

Clinical applications of choroidal imaging technologies

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Choroid supplies the major blood supply to the eye, especially the outer retinal structures. Its understanding has significantly improved with the advent of advanced imaging modalities such as enhanced depth imaging technique and the newer swept source optical coherence tomography. Recent literature reports the findings of choroidal changes, quantitative as well as qualitative, in various chorioretinal disorders. This review article describes applications of choroidal imaging in the management of common diseases such as age-related macular degeneration, high myopia, central serous chorioretinopathy, chorioretinal inflammatory diseases, and tumors. This article briefly discusses future directions in choroidal imaging including angiography.

Key words: Choroid, enhanced depth imaging technique, swept source optical coherence tomography

Access this article online

Website:

www.ijo.in

DOI:

10.4103/0301-4738.159861

Quick Response Code:



The choroid, being the most vascular tissue of the eye, plays a very important role in pathogenesis of a variety of chorioretinal disorders. Indocyanine green (ICG) angiography has been used for many years to analyze the perfusion of the choroid, however, it does not provide any structural analysis of this deep tissue. Optical coherence tomography (OCT) is a noninvasive technique that provides high-resolution cross-sectional images of the posterior structures, especially the retina. With the advent of newest deep-penetration OCT technologies, such as the enhanced depth imaging (EDI) technique-OCT on spectral domain (SD)-OCT, or the newer swept source (SS)-OCT, we are now able to analyze not only the individual retinal layers, but also the fine details of the choroidal anatomy. Such OCT technologies provide image resolution that is, almost comparable to a histologic study of the retina and choroid.

Recent literature is swamped with reports on choroidal imaging in normal eyes as well as in ocular and systemic pathologies. However, its clinical application has not been comprehensively elucidated to the clinicians for use in daily clinical practice. Here, we explore the utility of choroidal imaging in clinical situations and discuss about its future applications.

Choroidal Imaging - Technique

Enhanced depth imaging-optical coherence tomography enhances details of the choroid by displacing the zero delay line, which is the point of maximal OCT signal sensitivity. For a conventional OCT the zero delay line is positioned

at the posterior vitreous level to provide a clear image of vitreoretinal structures. By using EDI modality, the zero delay line is displaced deeper in the tissue to provide choroidal images with greater resolution.^[1] Image averaging, eye tracking, high-speed scanning, and low speckle noise result in an enhanced visualization of the choroidal morphology and enables reproducible quantitative measurement.

Swept source optical coherence tomography is a Fourier domain depth-resolved method distinct from SD-OCT. It uses a frequency swept laser with a narrow band light source that is, rapidly tuned over a broad optical bandwidth that enables the measurement of interference at different optical frequencies or wavelengths sequentially over time.^[2] No spectrometer or line camera is needed for the Fourier transformation. This increases the imaging speed up to 300,000 axial scans per second and allows a deeper penetration of the sampling beam. SS-OCT offers several potential advantages over SD-OCT, including increased sensitivity through the full imaging depth, decreased fringe washout, better axial resolution over a broad imaging range, and higher detection efficiencies. Since it uses a longer wavelength, it has the potential to image the choroid and even the scleral tissue better than conventional SD-OCT.^[2,3]

Multiple studies have evaluated the image quality between these two deep-penetration OCT techniques, and other studies have assessed the agreement between these EDI-OCT and SS-OCT in measuring choroidal thickness, which is the most used parameter to study and differentiate primarily choroidal diseases. Tan *et al.* reported that the subfoveal choroidal thickness measurements taken using SS-OCT and SD-OCT devices were very similar, with mean differences ranging from only 7 to 15 μ between the two OCT systems.^[4]

With EDI, as the point of maximum sensitivity (zero delay line) moves to the choroid, detection of the inner retinal surface is reduced, and the posterior vitreous is not visible. To overcome this limitation and to obtain a single comprehensive image of both vitreo-retinal interface and choroid a novel imaging method called combined depth imaging can be performed

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Manuscript received: 25.02.15; **Revision accepted:** 30.03.15

using a commercially available SD-OCT device, which is easy, fast, and sensitive to visualize posterior vitreo-retino-choroidal structures into a single, comprehensive image.^[5,6]

A study from India reported the mean subfoveal choroidal thickness in third decade $294.8 \pm 46.5 \mu$ and that of in eighth decade $249.6 \pm 36.0 \mu$ ^[7] [Fig. 1].

