]. On the basis of this conclusion, Firat *et al*^[53] selected 52 healthy subjects, 56 with normal tension glaucoma (NTG), and 61 POAG patients with SD-OCT to detect. After analyzing and comparing MT, GCC, and RNFL, as well as the AUCs corresponding to these parameters, they found that GCC and RNFL have similar performance and a high degree of consistency with respect to glaucoma detection ($P < 0.05$). Superior RNFLT is the single independent variable in the differentiation between POAG and NTG with respect to all parameters [odds ratio (OR)=0.942, $P=0.004$, 95%CI=0.905-0.981]. Yang *et al*^[61] detected the mGCIPL, mGCC, and cpRNFL thickness of 106 glaucomatous and 41 normal eyes with SS-OCT and SD-OCT, including the parameters of AUCs, and concluded that average thickness of macular ganglion cell inner plexiform layer (mGCIPL) and mGCC detected by SS-OCT are all smaller than the results of SD-OCT regardless of the presence or absence of glaucoma. The average diagnostic accuracy of all quadrants of macular

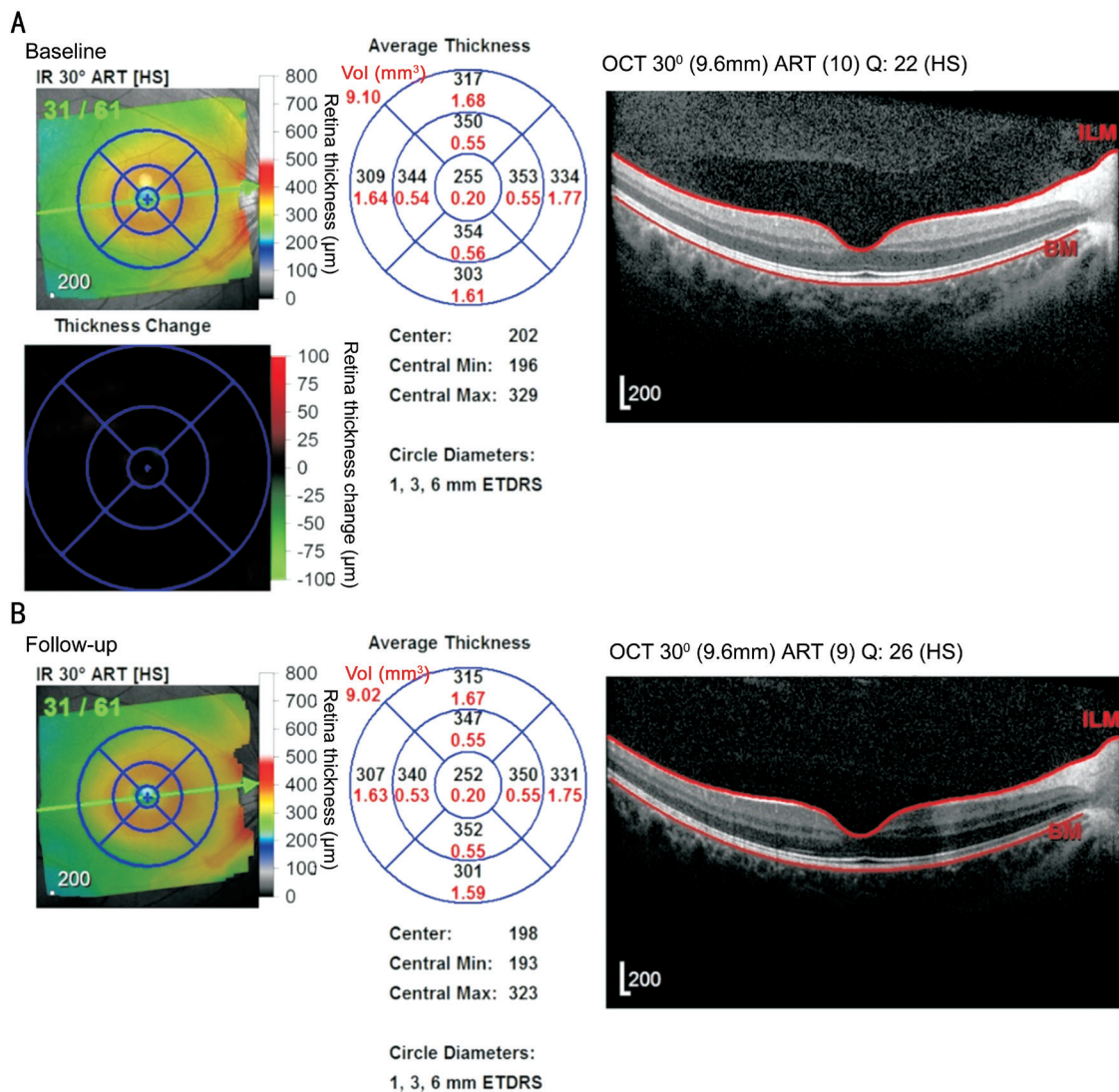


Figure 2 Thickness image and gray scale map of retina and macular layer obtained from Spectralis OCT in a patient with glaucoma. Thickness image is marked in black and gray, while the scale map is marked with red. Baseline was obtained on December 12, 2014 (A) and after 4mo of follow up was obtained on April 17, 2015 (B). The macular area is divided into nine sectors including the global part in the center and average volume marked with red in the top left hand corner of the circle. Over time, the thickness of the retina and macular layer decreased in the right eye of the patient.

