Guest Editorial

Kirti Singh

Challenges In Optical Coherence Tomography Interpretation For Diagnosing Glaucoma In Myopic Eyes

Optical coherence tomography has witnessed a rapidly evolving technology since its debut by David Huang in 1991, to its present finesse. The non- invasive nature of this imaging tool coupled with speed, reliability and test re-test reproducibility in analyzing structural damage has made it the cornerstone imaging device for glaucoma. Intricate and precise segmentation algorithms delineating structure have further enhanced disease understanding and paradigm of glaucoma management .Increasing prevalence of myopia worldwide with 80- 90% young adults of Asia being affected, one fifth of them with high myopia, is generating a population who would be screened for glaucoma at some time of their life.[1,2] Since the segmentation algorithms, so critical for glaucoma diagnosis, are tailored for normal retinal anatomy, variations from this normal in form of high refractive errors raises pertinent concerns regarding accuracy and reliability of OCT in these cases. This concern is underscored by evidence that myopes are 2-3 times at risk for developing glaucoma despite correcting for axial length and intraocular pressure. As this myopia cohort of young adults age, their proportion as glaucoma suspects would rise exponentially over coming decades. Understanding relevant optics and anatomical variations affecting interpretation of OCT in myopia, is thus essential to prevent mistaken diagnosis of red (false positive) or green (false negative) disease.

Optical coherence tomography uses optical interferometry to measure time delay of reflected light in near infra-red visible spectrum (810 - 1056 nm) and is therefore affected by refractive status and media opacities. Standard scanning protocols used for glaucoma diagnosis are - Circum-papillary Retinal nerve fibre layer quadrant scan (cp RNFL), Optic nerve head scan (ONH), Macular scan (macular ganglion cell complex, mGCC), Glaucoma progression analysis, with some new machines incorporating disc damage likelihood scale (DDLS) nomograms.

Segmentation software algorithms (layer seeking algorithms) to detect glaucoma have been tailored based on anatomy of retinal nerve fibre at disc and macula. Axons of ganglion cells (Retinal nerve fibres) arch in the macular area to converge on superior and inferior poles of disc. The circum-papillary Retinal nerve fibre layer scan (cpRNFL) protocol identifies and plots RNFL thickness starting from temporal to nasal quadrant in each eye following the Temporal, Superior, Nasal, Inferior and Temporal (TSNIT) sequence. This is depicted as the double hump pattern in the TSNIT plot (Figure 1). Macular cube

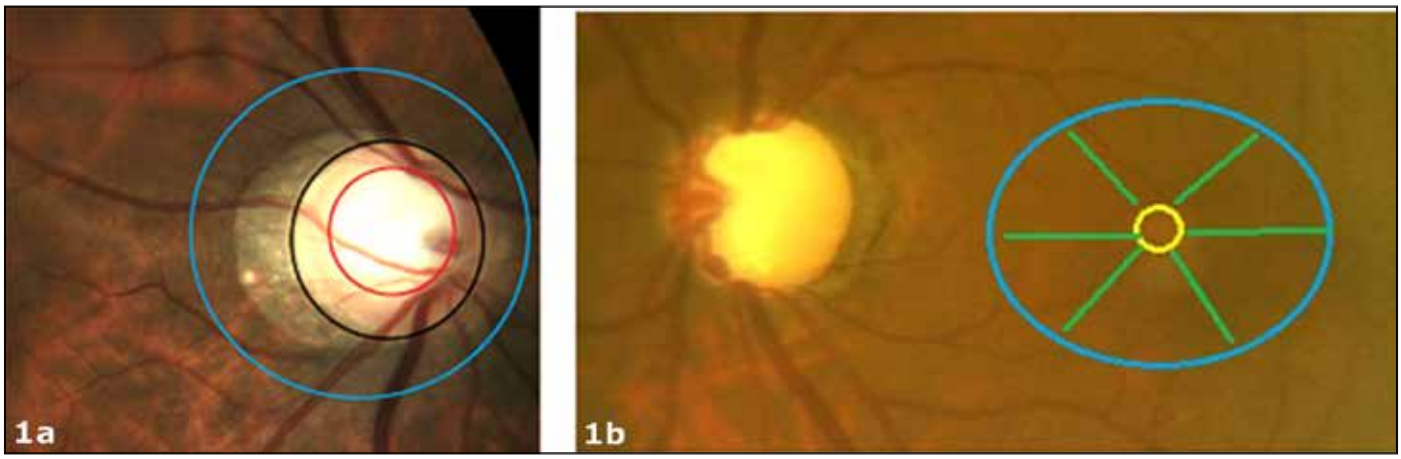

Figure 1: *The Optic disc cp RNFL 1b. Macular cube (macular ganglion cell complex) scanning protocol for glaucoma diagnosis*

protocol scans a 6 X 6 mm² area, measuring Retinal nerve fibre layer (axons) + Ganglion cell body + Inner plexiform layer IPL (dendrites), collectively called ganglion cell complex (mGCC). The central area, the foveola, which is devoid of ganglion cells is masked in the macula scan. (Figure 1). Probability levels for RNFL thickness are then displayed on four colour scale with red depicting thickness below thinnest 1 % percentile, yellow for measures within thinnest 1-5% of normative database, green for within 95% percentile and white for values beyond 95% percentile. This colour coding is arrived from population derived normative database involving adult patients over 18 year age and few races.

Myopic challenge in OCT interpretation

Axial myopia results in stretching of globe and thinning of retina. This thinning manifests as thinned retinal nerve fibre layer.[3,4] Current machines do not incorporate normative data from eyes with high refractive error in their internal database, therefore scans of myopic eyes with such thinned out RNFL, are interpreted as pathological (red disease). Most machines have only data from patients with emmetropia or low myopia incorporated.

Red Disease

This is the sobriquet given to false positive errors in interpreting OCT test, with the non - glaucomatous patient being erroneously labelled as glaucoma. Causes of red disease in myopia can be due to: from poor centration of measurement circle on optic disc due to poor fixation by patient, lack of normative database for high refractive errors, altered distribution angle of RNFL with temporal crowding of nerve fibres, magnification factor in axial myopia, split and shifted RNFL peaks to disc size/ shape variations and lamina cribrosa biomechanics. The following text details these variations in myopic fundus in conjunction with screening protocol used, for ease of understanding their impact on interpreting scans.

