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Advances in Optical Coherence Tomography

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On improving the use of OCT imaging for detecting glaucomatous damage

Donald C Hood,1,2 Ali S Raza1,3

ABSTRACT

Aims To describe two approaches for improving the detection of glaucomatous damage seen with optical coherence tomography (OCT).

Methods The two approaches described were: one, a visual analysis of the high-quality OCT circle scans and two, a comparison of local visual field sensitivity loss to local OCT retinal ganglion cell plus inner plexiform layer (RGC+) and retinal nerve fibre layer (RNFL) thinning. OCT images were obtained from glaucoma patients and suspects using a spectral domain OCT machine and commercially available scanning protocols. A high-quality peripapillary circle scan (average of 50), a three-dimensional (3D) scan of the optic disc, and a 3D scan of the macula were obtained. RGC+ and RNFL thickness and probability plots were generated from the 3D scans.

Results A close visual analysis of a high-quality circle scan can help avoid both false positive and false negative errors. Similarly, to avoid these errors, the location of abnormal visual field points should be compared to regions of abnormal RGC+ and RNFL thickness.

Conclusions To improve the sensitivity and specificity of OCT imaging, high-quality images should be visually scrutinised and topographical information from visual fields and OCT scans combined.

INTRODUCTION

At one time, there was only one commercially available optical coherence tomography (OCT) machine and glaucoma specialists depended upon the summary report (figure 1A) based upon the most commonly used protocol. Numerous studies using this time-domain (td) OCT machine found that the average retinal nerve fibre layer (RNFL) thickness (arrow 1), clock hour thickness (2), and quadrant thickness (3) provide good sensitivity and specificity for detecting glaucomatous damage (see references1–4 for reviews). These RNFL thickness measures were obtained separately from three scans and averaged for this report; the machine was too slow to average multiple images within a scan protocol. One of these scans is shown in figure 1A (4) and the raw data for this same scan is enlarged and presented in grey scale in figure 1B. Given the relatively poor resolution of this peripapillary image, the success of this report is a testimonial to the robustness of these derived RNFL measures, as well as to those who developed the technique and this report.5–8

With the advent of newer technology, such as the spectral domain (sd) OCT, the quality of the images became substantially better. For example, compare the scan in figure 1B to the sdOCT scan in figure 1C. The improvement in quality was partly due to improved spatial resolution, but was largely due to the averaging of multiple images within a scan (50 in the case of figure 1C) made possible by a substantially faster scan rate. In addition, because of these improvements, so-called three-dimensional (3D) scans (ie, cube or volume scans) of the regions around the disc and macula became possible. In particular, multiple lines scans can be obtained within a single scan protocol. From these images, 2D measures of the retinal ganglion cell (RGC) and RNFL thickness can be derived.

While the sdOCT allows us to see spatial detail not easily seen on the earlier tdOCT scans, our analyses have not kept pace in at least two ways. First, one of the advantages of sdOCT is that it provides topographical information about RGC and RNFL abnormalities. Thus, local RGC and RNFL loss can be topographically compared to local loss in visual field (VF) sensitivity,9–10 as patients are routinely tested with static automated perimetry (SAP). This should improve sensitivity and specificity for detecting glaucomatous damage as SAP measurement errors should be largely independent of OCT measurement errors. Second, the improved sdOCT images allow for a direct visual analysis of the scans, much the way MRI scans are analysed, rather than depending entirely upon computer-driven summary statistics.

The purpose here is to describe two approaches for improving the detection of glaucomatous damage; one approach combines a topographical comparison of OCT and VFs and a second involves a qualitative analysis of OCT scans. These approaches are illustrated below in a one-page report.

METHODOLOGY

The data from five eyes of five patients, were used to illustrate our approach. All five had glaucomatous optic neuropathy on stereophotography evaluation and all were part of previously published studies.11,12 They had 24-2 and 10-2 VFs tests obtained with the SITA-standard protocol (Humphrey VF Analyzer; Carl Zeiss Meditec, Dublin, California, USA); for inclusion, the mean deviation (MD) on the 24-2 VF had to be better than −6 dB.12 Written informed consent was obtained from all of the participants. Procedures followed the tenets of the Declaration of Helsinki, and the protocol was approved by the institutional review board of Columbia University.

OCT protocol

A sdOCT machine (3D OCT-2000, Topcon) and the following three scan protocols were used: 6.0×6.0 mm 3D disc (512 A-scans by 128 B-scans); 6.0×6.0 mm 3D macula (512 A-scans by 128 B-scans); and 3.4 mm dia. circle (average of 50 scans; 1024 A-scans). The circle protocol involved...
averaging 50 individual scans and thus produced an image of relatively high-quality. (Note that shadowgrams (see inset in panel E of figures 3 (green arrow), 5 and 6) can be examined for artefacts such as excessive eye movements, blinks, etc.)

OCT analysis
Peripapillary RNFL analysis
The high-quality peripapillary image produced by the circle scan was qualitatively analysed as described in the Results. In addition, this image was segmented by the machine’s software and a RNFL thickness plot produced. While the circle scan has the advantage of being of high quality, it can be off-centre if the patient has considerable trouble fixating or the operator is not careful. The fundus photo with the superimposed scan location (inset in panel A of figures 2, 3, 5 and 6) provides some information about how well centred the scan was.

The commercial software also derives a peripapillary RNFL thickness plot from the segmentation of the 3D disc scan, by centring a circle after the scan is obtained. To distinguish this plot from the one based upon the high-quality averaged circle data, the software uses a different algorithm and different parameters to calculate the thickness values.
3D RNFL and RGC+ thickness maps
As previously described,9 RGC+ and RNFL thickness maps were derived from the macular and disc 3D scans and turned into probability plots by comparing the thicknesses to normative values.

RESULTS
Below we describe elements of a report for detecting RGC/RNFL damage based upon sdOCT imaging. The report is designed to illustrate the power of combining VF and OCT information, as well as the value-added in carefully examining the OCT images.

Reports should display RNFL thickness plots as NSTIN, not TSNIT plots
In the original tdOCT report, the peripapillary circle scan (arrow 4 in figure 1A) was presented with the nasal quadrant (N) in the middle and the temporal (T) quadrant divided between the left and right ends. The accompanying RNFL thickness plot (arrow 5 in figure 1A) has been called the ‘TSNIT plot’. Instead, we recommend using a ‘NSTIN plot’, in which the most important portion of the disc for visual function, the temporal quadrant, is in the middle (figure 1D). As illustrated in the original report, the peripapillary circle scan (arrow 4 in figure 1A) was presented with the nasal quadrant (N) in the middle and the temporal (T) quadrant divided between the left and right ends. The accompanying RNFL thickness plot (arrow 5 in figure 1A) has been called the ‘TSNIT plot’. Instead, we recommend using a ‘NSTIN plot’, in which the most important portion of the disc for visual function, the temporal quadrant, is in the middle (figure 1D). As illustrated

Figure 2 Visual field (VF) and spectral domain optical coherence tomography (sdOCT) data for Patient 2 along with models relating VF locations to OCT, all shown as if for right eye. (A) The NSTIN averaged circle sdOCT image with computer-derived retinal nerve fibre layer (RNFL) segmentation (green lines) and corresponding circle scan path on top of fundus (inset). (B) The averaged circle RNFL thickness (grey dashed line) calculated based on the segmentation in (A) and the extracted circle RNFL thickness (solid black line), with regions corresponding to the superior (magenta) and inferior (dark blue) macula in unique colours. Both RNFL thickness plots are superimposed on coloured regions indicating the 95% to 5% (green), 5% to 1% (yellow), and less than 1% (red) ranges of normative data. The red vertical lines indicate the average location of the major blood vessels in a group of patients. (C) The 24-2 VF for the same patient with (D) a model relating the locations of the VF to regions of the circle scans. (E) The 10-2 VF for the same patient with (F) a model relating the locations of the VF to regions of the circle scans. The bold dark blue line indicates the macular vulnerability zone (MVZ).
below, this allows for easier visualisation of the relationship between RNFL thinning and VF defects.

Reports should contain an enlarged image of the circle scan
Figure 2A shows the averaged circle scan from Patient 2 with the computer-derived borders of the RNFL in green. There are two reasons for including an image larger than seen in the tDOCT report in Figure 1A (arrow 4). First, the validity of the computer-marked borders can be assessed. All current OCT computer algorithms make mistakes (segmentation errors), which will be typically overlooked if the scan image is presented as a small inset as in figure 1A. Epiretinal membranes, vitreous detachments, and poor image contrast can lead to segmentation errors and thus errors in the associated RNFL thickness measures. The enlarged, averaged circle scan has sufficient detail so that these errors can be identified.

Second, the high-quality image allows for a qualitative assessment of the details of the scan. For example, in figure 2A local RNFL thinning can be seen in two regions (see white arrows). Other details of interest can be seen in some circle scans as illustrated below.

Look for regions of abnormal thinning on the RNFL plot and compare to scan
After scrutinising the averaged circle scan image, the RNFL thickness plots should be examined. The dashed and solid curves in Figure 2B are the RNFL thickness plots from the averaged circle and 3D scans, respectively. If these curves agree and the segmentation seen on the scan appears accurate, these plots can be trusted. If they disagree, it is usually possible to decide why.

For example, the averaged circle (dashed) and extracted circle (solid) RNFL thickness plots from Patient 3 in Figure 3B disagree in two locations. First, the thickness in the temporal quadrant and part of the superior quadrant is slightly greater in the case of the averaged circle, probably because the circle scan is off-
centre; see the fundus photograph (inset in panel A). Second, and more important, there is a suggestion of a small local defect on the extracted circle RNFL plot (solid), but not on the averaged circle plot (dashed). A close examination of the scan in panel A, indicates a small, local thinning, which the algorithm appears to underestimate on the averaged circle scan. This is discussed further below.

After assessing the veracity of the RNFL plot (figure 2B), the regions of abnormal thinning can be identified. In this case, the RNFL plot falls well below the 99% confidence limit in the same regions (black arrows in figure 2B) that show local thinning on the scan in figure 2A (white arrows).

Examine the general topographical agreement between peripapillary RNFL thinning and loss in VF sensitivity

With a little practice, the topographical agreement between peripapillary RNFL thinning and VF defects can be assessed qualitatively. To make this assessment, one needs to take into consideration the relationship between regions of the disc and regions of the VF.

Figure 2 illustrates this relationship. The 24-2 pattern deviation (PSD) plot for this eye is shown in panel C. The red and light blue arrows in panel B mark the temporal half of the circle scan, that is, they extend from +90° to −90° as shown in panel D. The corresponding region of the 24-2 VF is enclosed within the light blue and red contours in panel C. These contours were drawn to be in general agreement with previous work. While these contours are approximate, and will differ somewhat among individuals, they are useful for deciding whether there is agreement among the OCT and VF findings.

The dashed red and blue horizontal lines along the x-axis in figure 2B show the regions of the RNFL plot that correspond to the abnormal regions of the VF (ie, the points falling within the dashed ellipses in C). In this case there is excellent agreement.

The RNFL plot also suggests there is damage in the macula, defined here as the central ±8°. To facilitate the detection of macular damage on the RNFL plots, the regions of the scan associated with the RGC fibres from the central ±8° retina are coded as magenta (superior retina/lower VF) and dark blue (inferior retina/upper VF). These boundaries (see panel F), as well as the corresponding regions on the 10-2 (panel E), are based upon a recent map of the macula. Note that macular damage is confirmed by the 10-2 VF in panel E.

Figure 4 (A) The 24-2 and (B) 10-2 visual field (VF) data for Patient 3. (C) The 10-2 VF data for Patient 4, (D) the 24-2 VF data from 2013 for Patient 5, and (E) enlargements of a hole observed in the averaged circle scan of Patient 5 in both 2013 (left) and 2010 (right).

Look for macular damage especially in the macular vulnerability zone

We have identified two types of macular damage on OCT scans. One type, considered below, is diffuse/widespread and is typically relatively shallow and difficult to identify with RNFL scans. The second tends to be deeper and to occur in a relatively narrow portion of the inferior disc labelled macular vulnerability zone (MVZ) in figure 2F.

This local macular damage easily can be missed if one does not look closely at the high-quality averaged circle scan and the RNFL plots. Figure 3A,B shows what appears to be a relatively normal RNFL thickness plot, although there is probably local nasal thinning far outside the 24-2 VF. The commercial report (not shown) indicated normal RNFL thickness in the inferior, temporal and superior quadrants and the associated clock hours. The 24-2 VF (figure 4A) appeared normal as well with a MD of −1.50 dB, a PSD of 1.16 dB, and a glaucoma hemifield test (GHT) within normal limits. However, as mentioned above, the extracted circle RNFL plot from the 3D scan (solid curve in figure 3B) shows a very local abnormal region (arrow). Given the VF results, this local abnormality could easily be overlooked. In any case, the scan in figure 3A shows a small local thinning (white arrow). This local thinning is in the middle of the MVZ, which is shown as the horizontal dark blue line. The damage in the MVZ can be missed on 24-2 VF tests because they poorly sample the region of glaucomatous damage of the macula seen on OCT.

The patient’s 10-2 VF (figure 4B) shows a subtle defect in the general region one would expect from the model of macular damage. However, given the subtle nature of both the OCT and VF changes, there is reason for scepticism. Figure 3 is our one page report of RGC/RNFL damage; the other panels, described below, confirm the damage is real.

Examine the RGC layer thickness maps obtained from the macular 3D scan

RGC thickness maps are useful for identifying macular damage, which can be missed on peripapillary RNFL analysis. In general, the commercial machines supply an analysis of macular 3D scans that includes RGC thickness. In some cases, this is the thickness of the combined RGC, inner plexiform layer (IPL) and RNFL, while in others it is the thickness of the combined RGC+IPL (called here RGC+). Figure 3D (right panel) shows the patient’s RGC+ thickness derived from the macular 3D scan and displayed in pseudo-colour. By

Figure 5  The single-page spectral domain optical coherence tomography report for Patient 4 as in figure 3 showing diffuse retinal ganglion cell (RGC)+ thinning (panel D, right). The agreement of the RGC+ (panel F) and retinal nerve fibre layer (RNFL) (panel E) probability plots with the visual field (VF) probability plot suggests diffuse macular damage.
comparing the local thickness values to healthy controls, a probability plot can be created as shown in figure 3F. This probability plot is displayed in field view. The abnormally thin RGC+ layer (black arrows in figure 3D,F) argues for macular damage in this eye.

Examine the RNFL layer thickness maps obtained from macular and disc 3D scans

From the 3D scans of the disc most commercial machines produce RNFL thickness plots as shown in figure 3C. A RNFL thickness plot can also be produced for the macular 3D scans as shown in figure 3D (left). By comparing the thickness values to healthy controls, this thickness plot can be turned into a probability plot. For the report, the RNFL probability plots from the macular and disc 3D scans are combined by aligning the blood vessels and then displayed in field view (figure 3E). The local macular damage is clearly apparent in this RNFL thickness analysis as indicated by the red arrows in panels C, D (left) and E.

Examine the topographical agreement between local RNFL and RGC+ thinning and local loss in VF sensitivity

The best way to assess the topographical agreement between RNFL thinning and VF sensitivity loss is to superimpose the probability plots for each as previously described. This analysis is shown on the right side of our report. Figure 3F shows the points from this patient’s 10-2 VF (figure 4B) superimposed on the field view of the RGC+ probability plot. The significance levels of the 10-2 points and RGC+ thickness are colour-coded using the same continuous probability scale. To make this comparison, the locations of the VF points need to be adjusted to account for the displacement of the RGCs in the fovea.

In a similar manner, in figure 3E the points of the 24-2 and 10-2 VF are superimposed upon the RNFL probability plot.
(field view) and coded with the same continuous probability scale. There is good local agreement between the OCT and VF results for the upper VF/inferior retina.

While it may be difficult for manufacturers to incorporate VF data into their software, it should be relatively easy for them to indicate the 24-2 and 10-2 locations on the OCT probability plots and leave it to the clinician to circle the VF points that are abnormal.

Using the report to detect diffuse macular damage
The report for Patient 4 in figure 5 illustrates an example of what we believe is diffuse macular damage.12 This patient’s 10-2 VF (figure 4C) had a MD of −4.15 dB (p<1%) and the total deviation values showed a relatively homogeneous loss across the VF. Given that the PSD was normal, many would attribute this diffuse loss of sensitivity to non-glaucomatous factors. The peripapillary RNFL plot in figure 5B is also ambiguous with the region corresponding to the macula (magenta and dark blue) falling in the normal (green) or borderline (yellow) region. The comparison of RGC+ and VF abnormalities in panel E, however, suggests diffuse macular damage. The RNFL and VF comparison in panel F agrees. On exam, this patient did not have cataracts, but did have a best corrected visual acuity (BCVA) of 20/50, also consistent with diffuse damage.