ganglion cell inner plexiform layer thickness (mGCIPLT) in SS-OCT and SD-OCT were extraordinarily similar. Statistically significant differences could not be seen in three parameters of AUCs regarding average cpRNFLT, mGCC, and mGCIPL that were obtained with the two types of OCT. Similar diagnostic capabilities were found between RNFL and GCC in the early, mid, and terminal stages of glaucoma in Kim *et al*'s^[66] study. Another study by Cho *et al*'^[67] about the average sensitivity of vision, GCC, and RNFLT show similar consistent results in glaucoma diagnostics.

From the above-mentioned findings mGCIPL and mGCC can be proven to have high potential in the diagnosis of early primary glaucoma, and with great consistency with the results of cpRNFLT; all of these can be used as significant and unprecedented parameters in monitoring the changes of glaucomatous eyes in the long-term clinical follow-up.

OPTIC NERVE HEAD CHANGES IN THE PROGRESSION OF GLAUCOMA

General Change in Optic Disc Structure Morphological structural changes of the optic disc contribute to another important feature during the progression of primary glaucoma, which can be seen in the ocular fundus as an expanded visual cup, narrowed disc-rim, increased cup-disc ratio (CD), *etc.* Lee *et al*'^[68] detected optic disc with Cirrus HD-OCT before concluding that significant consistency existed between RA and RNFLT either in normal population or in glaucoma group who has less figure significantly. Suh *et al*'^[54] who studied 78 patients with early primary glaucoma and 80 individuals with healthy eyes by using the same kind of OCT showed that the results of AUCs of RA were greater than the AUCs of the nasal quadrant on RNFLT and in the 1-5 o'clock position. No significant difference was found in the other regions of