1. Disc Size/ Shape Variations

The disc parameters studied Optic nerve head protocol are vertical cup disc ratio, rim area and mean RNFL thickness. Segmentation algorithms inbuilt in OCT software are designed for optic disc sizes and shapes within the Gaussian curve of emmetropic or low myopic populations with disc area between 1.3 - 2.5 mm². Discs larger or smaller than this, make interpretation beyond scope of normative database, with erroneous labelling of pathological disease. For such discs, common in myopia, the measurement circle placement need to be checked and manually placed, prior to interpretation.

Disc margin on OCT is identified, as termination of Bruch's membrane opening (BMO) and neuro-retinal rim is measured as the shortest perpendicular from that point to internal limiting membrane, called Minimum rim width (MRW).[5] Tilted or dysplastic disc, often associated with myopia, would pose difficulties in identification of Bruch's Membrane Opening BMO, the OCT landmark for disc margin identification, with subsequent erroneous rim measurement. (Figure 2) Myopic discs larger than 3.46 mm, would be erroneously labelled as damaged, since more distal dispersed peripapillary RNFL would get imaged. However there is a caveat to this, as evidence exists that circumpapillary

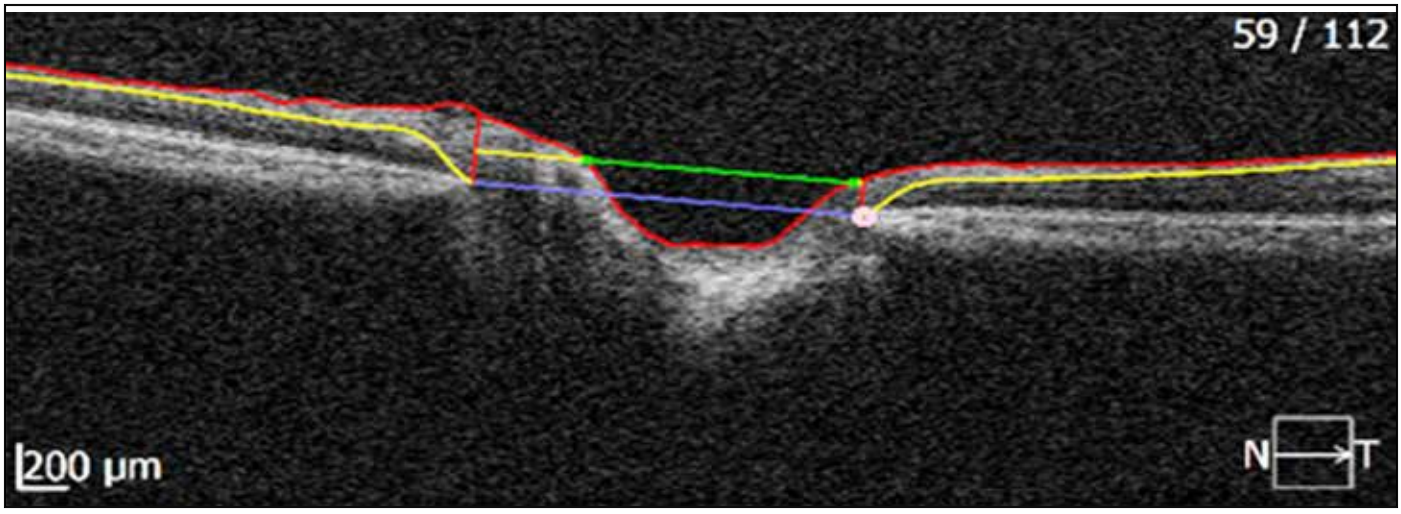

Figure 2: *OCT optic disc cube. The red line marks the internal limiting membrane and yellow the Retinal nerve fibre layer. The pink dot is the Bruch's membrane opening (BMO) which identifies the optic disc*

RNFL thickness is positively correlated with optic disc size, with smaller discs having less and larger discs having more nerve fibres.[6] This is in contravention to accepted anatomy of nerve fibres being constant in all sized discs.

2. Circumpapillary RNFL Thinning

Retinal nerve fibres are both actually and artifactually thinner in myopia. Let us understand this. Axial myopia results in scleral stretching with ganglion cell axons spreading out to cover the wider globe area, therefore resulting in actual diffuse thinning of RNFL. This reduction in RNFL thickness with increasing axial length, is reported to be in the range of 2.2 -3.7 microns /mm. or 1.30 µm for every 1 diopter sphere increase in negative SE.[7] Indian subcontinent data has verified thinned RNFL at 78.7 + 5.7 µ in high myopia, compared with 83.8 + 3.4 µ in moderate myopia and 91.3 + 2.99 in emmetropic eyes[8,9]

3. Magnification Factor while scanning ONH

Increasing axial length, results in expanding circumference of cpRNFL measuring circle from 3.46 mm, due to magnification factor, especially for myopia greater than - 4 D.[10] A myopic eye would result in increase of 3.46 mm scan circle, to 4.0mm for a 28 mm axial length myopia.[11] A longer myopic eye, generating an expanded measurement circle, measures RNFL at distance further from optic disc (Figure 3). Since nerve fibres fan out distal to optic disc, it would make nerve fibres appear more dispersed and artefactually less in number. To counteract this Littmann's magnification factor correction needs to be applied for longer eyes. Some authors do not however ascribe to use of this magnification factor citing occurrence of larger discs in myopia, which in any case have diluted the effect of circle expansion.[8]

4. Retinal nerve fibre layer distribution Pattern / Temporal Displacement Of RNFL Peaks

Volume-rendering MRI reveal globe shape in emmetropic eyes to be consistently spherical, with myopic eyes having symmetrical or asymmetrical anteroposterior elongation and posterior protrusions. With increasing myopia this asymmetrical anteroposterior elongation makes superotemporal (ST) and inferotemporal (IT) RNFL bundles converge

