Optical coherence tomography: history, current status and laboratory work

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Abstract

Optical coherence tomography (OCT) imaging has become widespread in ophthalmology over the past 15 years due to its ability to visualize ocular structures at high resolution. This article reviews the history of OCT imaging of the eye, current status and laboratory work that is driving the future of the technology.

A Brief History of Optical Coherence Tomography in Ophthalmology

Optical coherence tomography (OCT) has advanced considerably since it was first applied to the eye.[1-7] OCT is an extension of a technique called low-coherence interferometry, which was initially applied to ophthalmology for *in-vivo* measurements of eye axial length.[1] At the time of introduction, OCT was used to obtain *in-vivo* optical cross-sections of the anterior segment[6] as well as retinal pathologies such as macular detachment, macular hole, epiretinal membrane, macular edema and idiopathic central serous chorioretinopathy.[4] OCT cross-sections were also used to evaluate the optic disc and retinal layers[5, 8] such as the retinal nerve fiber layer (RNFL).[9] Scan patterns that enabled reproducible measurements were developed[10] and these eventually became incorporated into a commercial system, which had an axial resolution of ~10μm.

The first clinical system was limited to a scanning speed of 400 axial-scans (A-scans)/second due to a physical constraint: a moving reference mirror. OCT uses low coherence interferometry to obtain A-scan intensity profiles, and this requires light to be split and sent to both a reference arm with a mirror and to the sample. Provided the path length to the reference mirror and tissue match to within the coherence length of the light source, when the reflected beams recombine, interference occurs. Intensity information, in the form of a reflectivity profile in depth, can be extracted from the interference profile. Changing the location of the reference mirror allows backscattered tissue intensity levels to be detected from different depths in the tissue sample. This approach is referred to as time-domain (TD)-OCT because time-encoded signals are obtained directly. Several improvements in OCT hardware have been introduced since the first commercial TD-OCT system became available. Better axial resolution[11-13] and increased scanning speed[14-23] are the two main advancements that have recently become incorporated into commercial systems.

The implementation of broad-band light sources into OCT systems[11] improved the axial resolution from ~10μm to as high as 2μm in tissue.[24] Acquisition speed has improved considerably by detecting backscattering signals in the frequency domain,[14-23] which means backscattered depth information at a given location can be collected without the movement of a reference mirror. Frequency information is acquired using either a broad bandwidth light source, charge-coupled device (CCD) camera and spectrometer,[14, 17, 18, 20] or by sweeping a narrow bandwidth source through a broad range of frequencies and using a photodetector.[16, 21-23] The approach using a broadband light source is often referred to as spectral domain (SD)-OCT, while the latter is termed swept-source (SS)-OCT. In both approaches, intensity profiles (A-scans) are obtained using a Fourier-transform of the detected frequencies, and this facilitates rapid A-scan collection. In addition to improved scanning speed, frequency-domain OCT also offers the advantage of higher detection sensitivity, i.e., it will exhibit higher signal-to-noise given a perfect reflector.[23, 25] A summary of OCT detection techniques can be seen in Table 1.

With these speed and sensitivity improvements, it is now feasible to collect volumetric (three-dimensional; 3D) scans of tissue whereas in the past, the amount of time required to do this would have been prohibitive. Broadband volumetric retinal imaging with SD-OCT at speeds of up to 312,500 A-scans/sec[26] and SS-OCT 249,000 A-scans/sec[27] have been demonstrated. To date, most clinical systems operate at an acquisition rate of ~27,000 A-scans/sec and an axial resolution of 5-6 µm. A summary of the currently commercially available retinal imaging systems is presented in Table 2.

Current Status of Optical Coherence Tomography in the Clinic

Glaucoma

Conventionally, the most common scan patterns in TD-OCT glaucoma imaging were a 3.4 mm scan around the optic nerve head (ONH), and six equally spaced radial scans through the macula (6 mm) and optic nerve (4 mm). RNFL thickness is obtained via automated RNFL segmentation in the circumpapillary scan protocol, while macular thickness (internal limiting membrane, ILM, to the photoreceptor inner segment-outer segment junction (IS-OS)) is automatically segmented in the macular scan pattern. The optic nerve scan is used to obtain cup area, disc area, cup diameter, disc diameter and rim area. These ONH parameters are obtained automatically: the software detects the ONH margin/RPE tips, but the user can modify the location if the ONH margin detection algorithm is inaccurate.

The ONH and RNFL scan protocols have been used since TD-OCT became commercially available, and RNFL and ONH parameters have been shown to differ between glaucomatous and healthy eyes.[9, 28-33] Glaucoma discriminating ability, measured by the area under receiver operating characteristic curves (AROC) of RNFL (AROC = 0.94) and disc parameters (eg, rim area AROC= 0.97) have been reported to be higher than macular volume and thickness (AROC both 0.80).[34] A similar glaucoma discriminating ability is seen in comparing TD-OCT imaging and SD-OCT imaging when similar parameters are examined.[35] However, it may be possible to further improve glaucoma discrimination using parameters obtained from 3D scanning. With the commercialization of rapidly scanning SD-OCT systems, 3D volumes of tissue are now easily acquired. A 3D dataset not only allows a quantitative analysis from more locations but, once a volume has been collected, OCT fundus (*en face*) images can be obtained by integrating A-scans.[20] These can be used for a subjective assessment of signal quality and to assist with evaluating and/or correcting eye motion that may have occurred throughout the scan. The OCT fundus image also allows registration of OCT cross-sections to precise retinal locations.

Acquisition of 3D datasets has led to the advancement of software methods for efficiently analyzing and summarizing these vast amounts of data. One method for obtaining RNFL thickness measurements has been sampling the 3D volume (eg, 6.0 x 6.0 x 2.0 mm, centered on the ONH) after acquisition, at a diameter of 3.4 mm centered on the ONH (Figure 1). This method has been shown to have higher reproducibility than the conventional TD-OCT 3.4 mm scan circle, where the image is acquired along the circle only.[36] One explanation for the improved performance is that, with TD-OCT, scan placement is dependent upon the user and can be variable, but with SD-OCT, the circle can be consistently placed in the same location using landmarks within the 3D volume.

While sampling 3D volumes after acquisition may be an effective way for summarizing RNFL measurements, it is doing so at a cost: data outside the 3.4 mm band are not being used. Subjectively, wedge defects and global thinning may be easy to spot, but subtle changes or deviations from normal outside the 3.4 mm sampling band may be missed. One way of addressing this is to create an RNFL thickness map, which consists of all thickness measurements outside of the ONH. From this, thickness measurements from one subject can be compared to population thickness measurements. To date, however, commercial software is available for looking at deviation from normal, but there is no quantitative assessment utilizing all of the available RNFL information.

Different approaches have been proposed for quantifying 3D data. 3D RNFL thickness was analyzed in terms of a thickness profile as distance from the ONH increased.[37] In healthy eyes, the slope of RNFL thickness increased near the margin of the ONH, peaked, and then decreased with increasing distance from the ONH center in all but the nasal quadrant, which linearly decreased starting from the disc margin. Another approach (Ishikawa H, et al. IOVS 2009;50:ARVO E-Abstract 3328) exploits 3D macular data, which have been summarized using segmentation of the inner retinal complex (IRC: retinal ganglion cell layer (RGC), inner plexiform layer (IPL), inner nuclear layer (INL); Figure 2).[38] This approach reduces IRC data to superpixels (4x4 adjacent sampling points) and compares these superpixels to a normative thickness superpixel dataset. By condensing measurements into superpixels, it is less likely that small imaging artifacts or algorithm failure will have an effect.