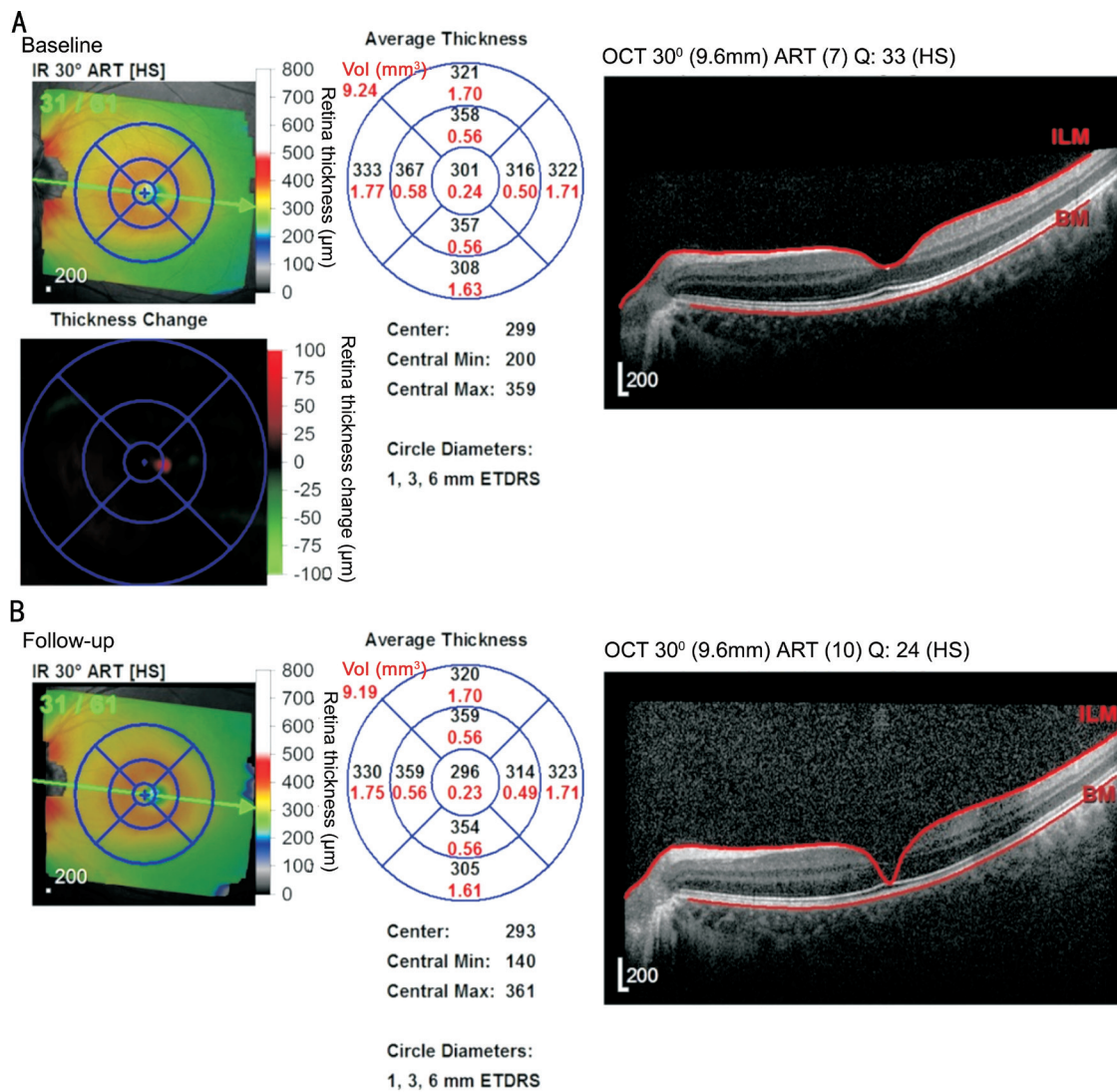


Figure 3 Over time, the thickness of the retina and macular layer decreased in the left eye of the patient.

cpRNFL. Rate ratio (RR) measurements (integrated calculation of the RA and RNFLT) perform better than RA and the 7+11 o'clock (regions that contain 7 and 11 o'clock) of RNFLT in the level of AUCs (RA: 0.931; RNFLT: 0.933; RR: 0.968). Berthold *et al*^[17] showed that there was a significant correlation ($P<0.05$) between MD and RNFL ($r=0.603$), as well as RNFL of the inferior quadrant ($r=0.620$), RA ($r=0.552$), and average CD ratio ($r=-0.551$). The best correlation for the ONH analysis was found between MD and vertical CD ratio ($r=-0.568$).

Therefore, RA, CD, and other ONH structures detected and analyzed on SD-OCT have an important role in the detection of glaucoma progression and have a synergistic effect with RNFLT that can also reflect transition in early glaucoma well.

Changes of Internal Morphology of the Optic Nerve Head

With the continuous improvement of scanning resolution and depth of OCT, its domain applied to glaucoma monitoring has penetrated to the detection and evaluation of LC^[35,69-71]. Omodaka *et al*^[35] scanned the area measuring 3×3-mm deep within the ONH, and ultimately, constructed a 3D model corresponding to this region of the LC structure and calculated

out the average lamina cribrosa thickness (avgLCT). They found a high pertinence between avgLCT and cpRNFLT with the correlation coefficient of both as 0.64 ($P<0.01$). The former coefficient of variation was 5.0%. There were significant differences in the avgLCT among the normal, preperimetric glaucoma (PPG), and NTG groups, which indicate that LCT obtained with SS-OCT could be refined as a new parameter for glaucoma diagnosis and follow-up. With images from SD-OCT, Shoji *et al*^[69] identified the inner surface of the Bruch's membrane opening (BMO) and measured the horizontal and vertical intersectional angles between the BMO line and the edge of LC, which approximately matched with the best-fitting line. The parameter of the vertical-inclined angle to the internal LC edge was associated with glaucoma and corresponded to