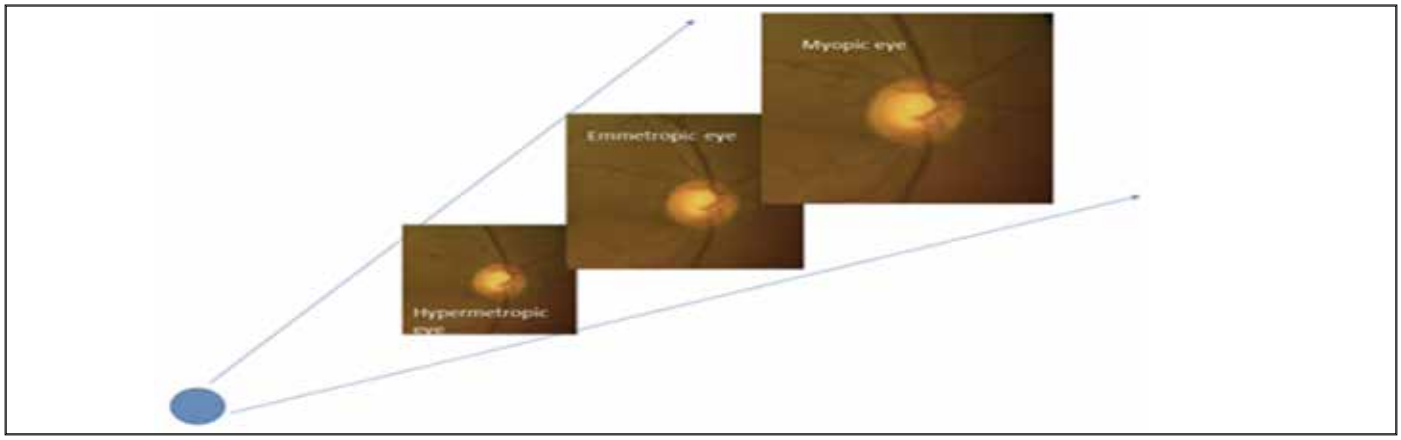

Figure 3: *Magnification of measuring circle in OCT commensurate with increasing axial length*

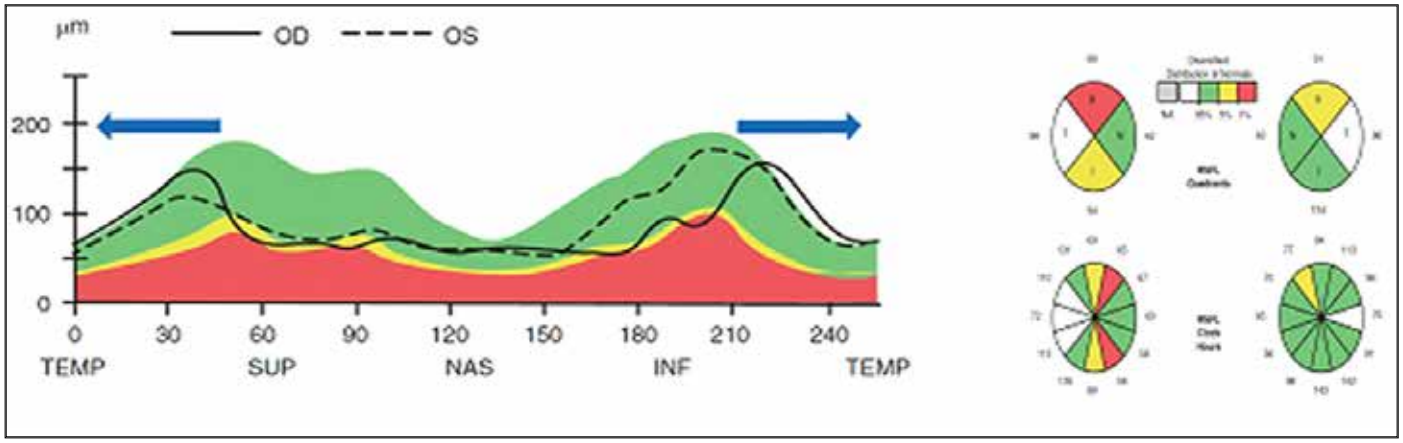

Figure 4: *Temporal displacement of RNFL peaks, resulting in thickening of RNFL in temporal quadrants, apparent thinning in superior & inferior quadrants in Right eye. Reproduced from Akman A, Bayer A, Nouri-Mahadavi K. In Optical Coherence tomography in glaucoma pg 201*

temporally due to retina being dragged temporal to disc. The condition called as "Temporal displacement or convergence, reduces distribution angle bounded by ST and IT bundles and displaces RNFL peaks temporally, resulting in erroneous interpretation of thickened temporal RNFL and thinned nasal RNFL.[7] (Figure 4) This temporal crowding in myopic eyes, could either be a result of an anatomical variation or image artefact due to increased vertical curvature of retina.[12] The RNFL distribution angle has been shown to be negatively associated with axial length, with a 3.4 decrease for every 1-mm increase in axial length, and positively associated with spherical error, with a 2.7 increase for every 1.0 D increase in spherical error.[7] This negative association between area of abnormal RNFL measurement and RNFL distribution angle persists even after adjustment of axial length and spherical error. This finding implies, that even if normative database including high myopia is incorporated in machine software, RNFL thickness analysis would be erroneous in eyes with a small RNFL distribution angle.