One commercially available system has developed an approach for summarizing macular data called the Ganglion Cell Complex (GCC; RTVue, Optovue, Inc) which consists of essentially the same layers as the IRC: the RGC (retinal ganglion cell bodies), RNFL (RGC axons) and IPL (RGC dendrites). The GCC measurements are then directly compared to a normative database and thickness difference and significance maps are available (Figure 3).

While a comparison to a normal population may reveal differences, structural changes may be occurring while a patient remains within normal limits and therefore go undetected. Ideally, a longitudinal comparison could be made for a given individual to look for subtle structural changes attributed to disease progression. One approach has been proposed by Kim *et al* to allow compatibility between TD-OCT and 3D OCT device iterations.[39] Since TD-OCT devices have been commercially available longer than 3D imaging systems, years of patient information may be available. The method presented by Kim *et al* resamples a 3D-OCT dataset for every possible 3.4-mm circular scan location within the boundaries of the 3D-OCT volume. It then uses cross correlation between these virtual circular scans and the TD-OCT 3.4-mm scan to automatically match the TD-OCT scan circle location within the volume.

To longitudinally compare 3D volumes, however, image registration techniques must be developed to spatially align 3D scans before they can be compared. This may be accomplished using cross-correlation,[40, 41] or by using landmarks within the OCT fundus image, such as blood vessels.[42, 43] Eye motion during acquisition has been shown to alter scan location,[44-46] and the effect of eye motion is visible on OCT *en face* images as discontinuous blood vessels. Detecting and correcting blood vessel location to align the OCT fundus can help correct eye motion,[42] which may be useful for cross-sectional analysis.

Longer wavelength imaging (~1μm center wavelength) of the lamina cribrosa[27] and birefringence imaging of the RNFL using polarization-sensitive (PS)-OCT[47-49] are two techniques under development that may improve the diagnosis and monitoring of glaucoma. These are further described in the Pre-clinical and Laboratory Studies section of this review.

Retina

The macular scan pattern discussed above – 6 radial macular scans, 6 mm long, spaced 30^o apart – has traditionally been used in TD-OCT imaging to assess retinal parameters such as total retinal thickness and the IRC. Three-dimensional imaging, however, has revolutionized the examination of retinal pathologies.[50-55] By examining the 3D structure of the retina, as opposed to just six radial scans, subtle structural changes may become apparent. For example, using high-resolution 3D imaging to observe the photoreceptor inner segment/outer segment junctions may be an indicator of visual outcomes after macular hole surgery.[56-58]

At present, one application of 3D OCT of imaging retinal pathologies that has considerable clinical potential is surgical planning and the evaluation of surgical outcomes. The use of OCT for planning an access point to release the hyaloid for vitrectomy using the six radial scan pattern in TD-OCT has been described.[59] While this was effective for minimizing traction forces on the macula during surgery, a detailed 3D map of the hyaloid membrane and subhyaloid space could further inform the clinician. Falker-Radler et al have used 3D imaging to visualize the vitreomacular interface in subjects that were undergoing surgery for epiretinal membrane.[60] Others have used OCT for evaluation of structure after surgery for macular hole[57, 58, 61] and vitreomacular traction.[52, 62-64] The use of 3D imaging for surgical preparation and evaluation of surgical outcomes has the potential to improve with the use of longer wavelength imaging, which is described later in this review. Automated segmentation of structures of interest, when possible, may provide objective measurements to clinicians for pre- and post-surgical evaluation.

Quantification of thickness is possible in certain pathologies,[65, 66] especially with early stage changes.[67, 68] The reproducibility of SD-OCT retinal thickness measurements is higher in than that of TD-OCT.[69] Thickness has been shown to correlate with best-corrected visual acuity in diabetic macular edema[70] and ERM.[71] While thickness may be a clinically useful correlate of visual function, however, there are cases and pathologies where no correlation to thickness is seen and thus clinicians need to exercise caution in interpretation of thickness measurements.[72]

Drusen volume may be a predictor of progression of age-related macular degeneration,[65] and efforts are underway for automated assessment.[66] While accurate quantification of volumetric tissue changes will assist with longitudinal monitoring of disease, fully automated segmentation may not be reliable because of shadowing from fluid in the retina[73, 74] or because of pathologies which disrupt normal retinal structures, such as macular hole, subretinal fluid, pigment epithelium detachment and others.[75, 76]

In cases where fully automated segmentation fails, C-mode visualization of structures may augment subjective analyses.[77] A 3D volume of data can be sectioned in any plane after acquisition, and for C-mode visualization, data are sectioned perpendicular to the retina. The section can be of any thickness, so structures embedded within a volume can be exposed. Often, since the true structure of the retina is curved, exact perpendicular sections slice through several layers simultaneously,[78, 79] so aligning the volume to structures such as the ILM or RPE assists with isolating structures of interest.[77] Figure 4 shows an example C-mode section taken after aligning a macular SD-OCT 3D volume to the RPE. By moving axially, past the retina and RPE, choroidal blood vessels can be visualized. This is not apparent in the corresponding SD-OCT fundus image because of highly reflective layers superficial to the choroid. C-mode provides alternative viewing perspective for many retinal pathologies, such as cystoid macular edema, central serous retinopathy, vitreoretinal traction, and age-related macular degeneration,[77] and this can improve the visualization of these pathologies.

It is also possible to image the choroid by focusing the illuminating OCT beam deeper and moving the choroid closer to zero delay.[80] In addition, longer wavelength imaging at ~1µm[81] allows for deeper penetration of light into the retina and choroid. A combination of these approaches may improve the current understanding of choroidal diseases.

Correcting ocular aberrations with adaptive-optics (AO)-OCT[82] may also provide a unique viewing perspective for retinal pathologies. This technique has been applied to view photoreceptors[83] and RNFL.[84] The utility of longer wavelength imaging and AO-OCT is under investigation and described in the Pre-clinical and Laboratory Studies section below.

Anterior Segment

Anterior segment OCT (AS-OCT) provides structural information of the cornea and anterior chamber without contacting the eye, offering an ease of image acquisition and a considerable advantage over ultrasound biomicroscopy (UBM). While it cannot be used to image deep structures, such as the ciliary body, as UBM can, AS-OCT has higher axial resolution (5-10 µm for AS-OCT as compared to 25 µm for UBM).[85]

It is possible to acquire high-resolution images of the sclera, angle and iris with AS-OCT imaging at longer wavelengths (1.3 µm).[86] High-resolution images of anterior chamber angle can also be obtained using 850 nm systems, and this has lead to the visualization of the trabecular meshwork and Schlemm's canal.[87-89]

Raster scanning and radial scanning of the cornea have been used to measure thickness,[90] resulting in reliable pachymetric mapping.[91, 92] Pachymetric measurements obtained with AS-OCT may assist with planning or follow-up of LASIK patients,[93] or used to diagnose keratoconus.[94]

In addition to its potential benefits in the evaluation of the anterior chamber angle and cornea, AS-OCT has also been shown to be applicable in the assessment of lens thickness in phakic eyes[95] or intracorneal ring placement.[96] This can provide an alternate, non-contact, method of pre- and post-surgical assessment.