its pathological changes. Changes in these parameters are of great significance in the monitoring of myopia, glaucoma, and LC morphological characteristics. Kim *et al*^[70] reached a similar conclusion with their study. With the LCT measured by SD-OCT, Sawada *et al*^[71] found that the LC of POAG moved backward when compared to healthy eyes.

These research studies have proved that LC as a portion of the ONH can be used to monitor and identify early glaucomatous eyes from normal eyes, because the changes in thickness and depth of LC attributable to the glaucomatous pathology were prominent and conspicuous. We can learn more about the variation of retinal and ONH or other structures in glaucoma by using SD-OCT to detect each layer of the retina and evaluate the relationship between all parameters and glaucoma.

OTHER POTENTIAL CHANGEABLE PARAMETERS

The Change of Choroidal Thickness and Choroidal Area

With the exception of RNFL, GCC, and ONH, peripapillary thickness and choroid volume can also be applied to distinguish glaucoma and ocular hypertension diseases from healthy eyes, by SD-OCT^[72]. Several studies have shown its change in the progression of glaucoma. Lamparter *et al*^[72] studied 213 eyes with open angle glaucoma (OAG), 73 eyes with ocular hypertension, and 152 healthy control eyes. This prospective data was collected and calculated by a linear mixed model fitted with provision for age and disease. The peripapillary choroidal thickness in glaucomatous eyes was the thinnest, whereas it was the thickest in eyes with ocular hypertension. Furthermore, the thickness parameters are different among every sector of peripapillary choroid, thickest in the superior sector and thinnest in the inferior sector. Most importantly, the temporal-inferior sector is thinnest in the choroidal area, which is one of the regions where glaucomatous damage begins. Chebil *et al*^[73] described macular choroidal thickness (MCT) in POAG patients with high myopia and confirmed that foveal choroidal thickness (FCT) reduced significantly in these patients. Choroidal thinning can be a useful parameter for the diagnosis and follow-up of highly myopic patients with glaucoma.