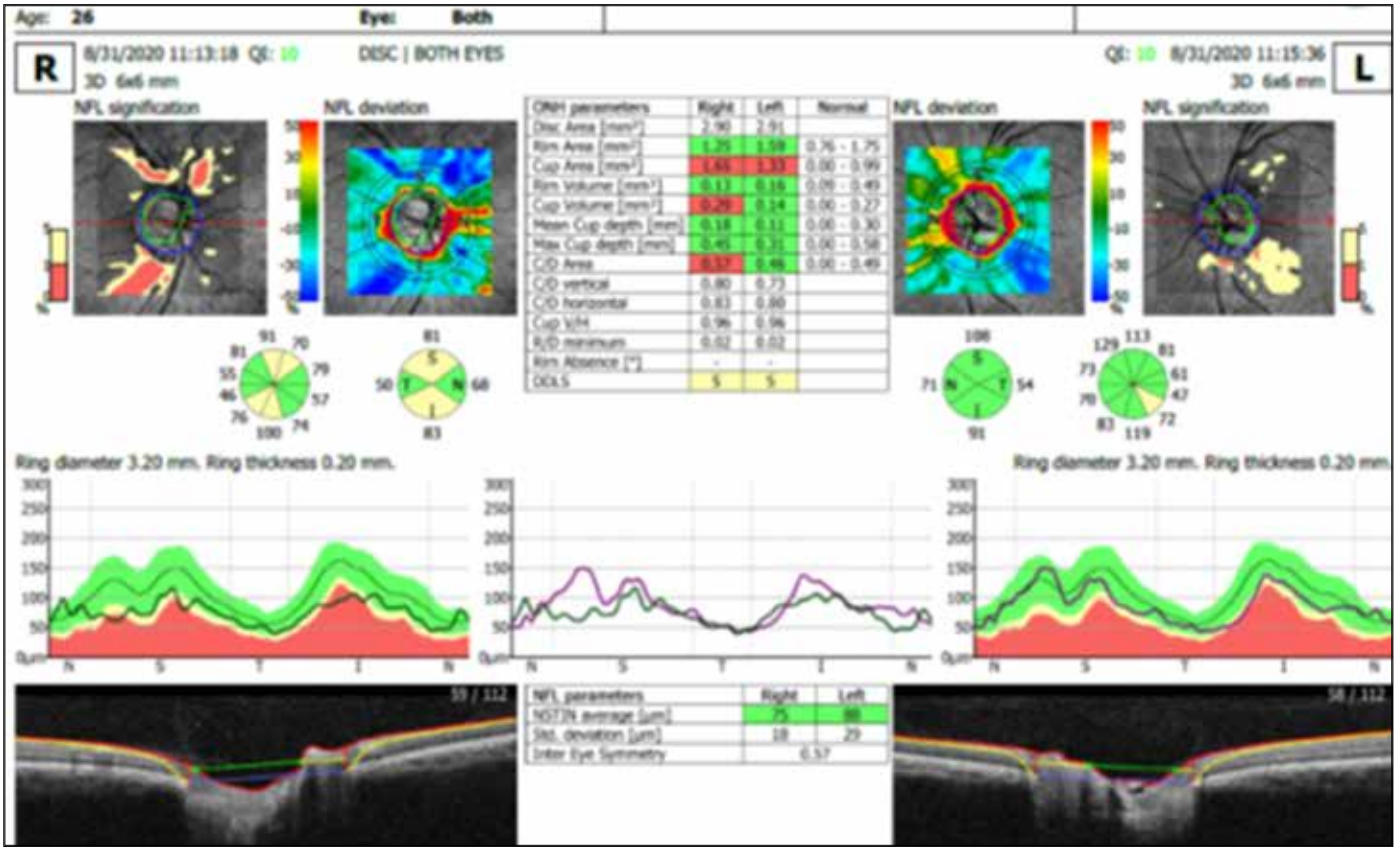

Figure 5: *Split nerve fibre bundle in left eye superior pole. The split is still within the 95% perecentile, it is falls short of manifesting as red diseases*

5. RNFL split / segmentation

Split or segmented RNFL are anatomical variants of the RNFL bundles entering poles of disc. This variation initially identified as an artifact by the earlier GDx machine, is often seen in high myopes with peripapillary atrophy (PPA). In this condition retinal nerve fibres converging on superior and inferior poles of disc do not enter as complete bundles, but instead split in two. The space between two bundles masquerades as a local RNFL defect (Figure 5).

6. Peri-papillary atrophy (PPA)

The presence of peripapillary atrophy with alpha and beta zones, has long been considered soft sign of glaucomatous disc damage and often known as halo ***glaucomatosus.*** *Three zones namely alpha, beta and gamma have been identified in PPA. Alpha zone α is due to hyper or hypopigmentation (usually former) of RPE at edge of PPA along with slight thinning of choroidal tissues. Beta zone β, present between α zone and disc margin, is visible as a white grey scleral crescent with loss of RPE, marked atrophy of photoreceptor layer and choriocapillaries. It is characterized by visibility of large choroidal vessels and sclera. Refined imaging by OCT advances, has identified two subtype of β PPA namely beta zone PPA and gamma zone PPA in some myopic eyes. Gamma zone γ, previously called as myopic temporal crescent, is white coloured area interspersed between beta zone and optic disc border. Gamma zone differs from beta zone in lacking a Bruch's membrane. Since OCT algorithms identify disc margin as Bruch's membrane termination /opening, the presence of gamma zone γ would spuriously*

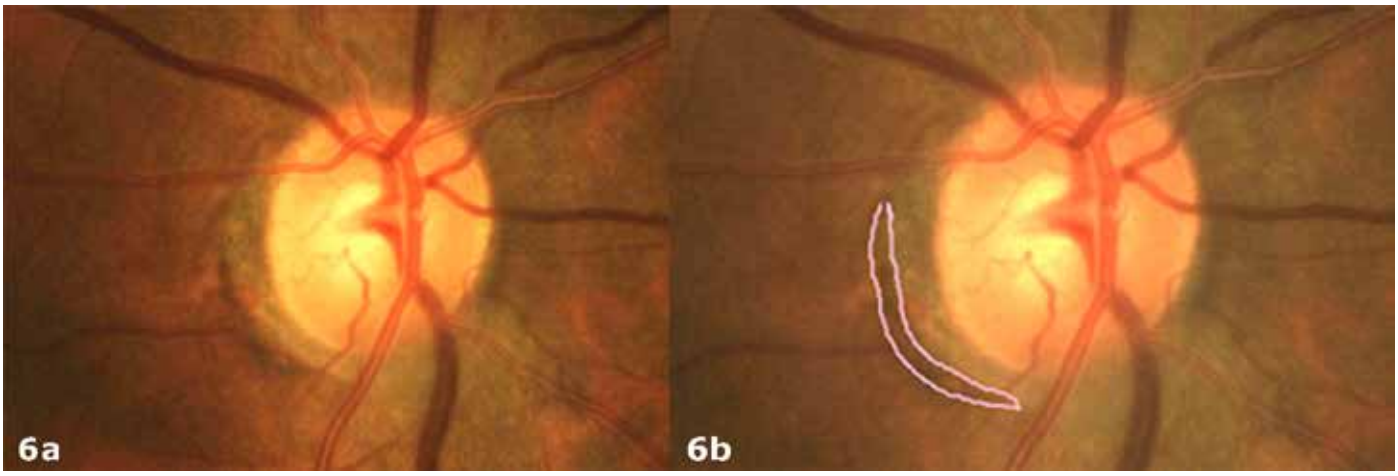

Figure 6: *a & 6 b Peripheral pigmented part of peripapillary atrophy (infero-temporal to disc) demarcated in pink is α zone*