Pre-clinical and Laboratory Studies

Swept-Source Optical Coherence Tomography and Longer Wavelength Imaging

As previously discussed, SS-OCT obtains time-encoded spectral information by sweeping a narrow bandwidth laser through a broad optical spectrum. Backscattered intensity is detected with a photodetector. This is in contrast to SD-OCT, which uses a broad bandwidth light source and detects the interference spectra with a CCD camera and spectrometer. While the use of spectrometer-based SD-OCT has become widespread in the clinic, there are some benefits to photodetector-based SS-OCT systems. Like SD-OCT, SS-OCT offers speed and sensitivity advantages over TD-OCT.[23, 27] To date, speeds of up to 249,000A-scans/sec have been attained in the eye.[27] This means that eye motion artifacts can be greatly reduced compared to TD-OCT.[22]

One advantage of SS-OCT over SD-OCT is that it does not require a CCD camera and spectrometer and instead uses a simpler photodetector.[27] A drawback to camera-based SD-OCT detection is a drop-off in signal with depth of scanning due to the finite pixel size of the CCD camera.[25, 97] While this can be improved by reducing the camera pixel size,[97] it increases the complexity and therefore cost of the CCD array. A noticeable drop-off in signal with depth typically does not occur with SS-OCT imaging due to the narrow bandwidth of the light source.[23, 97]

At this time, one disadvantage of SS-OCT is that the majority of systems are now operating at longer wavelengths (λ=1-1.3 μm), with very few studies demonstrating SS-OCT in the 800 nm range.[98, 99] Water absorption limits the usable bandwidth at 1 μm and 1.3 μm[99] and this limits the axial resolution; the water absorption window at 850 nm is larger so higher axial resolution can be achieved.

While axial resolution at longer wavelengths may not be as fine as at 850 nm, there are advantages to using ~1µm and 1.3µm sources. Posterior segment imaging using ~1µm (1040-1060nm)[81, 100, 101] center wavelengths has allowed deeper penetration into the retina, optic nerve head and choroid,[81, 102] which may be beneficial for imaging choroidal vessels, lamina cribrosa and pathologies such as choroidal neovascularization.[103] The water absorption window at 1.3µm offers even deeper penetration of light and may be useful for cornea and anterior segment imaging.[16, 22, 23, 104-106] Anterior chamber imaging at 1310 nm has been applied to visualize anterior segment structures anterior and posterior to the iris, Schlemm's canal, trabecular meshwork, and the scleral spur,[107] as well as the anterior chamber angle.[108]

While SS-OCT systems at any wavelength are not yet commercially available for clinicians, in part due to the cost of the light source, there is clinical potential for such devices. No signal drop-off with depth in SS-OCT, in combination with deeper penetration from longer wavelengths, may improve delineation of the outer retina, RPE and choroid thereby enhancing the performance of segmentation algorithms. In addition, high speed 1.3µm imaging may be expand the use of anterior segment OCT imaging.

Adaptive Optics Optical Coherence Tomography

Ophthalmic systems that employ adaptive optics (AO) dynamically adjust their optical characteristics to compensate for monochromatic aberrations that occur naturally in the eye. AO was initially proposed[109] and later employed by astronomers to correct distortions of light passing through the atmosphere.[110] In 1997, AO was demonstrated in the eye by Liang *et al*, who used a Hartmann-Shack wavefront sensor and a deformable mirror to correct contrast sensitivity and improve quality of vision for human subjects, and to obtain higher resolution images with an AO-fundus camera.[111] Shortly thereafter, individual cone mosaics were imaged.[112]

AO-OCT was first reported by Miller *et al* in 2003[82] to improve transverse resolution. Uncorrected, conventional OCT beams 1 mm in diameter have a transverse resolution limited to ~15-20 µm.[113] This makes it difficult to visualize individual cellular structures. One way to improve transverse resolution is to increase the numerical aperture, which in practice means increasing the diameter of the OCT beam entering the eye, since this would decrease the spot size on the retina. However, the theoretical diffraction-limited resolution cannot be attained due to ocular aberrations[114] that occur when the pupil is dilated.[115, 116] AO-OCT measures and corrects these aberrations using wavefront sensing and deformable mirrors, thereby minimizing spot size and improving transverse resolution. It should also be noted that aberrations can also be dependent on the bandwidth of the light source used for OCT imaging,[116] and these may be improved using an achromatizing lens.[117]

Ultrahigh (axial) resolution AO-OCT was presented in 2004, improving transverse resolution to 5-10µm in the retina.[113] Zhang *et al* developed an AO SD-OCT system and saw an enhancement of the photoreceptor inner segment/outer segment junction *in-vivo* with AO.[118] C-mode sectioning of 3D datasets have also facilitated the visualization of axon bundles in the RNFL[84] and cone photoreceptor mosaics from healthy subjects,[83, 119] and subjects with structural abnormalities[120] and optic neuropathies.[121]

One disadvantage of AO imaging is that the depth of focus is narrow, which means focusing simultaneously at different depths is difficult. For example, photoreceptors, located deep in the retina, and superficial retinal ganglion cells cannot be brought into focus at the same time. This may be able to be addressed by scanning in depth and varying the focal plane,[122] or by stitching together volumes.[123] Another limitation to AO imaging is that the field of view is restricted to approximately 1-3 degrees; the use of an eye tracking system to acquire a series of neighboring scans and gradually build up an image covering a larger volume may provide one solution to this limitation.[124]

One potential advantage of improved lateral resolution with AO-OCT is improved understanding of normal and pathologic retinal function *in-vivo*. AO may also help improve the overall quality of images obtained from eyes that have with more aberrations. Enhanced lateral resolution and improved image quality may then lead to better performance of automated segmentation algorithms and assist with disease diagnosis and follow-up.

Polarization-Sensitive Optical Coherence Tomography

Polarization-sensitive (PS)-OCT detects polarization changes in circularly polarized light.[125] PS-OCT was initially applied to characterize the birefringence of tooth enamel,[126] skin,[127] and cartilage.[128] In 2001, PS-OCT was first used in the eye[129] to measure birefringence of the RNFL in rhesus monkeys. RNFL birefringence was measured in humans by Cense *et al*,[47-49] who found that, unlike RNFL thickness, birefringence does not change as a function of increasing radius from the ONH.[48] It does, however, vary by sector around the ONH, with higher birefringence in thicker areas.[48] Because birefringence may change with disease, RNFL birefringence obtained with OCT may eventually provide an additional indicator of glaucomatous change. The utility of PS-OCT in glaucoma detection and monitoring is currently under investigation. In addition to measuring RNFL birefringence, a longer wavelength (λ=1.3µm) PS-OCT system has been used to observe the anterior chamber in subjects after glaucoma surgery.[108] A swept-source PS-OCT system at 1µm center wavelength was used to image sclera and lamina cribrosa,[130] which may provide insight into structural changes occurring in the ONH in glaucoma.