Carefully examine the actual scan images
There is much to be learned by carefully examining the actual OCT scan images. Below, we illustrate three examples.

False positives and the location of blood vessels
Figure 6 shows our report for the right eye of Patient 5. A glaucoma specialist noted peripapillary atrophy and diffuse thinning on fundus stereo photographs. The report from the commercial machine showed abnormal RNFL thinning in the inferior quadrant. Our report appeared to confirm this finding (black arrows in figure 6B). However, while the OCT analysis was consistent with local damage, the fundus exam and VF (figure 4D) were consistent with diffuse damage. On closer analysis, we concluded that the OCT result was a false positive, an example of what has been called ‘red disease’.17 Notice the abnormally thick RNFL in the temporal quadrant in figure 6A,B. The major blood vessels (BVs) in this eye are located more temporally than the average location for the controls. The red lines in panel B show the average locations of the major four groups of BVs for a group of patients.18 The red arrow in panel A indicates the location of the inferior-temporal (IT) BVS in this eye, while the purple arrow shows the average location of the IT BVS. As expected, the location of the IT BVS correspond to the location of the inferior peak of the RNFL plot (peak of green in panel A) in healthy controls.19 This is, in part, due to the direct contribution of the BVS to the RNFL thickness and in part due to the fact that the thickest region of RNFL tends to be close to the major BVS.19 In any case, the location of the IT BVS in this eye is probably the reason for the abnormally thick RNFL in the temporal quadrant and the abnormally thin RNFL in the inferior quadrant. The 24-2 VF is probably a false positive as well. Note that the 24-2 test from 2012, 1 year earlier, was normal, while the 24-2 VF obtained 2 years earlier showed diffuse loss.

Hypodense (holes)
While the inferior quadrant of the RNFL profile of this eye illustrates a false positive OCT result, the scan in figure 6A has evidence of local damage in the superior quadrant of the disc. In particular, there is a hypodense region (white arrow in figure 6A). We have shown that these holes are actually tunnels that follow an arcuate pattern and are almost surely very local, and very small, RNFL bundle defects.20 We have only seen them in patients with glaucoma or patients who are glaucoma suspects.21 They also show progression as seen for this eye in figure 4E.

Examine horizontal and vertical macular scans for outer retinal damage
Finally, we routinely examine the 3D macular scans, as well as a high-quality horizontal line scans through the macula, for signs of outer retinal damage. This is particularly important in eyes with reduced visual acuity. It is common to see previously unnoticed signs of epiretinal membranes, age-related macular degeneration, oedema, and macular holes in glaucoma patients and suspects.22

DISCUSSION
While once there was a single OCT report used to identify glaucomatous damage, now every commercial machine offers more than one glaucoma report. However, by and large, these reports fail to take full advantage of the spatial detail available. We argued above that the effectiveness of the OCT could be improved by a qualitative analysis of enlarged, high-quality images and by a topographical comparison of the abnormal regions seen on OCT to those seen on VFs. Our one-page report was developed to incorporate this information.

However, no one report will suffice. The high-quality OCT scans have all the complexities of MRI scans, as well as better spatial resolution. Yet, MRI scans are not analysed by computer algorithms and summarised in simple summary statistics and diagrams, as is typically the case with OCT scans. In fact, relying solely on summary statistics plays a major role in apparent disagreements between the results of VF and OCT tests.23 In the case of MRI scans, radiologists read and interpret the scans for other specialists, while in the case of OCT scans, ophthalmologists are left to interpret the scans on their own.

While the report developed here is meant to help ophthalmologists in this interpretation, it will not suffice. On one hand, the summary statistics and diagrams seen in figure 1A are still of use and new summary statistics combining VF and OCT information are being developed.24–30 The sensitivity and specificity of these various summary statistics need to be compared to alternative analyses, such as the report described here with and without summary statistics. On the other hand, the full power of the OCT will rely on a careful analysis of high-quality images performed by individuals trained to read these scans, much the way a radiologist reads an MRI. This is by far the most complex task, even for the most experienced OCT analyser.

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REFERENCES


Characterisation of Schlemm’s canal cross-sectional area

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ABSTRACT

Purpose To compare three methods of Schlemm’s canal (SC) cross-sectional area (CSA) measurement.
Methods Ten eyes (10 healthy volunteers) were imaged three times using spectral-domain optical coherence tomography (Cirrus HD-OCT, Zeiss, Dublin, California, USA). Aqueous outflow vascular structures and SC collector channel ostia were used as landmarks to identify a reference location within the limbus. SC CSA was assessed within a 1 mm segment (±15 frames of the reference, 31 frames in all) by three techniques. (1) Using a random number table, SC CSA in five random frames from the set of 31 surrounding the reference were measured and averaged. (2) The most easily visualised SC location (subjective) was measured, and (3) SC CSA was measured in all 31 consecutive B-scans, and averaged (comprehensive average, gold standard). Subjective and random CSAs were compared with the comprehensive by general estimating equation approach (linear regression); producing high estimates of SC CSA. SC assessed by these studies varied widely, failing to account for SC CSA variability in their study design. Further, no study has objectively quantified the magnitude of local variation in the healthy SC CSA, or supported a method of SC CSA assessment compared with a comprehensive assessment throughout a volumetric image. We hypothesised that: (1) SC cannot be accurately characterised by a single radial cross-sectional measurement, and (2) SC can be accurately and efficiently characterised by an a priori randomisation of SC CSA measurement locations to remove observer bias. The purpose of the present study was to test and compare an average of randomised SC CSA measurements, and a single subjective CSA measurement with the average of measurements from every scan within a 1 mm segment of SC.

RESULTS

The average from five random locations (4175 ±1045 μm²) was not significantly different than that obtained from the gold standard comprehensive assessment (4064±1308 μm², p=0.6537). Subjectively located SC CSA (7614±2162 μm²) was significantly larger than the comprehensive gold standard SC CSA (p<0.0001). The average of five random frames produced significantly less bias than did subjective location, yielding a calibration line crossing the ‘no-bias’ line.

DISCUSSION

Subjectively located SC CSA measurements produce high estimates of SC CSA. SC assessed by measuring five random locations estimate CSA was similar to the gold standard estimate.

INTRODUCTION

Glaucoma is the second leading cause of irreversible blindness in the world.1 Elevated intraocular pressure (IOP) is the greatest risk factor for the presence and progression of glaucoma.2-4 Reduction of IOP is the only Food and Drug Administration approved outcome of glaucoma medications and procedures.5 IOP is regulated by a balance between aqueous humour production and outflow. Reducing outflow resistance is the most common technique for IOP reduction; however, there is no clinically viable technique to assess outflow structure.2

Previously we reported that Schlemm’s canal (SC) cross-sectional area (CSA) as measured from spectral-domain optical coherence tomography (SD-OCT) is much smaller adjacent to collector channel ostia (SC—collector channel branch points). Specifically, within 160 μm of an ostium along its circumferential arc, SC CSA drops by 50%.8 This implied that SC CSA varies rapidly within short distances along its arc. Since that report, a number of publications have measured SC morphology with no strategy to address rapid variations in SC CSA.9-14 Being from multiple investigators, and with no existing consensus on assessment methodology, the techniques employed by these studies varied widely, failing to account for SC CSA variability in their study design. Further, no study has objectively quantified the magnitude of local variation in the healthy SC CSA, or supported a method of SC CSA assessment compared with a comprehensive assessment throughout a volumetric image. We hypothesised that: (1) SC cannot be accurately characterised by a single radial cross-sectional measurement, and (2) SC can be accurately and efficiently characterised by an a priori randomisation of SC CSA measurement locations to remove observer bias.

METHODS

The study was conducted in accordance with the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act. The institutional review board of the University of Pittsburgh approved the study. All subjects gave written informed consent before participation.

Study protocol

The nasal limbus of normal healthy eyes was scanned three times by SD-OCT using a volumetric raster scan pattern.15 These scans were analysed by three techniques: (1) Using a random number table, CSA measurements at five random locations within a 1 mm segment of SC were made and averaged as an estimate of overall CSA (Random); (2) A single CSA measurement was made at a location within the 1 mm segment at which SC was easily visualised (Subjective) and (3) CSA was measured in all 31 scans within the 1 mm segment. The ‘comprehensive’ analysis was performed first. Once completed, the ‘random’ data were drawn from the comprehensive data set using a random number
table to identify five random locations. Finally, the ‘subjective’ location was identified by reviewing the images within the region measured for the ‘comprehensive’ data. When SC was determined to be most prominent, the measurement of SC at that location within the existing ‘comprehensive’ data set was identified and used as the ‘subjective’ measurement.

The average of the 31 measurements provided the gold standard estimate of SC CSA for that segment. (Comprehensive, figure 1). In addition, within the 31 comprehensive measurements, change was quantified as the absolute difference in SC CSA between adjacent B-scans within each volume.

**SC imaging**

Ten healthy volunteers were recruited from the staff and faculty of the UPMC Eye Center. At one visit, three ‘Anterior Segment 512×128’ volumetric scans were obtained (Cirrus HD-OCT; Zeiss, Dublin, California, USA). Each scan comprised a 4×2×4 mm (512×1024×128 samples) volume of the limbus region from the right eye (nasal quadrant). Chin and forehead rests were used to centre the eye in the image frame, and verbal commands were used to direct the volunteer to move their eye and centre the desired region of the limbus in the field of view. This procedure produces SD-OCT scans with the limbus oriented orthogonally to the laser beam. Twenty-seven thousand A-scans were acquired per second. B-scans were evenly distributed and separated by 31.25 μm. The scan time was 2 s.

**Image processing**

The routine used in our previous studies was applied to the present image set.15 Briefly, images were blurred and contrast enhanced by local contrast enhancement using adaptive histogram filtering in Fiji (ImageJ 1.45q, NIH, http://imagej.nih.gov/ij/). Images were resampled to create isotropic pixels, facilitating measurements. An adjustment of contrast and brightness was applied to the entire image stack. B-scans were excluded if SC’s borders were not visible or excessive noise or shadowing were present. Using vasculature and collector channels as landmarks, one location contained in each of the three scan volumes was identified and used to ensure that the same region of the limbus was analysed throughout. Manual segmentation was performed as described previously,8 using a subjective full-width half-height approach.15 SC was traced using the freehand tool in Fiji, and area calculated automatically (figure 1).

**Statistics**

All CSA measurements are presented as mean±SD. The distributions of all comprehensive SC CSA measurements and of positional SC CSA fluctuation values are presented in histograms. Subjective and random SC CSA means were compared with the gold standard comprehensive mean. To account for correlation of data obtained in three scans of the same eyes, averages were compared by general estimating equation analysis. Structural equation modelling was used to quantify agreement between the three analysis techniques, and generate calibration equations between them. Agreement is displayed by scatter plot. Unlike regression, which only quantifies imprecision between data sets, a calibration equation quantifies imprecision and bias. For example, data sets of 1, 2, 3, 4, 5 and 1001, 1002, 1003, 1004, 1005 would produce a r² value of 1.0 (no imprecision) with regression analysis, and fail to describe the enormous bias. A calibration equation quantifies both.

With a reported coefficient of variation of 11% in measurements of SC using the technique described above,8 and reported SC CSA of 12 890 μm², this study has 90% power to detect a difference in the measurement of SC CSA as small as 1321.2 μm², as significant.

**RESULTS**

**Demographics**

The average age of the 10 healthy volunteers (3 male, 7 female) was 41 years (range 22–63 years). In total, 29 scans were analysed; one of the three volumetric scans from subject 8 was...
excluded from the reproducibility analysis due to eye movements during acquisition.

**Data distributions**

Thirty-one measurements from each of the 29 analysed scans yielded 899 measurements of SC CSA, and 870 B-scan to B-scan absolute differences within the normal cohort. The distribution of the SC CSA measurements is provided in figure 2. Note that 31 scans (5.7%) presented with SC CSAs between 0 μm² and 1000 μm². The remaining SC CSA values are distributed approximately normally around the mean value of 4064 μm² with 23 CSAs (2.6%) larger than 10 000 μm².

The absolute difference in B-scan to B-scan SC CSA, or positional fluctuation was 1223±1162 μm². Figure 2 shows the distributions of SC CSA and positional fluctuation for all subjects. Five hundred and forty-six (62.8%) of all frame to frame differences were less than 1000 μm², though approximately 15 instances (1.7%) of SC CSA changes larger than 4000 μm² were observed, with some approaching 10 000 μm².

**Cross-sectional area**

The comprehensive, subjective and random mean CSAs are provided in table 1. Subjective estimates of SC CSA were significantly higher than the comprehensive mean (table 1). There was no difference between comprehensive and random estimates of SC CSA. (table 1) Subjective (figure 3) and random (figure 4) estimates of SC CSA were in good agreement with the comprehensive means; however, as suggested by the differences found in the general estimating equation analysis, the subjective CSAs were significantly biased toward higher values compared with the comprehensive means (figure 4).

![Table 1](image)

<table>
<thead>
<tr>
<th></th>
<th>Comprehensive 31 B-scans</th>
<th>Subjectively identified frame</th>
<th>Random 5 frame</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSA (μm²)</td>
<td>4064±1308</td>
<td>7614±2162</td>
<td>4175±1045</td>
</tr>
<tr>
<td>GEE significance level</td>
<td>&lt;0.0001</td>
<td>0.6537</td>
<td></td>
</tr>
<tr>
<td>SEM goodness of fit</td>
<td>0.669</td>
<td>0.713</td>
<td></td>
</tr>
</tbody>
</table>

Significance levels of a general estimating equation comparison with the gold standard comprehensive measurements, and goodness of fit of the structural equation models are presented.

GEE, general estimating equation; SEM, structural equation modelling.

Figure 2 (Top) Histogram of cross-sectional area (CSA) measurements as the number of measurements. (Bottom) Histogram of CSA B-scan to B-scan change calculations as the total number of calculations.
Previous studies have used different combinations of these approaches. In our 2010 publication, we were not attempting to provide an overall characterisation of SC, but only to test a clinical observation of SC expansion at the location of collector channel ostia.\(^8\) In this instance, the utility of the volumetric scan was not in the supply of sufficient samples for general characterisation, but inclusion of enough tissue within the scan to facilitate identification of a landmark position available within all three scans. Once located, adjacent 'non-ostium' sections of SC could be measured and compared. While confirming the hypothesis that SC expands at ostia, the large difference observed suggested that SC CSA might present with large variations in extremely short circumferential distances. The present study approaches the more general problem of characterisation of SC, at least on a regional basis. Herein, the present data suggests that a sample of five random locations provides an estimate of SC CSA similar to that of a comprehensive measurement of all available sequential frames within a region. This is important due to the processing time required for high quality measurements. Image processing times are minimal, requiring approximately 2–3 min to prepare a volume for manual segmentation; however, the actual segmentation of SC can take as much as 1–2 min per frame. A comprehensive analysis of a 1 mm segment might, therefore, require half an hour for a single volume. This represents \(\sim 15\) h of manual segmentation time for the data set in the present study. Reducing the task to five random samples per volume reduces the overall processing time of the same data set from \(15\) h to a little over \(2.5\) h. While sampling provided an accurate general quantification of SC, clinical applicability, such as canoplasty, may still require a comprehensive description of the distribution of all SC CSAs, especially the percentage of locations at which SC is completely collapsed.

The findings of the present study have important implications in the interpretation of recent publications. Hong \(^{et\ al}\)\(^1\) used SD-OCT to compare SC CSA in healthy eyes and those with primary open angle glaucoma in cohorts of Chinese persons. They found that eyes with primary open angle glaucoma have a reduced CSA compared with normal healthy controls, and observed a positive correlation between SC CSA and IOP. The CSAs observed in their study are consistent with those observed at the ostia\(^8\) and those observed in subjectively identified frames (present data). This is consistent with the scanning protocol used by Hong \(et\ al\). They used a single line scan, interrogating the limbus until a clear view of SC was obtained. In this case, it is likely that only the largest viewable regions of SC were measured. The positive correlation in the present data suggest that measurements obtained by a single subjectively identified sample are representative of actual SC CSA, but may overestimate the actual average SC CSA present in the cohort of examined eyes. However, in their study, they used a RTVue OCT device, and it is possible that systematic differences between devices could yield systematic differences in SC CSA measurements.