Central Serous Chorioretinopathy

Increased choroidal thickness is a common finding in central serous chorioretinopathy (CSCR), especially in the areas of increased choroidal permeability on ICG angiography [Fig. 2]. This supports the role of the choroidal vasculature in CSCR.^[8] In particular, visualizing an extremely thick choroid in CSCR can be helpful in the differential diagnosis with age-related macular degeneration (AMD), where choroidal thickness is generally decreased compared to age-matched healthy subjects.^[9] While evaluating the effect of treatments for CSCR, Maruko *et al.* reported a decrease in choroidal thickness following photodynamic therapy (PDT),^[10] but no change in choroidal thickness after laser photocoagulation.^[11] Considering that CSCR arises from an abnormally thick choroid due to increased choroidal permeability, choroidal thinning after PDT supports its role in CSCR treatment. Fellow eyes of CSCR patients have also an increased choroidal thickness compared with normal eyes.^[12] Thus, choroidal thickness assessment using deep-penetration OCT would be useful for monitoring this disease over time.

Age-related Macular Degeneration

Choroidal changes on SD-OCT in early AMD may not be very obvious, however, in the later stage of the disease, choroidal thinning has been reported compared to age-matched healthy individuals.^[12,13]

In reticular pseudodrusen, loss of small choroidal veins on histopathology can be seen as choroidal thinning in the areas where pseudodrusen are located.^[14] Also, eyes with reticular pseudodrusen have a generally thinner choroid compared to eyes with early AMD. This differentiation is

important as the eyes with reticular pseudodrusen are at higher risk of developing wet AMD.^[15] Choroidal imaging is also helpful in differentiating AMD from polypoidal choroidal vasculopathy (PCV). Previous studies have shown choroidal thinning in AMD eyes compared to PCV eyes showing choroidal hyperpermeability areas on ICG.^[16,17] Analyzing advanced forms of dry AMD, eyes with thinner choroid showed fast geographic atrophy (GA) progression. Perhaps, subfoveal choroidal thickness may be a predictor of disease progression in GA cases.^[18] Finally, for a specific form of wet AMD called retinal angiomatous proliferation (RAP), choroidal imaging showed a thinner subfoveal choroidal thickness compared to typical wet AMD, which may suggest compromised choroidal perfusion in the development of RAP lesions.^[19]

Utilizing EDI-OCT, Spaide described a new condition called, age-related choroidal atrophy, which is different from AMD. In this entity, choroid was reported to be very thin suggesting small choroidal vessels disease, which could explain vision loss in these patients.^[20]

Analyzing changes in choroidal thickness in response to anti-VEGF therapy for wet AMD, multiple studies have reported variable results. Few reports suggested a reduction in thickness, whereas other reports suggested no change in choroidal thickness after anti-VEGF injections.^[21-23] Kang *et al.* reported a significant reduction in subfoveal choroidal thickness in eyes with a favorable response to treatment with intravitreal ranibizumab for wet AMD, but no significant change in nonresponders.^[23] Possibly, the subfoveal choroidal thickness may be a predictive factor for visual outcome and treatment response in typical wet AMD after intravitreal anti-VEGF injections.