Polarization of the RPE may be important in the detection of macular disease.[131, 132] Gotzinger et al developed a segmentation algorithm based on what they refer to as “polarization scrambling effect” of the RPE,[132] which provides an alternative to conventional intensity-based quantification. A combined AO PS-OCT system was later used to measure RPE polarization scrambling.[133] Conventional PS-OCT was used to observe subjects with AMD,[134, 135] where abnormal birefringence was co-localized with exudative lesions.

PS-OCT has been used for anterior segment imaging to measure corneal birefringence[136, 137], and these measurements were used to compensate for corneal birefringence in retinal imaging.[138] A difference in polarization in healthy corneas versus those with keratoconus was demonstrated *in vitro*, suggesting PS-OCT may eventually provide insight into corneal pathologies *in-vivo*.[139]

The aforementioned studies indicate that PS-OCT offers an alternative approach for detecting changes of optical properties in tissue. If it can be established that a change in birefringence occurs prior to tissue thinning or thickening, this may allow earlier detection and the opportunity for earlier intervention.

Eye-Tracking OCT Systems

Subject eye motion can alter the intended location of an OCT scan. While attempts to correct eye motion using post-processing methods are under development, real-time eye-tracking systems may provide an alternate method for avoiding eye motion artifacts.[46] Menke et al showed that an SD-OCT system with built-in eye tracking can provide reproducible measurements,[140] but it is yet to be shown whether this yields higher reproducibility or better sensitivity and specificity than devices without eye tracking systems.

OCT Systems for Surgical Guidance

As described earlier in this review, OCT is already being used for surgical planning and follow-up. In addition, there has also been progress in the development of intraoperative OCT systems. Intraoperative OCT was first demonstrated in anterior segment surgery, where a 1310 nm system was coupled to an operating microscope.[141] The use of a handheld OCT retinal imaging device has also been demonstrated for use in patients undergoing vitrectomy, after removing either the ILM or epiretinal membrane, in order to better visualize the macular pathology.[142] It is possible that the development of an intraoperative approach may be further improved using a projection of a virtual OCT image over the surgical site and within the line of sight of the surgeon,[143] but the implementation of this technique for surgery still have to be investigated.

Animal OCT Imaging

The noninvasive nature of image acquisition together with the commercialization of systems optimized for laboratory use has resulted in a recent increase in the number of animal studies using OCT. Two- and three-dimensional scanning with OCT is appealing because the same animals can be followed over time, *in-vivo*, making longitudinal studies of ocular structures possible without the need to sacrifice animals at various time points and obtain histological sections. Not only does this reduce the number of animals required for experiments, but is superior to cross-sectional experiments which require different animals for different time points. The following briefly summarizes recent studies using OCT in animals, from small to large animal models.

The eyes of small animal models commonly used in developmental biology, such as xenopus laevis larvae[144] and zebrafish embryos[145] have successfully been imaged with OCT. Rodent imaging with OCT is becoming increasingly popular given their relatively low cost and short lifespan – and therefore shorter time for disease progression. In addition, many transgenic models are easy for researchers to access. OCT has been used to study ocular dimensions[146] and characterize normal eye growth[147] as well as growth of eyes in mouse models of myopia.[148] Mouse models of retinal degeneration have been imaged using TD-OCT,[149, 150] and healthy and degenerative mice with SD-OCT.[151-158]

Recently, methods for automatically obtaining measurements from mouse OCT images have been presented.[159, 160] Images taken in an anesthetized mouse, held in place using a stage with a glass cover slip to neutralize the strong refractive power of the mouse cornea were shown to be reproducible.[159] This indicates that 3D SD-OCT imaging of the mouse retina may be useful for longitudinal studies of retinal structure in mice.

Rats also provide an interesting platform for studying structural changes in the retina and optic nerve in response to injury or disease. Given their larger eyes, it is less complicated to focus on the retina than in the mouse. Retina and optic nerve imaging has been demonstrated in rat models of retinal degeneration,[151] retinal vein occlusion,[161] retinal ganglion cell degeneration post nerve-crush injury[162, 163] and elevated intraocular pressure,[164] suggesting there is also potential for rats to be used for longitudinal studies with OCT.

The eyes of larger animal models, such as chickens with retinal degeneration,[165] have been imaged. Researchers have also used OCT to examine birds of prey,[166] pigs,[167, 168] cats[169] and rabbits.[170-178] These animals have eyes that are comparable in size to the human eye, which means large modifications of the OCT system optics are not necessary.

Nonhuman primate models are especially appealing for studies with OCT, since their ocular size and structure closely matches the human eye. Nonhuman primate imaging may provide novel insight into the mechanical damage to the RNFL and ONH associated with increased IOP, as is often seen in glaucoma. PS-OCT has been used to look at birefringence of the RNFL,[129, 179, 180] and RNFL thickness was measured in eyes with unilateral, laser-induced ocular hypertension.[181, 182] Strouthidis et al examined 3D SD-OCT images of the optic nerve in nonhuman primate eyes.[183] They visualized the termination of Bruch's membrane, border tissue, and the anterior scleral canal opening and showed that these structures correlated to disc photos[184] and histology.[185] This set the stage for a study of alterations in the ONH that are due to increased intraocular pressure.[186]

Ultimately, longitudinal OCT studies of small and large animals may help evaluate the efficacy of pharmacological agents, stem cell therapies, surgical intervention, and retinal prosthetics while reducing the required number of animals. OCT has the potential to provide a better understanding of disease development and progression in transgenic and other models of disease, which may eventually translate to improved clinical assessment and understanding of disease.

Conclusion

The use of OCT imaging in ophthalmology has increased steadily in recent years, in part due to technological improvements such as scanning speed, sensitivity and resolution. The field continues to grow and transform the way glaucoma and retinal diseases are monitored. With 3D imaging, there are new ways to visualize pathology and corresponding challenges to overcome. Current approaches, such as RNFL thickness maps and C-mode visualization, attempt to summarize structural information. These methods are not necessarily optimized for efficient cross-sectional and longitudinal analysis, but with technological improvements such as longer wavelength imaging, SS-OCT, AO-OCT, and PS-OCT on the horizon, even more structural detail will be available. Translating these techniques to the clinic has already begun and many could eventually be made available to the clinician. A combined slit-lamp/OCT system that allows the clinician to access structural information during a routine examination may eventually be available, as may a portable operating-room system. The use of OCT in animal models has the potential to further understanding of disease while offering a platform for testing novel approaches to treatment, as well as for innovations of the OCT technique itself. The future of OCT is promising, but with some constraints that, if history is any indication, will become the basis for future advancement.

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Figure Legends

Figure 1 (Top) OCT fundus images and (Bottom) RNFL thickness maps obtained by segmenting RNFL at all locations outside of the optic nerve, for a healthy and glaucoma subject. The outer red circle indicates the location of a resampled 3.4mm peripapillary cross-section. Images acquired with Cirrus HD-OCT; 200x200 A-scans, 6x6 mm).