Day \(et\ al\) measured SC diameter and trabecular meshwork CSA by identifying landmarks denoting its boarders.\(^10\) Similar to Hong \(et\ al\), they used a line scan protocol to acquire limbus imagery. Unlike Hong \(et\ al\), the Day \(et\ al\) study used the depth of the inner wall of SC, the Schwalbe’s line and the location of the scleral spur to identify the borders of the trabecular meshwork. Though SC diameter was not measured in the present study, visualisation of its three-dimensional (3D) morphology suggests that the diameter that would be observed in cross section would vary widely in a fashion similar to CSA.\(^15\) Rapidly changing SC CSAs were subjectively observable in the present data (figure 5). Assuming that the same tendency to
seek locations of prominent visualisation of SC due to its larger than average local size, it is possible that the estimates of SC diameter are also larger than the average SC CSA within a given region. 

Shi et al used a swept-source OCT for the assessment of SC.13 As with the other studies, the authors have used a single line scan to represent SC, yielding an estimation of SC CSA of 7888.38±1472.58 μm². Their measurements are remarkably close to the 7614±2162 μm² obtained in the present study when a single subjective location was sought. 

There were several limitations in the present study. This study was completed on one SD-OCT device only. Some portions of the structures being studied may be too small to be visualised by the current generation of the SD-OCT device. The 3D reconstructions suggest that the structures visualised in the 2D slices indeed are aqueous outflow vasculature,9 but this does not ensure that the smallest structures were visualised completely. 

However, a subjective comparison with latex corrosion castings and fluorescent microsphere models suggests that SD-OCT images include sufficient outflow structure to afford their 3D reconstruction the same appearance and completeness as the gold-standard comparisons.18 Another limitation is the possibility that the processing alters the measured size of structures within the images. However, such a systematic alteration of SC size would affect measurements equally, and could not explain the significant difference between subjective and comprehensive analysis observed in the present data. Further, the present study only included normal healthy eyes. SC has been shown to be smaller in eyes with glaucoma.14 It is possible that the findings obtained in a population of larger SC CSAs may not be generalisable to a population of eyes with disease, and associated smaller outflow structures. The distribution of SC sizes in the healthy eyes herein appeared to be skewed to the right, though the mean and median values were nearly identical (unpublished data). It is possible that the distribution of SC CSAs in eyes with glaucoma may be worse, and non-parametric statistics would be required. 

The analysis used in the present study did not assume a normal distribution, though the potential for skewed data necessitates testing for normality. Finally, the present study only included a limited number of eyes. This data set cannot be used to anticipate or account for variations that may exist between different ethnic and age groups.

In conclusion, SC can be assessed efficiently in a small number of randomly sampled frames. When a measurement location is sought subjectively, the resulting estimate of SC CSA will be approximately twice the actual average CSA. If the purpose of a study is to accurately describe SC CSA, a high density of radial scans facilitating multiple measurements of SC CSA, as provided by a volumetric scan across the region of interest, is required.

Contributors All authors have contributed substantially to the conception or design of the work, or to the acquisition, analysis or interpretation of data for the work. In addition, all authors have contributed to editing and revising, and providing final approval of the version submitted, and will also provide approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing interests JSS receives royalties from Zeiss Inc, for intellectual property licensed from MIT.

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Ethics approval The institutional review board of the University of Pittsburgh.

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REFERENCES

OCT for glaucoma diagnosis, screening and detection of glaucoma progression

Igor I Bussel,1 Gadi Wollstein,1 Joel S Schuman1,2

ABSTRACT
Optical coherence tomography (OCT) is a commonly used imaging modality in the evaluation of glaucomatous damage. The commercially available spectral domain (SD)-OCT offers benefits in glaucoma assessment over the earlier generation of time domain-OCT due to increased axial resolution, faster scanning speeds and has been reported to have improved reproducibility but similar diagnostic accuracy. The capabilities of SD-OCT are rapidly advancing with 3D imaging, reproducible registration, and advanced segmentation algorithms of macular and optic nerve head regions. A review of the evidence to date suggests that retinal nerve fibre layer remains the dominant parameter for glaucoma diagnosis and detection of progression while initial studies of macular and optic nerve head parameters have shown promising results. SD-OCT still currently lacks the diagnostic performance for glaucoma screening.

INTRODUCTION
Glaucoma is a multi-factorial optic neuropathy characterised by progressive structural loss of retinal ganglion cells (RGC) that may result in vision loss and irreversible blindness. The ability to detect structural loss is fundamental in the diagnosis and management of glaucoma. While glaucomatous structural damage can be assessed subjectively by clinically examining the optic nerve head (ONH) and peripapillary retinal nerve fibre layer (RNFL), the introduction of ocular imaging modalities into clinical management has allowed for supplemental objective and quantitative evaluation of ocular structure.

Optical coherence tomography (OCT) is a commonly used imaging technology in the evaluation of glaucomatous structural damage. OCT was introduced over 20 years ago and is a non-invasive optical technique that allows for in vivo cross-sectional imaging of the ONH and retina.1,2 The recent commercially available iteration of the OCT technology, spectral domain (SD)-OCT, has theoretical advantages in glaucoma assessment over the earlier generation of time domain (TD)-OCT due to increased axial resolution and faster scanning speed that lead to lower susceptibility to eye movement artefacts. The evidence to date suggests that SD-OCT offers improved reproducibility; however, the glaucoma diagnostic accuracy of SD-OCT and TD-OCT is statistically similar.3,4

SD-OCT is rapidly evolving with faster scanning speeds, 3D image acquisition patterns, reproducible registration and advanced segmentation algorithms. The clinical utility of SD-OCT in glaucoma has primarily focused on the evaluation RNFL parameters because it enables a comprehensive assessment of all the RGC axons as they approach the ONH. However, the variability of the surrounding structures and the presence of coexisting pathology may impact reliable measurement. As such, the enhanced performance of SD-OCT allows for the assessment of macular parameters for glaucoma evaluation because the macula has the highest concentration of RGC in the retina (approximately 50% of the RGC of the entire retina); thus, loss of these cells may potentially be more readily detected in this area. Furthermore, given the ability of SD-OCT to produce 3D datasets, there is now potential to assess ONH parameters for glaucoma evaluation with greater accuracy and improved progression detection in consecutive testing by precise image registration. There are currently several commercially available SD-OCT devices with varying parameters and unique features. As such, the discussion of parameters and features provided in this manuscript may not be applicable across every SD-OCT device. In this manuscript, we review the recent advances in the use of SD-OCT for glaucoma diagnosis, screening and detection of progression.

GLAUCOMA DIAGNOSIS
The use of SD-OCT for glaucoma diagnosis has become a common clinical practice. Numerous studies have demonstrated that RNFL and macular thickness parameters are reproducible, and with high diagnostic sensitivity and specificity in discriminating between healthy and glaucomatous eyes (table 1).4,5

The diagnostic capabilities of SD-OCT for discriminating between healthy and glaucomatous eyes using average RNFL thickness have been reported to have an area under receiver operating characteristics curve value of around 0.9.6 However, the discrimination ability is dependent on the severity stage of glaucoma, with better performance in discriminating between healthy and more advance disease compared with discrimination of early stages of glaucoma.7

Acquisition of 3D images of the ONH region enables accurate and reproducible measurements of ONH parameters that include: disc and rim area, cup to disc ratio, cup volume and others. A diagnostic capability study with SD-OCT of glaucoma and age-matched healthy controls reported that these ONH parameters are able to discriminate between healthy and glaucomatous eyes similar to RNFL thickness.8 Another study with glaucoma, preperimetric glaucoma and healthy subjects demonstrated that RNFL thickness was better than any tested ONH parameter.9 The contradictory...
Table 1 Summary of selected glaucoma diagnostic accuracy studies

<table>
<thead>
<tr>
<th>Study, year (reference)</th>
<th>Subjects</th>
<th>Number of eyes</th>
<th>Baseline MD (dB)</th>
<th>Device</th>
<th>Scan region</th>
<th>Parameter</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mwanza 2011⁸</td>
<td>Glaucma</td>
<td>73</td>
<td>−10.4</td>
<td>Cirrus SD-OCT</td>
<td>ONH, RNFL</td>
<td>Vertical rim thickness</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>Healthy</td>
<td>146</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
<td>0.96</td>
</tr>
<tr>
<td>Sung 2012⁹</td>
<td>Glaucma Preperimetric glaucoma</td>
<td>229</td>
<td>−6.64</td>
<td>Cirrus SD-OCT</td>
<td>ONH</td>
<td>Rim area</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>Healthy</td>
<td>405</td>
<td>−0.66</td>
<td></td>
<td></td>
<td></td>
<td>0.96</td>
</tr>
<tr>
<td>Kotowski 2012¹⁰</td>
<td>Glaucma</td>
<td>63</td>
<td>−2.21</td>
<td>Cirrus SD-OCT</td>
<td>Macular</td>
<td>GCC average</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
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<td>49</td>
<td>−0.32</td>
<td></td>
<td></td>
<td></td>
<td>0.90</td>
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<tr>
<td></td>
<td>Glaucma suspect</td>
<td>51</td>
<td>−0.18</td>
<td></td>
<td>RNFL</td>
<td>GCIPL average</td>
<td>0.91</td>
</tr>
<tr>
<td>Mwanza 2012¹¹</td>
<td>Glaucma</td>
<td>58</td>
<td>−3.2</td>
<td>Cirrus SD-OCT</td>
<td>Macular</td>
<td>GCIPL minimum</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>Healthy</td>
<td>99</td>
<td>0.08</td>
<td></td>
<td>RNFL</td>
<td>GCIPL average</td>
<td>0.94</td>
</tr>
<tr>
<td>Jeoung 2013¹²</td>
<td>Glaucma Mild</td>
<td>164</td>
<td>2.68</td>
<td>Cirrus SD-OCT</td>
<td>Macular</td>
<td>GCIPL minimum</td>
<td>0.90, 0.96</td>
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<tr>
<td></td>
<td>Healthy</td>
<td>142</td>
<td>−12.41</td>
<td></td>
<td>ONH</td>
<td>GCIPL average</td>
<td>0.82, 0.91</td>
</tr>
<tr>
<td>Takayama 2012¹³</td>
<td>Glaucma Early</td>
<td>38</td>
<td>−2.33</td>
<td>Cirrus SD-OCT</td>
<td>Macular</td>
<td>GCIPL minimum</td>
<td>0.94, 0.90, 0.99</td>
</tr>
<tr>
<td></td>
<td>Healthy</td>
<td>20</td>
<td>−14.2</td>
<td></td>
<td>RNFL</td>
<td>GCIPL average</td>
<td>0.87, 0.82, 0.96</td>
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<tr>
<td>Lisbona 2013¹⁴</td>
<td>Preperimetric glaucoma</td>
<td>48</td>
<td>−0.81</td>
<td>RTVue</td>
<td>Macular</td>
<td>GCIPL average</td>
<td>0.92, 0.89, 0.96</td>
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<tr>
<td></td>
<td>Healthy</td>
<td>94</td>
<td>0.02</td>
<td>SD-OCT</td>
<td>ONH</td>
<td>RNFL average thickness</td>
<td>0.79</td>
</tr>
</tbody>
</table>

AUC, area under receiver operating characteristics curve; GCC, ganglion cell complex; GCIPL, ganglion cell inner plexiform layer; MD, mean deviation; ONH, optic nerve head; RNFL, retinal nerve fibre layer; SD-OCT, spectral domain-optical coherence tomography.

results of these two studies may be attributed to difference in glaucoma severity within the study samples. However, both studies reported similar diagnostic capability with rim area and average RNFL thickness in advanced glaucoma. The role of SD-OCT ONH analysis in glaucoma diagnosis is yet to be determined.

While total macular thickness (TMT) has been associated with glaucoma, the diagnostic capabilities have been reported to be worse than with RNFL thickness. However, SD-OCT segmentation algorithms have enabled quantification of individual layers in the macular region that are particularly impacted by glaucomatous damage, specifically, macular RNFL (mRNFL), ganglion cell layer with inner plexiform layer (GCIPL) and ganglion cell complex (GCC=mRNFL+GCIPL). Recent studies reported similar area under the receiver operating characteristics diagnostic capability of GCC that was comparable with RNFL¹⁰⁻¹¹ and ONH parameters.¹⁻¹² Furthermore, of the various GCIPL-specific parameters (average, minimum, sectoral), minimum GCIPL has been reported to be the most sensitive for the diagnosis of glaucoma.¹²⁻¹³

SD-OCT diagnostic studies have demonstrated that glaucomatous damage results in thinning of RNFL and GCIPL as well as ONH structural changes that allow for discrimination between glaucoma and healthy eyes. However, in most of these studies, the diagnostic accuracy may not translate when used in clinical practice for early stage glaucoma detection because the discrimination studies are usually based on differentiating healthy eyes from eyes with established glaucomatous visual field (VF) loss. A recent SD-OCT study compared the diagnostic ability of RNFL, ONH and macular parameters for diagnosing preperimetric glaucoma in an observational cohort with 13 years of follow-up.¹⁴ The investigators demonstrated that RNFL parameters performed significantly better than ONH and macular parameters for detecting preperimetric glaucomatous damage. It is plausible that a combination of parameters from the various scanned regions can improve diagnostic performance; however, this has yet to be evaluated.

Myopia is a risk factor for glaucoma and a confounder that complicates diagnosis because it presents with structural changes that can progressively lead to glaucomatosus-appearing VF defects.¹⁵ Myopic refractive error and longer axial lengths impact RNFL and macular thickness measurements due to the optical projection artefact of the scanning area. It has been demonstrated that non-glaucomatous myopic eyes tend to have thinner RNFL and macular parameters that are falsely classified as abnormal by OCT.¹⁶ Recent SD-OCT diagnostic performance studies on glaucomatous eyes with high myopia have demonstrated that RNFL and macular thickness parameters have similar ability to detect glaucoma.¹⁷⁻¹⁸

The quality of reporting of diagnostic studies for glaucoma using OCT has been demonstrated overall to be suboptimal with only 26.7% of selected papers reporting more than half of the standards for the reporting of diagnostic accuracy studies (STARD) criteria items.¹⁹ Using the same criteria, 100% of the
selected diagnostic studies in this review reported more than half of the STARD items (mean 71.4%; range 54%–92%).

In summary, the literature to date suggests that RNFL thickness remains the most diagnostically accurate parameter for detecting glaucoma. Though there have been some conflicting reports, several studies suggest that the diagnostic performance of segmented macular and ONH parameters are comparable with RNFL parameters. Furthermore, there is a reported difference in RNFL thickness measurement between different SD-OCT devices attributed to variation in optical properties and segmentation algorithms, and therefore the measurements are not inter-changeable between devices.20 However, despite these variations, the devices have demonstrated similar diagnostic capabilities.21

GLAUCOMA SCREENING

Individuals with glaucoma are usually asymptomatic until late in the disease processes and it is possible to either slow or prevent the progression of vision loss if detected early by adequate treatment. Therefore, a glaucoma screening tool for the general population is desirable. Population-based glaucoma screening is currently not cost-effective but it may be more beneficial and cost-effective in a targeted high-risk population such as older African Americans and Hispanics or those with a family history of glaucoma. Screening for glaucoma in a community-based high-risk population with TD-OCT resulted in moderate sensitivity and high specificity for definitive glaucoma suggesting that the device does not have adequate sensitivity to be used alone but may have utility in excluding subjects from further evaluation.22 However, SD-OCT has been reported to have higher sensitivity than TD-OCT in glaucoma screening and may have potential for early detection in a high-risk population.7 As of this writing, the use of SD-OCT for glaucoma screening in high-risk populations has not been reported. The United States Agency for Healthcare Research and Quality evaluated the evidence from the primary studies that investigated the diagnostic performance of OCT and reported that all the studies had appreciable heterogeneity and were at risk of investigating subjects that did not reflect the general or the clinically relevant population (spectrum bias).8 In summary, OCT currently lacks the necessary diagnostic performance for general population glaucoma screening.

GLAUCOMA PROGRESSION

Once glaucoma is diagnosed, a sensitive method for detection of progression is essential because appropriately intensifying treatment can slow RGC loss and preserve vision. The detection of glaucoma progression with OCT remains a challenge because when assessing structural changes over time, it is difficult to discriminate between glaucomatous structural damage and measurement variability or age-related structural loss. A prospective study assessing age-related loss enrolled 100 healthy subjects for cross-sectional evaluation and then randomly selected 35 subjects for 30 months of longitudinal evaluation.23 Cross-sectional analysis of healthy subjects demonstrated a significant negative correlation between age and average RNFL thickness of −0.33 μm/year while the longitudinal analysis reported a −0.52 μm/year rate of age-related loss of RNFL. Furthermore, the same study reported that age-related structural loss varies as a function of baseline RNFL where a higher baseline thickness is subject to higher rates of decline.