One of the major differential diagnoses for wet AMD is adult onset foveomacular vitelliform dystrophy (AOFVD). This specific macular dystrophy may resemble a wet form of AMD because subretinal fluid accumulation, typical of active choroidal neovascularization (CNV), is also generally seen in AOFVD. However, while in wet AMD subretinal fluid is related to the abnormal permeability of the CNV complex,

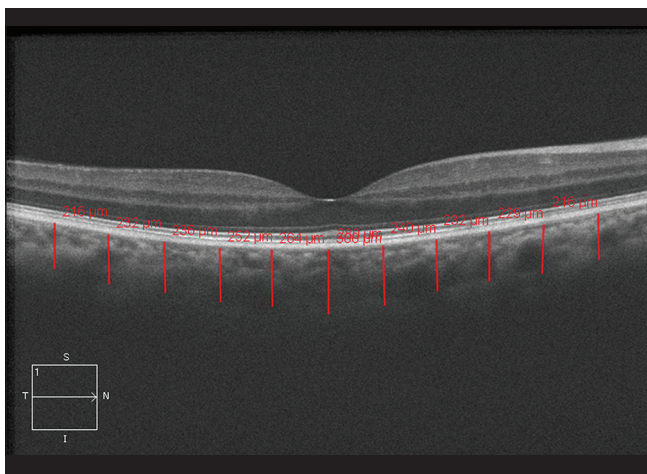


Figure 1: Choroidal scan, obtained using enhanced depth imaging mode with spectral domain optical coherence tomography in a healthy volunteer showing measurements of choroidal thickness at 500 μm from fovea in both directions

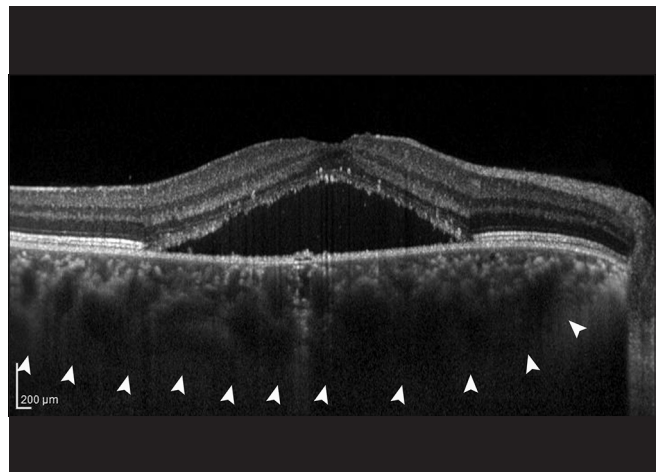


Figure 2: Choroidal scan, obtained using enhanced depth imaging mode with spectral domain optical coherence tomography in a patient with central serous chorioretinopathy, shows presence of subretinal fluid with thickened choroid (arrow-heads showing outer boundary of choroid)

in AOFVD subretinal fluid is the result of lipofuscin material reabsorption without evidence of CNV. Coscas *et al.* reported choroidal thickening in AOFVD that is, in contrast with the typical choroidal thinning observed in advanced AMD. These findings suggest that the pathogenic mechanisms of AOFVD are different from those of wet AMD. Choroidal thickness measurement could, therefore, help physicians in the challenging diagnosis between these two distinct retinal disorders.^[24]

Finally, a special mentioning must be done for the latest evidence in wet AMD using the promising technology called "OCT angiography." This noninvasive technology constructs microvascular flow map of the superficial retinal plexus, deep retinal plexus, and choriocapillaris using rapidly performed SD-OCT or SS-OCT scans of retino-choroidal areas and analyzing for variation in some measure of reflectivity, phase shift, or phase variance.^[25] OCT angiography helps to visualize the stromal choroidal vessels as well in addition to choriocapillaris. Jia *et al.* have recently shown that such technology is able not only to delineate the CNV complex in wet AMD without any dye injection, but can also provide quantitative information regarding CNV flow and area.^[26] This promising technology is still under development. However, there is a large consensus in the ophthalmology community that this is the future way to diagnose and follow-up chorioretinal disorders such as wet AMD. Additional studies evaluating change in CNV structure, CNV area, and flow index while under treatment with anti-VEGF agents are needed to clarify the clinical usefulness of the large amount of new data that this OCT angiography provides to physicians.