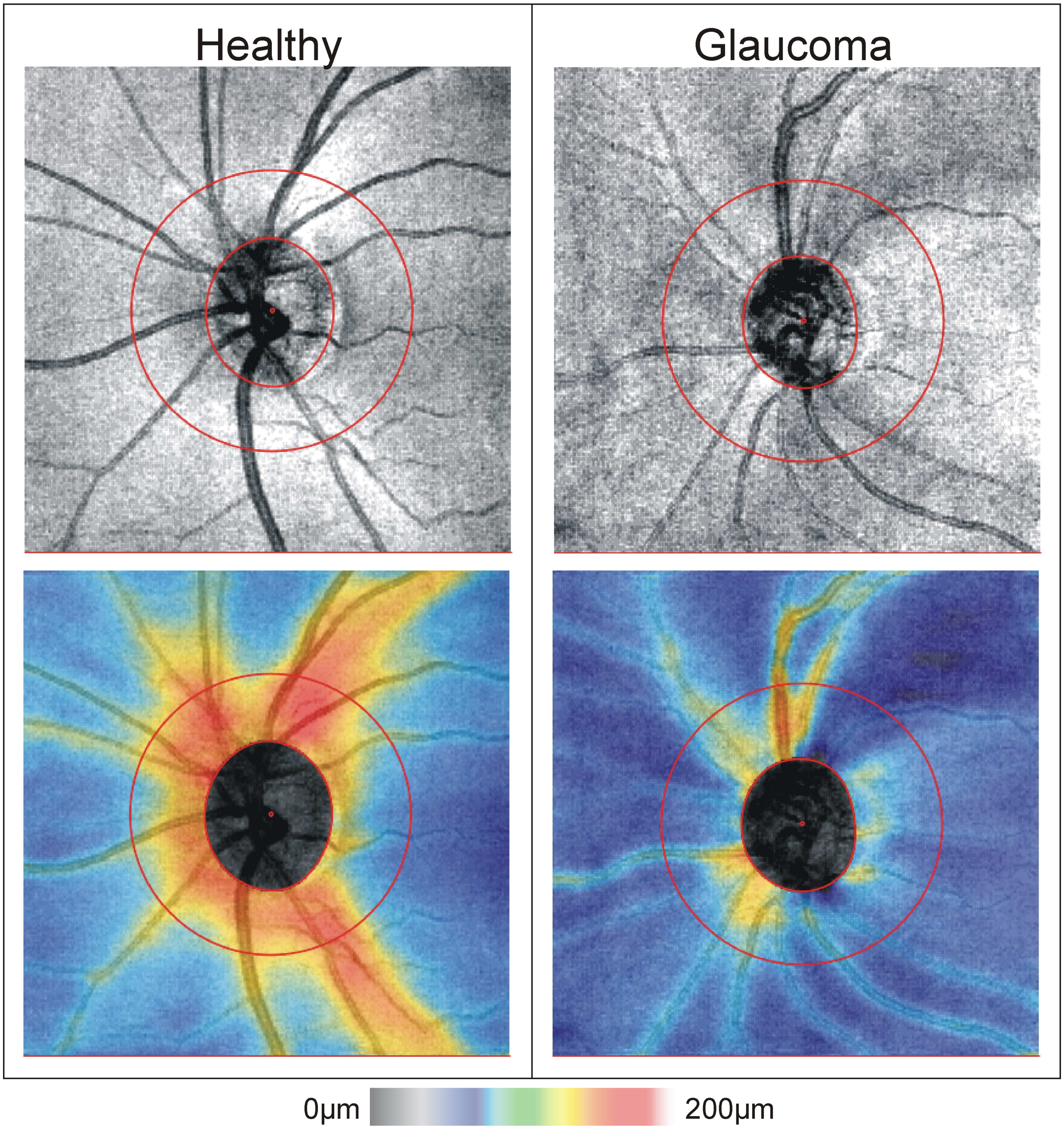


Figure 2. (Left) SD-OCT macular thickness map (inner retinal complex) and (Right) cross-sectional image showing automated segmentation results for one frame of the 3D volume. Image acquired with Cirrus HD-OCT; 200x200 A-scans, 6x6 mm); Blue lines, from inner to outer retina, indicate the outer border of the retinal nerve fiber layer, outer border of the inner plexiform layer, outer border of the outer plexiform layer and RPE