Table 2 Summary of selected longitudinal studies of glaucoma progression detection

<table>
<thead>
<tr>
<th>Study, year (reference)</th>
<th>Duration (years)</th>
<th>Subjects</th>
<th>Number of eyes</th>
<th>Device</th>
<th>Progression standard</th>
<th>Progression parameters</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wollstein 200525</td>
<td>4.7</td>
<td>Glaucoma</td>
<td>55</td>
<td>Prototype</td>
<td>TD-OCT</td>
<td>Visual field</td>
<td>RNFL</td>
</tr>
<tr>
<td>Wessel 201326</td>
<td>3</td>
<td>Glaucoma</td>
<td>38</td>
<td>Spectralis</td>
<td>SD-OCT</td>
<td>Optic disc photos</td>
<td>RNFL</td>
</tr>
<tr>
<td>Naghizadeh 201327</td>
<td>2</td>
<td>Glaucoma</td>
<td>51</td>
<td>RTVue</td>
<td>SD-OCT</td>
<td>Visual field</td>
<td>RNFL</td>
</tr>
<tr>
<td>Na 201228</td>
<td>2.1</td>
<td>Glaucoma</td>
<td>141</td>
<td>Cirrus</td>
<td>SD-OCT</td>
<td>Optic disc photos, red-free RNFL photos</td>
<td>RNFL</td>
</tr>
<tr>
<td>Sung 201229</td>
<td>2.2</td>
<td>Glaucoma</td>
<td>98</td>
<td>Cirrus</td>
<td>SD-OCT</td>
<td>Optic disc photos, red-free RNFL photos, visual field</td>
<td>RNFL</td>
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<td>Na 201320</td>
<td>2.2</td>
<td>Glaucoma</td>
<td>279</td>
<td>Cirrus</td>
<td>SD-OCT</td>
<td>Optic disc photos, red-free RNFL photos, visual field</td>
<td>RNFL</td>
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GCC, ganglion cell complex; GCPI, ganglion cell inner plexiform layer; OCT, optical coherence tomography; ONH, optic nerve head; RNFL, retinal nerve fibre layer; SD-OCT, spectral domain-optical coherence tomography; TD-OCT, time domain-optical coherence tomography; TMT, total macular thickness.
Supplement

SD-OCT has been reported to be more sensitive than TD-OCT in detecting RNFL changes in glaucoma progression. SD-OCT glaucoma progression algorithms measure changes based on either event-based or trend-based analysis. Event-based analysis detects progression when a follow-up measurement exceeds a pre-established threshold for change from baseline. This analysis identifies a gradual change over time that eventually crosses a threshold or an acute event that exceeds a threshold. The limitation of this approach is the susceptibility to the effect of outliers that can be inappropriately labelled as progression. Trend-based analysis detects progression by evaluating the slope of measured parameter over time. Trend analysis is less sensitive to measurement variability and identifies a rate of progression that may be extrapolated for time-to-event predictions. The limitation of this approach is the requirement for a large number of tests before the analysis can be considered as reliable. Furthermore, trend analysis has an a priori assumption of a linear rate of structural loss, which might not be applicable for all eyes.

Table 2 summarises selected longitudinal studies of glaucoma progression. The first study to show the potential of OCT in detecting glaucoma progression used an event-based approach to evaluate TD-OCT RNFL thickness measurements over time and reported a mean loss of average RNFL thickness of 11.7 μm over 4.7 years in glaucoma subjects. In a longitudinal SD-OCT study of glaucoma and healthy eyes followed for 3 years, the investigators reported a significantly greater rate of RNFL loss in glaucoma compared with non-progressors. A 2-year study of perimetric glaucoma and healthy eyes with SD-OCT scans demonstrated superior detection of early glaucomatous progression with measurement of GCC global loss volume and focal loss volume compared with ONH, RNFL thickness and average GCC parameters.

A longitudinal study of glaucoma and healthy eyes reported that compared with RNFL, TMT and GCPII showed similar levels of sensitivity in glaucoma progression detection. A longitudinal study of eyes with advanced glaucoma, as determined by VF, demonstrated that the rate of average macular thickness loss was significantly greater in the progressed group versus the stable and undetermined groups. Furthermore, the rate of average RNFL thickness loss was similar among the groups, suggesting that macular thickness assessment may be used to detect progression in advanced glaucoma. Another longitudinal study of 279 glaucoma eyes reported that RNFL thickness, macular and ONH parameters decreased significantly faster in progressors versus non-progressors as determined by optic disc, RNFL and VF assessment. These studies indicate that the macular region is appropriate for detection of glaucoma progression; however, they are all limited by short follow-up periods that did not last more than 2 years.

Myopia confounds the evaluation of glaucoma progression because it is difficult to discern the difference between progression due primarily to myopia or glaucoma. Since it is not possible to distinguish glaucomatous from non-glaucomatous changes based on a single examination, it is appropriate to conservatively follow highly myopic patients with suspected glaucoma after establishing baseline structural and functional parameters. As of this manuscript, no study has attempted to evaluate the effect of myopia on detection of glaucoma progression. In summary, the literature to date suggests that RNFL thickness is a dominant parameter in detection of glaucoma progression. However, macular parameters might provide a useful alternative for glaucoma progression assessment. The results of all available studies need to be cautiously evaluated in light of the relatively short duration of follow-up in the context of the typically slowly progressing glaucoma.

CONCLUSIONS

SD-OCT is a valuable clinical tool for glaucoma diagnosis and detection of progression. RNFL parameters have been demonstrated to provide accurate information for disease diagnosis and sensitive method for disease progression. Initial studies evaluating macular and ONH parameters show encouraging results.

Contributors JJB: drafting the article. GW: revising the article critically for important intellectual content and final approval of the version to be published. JSS: final approval of the version to be published.

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Optical coherence tomography in the preoperative and postoperative management of macular hole and epiretinal membrane

Roger A Goldberg, Nadia K Waheed, Jay S Duker

ABSTRACT
Optical coherence tomography (OCT) imaging plays an essential role in the diagnosis and treatment of macular diseases, including those of the vitreomacular interface. OCT enables accurate diagnosis and differentiation of full thickness macular hole, lamellar macular hole and epiretinal membrane, with or without the presence of vitreomacular adhesion. This information enables earlier diagnosis and treatment when necessary, and can guide the choice of therapy. OCT is useful to facilitate discussions with patients and manage the visual expectations. Postoperatively, OCT can be helpful to optimise patient comfort and visual outcomes. As the technology continues to improve, OCT will become increasingly critical for all aspects of care for patients with macular hole and epiretinal membrane.

Since Puliafito et al first described optical coherence tomography (OCT) imaging of the macula in 1995, OCT has evolved to become the gold standard for the diagnosis, management and follow-up of many vitreoretinal diseases. OCT-guided treatment for chronic conditions like age-related macular degeneration and macular oedema has become a de facto standard of care. Similarly, OCT has an increasingly important role in the management of diseases of the vitreomacular interface (VMI)—including full thickness macular hole (FTMH), lamellar macular hole (LMH), epiretinal membrane (ERM), and vitreomacular traction (VMT). A new classification system for diseases of the VMI relying entirely on OCT data to classify FTMH subtypes, supplements the pre-OCT Gass staging system. OCT allows for accurate diagnosis and differentiation early in the disease process and assists in preoperative decision making and planning. Similarly, OCT’s role in postoperative management also helps optimise visual outcomes. This paper reviews the role of OCT in the preoperative and postoperative management of patients with FTMH and ERM.

PREOPERATIVE OCT
Diagnostic utility
Even when clinically apparent at the slit lamp, obtaining an OCT image at the time of diagnosis in patients with FTMH or ERM helps in staging, surgical planning and prognostication of anatomical and visual success. First, the OCT can confirm the diagnosis. For example, a FTMH must be distinguished from entities that can cause macular pseudohole, such as ERM, VMT or LMH. Patients with pseudoholes often retain good vision without risk of progressive photoreceptor damage, and can be more safely observed. OCT is now considered the gold standard for diagnostic confirmation of FTMH, surpassing clinical tests such as the Watzke-Allen slit beam test, in accuracy.

Similarly, in evaluating for ERM and VMT, OCT has been demonstrated to be superior to clinical exam. In a prospective study, Do et al asked six vitreoretinal specialists to examine patients with slit lamp biomicroscopy and determine whether ERM or VMT was present, and to make a determination as to whether surgery was indicated. These patients then received a time domain (TD) OCT (Stratus, Zeiss). The TD OCT was found to be more sensitive than clinical exam overall, and particularly for VMT cases. OCT was also able to more consistently detect the presence of macular oedema, which has been corroborated in other diseases.

Prognostic indicators
In addition to confirming the diagnosis, OCT can be helpful in discussions with patients and their families about the disease, treatment options and visual potential after successful macular hole (MH) or ERM surgery.

In patients with MH, OCT can be used to accurately measure the size of the hole, which is done by using the calliper function found on most spectral domain (SD) OCT platforms to draw a horizontal line connecting the two closest components of the retina (minimum linear dimension; figure 1). Other measurements such as the base diameter, macular hole inner opening, as well as derived measurements such as the macular hole index, have also been studied. The minimum linear dimension is a critical factor in determining the anatomical success rate of hole closure after surgery, and forms the basis for the new international OCT-based classification system for macular holes.

Similarly, in patients with ERM, the integrity of the photoreceptor inner segment/outer segment (IS/OS) junction line has proven to be an important indicator of postoperative visual acuity (figure 2). Using TD OCT (Stratus), Suh et al found that eyes with disruption of IS/OS junction had significantly lower postoperative best corrected visual acuity (BCVA) and BCVA differences between before and after surgery than those without disruption on preoperative OCT. Falkner-Radler et al performed a similar study using TD OCT and SD OCT, and confirmed that baseline IS/OS integrity was helpful to predict the functional outcomes after surgery. They noted that SD OCT allowed...
for a more precise evaluation of the IS/OS junction line and differentiation of the ERM from the retinal surface. The highest quality study investigating the IS/OS junction line was performed by Inoue et al. They prospectively divided 45 eyes of 45 patients based on the preoperative IS/OS junction: intact versus disrupted. They then analysed changes postoperatively in these two cohorts, and found that the intact IS/OS cohort had better final visual acuity and a better improvement in visual acuity. In fact, none of the 11 eyes in the disrupted IS/OS cohort ever had a normal appearing IS/OS junction at any time point up to 1 year postoperatively. This study used SD OCT, and indocyanine green (ICG)-assisted internal limiting membrane (ILM) peeling was performed in every patient. This study also did not find a significant correlation between preoperative central foveal thickness, presence of a macular pseudohole or presence of retinal cysts with the postoperative visual acuity.

In patients with MH and ERM, a preoperative OCT can be used to assess for other conditions that may limit postoperative best-corrected visual acuity even after successful surgery, such as underlying age-related macular degeneration. This can help inform the discussion with patients and enable them to make more informed decisions regarding surgery.

Surgical planning

Additionally, with the recent availability of ocriplasmin (Jetrea, Thrombogenics) for the treatment of VMT, understanding the nature and extent of the adhesion as delineated on OCT can guide decision-making. In the pivotal studies, one injection of ocriplasmin was able to close 40% of FTMHs smaller than 400 microns in diameter, compared with 10.6% of placebo-injected eyes. In FTMHs smaller than 250 microns, the anatomical closure rate with ocriplasmin was 58%. However, in the presence of co-existent ERM, fewer than 10% of patients had resolution of their vitreomacular adhesion. Thus ocriplasmin may be a viable alternative to surgery in small and medium sized holes with persistent VMT but no ERM on OCT.

In patients who do require surgery, the risks and benefits of peeling the ILM is debated among vitreoretinal specialists in ERM and FTMH cases. In FTMH cases, studies suggest that ILM removal may improve the success rate of hole closure. However, holes smaller than 400 microns in diameter have an equivalently high rate of closure (over 90%) whether ILM is peeled or not. This finding that 400 micron aperture size was important for anatomical success rate was corroborated by the ocriplasmin data, as ocriplasmin cleaves laminin and fibronectin at the vitreoretinal interface, but does not impact the ILM.

In patients with ERM, some surgeons advocate peeling ILM to prevent ERM recurrence. Some studies suggest a recurrence rate as high as 50% when the ILM is left in place, whereas the recurrence rate of ERM is <10% when the ILM is removed. The ILM may serve as a platform for residual glial cells, hyalocytes and myofibroblasts to proliferate and re-form another ERM. Despite this, concern has arisen regarding the effect of ILM peeling on visual acuity, contrast sensitivity and the creation of microcystomas. In a single-surgeon study comparing patients who underwent ERM peel alone versus those that underwent ERM plus ILM peel, Chang et al found that there was no difference in the postoperative visual acuity, despite a greater proportion in the ERM peel only group having residual ERM present.

Sometimes, regardless of the surgeon’s intent preoperatively, the ILM comes off with the ERM simultaneously. Seidel et al examined what factors on preoperative SD OCT were predictive of residual ILM after ERM peel. Residual ILM was determined intraoperatively by using ICG staining after the ERM peel. They found that persistent ILM was present in 50% of cases. Not surprisingly, they found that the factors most predictive of ILM persistence after ERM peel were a greater extent of ERM elevation (a looser connection between the ERM and the retinal surface) and thicker ERMs. This may help surgeons determine beforehand which patients may warrant a second staining with ICG.

Often, the most challenging aspect of membrane peeling is initiating the flap edge. Preoperative OCT can help guide surgeons where best to initiate the membrane peel. Areas on the preoperative OCT where the ERM is elevated above the retina are easier to initiate a peel, whereas membranes with closer adherence to the retinal surface are more difficult to separate from the underlying retina (figure 2). Similarly, OCT can be used to determine the thickest part of the membrane, as well as an identifiable edge of the membrane.

POSTOPERATIVE OCT

Guiding prone positioning

Vitreoretinal surgeons often debate to what extent—if at all—prone positioning is needed postoperatively to maximise the rate the of hole closure after FTMH surgery. Anatomical success rates of >90% are now routinely reported in surgical series of FTMH, leading some to question the value of face-down positioning. Several groups have demonstrated that obtaining OCT scans through gas-filled eyes is feasible, though
scan quality can vary considerably.23–25 This requires the use of an OCT system using the macular cube scan feature to ensure that B scans through the fovea are obtained. These scans enable OCT-guided positioning postoperatively.

In a study by Shah et al, 26 32 eyes underwent FTMH repair. Patients were instructed to maintain a facedown position overnight, and every patient received an OCT scan on postoperative day 1. If the OCT demonstrated a closed hole, patients were instructed to remain facedown for two additional days. If the hole was open or indeterminate, they were instructed to remain facedown for 1 week. Three-quarters of eyes had closed holes on postoperative day 1, and of these, 96% remained closed. Of the eight eyes with open or indeterminate holes on day 1, all were >400 microns in diameter preoperatively, and six had closed by postoperative week 1. Using this algorithm of OCT-guided prone positioning, the authors achieved an overall single-procedure closure rate of 90.6%.

Similarly, Masuyama et al followed patients daily with postoperative OCT.24 As soon as the hole was closed on OCT, prone positioning was stopped. With this algorithm, 16 of 16 FTMHs closed by postoperative month 1. The authors suggest that as soon as the hole is closed on OCT, prone positioning is no longer needed. Of course, these studies do not address whether facedown positioning is necessary at all,27 28 but offer the opportunity for surgeons who do recommend prone posturing to tailor their recommendations based on OCT evidence.

Explaining visual outcomes
Postoperative OCT can also be helpful in determining why some patients have poor visual outcomes despite successful surgery. For example, OCT can easily detect subretinal or intraretinal fluid that can develop after macular surgery (figure 3). OCT can help identify this fluid, and help monitor response to therapy. Treatment options for postoperative cystoid macular oedema include topical non-steroidal anti-inflammatory drugs and corticosteroids, sub-Tenon’s or intravitreal steroids or a dexamethasone intravitreal implant.

Additionally, disruptions to the retinal pigment epithelium and photoreceptors can correlate with visual outcomes. Dissociated nerve fibre layer, recurrent ERM, and photoreceptor and retinal pigment epithelium disruptions have all been reported after surgery for FTMH and ERM.29

At this point, it is not clear if one single parameter or time point on SD OCT correlates best with visual acuity. Itoh et al30 reviewed 51 patients with surgically closed macular holes, and correlated the length of the foveal cone outer segment tips (COST) as measured by SD OCT with the best-corrected visual acuity at postoperative months 1, 3, 6, 9 and 12. They found that the length of the COST line defect correlated significantly with BCVA at all time points, and that the COST line defect was gradually restored in a centripetal fashion during the postoperative period.