Nowadays, the high resolution of choroidal structures can be acquired by long-wavelength SS-OCT for its higher acquisition speed and deeper tissue penetration and will become clearer in the near future^[34]. This study analyzed the visualization of the choroidal and scleral interface and showed that choroidal thickness and area may have better clinical utility in chorioretinal diseases including glaucoma. Thus, systematic studies are important to excavate the relationship between choroidal thickness and glaucoma.

Optic Disc Perfusion in Glaucoma As a consequence of increased intraocular pressure, the optic nerve becomes compressed, which can lead to reduction of optic disc perfusion and blood supply. Based on this theory, we can detect the bloodstream circled ONH and resistive index of the central retinal artery through OCTA^[74-77]. The split-spectrum amplitude-decorrelation angiography (SSADA) algorithm was used to compute the 3D optic disc angiography. Jia *et al*^[76] found that the disc flow index reduced in the glaucoma group and was highly correlated with VF pattern standard

deviation and even significant after adjusting for age, CD area ratio, NFL, and RA. This result also suggests that disc blood flow index may contribute to the diagnosis of OAG. Liu *et al*^[77] reported that peripapillary retinal perfusion as well as peripapillary flow index and peripapillary vessel density can be visualized in glaucomatous eyes. They all have high repeatability and reproducibility with OCTA in glaucoma evaluation.

Optic disc perfusion measured by OCTA is important for the monitoring and evaluation of glaucoma and its progression. Quantitative OCT angiography is of great utility to determine the value in future studies in glaucoma evaluation. With the improvement of glaucoma, visual function decreased severely, especially in the advanced period. From the discussion, the progression of OAG could be monitored by OCTA because of the close correlation between the flow index/vessel density and MD, RNFL, and GCC thickness. In a subsequent study, we can take optimize this indication for glaucoma diagnosis.

CONCLUSION AND OUTLOOK

Developed by Huang *et al*^[25] in the 1990s as a new diagnostic tool, OCT has thus far been extensively used in the clinical diagnosis of related diseases, especially for primary glaucoma. Use of the Fourier technique results in enhanced resolution, scanning speed, and depth of OCT, and come out the Fourier-domain that is SD-OCT, which can discover the reduction of RNFLT, mGCC, ONH parameters, and LCT before excessive damage to the visual field. This allows us to correctly and accurately diagnose glaucoma in the early stages, and offer appropriate treatment to postpone or prevent further disease progression. Improvements in OCT-based diagnostics have been rapid, with the emergence of more and more parameters for more rapid detection of optic neuropathies. Although abundance of optic nerve related parameters are available to manage the progression of glaucoma, visual functional damage still occurs in very few cases of glaucoma-related nerve head disease when irreversible atrophic damage occurs in the optic nerve. There are still plenty of challenges in finding better and improved high-sensitivity parameters that can aid in the detection of neural losses that contribute to early primary glaucoma diagnosis. Therefore, glaucomatous patients would benefit from earlier diagnosis and better therapy with more accurate ability of detection with SD-OCT screening.

ACKNOWLEDGEMENTS

Foundations: Supported by the National Natural Science Foundation of China (No.81300755); the Key Project of the Natural Science Foundation of the Higher Educational Bureau of Anhui Province (No.KJ2013A147).

Conflicts of Interest: Tao YL, None; Tao LM, None; Jiang ZX, None; Liu HT, None; Liang K, None; Li MH, None; Zhu XS, None; Ren YL, None; Cui BJ, None.