Vogt-Koyanagi-Harada Syndrome

The choroid is the primarily ocular target in Vogt-Koyanagi-Harada (VKH), a granulomatous inflammatory disorder that frequently occurs in patients of Asian, American Indian, or Hispanic descent, affecting eyes, meninges, and skin. This inflammatory disease, if not treated adequately, leads to multiple exudative retinal detachments that may become sight-threatening.

Markedly increased choroidal thickness is a well-known feature of this disease, as shown by various authors using EDI-OCT.^[27,28] It is possible to monitor quantitatively the change in choroidal thickness with great accuracy using deep-penetration OCT, which is extremely useful in assessing the treatment response to steroids. A significant increase in choroidal thickness happens during the acute stage of the disease, whereas during treatment progressive thinning occurs and correlates with decreasing inflammatory activity.^[29] EDI-OCT could be guide physicians in the early diagnosis of disease activity recurrence. On the contrary, choroidal atrophy is a common feature for long-standing VKH, along with changes in reflectivity of the choroidal stroma on EDI-OCT. Loss of small choroidal vessels with stromal scarring are prominent features of chronic VKH.^[30]

In addition, choroidal imaging can also reveal the presence and characteristics of VKH-associated granulomatous lesions. Choroidal granulomas can be visualized by funduscopic examination as deep, round-shaped, yellowish lesions. However, ICG angiography can help physicians in evaluating thickness of such lesions; most commonly full-thickness

granulomas appear as hypo-cyanescent areas for the whole angiogram duration, whilst partial thickness granulomas gradually disappear in the late phases of the exam.^[31] On EDI-OCT these lesions usually correspond to areas of increased homogeneity within the choroid caused by the loss of the typical vascular pattern.^[32] In addition, EDI-OCT can also reveal the depth and characteristics of VKH-related granulomas within the choroidal tissue.^[32]

Sakata *et al.* reported a unique finding in VKH patients in the nonacute uveitic stage, the "choroidal bulging," which seems to be related to active posterior segment inflammation. It is characterized by a localized thickening of the choroidal compartment with consequent bulging of the retinal pigment epithelium (RPE)/Bruch's membrane reflective complex anteriorly, without an associated retinal thickening or any obvious nearby retinal lesion to justify this finding. This could be a new sign indicative of posterior segment inflammation in a noninvasive manner.^[33]

Birdshot Chorioretinopathy

Birdshot chorioretinopathy is an immune-mediated inflammatory disorder apparently involving only the eyes. As indicated by its name, the inflammatory process involves both the retina and the choroid.^[34] ICG angiography has an essential role in the diagnosis of this disease. In 100% of the patients, ICG angiography reveals regularly distributed hypocyanescent dark dots, which are consistent with choroidal granulomatous infiltrates.^[35] In addition, ICG angiography can also differentiate between stages of the disease. In the active stage, infiltrates appear as hypocyanescent lesions in mid-phase and either disappears (partial-thickness infiltrates) or persist (full-thickness infiltrates) late-phase ICG angiography. On the contrary, in chronic disease most hypocyanescent lesions persist up to the late-phase ICG angiography; these lesions are interpreted as either chronic granulomas or stromal scars.^[35]

Sarcoidosis

Because sarcoidosis is a primarily choroidal inflammatory disease, choroidal imaging is very helpful also in this disorder. Noncaseating inflammatory infiltrates (granulomas) are common in ocular sarcoidosis.^[36] On SD-OCT, sarcoid granulomas generally appear as homogenous, hyporeflective, well-demarcated choroidal lesions.^[32,37] The adjacent choroidal tissue may be normal,^[37] or may present loss of the typical vascular pattern.^[32] After initiating proper immunosuppressant treatment, such lesions reduce in diameter.^[37] On early-phase and mid-phase ICG angiography, granulomas generally appear as confluent hypocyanescent areas that may or may not disappear on late-phase angiography depending on their thickness.^[31] Choroidal imaging could be useful in confirming the diagnosis and assessing the treatment response in ocular sarcoidosis.