A similar study by Kao et al31 examining 77 eyes with closed macular holes found that an intact external limiting membrane at postoperative month 1 after surgery correlated best with visual outcome, regardless of the photoreceptor IS/OS status at that time. In contrast, Oh et al found in 23 patients after macular hole surgery that poorer postoperative vision did correlate with the size of the IS/OS defect, as measured by linear (raster) and composite (partial fundus image) scans.32

FUTURE DIRECTIONS
New software updates to SD OCT systems now enable en face imaging of the retinal surface. Rispoli et al33 examined 20 consecutive patients with idiopathic ERMs using en face OCT imaging, and identified areas of small craters and pits adjacent to the plaque membrane. They hypothesise that membrane contraction causes localised tearing and folding of the ILM, exposing the bare retinal nerve fibre layer underneath. These would not be good places to initiate membrane peel during surgery. Postoperatively, the authors identified areas of dimpling of en face imaging that they speculate are consistent with previously described reports of dissociated optic nerve fibre layer, though they suggest that they may be Muller cells regenerating their end feet. How en face imaging may be useful is yet to be determined.

Intraoperative OCT offers another exciting aid to the vitreoretinal surgeon during FTMH and ERM surgeries. Though no real-time, integrated system yet exists to provide the surgeon with live feedback of the precise layers being grasped, active research in this area is being pursued.34

Finally, swept source (SS) OCT imaging may further add to our understanding of MH and ERM pathophysiology and surgical outcomes. SS OCT can image at speeds of 100 000–400 000 axial scans per second with a 1050 nm light source, enabling wide-field imaging, improved deep choroidal imaging and faster acquisition speeds.35 What role SS OCT will play for patients with ERM and MH is yet to be determined.

CONCLUSION
OCT has revolutionised all facets of our management of patients with FTMH and ERM. Over the past decade, OCT has become an essential component of the preoperative evaluation of FTMH and ERM, confirming the diagnosis, aiding in surgical planning and explaining visually to patients what these diagnoses mean. Similarly, postoperatively, OCT can help predict and explain the visual outcome, guide therapeutic decision-making such as prone positioning or the need for—and response to—treatment for cystoid macular oedema. New advances currently in development will likely expand the role of OCT even further, for the benefit of our patients with FTMH and ERM.

Figure 3 Postoperative macular oedema. This optical coherence tomography shows cystic intraretinal fluid after vitrectomy and membrane peel. The patient was treated with topical steroid and non-steroidal anti-inflammatory eye drops. The intraretinal fluid resolved and the visual acuity improved.
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Optical coherence tomography imaging of macular oedema

George Trichonas, Peter K Kaiser

ABSTRACT
Macular oedema (ME) occurs in a wide variety of pathological conditions and accounts for different degrees of vision loss. Early detection of ME is therefore critical for diagnosis and therapeutic management. Optical coherence tomography (OCT) is a non-contact, diagnostic method that uses infrared light, which allows the analysis of the retinal structure by means of high-resolution tomographic cross sections. The identification, localisation, quantification and long-term follow-up of fluid collections are the most important capabilities of OCT. Since the introduction of OCT in clinical practice, it has become an invaluable diagnostic tool and different patterns of ME have been reported. The purpose of this manuscript is to review OCT profiles of ME according to the aetiology and describe what has been reported regarding intraretinal features in vivo.

INTRODUCTION
Traditional methods of accessing macular oedema (ME) include contact and non-contact slit lamp biomicroscopy, indirect ophthalmoscopy, fluorescein angiography and fundus stereo photography. However, since the introduction of optical coherence tomography (OCT) in 1991, it has become an invaluable tool in the diagnosis and management of different retinal disorders including ME. OCT is a non-contact, micron-level, high-resolution diagnostic method that uses infrared light in the 800–840 nm wavelength range to provide real-time non-invasive imaging of the retina. OCT is based on the principal of Michelson interferometry. An interference pattern is produced by splitting a beam of light into two paths, bouncing the beams back (one from the targeted tissue, the other from a reference mirror) and recombining them by using semitransparent mirrors. OCT measurements are similar to those of ultrasound B-mode examinations, but have much higher resolution since light is used instead of sound waves. Ultrasound B-mode examinations have a resolution of 150 μ, while current OCT scanners have less than 5 μ resolution. Spectral or Fourier domain OCT technology has replaced the older, and slower, time domain OCT. Initial SD OCT could acquire images at higher rates up to 20 000 axial scans per second with almost 5 μm resolution. Today, state-of-the-art SD-OCT can acquire between 40 and 70 000A-scans per second. In the future, swept source and longer bandwidth light sources will improve even those numbers.

The normal retinal tissue has different reflectivity patterns on OCT. The nerve fibres and the retinal pigment epithelium display high reflectivity. Theplexiform and the nuclear layers display medium reflectivity. The photoreceptors display low reflectivity. There are several scan protocols that are currently used in clinical practice, and the most common are the line and cube or volume scans. The OCT software measures retinal thickness automatically while it is evaluating variations and deviations from the normal values. The distance between the vitreoretinal interface and the anterior surface of the retinal pigment epithelium is generally 200–275 μ. The foveal depression ranges from 170 to 190 μ. The mean thickness measured by OCT in the peripheral retina is generally 220–280 μ. Using several mathematic algorithms, cube scans also allow measurement of the volume of the macula.

OCT has been routinely used in measuring retinal thickness for the evaluation of ME caused by diseases such as age-related macular degeneration, diabetic retinopathy, hereditary retinal degenerations, retinal vein occlusion, after cataract surgery, epiretinal membrane (ERM) and uveitis. Given its excellent reproducibility, OCT can be used to quantitatively and qualitatively follow retinal thickness over time. Images acquired with OCT today have been found to correlate well with retinal histology as demonstrated with light microscopy. Furthermore, topographical studies have shown that subclinical ME caused by different diseases may only be detected by OCT. The advantages of OCT over other imaging modalities available include its non-invasive approach, quick imaging acquisition and safety profile. This review highlights the use of OCT in the diagnosis of ME in patients with different diseases and the different patterns that have been reported.

MACULAR OCT FINDINGS
Patterns of ME
OCT has provided new insights into the morphological changes that occur in patients with ME. There are many causes of ME (table 1). Studies using OCT in diabetic patients have reported different patterns of fluid accumulation in diabetic macular oedema (DME). Otani described three patterns of structural changes in DME: diffuse retinal thickening (DRT), cystoid macular oedema (CME) and serous retinal detachment (SRD). Focal or diffuse oedema first appears as a reduction in the reflectivity of the tissue and as increased retinal thickness. Later the retina appears ‘spongy’. CME includes the accumulation of intraretinal fluid in well-defined spaces (figures 1 and 2). Cystoid spaces are formed in the vicinity of the outer plexiform layer, and the rosette appearance seen in late views on fluorescein angiography is caused by the anatomical structure of the plexiform layer. The arrangement of the cystoid cavities is determined by the Müller fibres, which are vertical. The anatomy is clearly delineated on OCT and also
DME was DRT with prevalence of 88% and 60%, respectively. Yamamoto, who showed that the most common OCT finding in patients with DME, Kim et al reported that a 100 μm increase in retinal thickening corresponds to worsening of visual acuity by 0.16 logMAR units. The OCT pattern that was found to be associated with worse visual acuity was CME. The mere presence of CME corresponded to a mean reduction in logMAR acuity of 0.40 compared with 0.16 for other patients.

Hassenstein et al were the first to describe the use of OCT in patients with uveitis and found it to be very useful especially when trying to detect early ME and treatment efficacy, especially in the presence of vitreous cells. Markomichelakis et al defined specific OCT patterns that were identified in uveitic ME. They studied 60 patients with uveitis and uveitic ME and noted three different patterns of fluid accumulation that were similar to the ones reported in diabetic ME by Otani: diffuse macular oedema (DME), CME and SRD. Lannetti et al also reported OCT findings in patients with ME from uveitis. Out of 43 eyes that were imaged with OCT, 58% had CME and 42% had DME. SRD was noted in 28% of all cases.

Spaide et al evaluated the incidence of SRD secondary to branch retinal vein occlusion (BRVO) by OCT. Out of 14 eyes that he evaluated, he found that 10 (71.4%) had SRD involving any portion of the macula. That was an interesting finding given that SRD was rarely discovered on clinical examination in the past. In addition, subretinal haemorrhage can occur in patients with BRVO and the authors propose that blood gravitates through the subretinal fluid to settle behind the retina.

Table 1 Causes of macular oedema

<table>
<thead>
<tr>
<th>Frequent causes</th>
<th>Less frequent causes</th>
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<tr>
<td>Diabetic retinopathy</td>
<td>Macular telangiectasis</td>
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<td>Age-related macular degeneration</td>
<td>Coats’ disease</td>
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<td>Venous occlusion</td>
<td>Leber’s disease</td>
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<td>Retinal arterial macroaneurysm</td>
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<td>Uveitis and iridocyclitis</td>
<td>Metastatic tumour</td>
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<td>Birdshot retinopathy</td>
<td>Retinal surgery</td>
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<td>Retinitis pigmentosa</td>
<td>Local epinephrine toxicity, prostaglandin analogues</td>
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becomes very clear in late fluorescein angiography where one sees the typical petalloid leakage. Serous detachment of the retina is usually due to chronic oedema (figure 3). In these patients, the sensory retina is elevated and the cystic cavities often merge.

We first reported on OCT findings in a subset of diabetic patients with macular oedema (DME) from posterior hyaloidal traction (PHT),13 The patients all had a subclinical tractional retinal detachment (TRD) that was only visible on OCT. These patients are better treated with surgery instead of medical therapy. We later reported five OCT patterns of DME—the fifth pattern was PHT without TRD. In retrospective, observational, case series 276 scans of 164 patients were analysed and the prevalence of these five OCT patterns were 97% for DRT, 55% for CME, 7% for SRD, 12.7% for PHT without TRD and 2.9% for PHT with TRD14 (figures 4 and 5). The actual OCT image of patients with DRT shows increased retinal thickness with areas of reduced intraretinal reflectivity. CME demonstrates large ovoid areas of low reflectivity, separated by highly reflective septae that represent intraretinal cystoid-like cavities. PHT appears as a highly reflective band over the retinal surface. SRD appears as a dark accumulation of subretinal fluid beneath the high reflective and dome-like elevation of detached retina. The highly reflective band, which represents the outer surface of the detached retina, helps differentiate SRF from intraretinal fluid. TRD is identified as the area of low signal underlying the highly reflective border of detached retina. TRD often take a peaked-shaped configuration. These results were similar to reports by Otani and Yamamoto, who showed that the most common OCT finding in DME was DRT with prevalence of 88% and 60%, respectively.

CME was similar with 47% prevalence by Otani and 40% by Yamamoto.15 All these studies also agree that there is a correlation between retinal thickness and visual acuity in patients with DME. Kim et al reported that a 100 μm increase in retinal thickening corresponds to worsening of visual acuity by 0.16 logMAR units. The OCT pattern that was found to be associated with worse visual acuity was CME. The mere presence of CME corresponded to a mean reduction in logMAR acuity of 0.40 compared with 0.16 for other patients.

Figure 1 Optical coherence tomography appearance of cystoid macular oedema (CME).

Figure 2 Optical coherence tomography appearance of cystoid macular oedema (CME) with associated subretinal fluid.
Catier et al retrospectively reviewed OCT images from patients with different retinal diseases including diabetic retinopathy, central retinal vein occlusion (CRVO), pseudophakia, posterior uveitis and retinitis pigmentosa. They reported that ME was located in the outer retinal layers 92% of all cases. Serous retinal detachment was present in 37% of cases, and it was more frequent in central retina vein occlusion. This detachment did not correlate with poorer visual acuity. Macular thickening only correlated with visual loss in diabetic retinopathy and pseudophakia. Also, there is a correlation between angiographic leakage and patterns of ME. Brar et al retrospectively reviewed fluorescein angiography and SD-OCT images of 87 patients with ME due to diabetes, ERM, uveitis, pseudophakia and vein occlusion. They concluded that cystoid leakage on FA is always associated with cystic changes on SD-OCT. Furthermore, diffuse non-cystoid angiographic ME may show microcysts on SD-OCT, but diffuse oedema is more commonly associated with thickening and distortion of the retinal layers without cyst formation.

Choroidal neovascularisation (CNV) in wet age-related macular degeneration and other causes is associated with intraretinal fluid, subretinal fluid accumulation and pigment epithelial detachments as seen by OCT. Sandhu et al analysed 131 eyes of 118 patients and found that OCT with stereo images is 94% sensitive and 89% specific compared with fluorescein angiography in detecting new CNV lesions. Khurana et al had similar results and also demonstrated the superiority of SD-OCT versus TD-OCT.

Drugs like prostaglandin analogues have been reported to induce CME presumably by inducing an inflammatory reaction that causes breakdown of the blood retinal barrier. Similar is the effect of epinephrine and epinephrine-like drugs. CME can be seen on OCT without leakage on FA and a well-recognised cause is the use of nicotinic acid to treat hypercholesterolaemia. Other causes are the oncology drugs docetaxel and paclitaxel. Also, there are some reports that thiazolidinedione agents (pioglitazone and rosiglitazone) can exacerbate ME in 5–15% of patients.

Intraocular vascular tumours like choroidal hemangiomas, retinal hemangioblastomas, vasoproliferative tumours can cause leakage and cystoid oedema of the retina. Sayanagi et al used 3D SD-OCT and analysed 67 eyes with different choroidal tumours and showed that subretinal deposits, subretinal fluid and intraretinal oedema were detected significantly more...
Vitreoretinal interface disorders and ME

Epiretinal membrane
ERM is an avascular, fibrocellular membrane on the inner surface of the retina (figure 6). ERM, also known as cellophane retinopathy, results from proliferative changes at the vitreoretinal interface and can be either idiopathic or secondary to other ocular conditions. Secondary causes include retinal tears, retinal vascular diseases (BRVO and CRVO), uveitis, trauma or retinal detachment surgery. Idiopathic premacular membranes have a wide range of severity. Tangential traction from ERM may cause macular thickening with or without fluorescein leakage. Also, ERMs can cause significant distortion of the underlying retina and create cystoid spaces.

In clinical practice, SD-OCT has proven useful in the evaluation and treatment of ERMs. Using SD-OCT, one can almost always differentiate the posterior hyaloid, a minimally reflective signal, from an ERM, which is highly reflective. Wilkins et al described two patterns of ERM adherence. In his study of 174 eyes, focal attachment was seen in 26% of eyes and 67% eyes had a globally attached ERM. Membrane thickness could be measured in 91% of eyes and was divided into thin (40–60 μm), intermediate (70–100 μm) and thick (120–260 μm). OCT has also been helpful in confirming the relationship between PVD and ERM and is valuable for following the natural history of ERMs. Partial or complete PVD has been found in 80–95% of eyes with idiopathic ERM. Johnson, in a retrospective observational case series of 43 eyes of 40 patients with idiopathic ERM and no biomicroscopic evidence for complete PVD, reported that all eyes were found by OCT to have partial (87% of eyes) or complete (13% of eyes) PVD. It is likely that idiopathic ERM is always associated with PVD and that eyes previously reported as not having PVD have indeed subtle vitreous separation in the macular area that could not be discerned clinically.

Vitreomacular traction
Vitreomacular traction (VMT) is characterised by partial, anomalous, posterior vitreous detachment that causes anteroposterior traction on the macula in areas of residual vitreous adhesion (figure 7). The adherent vitreous cortex results in a broad, often dumbbell-shaped region encompassing the macular area and optic nerve. This in turn causes cystoid thickening of the macula. During the Phase III MIVI-TRUST trials of enzymatic vitreolysis with ocriplasmin, assessment of retinal morphology with OCT was performed and confirmed the superiority of OCT to clinical examination. Specifically eyes from the MIVI-TRUST programme with concurrent SD-OCT and TD-OCT at baseline and day 28 were included, and the study concluded that SD-OCT may be superior for formal clinical trial grading due to greater inter-reader reproducibility. Based on SD-OCT data, it appears that there are two subclasses of VMT: focal (≤1500 μm) and broad (>1500 μm) adhesion.