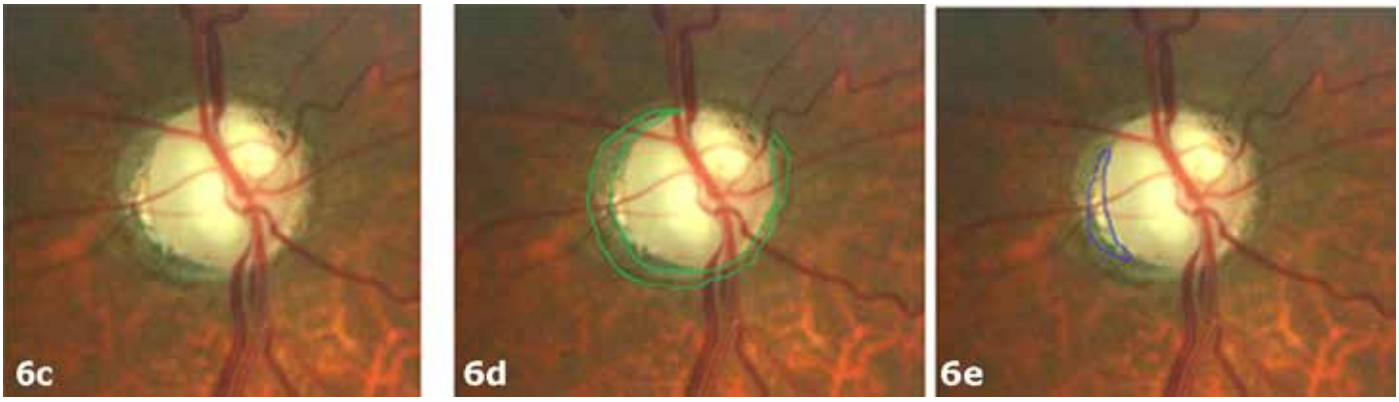

Figure 6: *6c, 6d & 6e Peripapillary atrophy , whitish grey zone with RPE loss, retinal and choriocapillary atrophy demarcated in green is β zone and that in blue could be γ zone (which is essentially an OCT finding)*

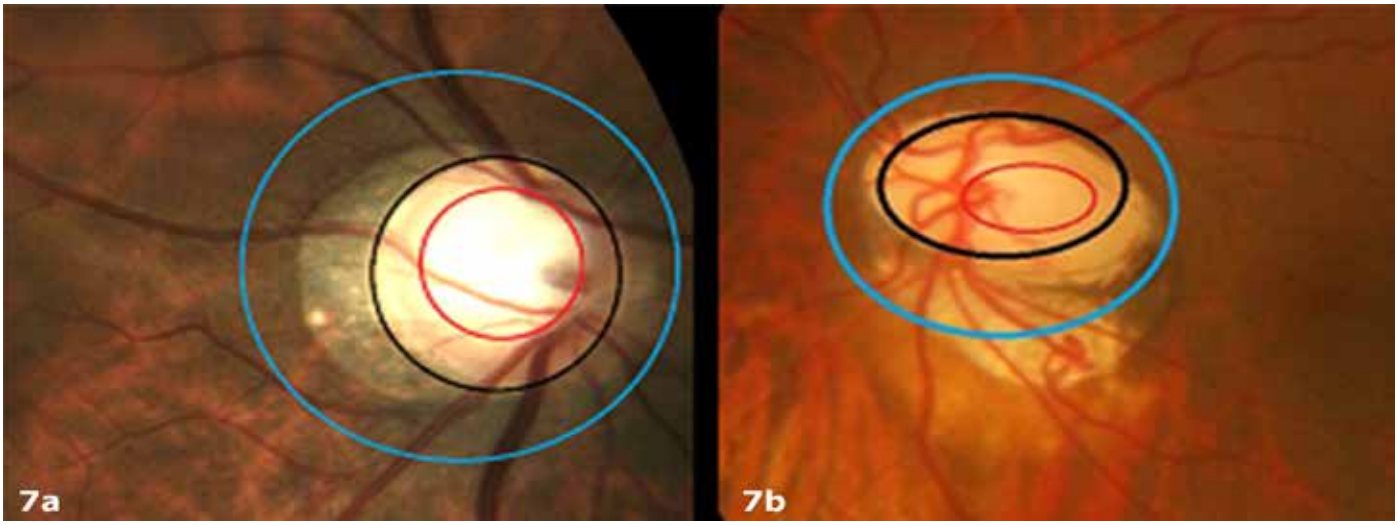

Figure 7: *Examples of Peripapillary atrophy 7a. RNFL calculation circle incorporates the PPA and therefore depicts less RNFL measure.7b Tilted disc with inferior PPA, the RCNFL calculation circle falls short of PPA and therefore depicts less RNFL measure. In addition the oval disc margin is not completely covered by Disc circle*

enlarge disc area in image interpretation. (Figure 6)

Peri-papillary atrophy is often present in myopic retina and results in discrimination errors to differentiate glaucomatous damage in myopic disc from a non-diseased myopic optic nerve head. Presence of PPA in addition, makes placement of OD circle with subsequent measurement of disc and RNFL parameters difficult. The scanning circle diameter for measuring optic disc in OCT machines is 3.46 -3.5 mm, which may fail to traverse extent of the PPA. Presence of large PPA extending