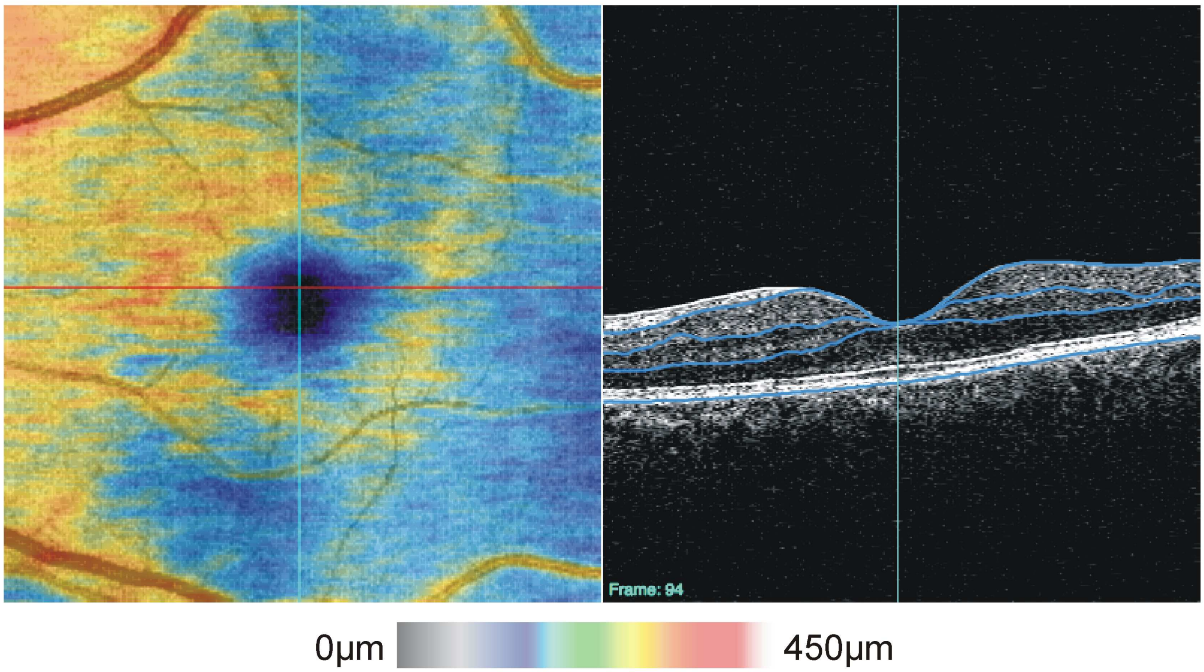
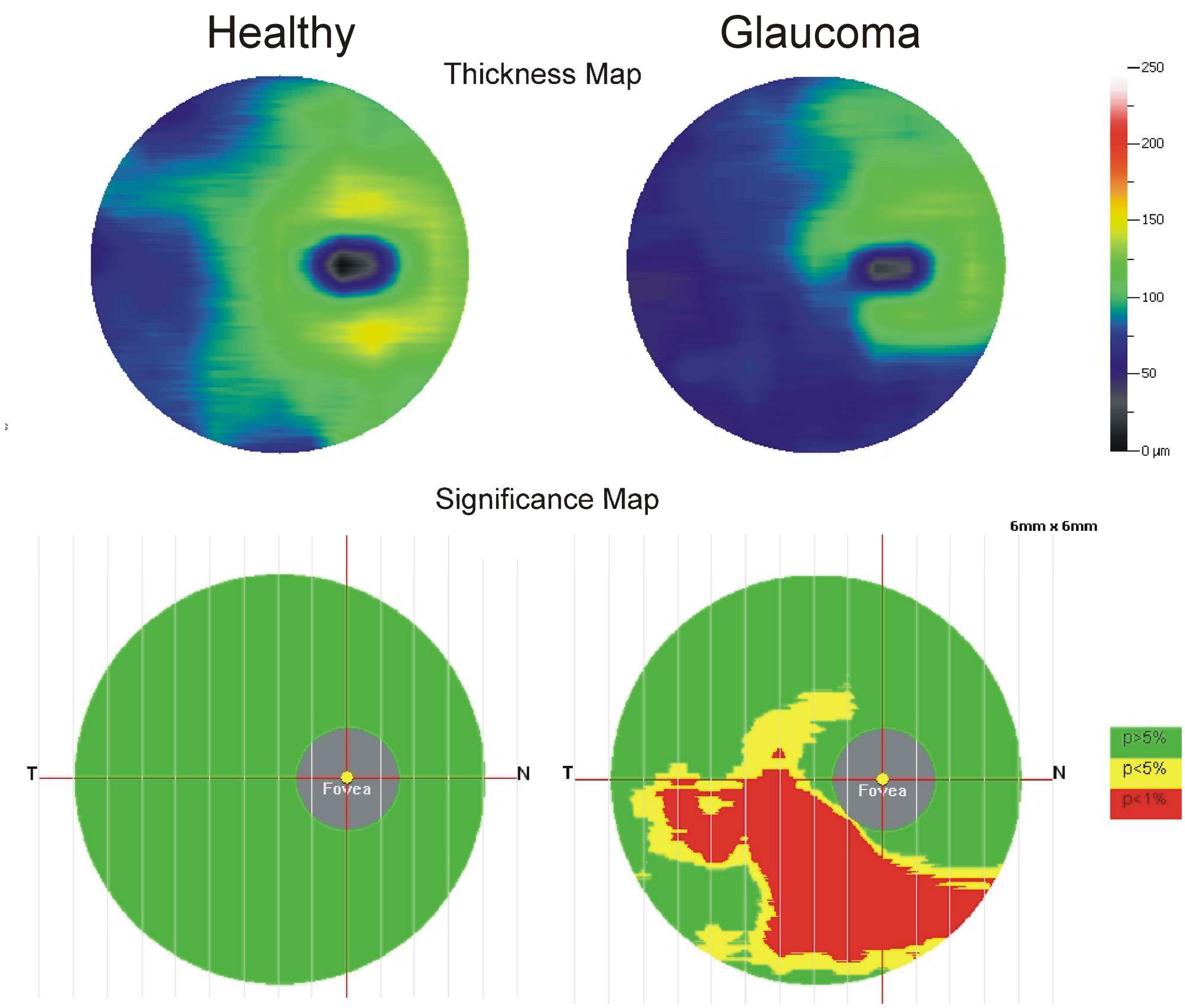


Figure 3. Ganglion cell complex thickness and significance maps for a healthy (left) and glaucoma (right) subject. The ganglion cell complex includes cell bodies, axons and dendrites of retinal ganglion cells. Images acquired with RTVue-100: 1 horizontal B-scan, and 15 vertical B-scans (separated by 0.5 mm). All B-scans consisted of 933 A-scans; 7 x 6 mm scan area).



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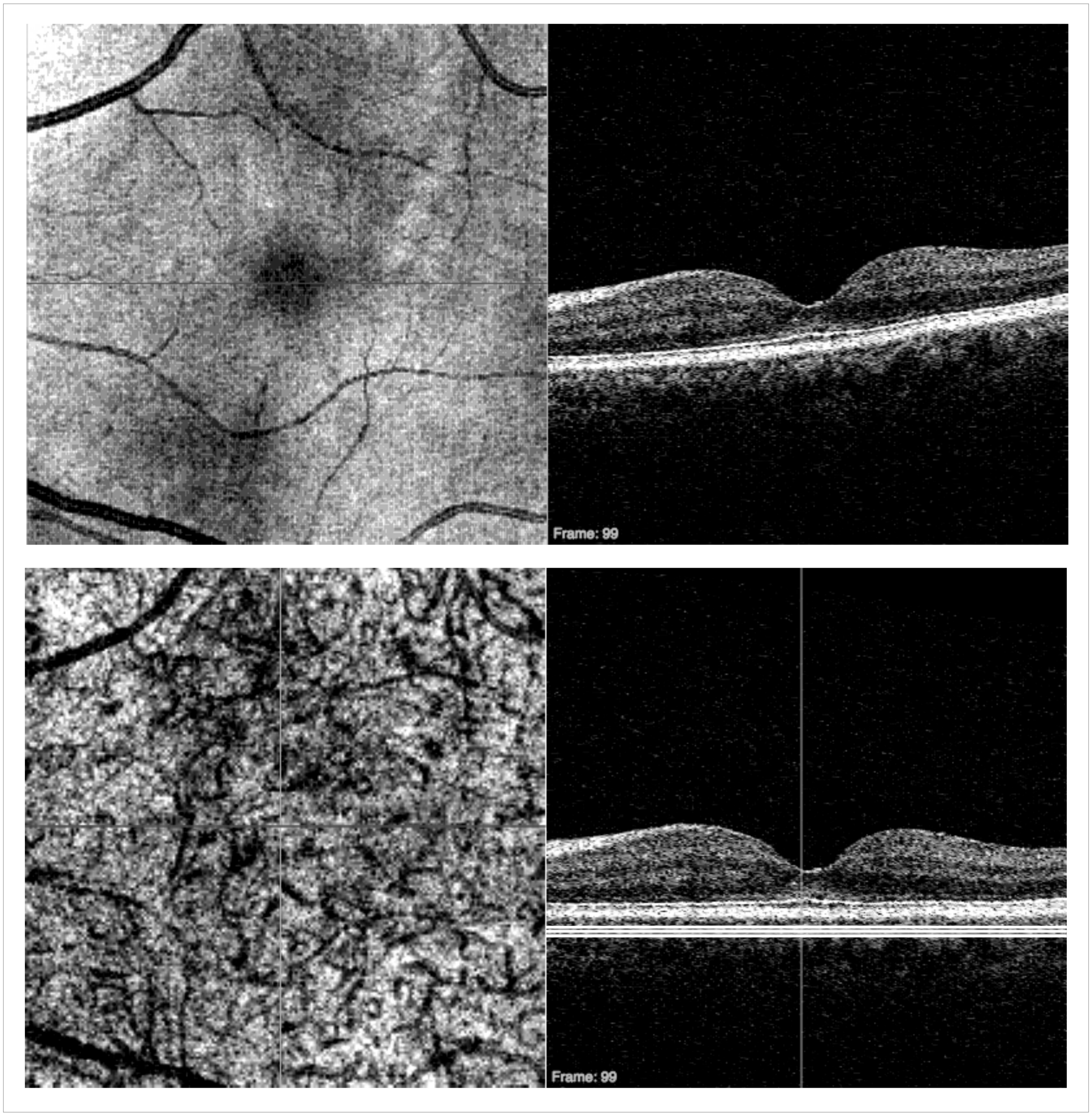