Koizumi et al showed that eyes with focal VMT showed a foveal cavitation, whereas eyes with broad VMT had more widespread CME. In VMT, the posterior hyaloid usually appears hyper-reflective and thickened on OCT. Yamada and Kishi suggested that the specific preoperative pattern of VMT may be useful in predicting the postoperative outcome. They described two types of partial PVD patterns. The first type had incomplete vitreous detachment nasally and temporally causing a V-shaped pattern with attachment only at the fovea. The second type had persistent nasal attachment with detachment temporal to the fovea. In their study, the first type of PVD had postoperatively better visual outcomes compared with the second type.

Myopic macular schisis
Retinal schisis or splitting is a phenomenon that is commonly seen in patients with high myopia and posterior staphylomas (figure 8). Biomicroscopically it can be challenging to diagnose, and OCT can be very helpful in these cases. Gaucher et al studied 29 high myopic eyes with OCT scans and revealed that the foveoschisis was associated with macular anomalies: a premacular structure was present in 13 (44.8%) of 29 eyes, a foveal detachment in 10 (34.5%) of 29 eyes and a lamellar macular hole in 6 (20.7%) of 29 eyes. Isolated foveoschisis was found in four eyes (13.8%). Shimada et al also used OCT and published the natural course of macular retinoschisis in highly myopic eyes without macular hole or retinal detachment. In the study, eight eyes were followed with OCT for 2 years. During follow-up, two eyes that had vitreoretinal adhesions developed a macular hole, one with and one without retinal detachment (RD), and two eyes without detectable vitreoretinal adhesion developed RD without a macular hole. The remaining four eyes did not develop complications, although the thickness of the macula increased significantly. In addition, Robichaud et al published two cases where subtle macular thickening was found on biomicroscopy and OCT confirmed the presence of macular schisis associated with VMT.

Macular schisis associated with optic nerve pits and colobomas
OCT is also helpful in characterising ME or schisis due to optic nerve pits or colobomas (figure 9). In these cases, there is intraretinal fluid accumulation and schisis-like cavity formation within
CONCLUSIONS

OCT has broadened our basic understanding and interpretation of ME and vitreoretinal interface disorders. It allows early, accurate diagnosis and better follow-up. OCT is now being used in daily practice, OCT has become today an invaluable tool in various etiologies by optical coherence tomography. Any change in macular edema associated with posterior hyaloidal traction. Am J Ophthalmol 2001;131:44–9.


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Optical coherence tomography shows retinal abnormalities associated with optic nerve disease

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ABSTRACT
Optical coherence tomography (OCT) of the macula in patients with primary optic neuropathy has revealed the presence of structural changes in the neurosensory retina in addition to the nerve fibre layer. Subretinal fluid has been documented in papilloedema and non-arteritic ischaemic optic neuropathy, and may account for decreased visual acuity in affected patients. Subretinal fluid has also been described from other causes of optic nerve head swelling including diabetic papillopathy and papillitis. Drugs used in the treatment of multiple sclerosis, such as corticosteroids and fingolimod can cause decreased vision due to central serous and cystoid macular oedema sometimes confused with recurrent optic neuritis. A subset of patients with various types of optic atrophy show microcystic changes in the inner nuclear layer on spectral domain OCT imaging. The pathophysiology and visual significance of these retinal changes remain unclear, but may affect the diagnosis and management of optic nerve disorders.

INTRODUCTION
Optical coherence tomography (OCT) is a well-established technique that has allowed qualitative and quantitative description of optic nerve disease with a degree of resolution and precision not previously afforded by clinical examination alone. Since OCT was first applied clinically at the New England Eye Center in the early 1990s, we have demonstrated structural changes in the retina and nerve in a variety of optic nerve disorders. As OCT imaging becomes part of the standard of care, a more thorough evaluation and understanding of these structural changes may aid in disease management.

SUBRETINAL FLUID IN PAPILLOEDEMA
Papilloedema mainly causes visual field loss from damage to the retina nerve fibre layer. Macular changes from papilloedema have been described since 1869 but have generally been viewed as secondary phenomena. Morris and Sanders described preretinal and subretinal haemorrhages, choroidal folds, macular exudates and retinal pigment epithelial changes associated with papilloedema. They proposed that a combination of haemodynamic and mechanical factors in papilloedema produced these changes which, in some cases, results in secondary visual loss. Gittinger and Asfourian hypothesised that tortuosity macular pigment observed in association with papilloedema may be due to macular oedema, similar to the pigmentary changes seen in cystoid macular oedema. Corbett et al described subretinal fluid in the peripapillary region in cases of papilloedema, causing enlargement of the blindspot, peripapillary hyperopia and refractive scotomas.

In 2001, we demonstrated the presence of subretinal macular oedema on OCT in patients with papilloedema and reduced visual acuity. Of 19 patients with macular OCT imaging during periods of acute, subacute, or recurrent papilloedema, seven patients had subretinal fluid involving the macula, all of whom had some reduction in visual acuity. Of the 12 patients without subretinal fluid, visual acuities were better than or equal to 20/20 in all but one eye in one patient (in which there was an altitudinal field defect). All the patients found to have macular subretinal fluid had improvement in central vision as the fluid resolved. Since then, we have seen this in about 10% of affected patients (figure 1). In some of these cases, a direct communication between the swollen optic nerve and the submacular space is identified, suggesting that the fluid may originate from the optic nerve. This idea is supported by Samuel’s histopathologic findings in 1938 suggesting that the intermediary tissue of Kuhnt can become disrupted with optic disc swelling and may allow escape of peripapillary fluid from the peripapillary choroid.

Savini et al also observed the presence of a hyporeflective subretinal space on OCT in 12 eyes with various types of optic disc oedema, and hypothesised that in addition to the previously proposed idea of peripapillary transudation and exudation of fluid into the subretinal space, extensive swelling of the optic nerve head may anteriorly displace the peripapillary nerve fibre layer producing a tractional separation between the sensory retina and the retinal pigment epithelium. Johnson et al also documented the presence of a hyporeflective space on OCT imaging underlying the sensory retina which had differing characteristics in pathologic disc swelling compared with optic nerve head drusen. They found that this space was on average thicker and more likely to have a smooth internal contour with tapering ‘V’ pattern away from the nerve in cases of pathologic optic disc swelling in comparison to cases of optic disc drusen where the space was, on average, thinner with a more rounded internal contour. They postulated that the most plausible cause for this space was the extravasation of fluid from the optic nerve head percolating into and elevating the subretinal space. It was felt that, due to its longstanding nature, the subretinal fluid in optic nerve head drusen was limited by a homeostatic balance achieved between the capillary and interstitial tissue hydrostatic pressures, and the active transport of the retinal pigment epithelium. However, in cases of recent-onset acute
cases of papilloedema.7 Patient with blurred vision, headaches and nosebleeds. The patient had more rather represents artefact secondary to a thickened and hyporeflective space in some cases as previously described.8 Finally, Scott et al proposed that the hyporeflective subretinal space seen on OCT in papilloedema does not necessarily represent fluid in all cases, but rather represents artefact secondary to a thickened and more reflective retinal nerve fibre layer which they described in cases of papilloedema.7

Kupersmith et al used OCT to quantify deformation of the peripapillary subretinal structures and found that peripapillary retinal pigment epithelium and Bruch’s membrane at the optic canal opening was more commonly deflected inward towards the vitreous in cases of papilloedema than in eyes with non–arteritic anterior ischaemic optic neuropathy (NAION) or optic neuritis. They felt these changes were secondary to an elevated pressure gradient between the retrolaminar subarachnoid peripapillary subretinal structures. The inward angulation of the retinal pigment epithelium and Bruch’s membrane was noted to resolve as papilloedema subsided.

VITREOPAPILLARY TRACTION
In 2006, we described two cases referred for evaluation of papilloedema in which OCT imaging demonstrated vitreopapillary traction with elevation of the optic nerve head and subsequent blurring of the disc margins with a subretinal hyporeflective space.11 However, these patients did not have true disc oedema, but rather the appearance of optic disc swelling created by tractional forces imposed by the contracting vitreous (figure 2). In one case, vitrectomy allowed the optic disc to return to normal.

DIABETIC PAPILLOPATHY AND PAPILLITIS
Nakamura et al described cases of serous macular detachment identified on OCT imaging in cases of diabetic papillopathy with minimal or no concurrent diabetic retinopathy. Based on fluorescein angiogram findings in these cases, they too concluded that the fluid resulted from leakage from the optic nerve head rather than a disruption of the blood–retinal barrier. Furthermore, they proposed that diabetes mellitus-induced glial dysfunction may accelerate transretinal fluid movement in such cases.12 We have also seen subretinal fluid on OCT in cases of papillitis associated with meningitis with improvement in visual acuity following resolution of the serous retinal detachment. Also, there appeared to be more hyper-reflective material below a clear area suggesting subretinal inflammation (figure 3).

SUBRETINAL FLUID IN ISCHEMIC OPTIC NEUROPATHY
In 2008, we described the presence of submacular fluid in patients with NAION.13 Of 76 patients with NAION from two institutions, 8 patients had subfoveal fluid on OCT, while 28 of the 44 patients from the New England Eye Center had peripapillary fluid and/or subretinal fluid extending towards but not into the fovea. Visual acuity reduction roughly correlated with the degree of increased macular thickness. It was proposed that subretinal fluid may contribute to some of the visual loss associated with anterior ischaemic optic neuropathy, and that resolution of the fluid may account for a portion of the visual improvement that often occurs with NAION. A fluorescein angiogram done in one of these patients did not show accumulation of dye in the macular region, indicating the fluid did not arise from the retinal vessels or directly from the choroid. Furthermore, it was suggested that there may be disruption of the glial tissues that comprise the intermediary tissue of Kuhnt, similar to what occurs in papilloedema. Subretinal fluid is allowed to escape from the peripapillary choroid into the subretinal space and track into the macula (figure 4). Visual acuity improved in five of eight patients described, as the subfoveal fluid resolved. In that study and in subsequent observations, macular fluid occurs in about 15% of patients with anterior ischaemic optic neuropathy. As our treatment of optic neuropathies evolves and new treatments become available, it becomes increasingly important to understand specifically what is being treated. Indeed, decreased vision due to associated subretinal fluid may be treated differently than visual acuity changes arising from the optic neuropathy itself.

DRUG-INDUCED RETINOPATHY
Secondary retinopathy in the setting of treatment of primary optic nerve disease is also well described. Corticosteroids are routinely used in the treatment of optic neuritis and recurrent demyelinating attacks in multiple sclerosis, but are also known to be associated with development of central serous retinopathy. Patients who have multiple sclerosis and loss of vision may be

Figure 1 Spectral domain optical coherence tomography line scan from five-line raster protocol through the optic disc and macula showing peripapillary and submacular fluid (arrows) in a middle-aged patient with blurred vision, headaches and nosebleeds. The patient had papilloedema associated with Waldenström’s macroglobulinemia.

Figure 2 Time domain optical coherence tomography line scan through the optic nerve and macula showing vitreous adhesions (arrows) apparently exerting anterior traction on the optic disc margins in an elderly patient who was referred for apparent optic nerve head swelling in the right eye.
misdiagnosed with optic neuritis when they actually have central serous retinopathy, making retinal evaluation of particular importance in patients with multiple sclerosis who routinely receive steroids as part of their disease management. Additionally, although neuro-ophthalmic evaluation for associated optic neuritis is often part of multiple sclerosis disease management, the ophthalmologist must be careful to not neglect associated vasculitis or uveitis that may also cause retinal abnormalities including cystoid macular oedema and a subsequent reduction in visual acuity.

Fingolimod has recently been approved as an oral treatment option for multiple sclerosis, and two phase III clinical studies demonstrated a significant reduction in the relapse rate in patients with relapsing-remitting multiple sclerosis compared with interferon and placebo. However, macular oedema was an adverse event reported in these and prior studies. Central foveal thickness measurements on OCT in such cases are often increased, and cross-sectional analysis demonstrates hyporeflective pockets or cysts within the retina, and an altered contour of the retina. Fingolimod is a structural analogue to sphingoine-1-phosphate (S1P) which plays a key role in the release of T lymphocytes from secondary lymphoid organs, thereby decreasing the population of circulating lymphocytes. However, the S1P receptor also plays a role in the regulation of vascular permeability and is implicated in the process of fingolimod-associated macular oedema, a well-described dose-dependent side effect more likely to occur in diabetics or patients with a prior history of uveitis.

MICROCYSTIC RETINAL CHANGES

Gelfand et al described macular microcystic changes predominantly involving the inner nuclear layer of the retina identified on spectral domain OCT images in patients with multiple sclerosis who did not have another reason for macular oedema. It was suggested in this paper that this finding may be a result of inner nuclear inflammation and microglial activation resulting in a breakdown of the blood-retinal barrier. These microcystic changes in the inner nuclear layer were also found in eyes with a prior history of optic neuritis in a significant portion of patients with neuromyelitis optica. However, similar microcystic changes in the inner nuclear layer have been recently described in cases of compressive optic neuropathy, optic atrophy due to glaucoma, Leber’s hereditary optic atrophy, dominant optic atrophy, trauma and hydrocephalus. We have recently seen these changes in a child with optic atrophy from hydrocephalus (Figure 5). The presence of these changes in inflammatory and non-inflammatory conditions, and the lack of leakage on fluorescein angiography, argue against a breakdown in the blood-retinal barrier. Vitreous traction has been proposed as a cause of retinal microcystic changes seen in optic atrophy, although recent studies have reported only cases in which the absence of vitreoretinal traction was confirmed with OCT. Microcystic changes may be due to trans-synaptic degeneration resulting from optic nerve damage. This theory is supported by the histopathologic finding of cavitory degeneration in the inner nuclear layer in optic nerve crush experiments in primates by Van Buren in 1963.

COEXISTENT PRIMARY RETINOPATHY

Independent primary retinopathy in the setting of known optic neuropathy can also coexist, and patients with retinopathy can also develop optic neuropathy. A thorough examination of the retina, with appropriate imaging when indicated, is an important component in the workup and management of all optic neuropathies, and patients with retinopathy should have periodic...
OCT scanning of the retinal nerve fibre layer, especially if vision loss seems out of proportion to the retinal findings.

CONCLUSION

OCT imaging has expanded our understanding of the pathology of many diseases of the retina and nerve, and has revealed structural changes in both that were previously unknown. OCT has further demonstrated the intimate connection between pathology in the neurosensory retina and optic nerve. Understanding the diagnostic and therapeutic value of these findings will improve the diagnosis and treatment of patients with optic neuropathy.

Contributors

All authors contributed to, reviewed and approved the manuscript. TRH and KLT designed, wrote the final version of the manuscript. TRH and KLT designed, wrote the final version of the manuscript. Guarantors: TRH, KLT.

Competing interests

None.

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REFERENCES

Recent advances in OCT imaging of the lamina cribrosa

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ABSTRACT
The lamina cribrosa (LC) is believed to be the site of injury to retinal ganglion cell axons in glaucoma. The ability to visualise this structure has the potential to help increase our understanding of the disease and be useful in the early detection of glaucoma. While for many years the research on the LC was essentially dependent on histology and modelling, a number of recent advances in optical coherence tomography (OCT) have dramatically improved the ability to visualise the LC, such that it is now possible to image the LC in vivo in humans and animals. In this review, we highlight recent advances in OCT imaging of the LC in the technology, processing and analysis, and discuss the impact that these will have on the ability to diagnose and monitor glaucoma, as well as to expand our understanding of its pathophysiology. With this manuscript, we aspire to share our excitement on the achievements and potential of recent developments as well as advise caution regarding the challenges that remain before imaging of the LC and optic nerve can be used routinely in clinical practice.

INTRODUCTION
Loss of vision in glaucoma occurs due to damage to retinal ganglion cell axons. This damage is believed to initiate at the level of the lamina cribrosa (LC), a network of connective tissue beams that provide structural and nutritional support to the retinal ganglion cell axons as they traverse the optic nerve head (ONH) to the brain.1 The resulting glaucomatous damage is characterised by distinctive changes in the ONH and patterns of visual field loss. Clinically, the disease is monitored by examining ONH morphology for signs of glaucomatous optic neuropathy, which if untreated will be recognised as a progressive deepening and enlarging of the cup and thinning of the neuroretinal rim.

Although the pathophysiology of the disease is still not completely understood, it is clear that glaucoma is a multifactorial disease with substantial variability in individual susceptibility and speed of progression. Despite decades of study, elevated intraocular pressure (IOP) remains the only modifiable risk factor for slowing the progression of disease, regardless of whether or not the IOP is elevated.2 Hence, to further understand the pathogenesis of glaucoma, improve diagnosis and enable novel means for preventing or treating glaucoma, it is of interest to understand the effects of IOP on the ONH, and in particular the biomechanics of the LC and surrounding sclera.3 Furthermore, it is necessary to understand how these effects vary from one individual to another, as well as how they may change with disease or ageing.