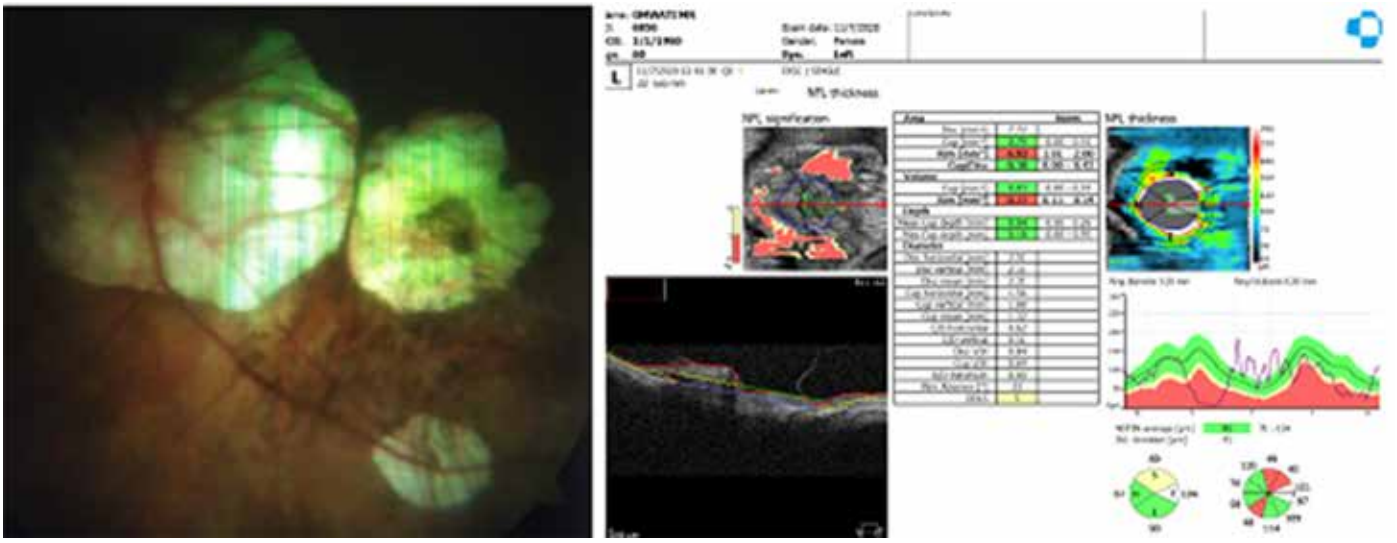

Figure 8: *Large peripapillary atrophy with posterior staphyloma. The cp RNFL print out gives erroneous results due to inability of measurement circle to stretch beyond the large PPA area.*

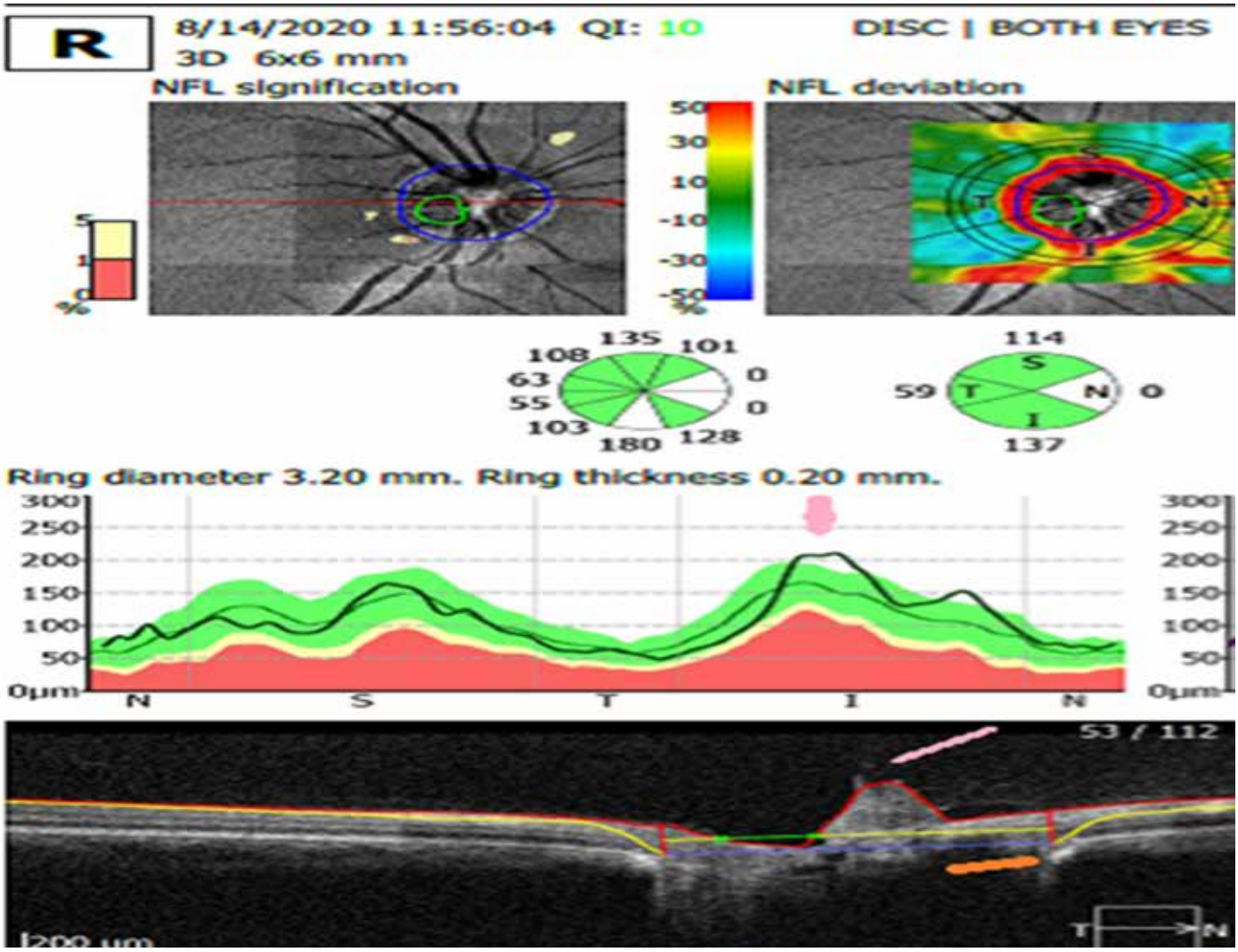

Figure 9: *Internal limiting membrane traction, resulting in artefactual increase in RNFL peak, Green disease*

beyond scanning circle diameter, would result in RNFL measured from beta zone outward, resulting in erroneously low measures (red disease). (Figure 7 and 8)New versions of Spectralis have options of 4.1 and 4.7 mm circles, to bypass the of area peripapillary atrophy.[13]