Toxoplasma Retinochoroiditis

Toxoplasma retinochoroiditis, simply known as ocular toxoplasmosis, is the most common cause of infections uveitis in immunocompetent patients.^[38,39] It is mostly the result of a congenital infection by *Toxoplasma gondii*, with possible reactivation later in life. Reactivation of toxoplasmosis is

characterized by focal retinitis adjacent to an old scar, usually associated with vitritis.^[40] The choroid is also involved by the inflammatory response to the infectious agent. During the active stage of the infection, a marked increase in choroidal thickness is commonly seen under the active lesion [Fig. 3]. After proper treatment, the choroid goes back to the normal thickness. The inactive stage of the infection is characterized by retinochoroidal scars, which may be associated with choroidal thinning (atrophic scars), normal choroidal thickness (elevated retinochoroidal scars), or significant choroidal thinning with loss of normal choroidal architecture (deep scars).^[41] The assessment of choroidal involvement during and after toxoplasma retinochoroiditis can be simply performed by the use of EDI-OCT, which can provide useful information about the treatment response for active toxoplasmosis.

Retinitis Pigmentosa

Retinitis pigmentosa (RP) is a genetic disorder characterized by degeneration of the RPE, attenuation of retinal vessels, loss of photoreceptors, sclerosis, and atrophy of the choriocapillaris. RP progressively lead to localized areas of clinically visible chorioretinal atrophy and consequently, a dramatic loss in visual function.^[42,43] Previous studies reported reduced choroidal thickness in patients with RP compared to healthy individuals.^[44,45] However, such studies had a very small sample size with poor distribution of patients in various age groups. Ayton *et al.* reported a significant correlation between choroidal thickness and visual acuity in RP, as well as duration of the disease. They also reported that the choroid is thinner in cases of poor visual acuity and longer duration of the disease. However, no correlation of the disease duration was found with visual acuity.^[46] Measurements of choroidal thickness in RP patients could be very useful for future therapies, such as suprachoroidal implantation of electrode arrays, to calculate the distance between the implant and the retinal ganglion cells. Therefore, a better understanding of the choroid in eyes with RP is needed.^[47]

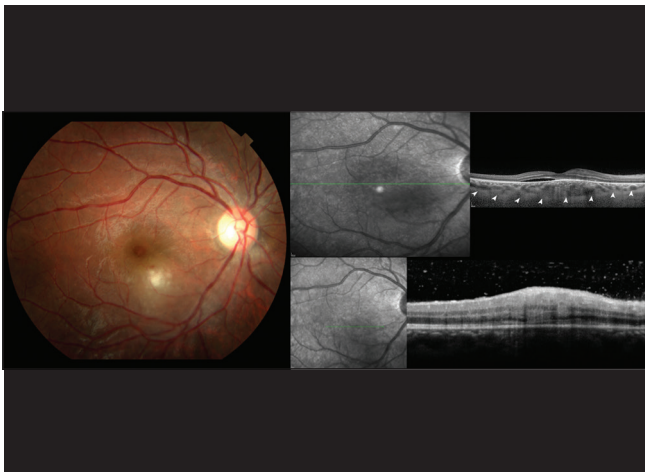


Figure 3: Color photograph shows a yellowish active chorioretinitis due to toxoplasmosis (left panel). Choroidal scan (top right panel) passing through fovea, obtained using enhanced depth imaging mode with spectral domain optical coherence tomography, shows thickening of the choroid (arrow-heads showing outer boundary of choroid). Choroidal scan (bottom right panel) passing through the lesion shows inner hyperreflectivity suggestive of retinitis and hyper-reflective dots suggestive of vitreous cells