Recent advances in optical coherence tomography (OCT) have made it possible to image in vivo the deep structures of the ONH, and in particular the LC.3-6 OCT has been widely adopted for clinical care to objectively assess small-scale changes in the eye, most commonly for retinal pathology but increasingly for glaucoma diagnosis and monitoring purposes. In glaucoma, OCT-derived structural parameters such as retinal nerve fibre layer (RNFL) and macular ganglion cell complex thicknesses have shown promise for early glaucoma detection and assessing glaucoma progression.7 It is hoped that glaucoma diagnosis and risk management could be improved if additional structural information from the LC could be extracted using the same OCT scans—but this remains an imaging challenge.

The purpose of this review is to highlight recent advances in OCT imaging of the LC, in the technology, processing and analysis, and the impact these will have on our ability for diagnosing and monitoring glaucoma as well as expanding our understanding of its pathophysiology.

TECHNIQUES OF OCT IMAGING OF THE LC
A fundamental challenge in imaging the LC using OCT is that the light signal is attenuated as the beam travels through the tissue. Therefore, it is difficult to obtain good images of structures deep within the ONH or of those behind highly reflective or absorbing tissues. Using conventional spectral domain (SD)-OCT, only a small fraction of the LC is visible during imaging. In particular, peripheral LC or regions posterior to large blood vessels typically remain difficult or out of reach for OCT imaging. Conventional wisdom is that this means typically LC visibility would be worse in healthy subjects who have thick prelaminar tissues, and better in individuals with glaucoma who had suffered loss of prelaminal tissue. Similarly, LC visibility would be worse in humans than in animals with thinner prelaminal tissues or shallower LCs, such as monkeys or pigs. Nevertheless, this remains to be demonstrated. Postprocessing techniques to improve LC visualisation are being developed and are discussed later.

An important consideration when imaging the LC is that longer scans are prone to increased ocular movements, leading to motion artefacts.8 Patients with poor fixation, particularly the elderly, may require faster, lower density scans, resulting in poorer LC visualisation and decreased reproducibility of quantitative measurements. The complexity...
of the LC architecture and the need to measure minute focal changes to detect disease progression make low scanning resolution especially problematic. Some commercially available OCT instruments incorporate eye tracking technologies (eg, FastTrack from Zeiss or TruTrack from Heidelberg Engineering) to detect eye motion and either discard the data or correct for the motion artefact. Recently, software tools have been developed to correct for small eye motions and oscillation artefacts. While promising, it is important to validate these tools to avoid introducing artefacts.

Optimal OCT images of the LC are acquired with a focal plane deeper than that which optimises images of the RNFL. This means that traditional images of the ONH intended for analysis of cup shape and RNFL thickness often produce suboptimal visualisation of the LC. A technique called enhanced depth imaging (EDI) has been developed to improve visualisation of deeper structures, such as the choroid and LC. In EDI, the imaging window is moved closer to the zero-delay, which has superior signal to noise ratio. Lee et al have used EDI to improve LC reflectivity and contrast compared with conventional SD-OCT. EDI-OCT offers perhaps the best method for visualising the LC using commercial scanners. A disadvantage of this setup is that current commercial scanners do not offer high density isotropic sampling of the LC. Commercial EDI-enabled OCT systems often use averaging of multiple frames in order to see the deep tissue. To keep imaging times reasonable, commercial scanners typically use radial patterns or have wide distance between B-scans.

An interesting recent development has been polarisation sensitive OCT, where intrinsic tissue properties such as phase retardation can be measured and visualised in conjunction with the structure. This technology has been used to image the LC and sclera in vivo, providing contrast to the structures not always visible in the intensity images.

A recently developed technology used for LC in vivo imaging is swept source OCT (SS-OCT). SS-OCT offers reduced sensitivity roll-off versus depth compared with SD-OCT (figure 1A, B). Because SS-OCT does not require averaging of multiple B-scans to visualise the deep tissues, it allows 3D raster scanning with excellent sampling density, enabling clearer observation of the 3D structure of the optic disc (figure 1C). Although isotropic sampling improves visualisation and simplifies postprocessing, it is not an absolute requirement if the interest is on the ONH macroarchitecture, such as the general LC shape, and several important studies have been conducted using anisotropic scanning patterns. For example, anisotropic sampling was used to show a nasal-temporal ridge in the anterior LC.

Another important recent advance has been the integration of adaptive optics (AO) into OCT (AO-OCT). AO-OCT corrects ocular aberrations, permitting improved transverse resolution, from 20 to 5 μm. This enables high quality images of the posterior pole and visualisation of the LC trabecular structure (figure 2A). Technologies currently in development include 1-micron resolution (axial and lateral) micro-OCT and ultra-high resolution OCT. The impact of these on ophthalmic imaging remains to be elucidated.

**LC CHANGES DURING IOP VARIATIONS**

A major area of interest has been in assessing the dynamic reaction of the LC to IOP changes (figure 3). Analysing single
B-scans through the ONH, Agoumi and colleagues measured compression of prelaminar tissue, without any changes in LC position (on average) following acute IOP elevation, produced using ophthalmodynamometry. The effects of acute increases in IOP on animal ONHs have also been studied using OCT imaging. In normal rhesus monkeys, increases in IOP produced significant posterior displacement of the anterior LC surface in some monkeys, but not in others. Numerical models of humans and monkeys suggest that whether their LC displaces or not following an acute change in IOP is largely determined by the biomechanical properties and anatomy of both the LC and sclera. Thus, the range of biomechanical effects of IOP on the LC over a population is due to the variability in LC and sclera properties and their complex interactions. Note that even without anterior–posterior LC movement, an acute change in IOP may still cause substantial lateral displacements, forces (stresses) and deformations (strains) within the LC. Combined experimental and numerical techniques to measure IOP-induced displacements and deformations of the LC are currently being developed and may shed further light on the biomechanical behaviour of the eye.

There is also considerable interest in measuring the effects on the LC of IOP-reducing surgery. Both Reis and colleagues and Lee et al found significant anterior lamina displacement following a decrease in IOP through trabeculectomy at 1 week postsurgery. It is well known that a reversal of optic disc cupping often occurs after successful glaucoma surgery in children, but is rarely observed in adults. EDI-OCT has revealed the reversal of the position of LC following IOP reduction, which suggests that the reversal of the optic disc cupping may result from the anterior movement of LC. Although the extent of reversal of LC position certainly reflects the amount of IOP lowering, it has not been elucidated whether detection of this phenomenon is clinically useful. The biomechanical paradigm of glaucoma

**Figure 2**  Adaptive optics optical coherence tomography (AO-OCT) for assessing lamina cribrosa (LC) microarchitecture. (A) C-mode section at the level of the LC through an AO-OCT scan of a glaucomatous eye acquired in vivo. (B) The beams (cyan) and pores (green) were identified using a semiautomated segmentation technique. (C) 3D structural view of LC beams; (D) 3D LC beam thickness was then measured at every voxel, where hotter colours represent thicker beams. Adapted with permission from Nadler et al.

**Figure 3** Effects of intraocular pressure (IOP) increase on non-human primates. (A and B) The acute effects of (A) 10 mm Hg (top) and (B) 45 mm Hg (bottom) IOP on spectral domain optical coherence tomography (SD-OCT) B-scans of a normal monkey eye. Bruch’s membrane (red dots) and the anterior lamina cribrosa (LC) surface (green dots) have been delineated. The area enclosed by the anterior surface of the LC and a plane defined at Bruch’s membrane opening (area shaded green) is larger in the scan at 45 mm Hg. There was no detectable lateral expansion of the scleral canal at Bruch’s membrane opening (vertical green lines). Using a second reference plane parallel to BM opening (dashed red lines), it is also visible that the BM is outwardly bowed at high IOP, which suggests that there is IOP-induced posterior deformation of the peripapillary sclera. While choroidal compression may contribute to this finding, we believe that the behaviour of BM is principally related to the behaviour of the sclera. (C) The chronic effects of IOP elevation on the morphology and position of the internal limiting membrane and anterior surface of the LC are compared in an early glaucoma monkey eye. (D) Anterior LC surface and neural canal opening at baseline (green), follow-up 1 (yellow) and follow-up 2 (red). Delineations were made on images acquired with SD-OCT. Adapted with permission from Sigal et al and Strouthidis et al.

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SUPPLEMENT


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proposes that LC reversal may represent a relief of potential pathological strain and stress levels, reducing biomechanical insult on the astrocytes, load bearing structures and vascular system.

SD-OCT imaging of monkeys has also been used to study the effects of unilateral chronic IOP elevation (figure 3C, D). The results demonstrate that it is possible to detect longitudinal structural changes in the anterior laminar surface and prelamellar tissues using SD-OCT imaging in an experimental model of glaucoma.27 These changes included posterior displacement of the anterior surface of the LC and of Bruch’s membrane opening, as well as thinning of the prelamellar tissues and a decrease of the minimum neuroretinal rim width. Interestingly, all of these changes occurred prior to the detection of peripapillary nerve fibre layer thinning, whether detected by SD-OCT, scanning laser polarimetry or multifocal electroretinogram.28 This suggests that LC imaging might be useful for detecting structural change prior to visual field damage in glaucoma.

In animals, IOP levels can be better controlled and sustained than on patients. A sustained increase in IOP offers certain advantages in assessing the biomechanical response of an eye compared with acute IOP elevation since the effects of acute increases in IOP are not instantaneous. Due to tissue properties, including viscoelasticity and fluid shifts within the eye, the mechanical response of the eye changes over time.29 This time-dependent biomechanical behaviour of the eye may aid in protecting the delicate structures of the eye, such as the nerves passing through the LC, from transient forces and increases in IOP, such as from ocular pulse or rubbing our eyes. The role of viscoelasticity on long-term disease is also unknown, but the ability to measure IOP-induced deformations on the LC is a necessary first step.

LC MICROARCHITECTURE AND DEFECTS
Several studies using OCT to image the LC have described focal LC defects, identified using both EDI-enabled SD-OCT30 31 and SS-OCT.32 The definition of a defect, however, is yet to be established, as these are sometimes described as laminar holes or dissections,33 laminar surface irregularities34 or as pits or cavities in the LC.35 The SD-OCT studies have reported that LC defects are associated with local glaucomatous optic disc changes such as neuroretinal rim thinning/notching or acquired pits of the optic nerve30 31 as well as disc haemorrhages.36 SS-OCT studies have revealed that LC defects are sometimes associated with disc haemorrhages and longer axial length.37 However, it should be noted that careful interpretation must be applied for the detection of the LC defects because of the potential for artefacts due to vascular shadowing. These shadow artefacts lead to LC defect-like artefacts even when using SS-OCT (figure 1C,D). Further investigations are needed to determine when LC defects occur and their association with glaucomatous optic neuropathy, and whether the regions of the lamina that can be visualised consistenly are sufficient to be representative of the LC as a whole.

Recently, 3D microarchitectural analysis has started to be reported using SD-OCT,35 36 AO-OCT,35 37 and AO-SLO.38 Microarchitectural analysis has generally aimed to identify changes in LC beam and pore structure associated with the development or progression of glaucoma. The studies using AO-SLO primarily used manual delineation of individual LC structure, whereas the SS-OCT and AO-OCT studies demonstrated a semi-automated segmentation analysis capable of segmenting and analysing individual LC beams and pores (figure 2B–D).35 The quantitative assessment of the LC beams and pores in vivo may provide important mechanistic insights into the pathogenesis of glaucoma. For example, a study using SS-OCT reported significant in vivo changes in LC microarchitecture of glaucoma subjects, such as a reduction in pore size and increased pore variability, which may be a cause or a result of axonal loss and beam remodelling.39 The potential clinical significance of such findings has been discussed elsewhere.1–3 40

IMPROVING VISUALISATION OF THE LC
Addressing the challenge of signal penetration and the need for improved visualisation of the LC and deep structures of the ONH, Girard, Mari and colleagues proposed postprocessing algorithms to enhance the contrast of OCT signals by compensating for light attenuation.31 42 They have demonstrated that these algorithms can help reduce shadowing from blood vessels and peripapillary structures, and increase confidence in identifying the LC region (figure 4), although the gains vary from one patient to another.42 Improved visualisation of the LC would allow extending the studies of the LC to larger populations and eliminate the bias that may arise with restricting analyses to cases with more easily visualised LC.

LIMITATIONS OF OCT IMAGING THE LC
Important challenges remain to the use of OCT imaging for the study of the LC and optic nerve. First, the resolution and contrast of OCT images is still inferior to that of other optical techniques such as histology or second harmonic generated imaging.43 While neither of these can be used to study the LC in vivo, they have proven important research tools. Second, OCT is not consistently capable of imaging the whole LC.

Several recent papers have reported SD-OCT defined LC thickness measurements, most notably observing a relationship between reduced LC thickness and reduced visual field mean deviation44 and reduced LC thickness and the presence of pseudoxofoveolative glaucoma as compared with non-pseudoxofoveolative glaucoma eyes with the same level of IOP and glaucoma damage.45 While the results of these studies are compelling (despite low numbers of subject eyes) and ‘fit’ with preconceptions regarding LC morphometry in glaucoma, one must not, however, underplay the fact that the LC is a complex 3D structure, likely under-represented by the single thickness measurements considered in these studies. Furthermore, the detection of the posterior surface of the lamina, even with EDI and compensation algorithms, is highly variable with many experts struggling to identify the posterior LC surface in some images. Often, large regions of the LC remain difficult to visualise. The detection of the posterior surface of the LC in OCT images must still be verified by comparison with histology, in both human and monkey eyes. There is a risk that the proliferation of articles on this topic may prematurely push laminar thickness measurements into clinical practice. It is perhaps preferable to wait until LC thickness measurements can be obtained consistently and it is better understood what these represent of the actual structures. Most importantly, it is necessary to understand how OCT defined measurements of LC thickness relate to visual function in glaucoma.

FUTURE OF LC ANALYSIS
A promising technique for analysing images of the LC involves the use of tracking to identify the short-term deformations (strains) and long-term remodelling caused by acute and chronic IOP changes (figure 5). These methods are currently being developed and demonstrated for both OCT21 and second harmonic generated imaging.22 Application of these methods may shed further light on the biomechanical behaviour of the eye;
for example, by helping identify regions of structural weakness that may predispose to disease, or in assessment of techniques aiming to reinforce an eye to reduce sensitivity to IOP. These techniques, combined with improved signal penetration and robustness to eye movement, will enable longitudinal analysis for risk stratification and improved management of glaucoma.

CONCLUSIONS

Further studies are needed to understand the effects of IOP on the LC and the optic nerve, and the roles these play in the pathophysiology of glaucoma. Nevertheless, recent advances in OCT imaging have dramatically improved the ability to visualise the LC. While for many years the research on the LC was essentially dependent on histology and ex vivo modelling, developments in OCT imaging have enabled in vivo visualisation. These are exciting times for imaging and analysis of the LC, with many promising avenues that can potentially improve the diagnosis, risk profiling and perhaps treatment of glaucoma and other diseases of the ONH.

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References


Optical coherence tomography imaging of ocular and periorcular tumours
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ABSTRACT
Optical coherence tomography (OCT) has become pivotal in the practice of ophthalmology. Similar to other ophthalmic subspecialties, ophthalmic oncology has also incorporated OCT into practice. Anterior segment OCT (AS-OCT), ultra-high resolution OCT (UHR-OCT), spectral domain OCT (SD-OCT) and enhanced depth imaging OCT (EDI-OCT), have all been described to be helpful in the diagnosis, treatment planning and monitoring response of ocular and periorcular tumours. Herein we discuss the role of OCT including the advantages and limitations of its use in the setting of common intraocular and adnexal tumours.

INTRODUCTION
Optical coherence tomography (OCT) has become pivotal in the practice of ophthalmology. Similar to other ophthalmic subspecialties, ophthalmic oncology has also incorporated OCT into practice. Spectral domain OCT quickly replaced conventional time domain OCT because of its superior speed, sensitivity and resolution (3–7 μm).2 Anterior segment OCT (AS-OCT), ultra-high resolution OCT (UHR-OCT), spectral domain OCT (SD-OCT) and enhanced depth imaging OCT (EDI-OCT), have all been described to be helpful in the diagnosis, treatment planning and monitoring response of ocular and periorcular tumours. As OCT technology quickly evolves to more portable units with higher resolution and the capacity to image more peripheral lesions, there is no question it will become increasingly important in clinical practice. Herein we discuss the role of OCT in the management of ocular tumours as well as the advantages and limitations of its use in the setting of common intraocular and adnexal tumours.