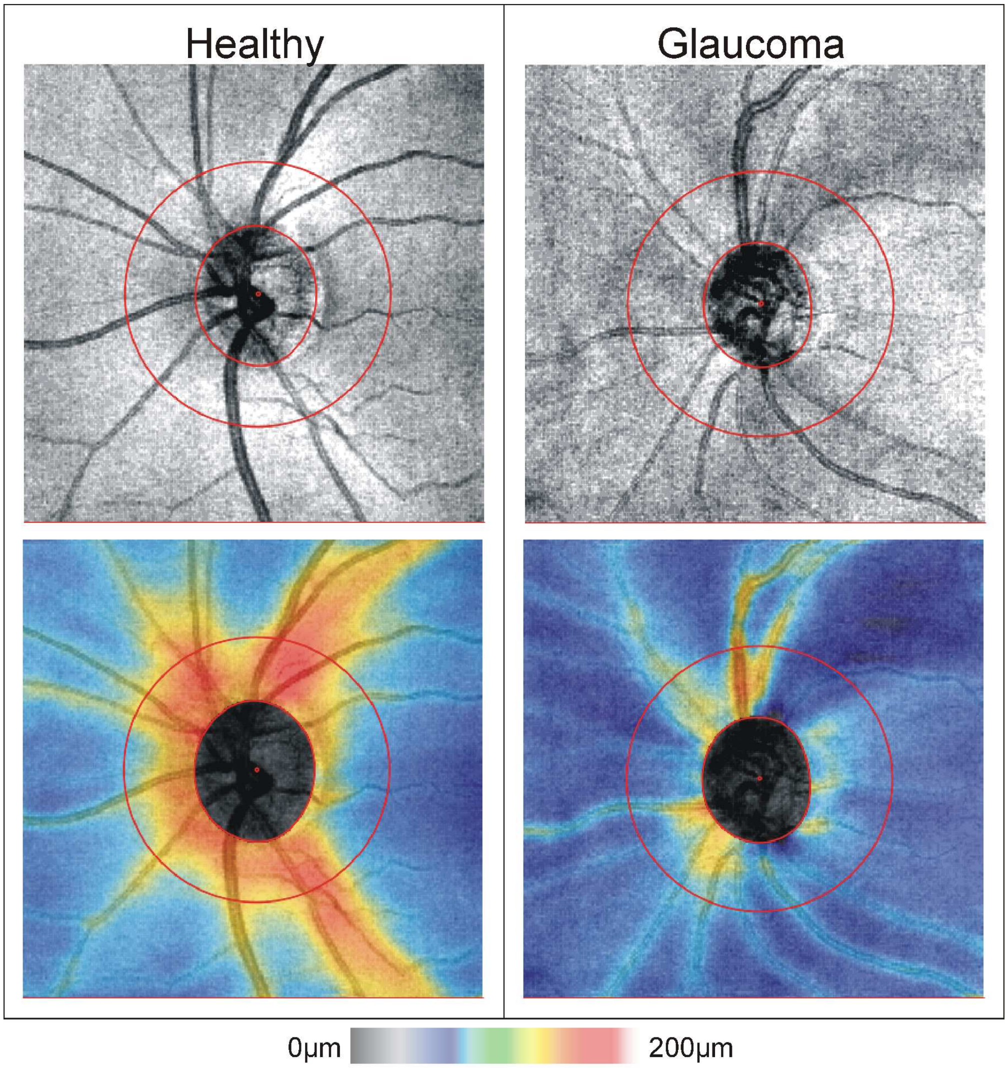
Table 1. Comparison of time-domain (TD-), spectral-domain (SD-) and swept-source (SS-) optical coherence tomography (OCT) devices

	Light source	Ophthalmic system commercially available?	Primary Advantages	Primary Disadvantages
TD-OCT	Broadbandwidth	Yes	Intensity information acquired in time domain; No complex conjugate image	Moving reference mirror required limiting acquisition rate
SD-OCT	Broadbandwidth	Yes	No moving reference mirror required; Higher sensitivity than TD-OCT; High scanning speed and axial resolution have been attained	Noticeable signal drop-off with depth
SS-OCT	Narrow band, swept through broad range	No	No moving reference mirror required; Higher sensitivity than TD-OCT; Very high scanning speeds can be attained; Minimal signal drop-off with depth	Most ophthalmic systems operating at longer wavelengths (λ=1-1.3 μm), with lower axial resolution

Table 2. Description of commercially available SD-OCT systems

Device (Manufacturer)	Description
3D-OCT 2000 (Topcon)	SD-OCT and high-resolution fundus camera; Axial resolution 5 μm, A-scan acquisition rate: 27 kHz.
Bioptigen SD-OCT (Bioptigen)	Designed for both clinical and research use and includes a hand-held probe and microscope setup; Axial resolution 4 μm, A-scan acquisition rate: 20 kHz

Cirrus HD-OCT (Carl Zeiss Meditec)	Software includes guided progression analysis for glaucoma progression detection; Axial resolution 5 µm, A-scan acquisition rate: 27 kHz.
RTVue-100 (Optovue)	Offers multiple scanning protocols for glaucoma detection, including ganglion cell complex analysis; Axial resolution 5 µm, A-scan acquisition rate: 26 kHz.
SOCT Copernicus (Optopol)	Software includes progression analysis software that incorporates disk damage likelihood scale, asymmetry between the discs, and RNFL thickness; Axial resolution 6 µm, A-scan acquisition rate: 27 kHz.
Spectral OCT SLO (Opko)	Combines SD-OCT, scanning laser ophthalmoscopy, and microperimetry. Axial resolution 6 µm, A-scan acquisition rate: 27 kHz.
Spectralis OCT (Heidelberg Engineering)	High-speed SD-OCT device with eye-tracking, fluorescein angiography, ICG angiography, and autofluorescence. Axial resolution 7 µm, A-scan acquisition rate: 40 kHz.