Larger β zone has been identified as a significant marker of glaucomatous damage. A recent report released from DIGS (Diagnostic Innovations of glaucoma study) states that the odds of having glaucoma get doubled for each 0.2 mm² larger β PPA area, after controlling for age, central corneal thickness and axial length.[14] *On the other hand larger γ zone is due to scleral stretching with myopic changes and is more often associated with healthy myopic, non-glaucomatous eyes.*[15,16] *Advances in measurement of β and γ zone have resulted in development of SALSA algorithms (San - Diego Automated Segmentation Algorithms), which measures areas of β PPA with intact Bruch's membrane, as surrogate indicators of glaucomatous damage*

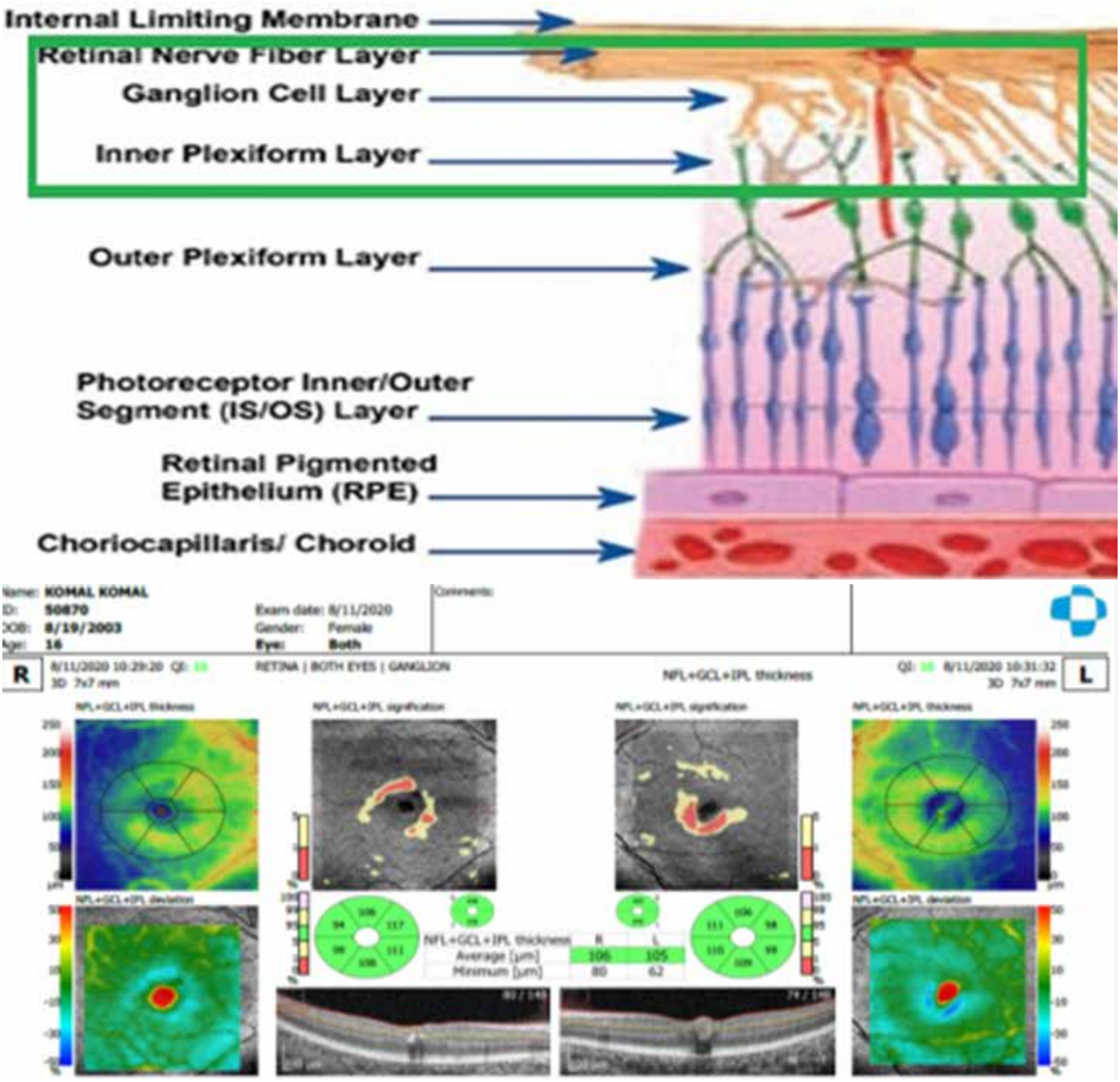

***Figure 10**: 10a Macular cube protocol measures etinal nerve fibre layer & ganglion cells and inner plexiform layer 10b. Ganglion cell complex OU print out*

Green disease

Myopic eyes suspected of glaucoma sometimes would be erroneously labelled as normal. This is seen in situations of epiretinal membrane, vitreoretinal tractions, Weiss ring or Internal limiting membrane (ILM) traction over optic nerve head, both causing artefactual increase in RNFL measurement (green disease).[17] (Figure 9) However, once total posterior vitreous detachment occurs, the membrane would obscure light reflectance and that could cause a localized red disease. In Peri-papillary retinoschisis conditions, a transient increase in RNFL thickness is noted, again a cause of green disease.