REFERENCES

- 1 Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. *JAMA* 2014;311(18):1901-1911.
- 2 Weinreb RN, Khaw PT. Primary open-angle glaucoma. *Lancet* 2004;363(9422):1711-1720.
- 3 Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol* 2006;90(3):262-267.
- 4 Medeiros FA, Lisboa R, Weinreb RN, Liebmann JM, Girkin C, Zangwill LM. Retinal ganglion cell count estimates associated with early development of visual field defects in glaucoma. *Ophthalmology* 2013;120(4):736-744.
- 5 Kuang TM, Zhang C, Zangwill LM, Weinreb RN, Medeiros FA. Estimating lead time gained by optical coherence tomography in detecting glaucoma before development of visual field defects. *Ophthalmology* 2015;122(10):2002-2009.
- 6 Seong M, Sung KR, Choi EH, Kang SY, Cho JW, Um TW, Kim YJ, Park SB, Hong HE, Kook MS. Macular and peripapillary retinal nerve fiber layer measurements by spectral domain optical coherence tomography in normal-tension glaucoma. *Invest Ophthalmol Vis Sci* 2010;51(3):1446-1452.
- 7 Fang Y, Pan YZ, Li M, Qiao RH, Cai Y. Diagnostic capability of Fourier-Domain optical coherence tomography in early primary open angle glaucoma. *Chin Med J (Engl)* 2010;123(15):2045-2050.
- 8 Le PV, Tan O, Chopra V, Ragab O, Varma R, Huang D. Regional correlation among ganglion cell complex, nerve fiber layer, and visual field loss in glaucoma. *Invest Ophthalmol Vis Sci* 2013;54(6):4287-4295.
- 9 Fortune B, Cull G, Reynaud J, Wang L, Burgoyne CF. Relating retinal ganglion cell function and retinal nerve fiber layer (RNFL) retardance to progressive loss of RNFL thickness and optic nerve axons in experimental glaucoma. *Invest Ophthalmol Vis Sci* 2015;56(6):3936-3944.
- 10 Le PV, Zhang X, Francis BA, Varma R, Greenfield DS, Schuman JS, Loewen N, Huang D; Advanced Imaging for Glaucoma Study Group. Advanced imaging for glaucoma study: design, baseline characteristics, and inter-site comparison. *Am J Ophthalmol* 2015;159(2):393-403.
- 11 Balendra SI, Normando EM, Bloom PA, Cordeiro MF. Advances in retinal ganglion cell imaging. *Eye (Lond)* 2015;29(10):1260-1269.
- 12 Kotowski J, Wollstein G, Ishikawa H, Schuman JS. Imaging of the optic nerve and retinal nerve fiber layer: an essential part of glaucoma diagnosis and monitoring. *Surv Ophthalmol* 2014;59(4):458-467.
- 13 Vizzeri G, Kjaergaard SM, Rao HL, Zangwill LM. Role of imaging in glaucoma diagnosis and follow-up. *Indian J Ophthalmol* 2011;59 Suppl:S59-S68.
- 14 Leung CK, Chiu V, Weinreb RN, Liu S, Ye C, Yu M, Cheung CY, Lai G, Lam DS. Evaluation of retinal nerve fiber layer progression in glaucoma: a comparison between spectral-domain and time-domain optical coherence tomography. *Ophthalmology* 2011;118(8):1558-1562.
- 15 Leung CK, Cheung CY, Weinreb RN, Qiu K, Liu S, Li H, Xu G, Fan N, Pang CP, Tse KK, Lam DS. Evaluation of retinal nerve fiber layer progression in glaucoma: a study on optical coherence tomography guided progression analysis. *Invest Ophthalmol Vis Sci* 2010;51(1):217-222.
- 16 Moreno PA, Konno B, Lima VC, Castro DP, Castro LC, Leite MT, Pacheco MA, Lee JM, Prata TS. Spectral-domain optical coherence tomography for early glaucoma assessment: analysis of macular ganglion cell complex versus peripapillary retinal nerve fiber layer. *Can J Ophthalmol* 2011;46(6):543-547.
- 17 Berthold AJ, Hoang AM, Just A, Wirbelauer C. Relevant parameters of optic nerve analysis from spectral domain OCT for glaucoma diagnostics. *Klin Monbl Augenheilkd* 2015;232(9):1086-1091.
- 18 Lisboa R, Paranhos A Jr, Weinreb RN, Zangwill LM, Leite MT, Medeiros FA. Comparison of different spectral domain OCT scanning protocols for diagnosing preperimetric glaucoma. *Invest Ophthalmol Vis Sci* 2013;54(5):3417-3425.
- 19 Fanihagh F, Kremmer S, Anastassiou G, Schallenberg M. Optical coherence tomography, scanning laser polarimetry and confocal scanning laser ophthalmoscopy in retinal nerve fiber layer measurements of glaucoma patients. *Open Ophthalmology J* 2015;9:41-48.
- 20 Chong GT, Lee RK. Glaucoma versus red disease: imaging and glaucoma diagnosis. *Curr Opin Ophthalmol* 2012;23(2):79-88.
- 21 Sullivan-Mee M, Ruegg CC, Pensyl D, Halverson K, Qualls C. Diagnostic precision of retinal nerve fiber layer and macular thickness asymmetry parameters for identifying early primary open-angle glaucoma. *Am J Ophthalmol* 2013;156(3):567-577.e1.
- 22 Medeiros FA, Zangwill LM, Bowd C, Vessani RM, Susanna R Jr, Weinreb RN. Evaluation of retinal nerve fiber layer, optic nerve head, and macular thickness measurements for glaucoma detection using optical coherence tomography. *Am J Ophthalmol* 2005;139(1):44-55.
- 23 Park HY, Shin HY, Yoon JY, Jung Y, Park CK. Intereye Comparison of cirrus OCT in early glaucoma diagnosis and detecting photographic retinal nerve fiber layer abnormalities. *Invest Ophthalmol Vis Sci* 2015;56(3):1733-1742.
- 24 Leung CK, Lam S, Weinreb RN, Liu S, Ye C, Liu L, He J, Lai GW, Li T, Lam DS. Retinal nerve fiber layer imaging with spectral-domain optical coherence tomography: analysis of the retinal nerve fiber layer map for glaucoma detection. *Ophthalmology* 2010;117(9):1684-1691.
- 25 Huang D, Swanson EA, Lin CP, Schuman JS, Stinson WG, Chang W, Hee MR, Flotte T, Gregory K, Puliafito CA. Optical coherence tomography. *Science* 1991;254(5035):1178-1181.
- 26 Polo V, Larrosa JM, Ferreras A, Mayoral F, Pueyo V, Honrubia FM. Retinal nerve fiber layer evaluation in open-angle glaucoma. Optimum criteria for optical coherence tomography. *Ophthalmologica* 2009;223(1):2-6.
- 27 Schrems WA, Schrems-Hoesl LM, Bendschneider D, Mardin CY, Laemmer R, Kruse FE, Horn FK. Predicted and measured retinal nerve fiber layer thickness from time-domain optical coherence tomography compared with spectral-domain optical coherence tomography. *JAMA Ophthalmol* 2015;133(10):1135-1143.
- 28 Hong S, Seong GJ, Kim SS, Kang SY, Kim CY. Comparison of peripapillary retinal nerve fiber layer thickness measured by spectral vs. time domain optical coherence tomography. *Curr Eye Res* 2011;36(2):125-134.