EYELID AND ADNEXA
Basal cell carcinoma (BCC) represents 80–90% of non-melanoma skin cancers of the eyelid.3 Adequately assessing the extent of the tumour is essential in achieving complete surgical excision without risking the integrity of the eye or cosmetic result. This is particularly true in the periorcular skin where redundant skin is scarce. Although diagnostic biopsy represents the gold standard for diagnosis, several groups have explored OCT as a diagnostic tool in dermatology.4–6 In the setting of BCC, OCT is capable of visualising the altered skin architecture with good histopathologic correlation. In a preliminary study, OCT matched histologic features of superficial, nodular, micronodular and infiltrative BCC.

In the context of Mohs micrographic surgery (MMS), lesion margin mapping with OCT was also used to determine if further resection is needed. In a study of 52 patients, OCT was used to identify the transition point between the lesion and benign tissue. With OCT guidance, the authors were able to predict prior to MMS, the cases in which the lesion extended past the clinically apparent margins.7

Pelosini and colleagues studied 15 patients with biopsy-proven periorcular BCC, and observed a strong positive correlation between the margins obtained with in vivo OCT and histology. Only a weak correlation for depth of invasion was observed, as the maximum imaging depth with current technology is limited to 1.5–2.0 mm.6 Dense architecture, light-scattering properties and the small size of anatomic components continue to present challenges to imaging human skin.7

CORNEA AND CONJUNCTIVA
Similar to eyelid skin lesions, differentiation of ocular surface lesions is mostly based on clinical examination. Non-invasive imaging techniques, such as OCT and confocal microscopy, can aid in the diagnosis of ocular surface lesions.8 With in vivo confocal microscopy, cellular characteristics suggestive of malignancy, such as enlarged nuclei with high nuclear to cytoplasmic ratio can be observed although clinical interpretation is often challenging. Several authors have assessed the role of AS-OCT in the diagnosis and management of ocular surface lesions.9–12 These studies have shown excellent correlations with histopathology. Furthermore, the introduction of UHR-OCT with a resolution of 3 microns has overcome some of the initial challenges of low-resolution images obtained with time-domain OCT.

In one study with 34 eyes of 34 patients with conjunctival lesions suspicious for ocular surface squamous neoplasia (OSSN) and pterygia, UHR-OCT revealed a significant degree of morphologic correlation with histopathologic results. Moreover, differences in the measured maximal epithelial thickness using UHR-OCT between OSSN and pterygia, were statistically significant. Using a cut of value of 142 um, the sensitivity and specificity of UHR-OCT for differentiating between OSSN and pterygia was 94% and 100%, respectively.10

In a second study, eyes that had been treated with interferon alfa-2b or 5-fluorouracil for conjunctival and corneal intraepithelial neoplasia (CCIN) were compared with patients who had undergone surgical excision of pterygia. Ultra-high-resolution OCT images were useful in guiding medical treatment, and could prevent premature termination of chemotherapy in the...
presence of subclinical disease. Images of patients with surgically excised pterygia demonstrated similar findings to resolved CCIN cases. The same group assessed 54 eyes of 53 patients with a variety of biopsy-proven ocular-surface lesions, including primary acquired melanosis, amelanotic melanoma, naevi, OSSN, histiocytosis, conjunctival lymphoma, conjunctival amyloidosis and pterygia. The authors reported UHR-OCT to be helpful in providing a non-invasive means of guiding diagnosis and management (figure 1).

Shields et al used AS-OCT to evaluate 22 eyes of 21 patients with conjunctival naevi. The anterior, posterior and lateral margins were visualised in 100, 82 and 86% of cases, respectively. By comparison with histopathology, AS-OCT detected intrinsic cysts with a sensitivity of 80% and specificity of 100%. The major drawback was optical shadowing of deeper structures from the pigment within the naevi.

**IRIS AND CILIARY BODY**
Ultrasound biomicroscopy (UBM) is the main imaging modality for assessing iris and ciliary body tumours. The main limitation of UBM is that it is cumbersome and time consuming, requiring an experienced technician and direct contact with the eye. Anterior segment OCT has only recently been used to image iris tumours. Although AS-OCT allows for a less complicated clinical examination without contact with the patient and minimal technical skill, it does suffer from limited penetration. This is particularly true when trying to image through pigmented tissue such as the posterior pigmented layer of the iris (figure 2). The usefulness of OCT in the setting of anterior segment tumours is therefore limited to the iris tumours, hypopigmented tumours and those with limited thickness.

Bianciotto et al studied 200 eyes with anterior segment tumours imaged with AS-OCT and UBM. Overall, UBM provided superior tumour visualisation (69% vs 31%) and better resolution of the posterior margin (74% vs 27%) compared to AS-OCT. Better resolution of the anterior margin (20% vs 80%) and anterior segment anatomy (21% vs 80%) was observed with AS-OCT. This and other studies conclude that UBM continues to be the best method for imaging and following tumours of the iris and ciliary body.

**CHOROID AND RETINA**

**Naevus and melanoma**
With reported prevalence rates from 0.2% to 30% in the white population, clinicians regularly face the challenge of differentiating common choroidal naevus from the much less common but potentially fatal melanoma. Although the latter usually presents as an elevated choroidal mass with associated orange pigment and subretinal fluid, approximately 30% are small and difficult to differentiate from naevi on clinical examination. In the setting of a suspicious naevus, small choroidal melanoma or intermediate melanocytic lesions, OCT has been a helpful tool in identifying potentially important signs. Subretinal fluid (91% vs 14%), retinal oedema (61% vs 14%) and subretinal deposits (61% vs 11%) all have a significantly higher prevalence in melanoma compared to naevus. Although OCT features of choroidal naevus have been extensively documented, the limited visualisation of the deeper layers of the choroid and sclera secondary to light scattering from the

![Figure 1](image-url) **Figure 1** Left eye conjunctival lesion noticed 4 months prior to referral to the oncology clinic after treatment with topical steroids failed. Slit lamp photographs reveal a vascularised cream-coloured lesion (A). Nasally, the lesion appeared to arise from the epithelium with two small pearl lesions consistent with leukoplakia while the temporal aspect was mainly subconjunctival. Optical coherence tomography revealed thickened epithelium with invasion into the subconjunctival space (B). Photomicrograph of H&E-stained slide of conjunctival invasive squamous cell carcinoma. The neoplastic epithelium is much thicker than the peripheral non-neoplastic epithelium, and exhibits disordered maturation toward the surface (C). At the right, the carcinoma is seen undermining the non-neoplastic conjunctival epithelium (original magnification ×31). The inset depicts a higher-power photomicrograph, wherein the atypical cytologic and architectural features as well as the irregular, invasive stromal interface characteristic of squamous cell carcinoma, are more easily observed (original magnification ×180).
retinal pigment epithelium (RPE) and choroid have limited these descriptions to the retina and anterior choroid. To overcome this, EDI-OCT has been used to visualise the choroidal anatomy. In this method, the OCT objective lens is pushed closer to the eye yielding an inverted image with improved resolution of the deeper layers of the choroid and sclera.

Shah and associates evaluated 104 eyes with choroidal naevus EDI-OCT found that only 51 (49%) displayed image detail suitable for study. The most common EDI-OCT imaging features in included choroidal shadowing deep to the naevus (partial 59%, complete 35%), choriocapillaris thinning overlying the naevus (94%), RPE atrophy (43%), RPE loss (14%), RPE nodularity (8%), photoreceptor loss (43%), inner segment outer segment (IS-OS) junction irregularity (37%), IS-OS loss, (6%), external limiting membrane irregularity (18%), outer nuclear and outer plexiform layer irregularity (8%), inner nuclear layer irregularity (6%) and subretinal fluid (16%). The authors also observed that EDI-OCT could allow for more precise measurements of naevus thickness and judgment of related effects on the surrounding structures (figure 3).

In another study, 37 eyes with small choroidal melanoma were imaged using EDI-OCT. Choroidal shadowing and choriocapillaris thinning was found in 100% of the eyes. Compared with similar sized choroidal naevus, statistically significant EDI-OCT features included intraretinal oedema, loss of photoreceptors, loss of external limiting membrane, loss of IS-OS junction, irregularity of inner plexiform layer and irregularity of ganglion cell layer. Elongated photoreceptors were observed overlying small choroidal melanoma in 49% of cases, but were not observed overlying choroidal naevus.

Our group reported on 23 eyes with amelanotic choroidal naevus, melanotic choroidal naevus, choroidal melanoma, circumscribed choroidal haemangioma (CCH) and choroidal metastasis. Using EDI-OCT, the authors were able to identify the tumour distinctly from the surrounding normal choroid. Maximum tumour diameter and thickness could be measured only by EDI-OCT in 10 cases, all of which were <9.0 mm in diameter and <1 mm in thickness (undetectable by ultrasonography). Consequently, we suggest that EDI-OCT may be used as a complementary technique to ultrasonography for measuring tumours less than 1 mm in height. Qualitative analysis revealed variable reflectivity and vasculature depending on the type of lesion imaged (table 1). A particular advantage of the OCT is the ability to simultaneously display the choroidal tumour and associated retina changes.

**Lymphoma**

Intraocular lymphoid tumours can be grouped into primary intraocular lymphoma, a variant of primary central nervous system lymphoma (PCNSL-O) with predominantly ophthalmic involvement and uveal lymphoma. PCNSL-O can masquerade as uveitis, and differential diagnosis should include all causes of
chronic posterior uveitis, such as syphilis, sarcoidosis and tuberculosis. Diagnosis may be challenging and is, therefore, usually delayed, sometimes even for years, after initial presentation. The gold standard for diagnosis of lymphoma involves biopsy of the involved tissue. Ancillary testing, such as OCT, has been shown to be helpful in the diagnosis. Fardeau et al. examined 61 eyes with biopsy-proven vitreoretinal lymphoma where OCT images showed nodular hyper-reflective lesions at the level of the RPE (figure 4). Others have shown the presence of hyper-reflective bands or nodules distributed across the retinal layers.

Uveal lymphoma may involve any portion of the uvea and are sometimes accompanied by conjunctival or orbital tumour. For lymphoma involving the choroid, OCT shows regular intermittent placoid choroidal thickening and loss of choriocapillaris with an unaffected RPE and retina. Ultrasonography is still recommended on these patients as, unlike OCT, ultrasonography can detect extrascleral extension.

Haemangioma
Choroidal haemangiomas represent benign hamartomatous vascular tumours that may be confined to the globe or be a manifestation of a widespread hemangiomatous disorder. Although the iris and ciliary body may be involved, these tumours most frequently affect the choroid where they can be classified as circumscribed or diffuse depending on the extent of choroidal involvement. The diagnosis of CCH can be challenging. The funduscopic appearance may be similar to that of other amelanotic choroidal lesions, such as an amelanotic choroidal melanoma, choroidal metastasis, posterior scleritis, choroidal granuloma, choroidal osteoma, varix of vortex vein ampulla, lymphoma or atypical central serous retinopathy. Although...
Figure 4  Patient with a 6-month history of vitritis that was initially treated as a posterior uveitis but subsequently noted to rebound and develop subretinal lesions. Fundus photographs show mild vitritis and a 7×6 mm infiltrative subretinal patch (A and B). On optical coherence tomography nodular hyper-reflective lesions in the retinal pigment epithelium are observed (C).

Figure 5  Patient with a history of stage IV adenocarcinoma of the right lung who presented to the clinic with decreased vision in the left eye. On fundus photography, an amelanotic choroidal lesion approximately 3.5×2.5×1.3 mm in size is observed superior to the fovea with subretinal fluid and no orange pigmentation (A). Enhanced depth imaging optical coherence tomography (OCT) reveals a hyporeflective band in the deeper choroid causing enlargement of the suprachoroidal space (B). Subretinal fluid and some retinal pigment epithelium (RPE) changes are observed. Fundus photograph 2 months after chemotherapy (C). Note a decrease in tumour size, resolution of subretinal fluid and increase in RPE mottling is observed. Enhanced depth imaging OCT (EDI-OCT) confirms these changes (D).
ultrasonographic findings and indocyanine green (ICG) are typically most helpful in diagnosis, OCT can also be used to evaluate secondary retinal morphologic changes, such as shallow subretinal fluid or cystoid macular oedema.

Ramasubramanian and colleagues described OCT findings in choroidal haemangiomas. For CCH, subretinal fluid, retinal oedema, retinal schisis, macular oedema and localised photoreceptor loss were observed in 19, 42, 12, 24 and 35% of the cases, respectively. For diffuse choroidal haemangioma, subretinal fluid, retinal oedema and photoreceptor loss were observed 28, 14 and 43% of the time, respectively. To determine the chronicity of the serous retinal detachment and, therefore, potential for visual function, OCT has been used to assess photoreceptor atrophy. On EDI-OCT, CCH appears as a low to medium reflective band with homogenous signal and intrinsic spaces.

Although traditionally fluorescein angiography and ICG have been used to monitor treatment results, currently, OCT is the primary imaging modality used to detect and quantify associated retinal changes, such as retinoschisis, photoreceptor loss, or atrophy and subretinal or intraretinal fluid.

Metastasis
Metastasis to the uvea is by far the most common intraocular malignancy, and the vast majority develop in the choroid. Breast cancer accounts for more than half of all patients with uveal metastases, followed by lung cancer, which accounts for another quarter of all patients. Uveal metastases are usually diagnosed in the setting of a known primary tumour making diagnosis straightforward, but they may, however, also arise as the initial manifestation of an unknown primary. In these cases, differential diagnosis includes all other intraocular tumours, in particular, amelanotic choroidal melanoma. Although OCT has been used to aid in the diagnosis of uveal metastasis, it has, perhaps, been more valuable in monitoring resolution of subretinal fluid and, hence, treatment response. Choroidal metastases usually appear as a hyporeflective band in the deeper choroid causing enlargement of the suprachoroidal space (figure 5). Overlying retinal changes on OCT are non-specific and include a dome-shaped elevation with overlying retinal atrophy, intraretinal oedema and subretinal fluid.

Retinoblastoma
Retinoblastoma is the most common primary intraocular tumour in children. It appears as a yellow-white retinal mass that may exhibit an endophytic or exophytic growth pattern. A rare diffuse pattern of growth characterised by horizontal growth can masquerade as uveitis. Individual tumours appear as thickening and disorganisation of the outer retinal layers with posterior shadowing. On OCT, calcification is sometimes observed. Unlike retinal astrocytic harmartoma which mainly involve thickening of the inner retinal layers, retinal thickening in retinoblastoma involves the outer retinal layers. Because OCT requires certain patient compliance seldom found in the young age group, reports on OCT of retinoblastoma were scarce in the past.

Recently, with the advent of intraoperative OCT, its use has become more popularised. Intraoperative OCT has aided in the diagnosis and management of treatment complications, such as cystoid macular oedema, epiretinal membranes and atrophic retinal holes (figure 6). It has also been helpful in visualising subtle retinal findings that are difficult to detect on indirect ophthalmoscopic examination.

Figure 6 Patient referred for evaluation of a possible retinal detachment. The past medical history is significant for retinoblastoma diagnosed at 2 months of age and treated with multiple cryotherapy and laser trans-pupillary thermotherapy sessions. She had been evaluated by multiple retinal surgeons who debated the presence of schisis and/or full thickness retinal hole. Fundus photograph of the right eye shows two large areas of chorioretinal atrophy due to prior treatment (A). The retina between these two lesions appears to be elevated. Intraoperative optical coherence tomography confirmed the presence of atrophic retinal hole and retinal detachment overlying the area of chorioretinal atrophy (B).

SUMMARY
New imaging modalities, such as SD-OCT, ED-OCT, AS-OCT and UHR-OCT offer improvements in diagnosis, treatment planning and monitoring response in patients with ophthalmic tumours. Furthermore, these technologies continue to evolve and become more readily available through ophthalmology practices. It is, however, important to understand the limitations of OCT, mainly its penetration into deep pigmented tissue. Whereas imaging of the cornea and conjunctiva is mainly limited by resolution, imaging of the skin and uvea is limited by penetration. Furthermore, imaging of pigmented and vascularised lesions is also limited. Although, OCT provides valuable information regarding the status of the retina, RPE and inner choroid, ultrasonography including UBM, are still essential in the majority of patients with intraocular tumours.

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