Macular cube: Macular Ganglion cell complex (mGCC)

Ganglion cell death is the hallmark of glaucomatous damage and macula has the unique position of containing 50% of ocular retinal ganglion cells. Due to the above defined confounders while measuring RNFL and optic disc parameters in the myopic suspect eye, macular GCC measurement has been explored as a more robust option to discriminate glaucoma patients from non-glaucoma subjects. Macular ganglion cell complex (mGCC) protocol measures ganglion cell, their dendrites (inner plexiform layer) and their axons (retinal nerve fibre layer). Some machines exclude RNFL and measure ganglion cell with inner plexiform layer (GC IPL). (Figure 10) A 6 by 6 mm2 area centered on macula is scanned , of which central elliptical region of 1.2 x 1.0mm, represents foveola (which lacks ganglion cells) being masked. (Figure 11)[18] Being less affected by anatomical vagaries in myopic eyes, macular scan has been established to have higher diagnostic power than cpRNFL parameters in detecting glaucoma in these patients.[19,20,21] However some studies have disputed this with both macular and optic disc protocols having equivalent diagnostic efficacy in myopic eyes.[22] Literature is equivocal on macular thickness in myopic eyes, with some authors reporting thicker macula[23] with others documenting no change.[24] In both situations a myopic normative database for ganglion cell internal plexiform layer (GCIPL) would improve glaucoma detection rate in myopic eyes.[25] In myopic eyes with macular thining/hole, posterior staphyloma and Foster Fuchs however, the macular cube scanning protocol should not be attempted. (Figure 11)

The commonest challenge faced in discriminating glaucoma in myopic eyes, remains lack of myopic normative data. Diagnostic Innovations in Glaucoma Study (DIGS 1995) and African Descent And Glaucoma Evaluation Study (ADAGES 2002) are longitudinal cohort studies designed to study participants with or without myopia and rectify this gap in imaging technology. Structural, functional and vascular testing by Spectral OCT, in Caucasian and African population, seeks to generate a reference database of healthy myopic and glaucomatous myopic eyes.[26]

Recent advances in OCT use extended depth imaging and adaptive optics have been used to study lamina cribrosa structure.[27] In myopic eyes, documenting changes in peripapillary sclera and lamina cribrosa dimensions may help in diagnosing glaucoma early.

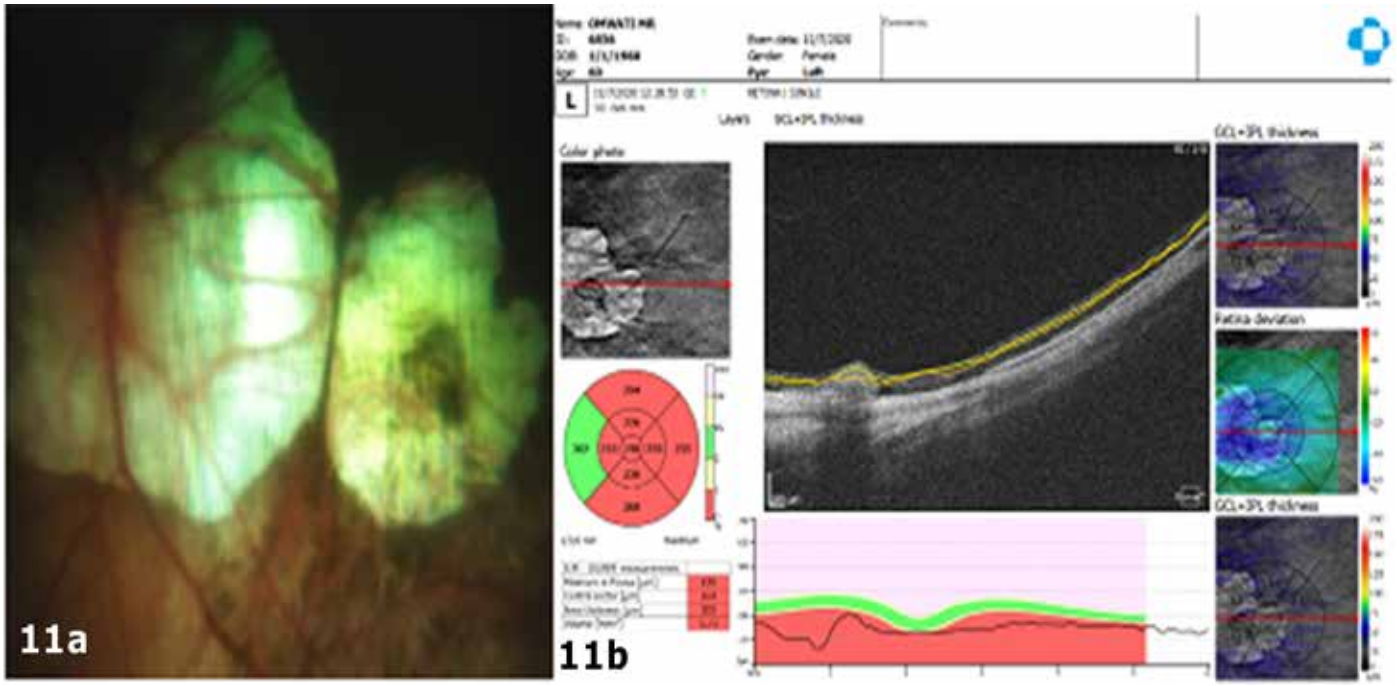

Figure 11: *11a. Pathological myopia with large annular crescent and Foster Fuchs spot*
11b Macular ganglion cell analysis protocol of same case, does not give any meaningful interpretation

Conclusion

Optical coherence tomography has become the imaging device of choice in diagnosing glaucoma. Its use in high to moderate myopia is limited by various anatomical alterations in myopic eye affecting scan acquisition and interpretation.[28] Knowledge of this challenging aspect of OCT is essential for the ophthalmologist keeping in mind the exponential increase in myopia globally. This would reduce the erroneous labelling of non-diseased myopic as glaucoma and also missing the pathology in myopic eyes.

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Kirti Singh
MD, DNB, FRCS, FAIMER
Dir Professor, Glaucoma Services,
Guru Nanak Eye Centre, Maulana
Azad Medical College, New Delhi

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