- 29 Mulak M, Cicha A, Kaczorowski K, Markuszewski B, Misiuk-Hojło M. Using Spectralis and Stratus optical coherence tomography devices to analyze the retinal nerve fiber layer in patients with open-angle glaucoma—preliminary report. *Adv Clin Exp Med* 2013;22(6):831-837.
- 30 Blumberg DM, Dale E, Pensec N, Cioffi GA, Radcliffe N, Pham M, Al-Aswad L, Reynolds M, Ciarleglio A. Discrimination of glaucoma patients from healthy individuals using combined parameters from spectral-domain optical coherence tomography in an African American population. *J Glaucoma* 2016;25(3):196-203.
- 31 Ng DS, Gupta P, Tham YC, Peck CF, Wong TY, Ikram MK, Cheung CY. Repeatability of perimacular ganglion cell complex analysis with spectral-domain optical coherence tomography. *J Ophthalmol* 2015;2015:605940.
- 32 Akashi A, Kanamori A, Nakamura M, Fujihara M, Yamada Y, Negi A. The ability of macular parameters and circumpapillary retinal nerve fiber layer by three SD-OCT instruments to diagnose highly myopic glaucoma. *Invest Ophthalmol Vis Sci* 2013;54(9):6025-6032.
- 33 Akashi A, Kanamori A, Nakamura M, Fujihara M, Yamada Y, Negi A. Comparative assessment for the ability of Cirrus, RTVue, and 3D-OCT to diagnose glaucoma. *Invest Ophthalmol Vis Sci* 2013;54(7):4478-4484.
- 34 Adhi M, Liu JJ, Qavi AH, Grulkowski I, Fujimoto JG, Duker JS. Enhanced visualization of the choroïdo-scleral interface using swept-source OCT. *Ophthalmic Surg Lasers Imaging Retina* 2013;44(6 Suppl):S40-S42.
- 35 Omodaka K, Horii T, Takahashi S, Kikawa T, Matsumoto A, Shiga Y, Maruyama K, Yuasa T, Akiba M, Nakazawa T. 3D evaluation of the lamina cribrosa with swept-source optical coherence tomography in normal tension glaucoma. *PLoS One* 2015;10(4):e0122347.
- 36 Langenegger SJ, Funk J, Toteberg-Harms M. Reproducibility of retinal nerve fiber layer thickness measurements using the eye tracker and the retest function of Spectralis SD-OCT in glaucomatous and healthy control eyes. *Invest Ophthalmol Vis Sci* 2011;52(6):3338-3344.
- 37 Patel NB, Wheat JL, Rodriguez A, Tran V, Harwerth RS. Agreement between retinal nerve fiber layer measures from Spectralis and Cirrus spectral domain OCT. *Optom Vis Sci* 2012;89(5):E652-E666.
- 38 Zhao L, Wang Y, Chen CX, Xu L, Jonas JB. Retinal nerve fibre layer thickness measured by Spectralis spectral-domain optical coherence tomography: The Beijing Eye Study. *Acta Ophthalmol* 2014;92(1): e35-e41.
- 39 Xiao GG, Wu LL. Optic disc analysis with Heidelberg Retina Tomography III in glaucoma with unilateral visual field defects. *Jpn J Ophthalmol* 2010;54(4):305-309.
- 40 Pablo LE, Ferreras A, Fogagnolo P, Figus M, Pajarin AB. Optic nerve head changes in early glaucoma: a comparison between stereophotography and Heidelberg retina tomography. *Eye (Lond)* 2010;24(1):123-130.
- 41 Arthur SN, Smith SD, Wright MM, Grajewski AL, Wang Q, Terry JM, Lee MS. Reproducibility and agreement in evaluating retinal nerve fibre layer thickness between Stratus and Spectralis OCT. *Eye (Lond)* 2011;25(2):192-200.
- 42 Leite MT, Rao HL, Zangwill LM, Weinreb RN, Medeiros FA. Comparison of the diagnostic accuracies of the Spectralis, Cirrus, and RTVue optical coherence tomography devices in glaucoma. *Ophthalmology* 2011;118(7):1334-1339.
- 43 Nukada M, Hangai M, Mori S, Nakano N, Nakanishi H, Ohashi-Ikeda H, Nonaka A, Yoshimura N. Detection of localized retinal nerve fiber layer defects in glaucoma using enhanced spectral-domain optical coherence tomography. *Ophthalmology* 2011;118(6):1038-1048.
- 44 Abe RY, Gracitelli CP, Medeiros FA. The use of spectral-domain optical coherence tomography to detect glaucoma progression. *Open Ophthalmol J* 2015;9:78-88.
- 45 Garvin MK, Lee K, Burns TL, Abramoff MD, Sonka M, Kwon YH. Reproducibility of SD-OCT-based ganglion cell-layer thickness in glaucoma using two different segmentation algorithms. *Invest Ophthalmol Vis Sci* 2013;54(10):6998-7004.
- 46 Leung CK, Choi N, Weinreb RN, Liu S, Ye C, Liu L, Lai GW, Lau J, Lam DS. Retinal nerve fiber layer imaging with spectral-domain optical coherence tomography: pattern of RNFL defects in glaucoma. *Ophthalmology* 2010;117(12):2337-2344.
- 47 Xu G, Weinreb RN, Leung CK. Retinal nerve fiber layer progression in glaucoma: a comparison between retinal nerve fiber layer thickness and retardance. *Ophthalmology* 2013;120(12):2493-2500.
- 48 Rolle T, Dallorto L, Briamonte C, Penna RR. Retinal nerve fibre layer and macular thickness analysis with Fourier domain optical coherence tomography in subjects with a positive family history for primary open angle glaucoma. *Br J Ophthalmol* 2014;98(9):1240-1244.
- 49 Sung MS, Yoon JH, Park SW. Diagnostic validity of macular ganglion cell-inner plexiform layer thickness deviation map algorithm using cirrus HD-OCT in preperimetric and early glaucoma. *J Glaucoma* 2014;23(8):e144-e151.
- 50 Wollstein G, Schuman JS, Price LL, Aydin A, Stark PC, Hertzmark E, Lai E, Ishikawa H, Mattox C, Fujimoto JG, Paunescu LA. Optical coherence tomography longitudinal evaluation of retinal nerve fiber layer thickness in glaucoma. *Arch Ophthalmol* 2005;123(4):464-470.
- 51 Vazirani J, Kaushik S, Pandav SS, Gupta P. Reproducibility of retinal nerve fiber layer measurements across the glaucoma spectrum using optical coherence tomography. *Indian J Ophthalmol* 2015;63(4):300-305.
- 52 Mansoori T, Viswanath K, Balakrishna N. Ability of spectral domain optical coherence tomography peripapillary retinal nerve fiber layer thickness measurements to identify early glaucoma. *Indian J Ophthalmol* 2011;59(6):455-459.
- 53 Firat PG, Doganay S, Demirel EE, Colak C. Comparison of ganglion cell and retinal nerve fiber layer thickness in primary open-angle glaucoma and normal tension glaucoma with spectral-domain OCT. *Graefes Arch Clin Exp Ophthalmol* 2013;251(3):831-838.
- 54 Suh MH, Kim SK, Park KH, Kim DM, Kim SH, Kim HC. Combination of optic disc rim area and retinal nerve fiber layer thickness for early glaucoma detection by using spectral domain OCT. *Graefes Arch Clin Exp Ophthalmol* 2013;251(11):2617-2625.
- 55 Park SB, Sung KR, Kang SY, Kim KR, Kook MS. Comparison of glaucoma diagnostic capabilities of Cirrus HD and Stratus optical coherence tomography. *Arch Ophthalmol* 2009;127(12):1603-1609.