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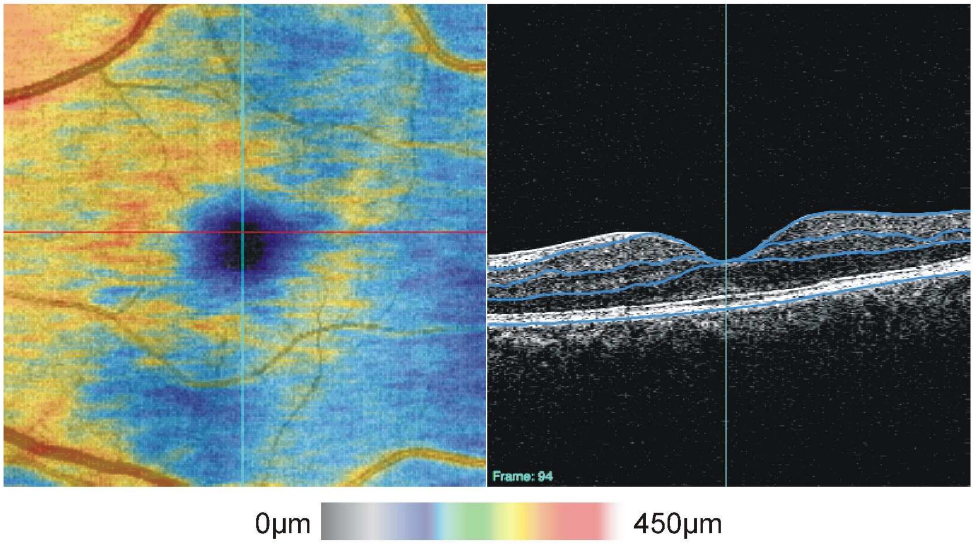

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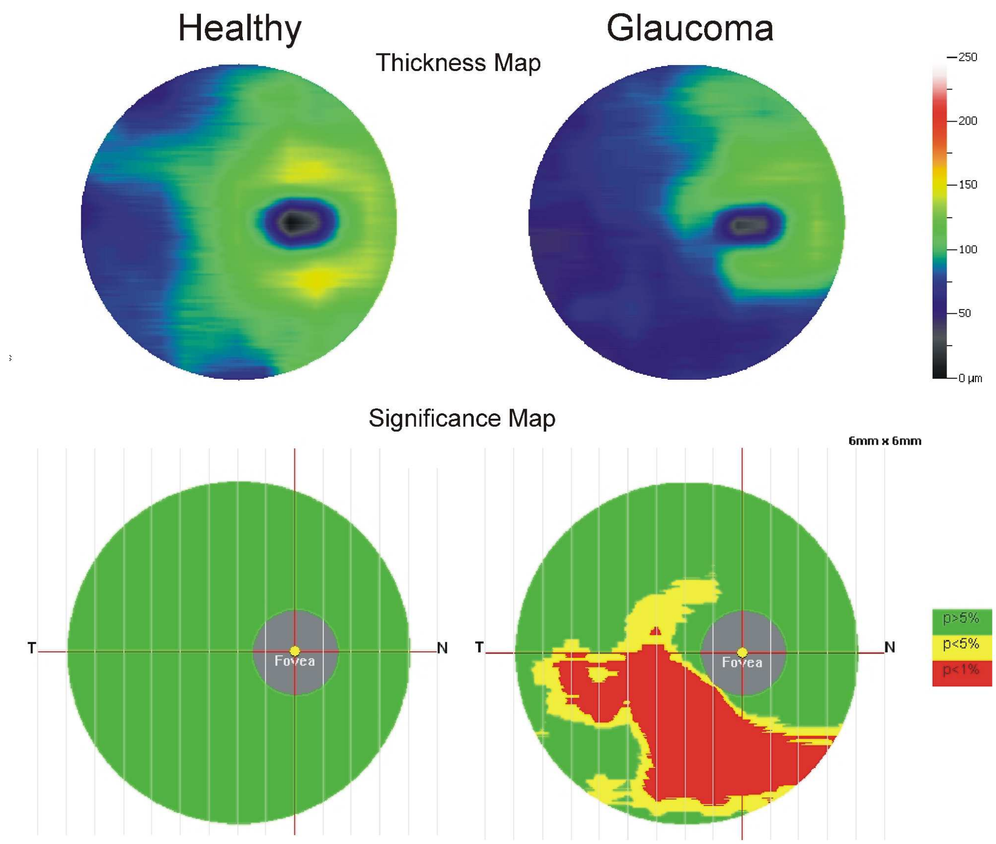

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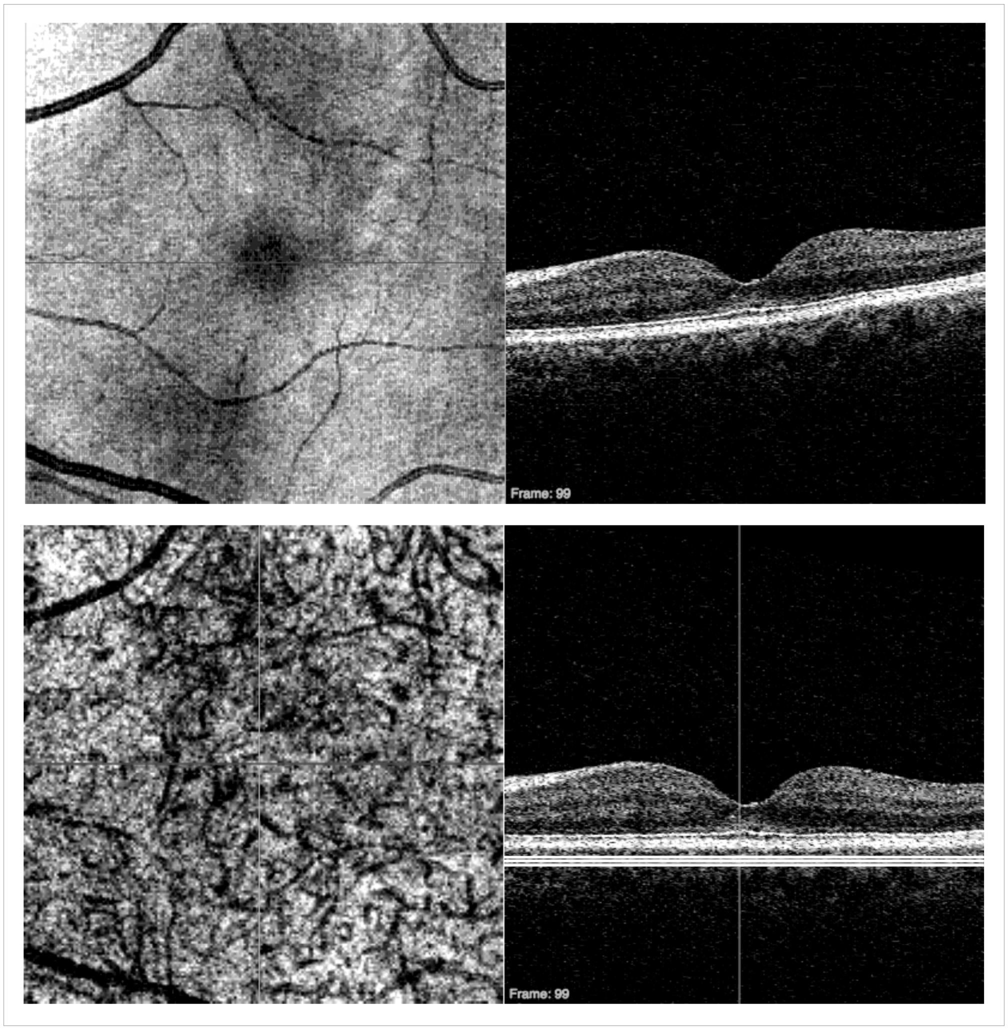

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