- 56 Nouri-Mahdavi K, Hoffman D, Tannenbaum DP, Law SK, Caprioli J. Identifying early glaucoma with optical coherence tomography. *Am J Ophthalmol* 2004;137(2):228-235.
- 57 Chen HY, Chang YC. Meta-analysis of stratus OCT glaucoma diagnostic accuracy. *Optom Vis Sci* 2014;91(9):1129-1139.
- 58 Tan O, Li G, Lu AT, Varma R, Huang D. Advanced Imaging for Glaucoma Study Group. Mapping of macular substructures with optical coherence tomography for glaucoma diagnosis. *Ophthalmology* 2008;115(6):949-956.
- 59 Kerrigan-Baumrind LA, Quigley HA, Pease ME, Kerrigan DF, Mitchell RS. Number of ganglion cells in glaucoma eyes compared with threshold visual field tests in the same persons. *Invest Ophthalmol Vis Sci* 2000;41(3):741-748.
- 60 Oli A, Joshi D. Can ganglion cell complex assessment on cirrus HD OCT aid in detection of early glaucoma? *Saudi J Ophthalmol* 2015;29(3):201-204.
- 61 Yang Z, Tatham AJ, Weinreb RN, Medeiros FA, Liu T, Zangwill LM. Diagnostic ability of macular ganglion cell inner plexiform layer measurements in glaucoma using swept source and spectral domain optical coherence tomography. *PLoS One* 2015;10(5):e0125957.
- 62 Padhy D, Rao A. Macular ganglion cell/inner plexiform layer measurements by spectral domain optical coherence tomography for detection of early glaucoma and comparison to retinal nerve fiber layer measurements. *Am J Ophthalmol* 2014;158(1):211.
- 63 Sung KR, Sun JH, Na JH, Lee JY, Lee Y. Progression detection capability of macular thickness in advanced glaucomatous eyes. *Ophthalmology* 2012;119(2):308-313.
- 64 Na JH, Sung KR, Lee JR, Lee KS, Baek S, Kim HK, Sohn YH. Detection of glaucomatous progression by spectral-domain optical coherence tomography. *Ophthalmology* 2013;120(7):1388-1395.
- 65 Leung CK, Ye C, Weinreb RN, Yu M, Lai G, Lam DS. Impact of age-related change of retinal nerve fiber layer and macular thicknesses on evaluation of glaucoma progression. *Ophthalmology* 2013;120(12):2485-2492.
- 66 Kim NR, Lee ES, Seong GJ, Kim JH, An HG, Kim CY. Structurefunction relationship and diagnostic value of macular ganglion cell complex measurement using Fourier-domain OCT in glaucoma. *Invest Ophthalmol Vis Sci* 2010;51(9):4646-4651.
- 67 Cho JW, Sung KR, Lee S, Yun SC, Kang SY, Choi J, Na JH, Lee Y, Kook MS. Relationship between visual field sensitivity and macular ganglion cell complex thickness as measured by spectral-domain optical coherence tomography. *Invest Ophthalmol Vis Sci* 2010;51(12):6401-6407.
- 68 Lee M, Yoo H, Ahn J. Comparison of disc analysis algorithms provided by cirrus oct and stereo optic-disc photography in normal and open angle glaucoma patients. *Curr Eye Res* 2013;38(5):605-613.
- 69 Shoji T, Kuroda H, Suzuki M, Baba M, Hangai M, Araie M, Yoneya S. Correlation between lamina cribrosa tilt angles, myopia and glaucoma using OCT with a wide bandwidth femtosecond mode-locked laser. *PLoS One* 2014;9(12):e116305.
- 70 Kim YW, Kim DW, Jeoung JW, Kim DM, Park KH. Peripheral lamina cribrosa depth in primary open-angle glaucoma: a swept-source optical coherence tomography study of lamina cribrosa. *Eye (Lond)* 2015;29(10):1368-1374.
- 71 Sawada Y, Hangai M, Murata K, Ishikawa M, Yoshitomi T. Lamina cribrosa depth variation measured by spectral-domain optical coherence tomography within and between four glaucomatous optic disc phenotypes. *Invest Ophthalmol Vis Sci* 2015;56(10):5777-5784.
- 72 Lamparter J, Schulze A, Riedel J, Wasielica-Poslednik J, König J, Pfeiffer N, Hoffmann EM. Peripapillary choroidal thickness and choroidal area in glaucoma, ocular hypertension and healthy subjects by SD-OCT. *Klin Monbl Augenheilkd* 2015;232(4):390-394.
- 73 Chebil A, Maamouri R, Ben Abdallah M, Ouderni M, Chaker N, El Matri L. Foveal choroidal thickness assessment with SD-OCT in high myopic glaucoma. *J Fr Ophtalmol* 2015;38(5):440-444.
- 74 Ghany AF, Botros SM, El-Raggal TM. Central retinal artery resistive index and optical coherence tomography in assessment of glaucoma progression. *Int J Ophthalmol* 2015;8(2):305-309.
- 75 Wang X, Jiang C, Ko T, Yu X, Min W, Shi G, Sun X. Correlation between optic disc perfusion and glaucomatous severity in patients with open-angle glaucoma: an optical coherence tomography angiography study. *Graefes Arch Clin Exp Ophthalmol* 2015;253(9):1557-1564.
- 76 Jia Y, Wei E, Wang X, Zhang X, Morrison JC, Parikh M, Lombardi LH, Gattney DM, Armour RL, Edmunds B, Kraus MF, Fujimoto JG, Huang D. Optical coherence tomography angiography of optic disc perfusion in glaucoma. *Ophthalmology* 2014;121(7):1322-1332.
- 77 Liu L, Jia Y, Takusagawa HL, Pechauer AD, Edmunds B, Lombardi L, Davis E, Morrison JC, Huang D. Optical coherence tomography angiography of the peripapillary retina in glaucoma. *JAMA Ophthalmol* 2015;133(9):1045-1052.