Diabetic Retinopathy

Scanning electron microscopy in eyes with diabetic retinopathy showed increased vascular tortuosity, dilation and narrowing, hypercellularity, vascular loop and microaneurysm formation, “drop-out” of choriocapillaris, and sinus-like structure formation between choroidal lobules.^[48,49] Using EDI-OCT, inconsistent results have been reported in the literature while assessing choroidal changes in diabetes. Xu *et al.* reported slight choroidal thickening in diabetic patients compared to normal; however, neither presence nor stage of diabetic retinopathy appeared to be associated with abnormal subfoveal choroidal thickness.^[50] Kim *et al.* also demonstrated increasing choroidal thickness with increasing severity of retinopathy.^[51] On the contrary, Querques *et al.* reported a significant thinning of subfoveal choroid in diabetic patients as compared to controls.^[52] Other reports suggested choroidal thinning in diabetics^[53-55] and increasing thinning with progressive retinopathy.^[53] Decreased choroidal thickness may be related to decreased choroidal blood flow; however, choroidal angiography may explain this further. In patients with severe nonproliferative diabetic retinopathy or early proliferative diabetic retinopathy, after panretinal photocoagulation the mean choroidal thickness increased significantly in the macular area and decreased significantly in the photocoagulated area. This might reflect a redistribution of choroidal blood flow, which may be critical for retinal metabolism.^[56]

Rayess *et al.* showed that the eyes with diabetic macular edema (DME) with a thicker baseline subfoveal choroidal thickness had better short-term anatomic and functional responses at 3 months.^[57] Baseline subfoveal choroidal thickness may help predict which patients with DME will respond more favorably in the short-term to intravitreal anti-VEGF agents. In contrary, Yiu *et al.* reported decrease in choroidal thickness after anti-VEGF therapy for DME at 6 months; however, choroidal thinning was not associated with functional or anatomic outcomes in eyes with DME.^[58]

Pathologic Myopia

Pathologic myopia is associated with excessive and progressive elongation of the globe and results in a variety of fundus changes such as lacquer cracks in Bruch’s membrane, CNV, and chorioretinal atrophy. Both photoreceptors and choriocapillaris are rarefied as compared with emmetropic eyes, and the RPE is diffusely depigmented. Compared to emmetropic subjects, myopic eyes have an extremely thin choroid that can be easily visualized by indirect ophthalmoscopy and measured by EDI-OCT [Fig. 4]. The longer is the eye, the thinner is the choroid within the macular area.^[59,60] In addition, specific choroidal findings may be associated with high myopia. For example, peripapillary intrachoroidal cavitations are often associated with tilted discs with myopic conus. Intrachoroidal cavitations are lesions with no internal elevation, likely related to the posterior bowing of the sclera in the region of the conus that extended around the nerve to involve the choroid secondarily.^[61]

Choroidal Masses

The differentiation between benign and malignant choroidal masses is crucial to understand if a specific treatment may be appropriate, however, the correct diagnosis may be

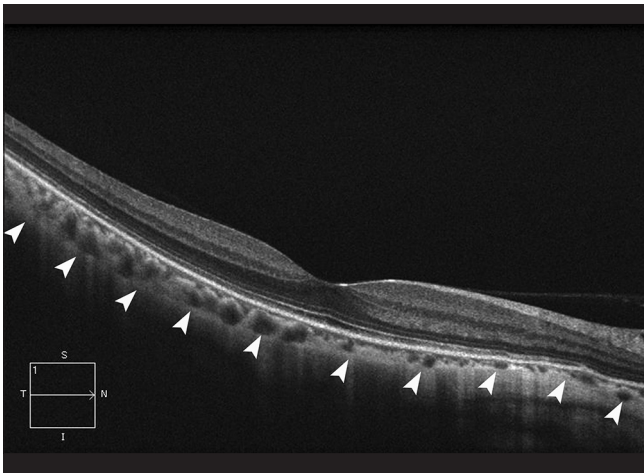


Figure 4: Choroidal scan, obtained using enhanced depth imaging mode with spectral domain optical coherence tomography in a high myope patient, shows thin choroid (arrow-heads showing outer boundary of choroid)

challenging. Considering the fact that most ocular malignancies arise within the choroidal tissue, choroidal imaging may be extremely useful in the differential diagnosis. Indeed, different choroidal features can be detected using EDI-OCT among tumors. Melanocytic tumors demonstrate a highly reflective band within the choriocapillaris with posterior shadowing, whilst amelanotic nevi appears homogeneous with a medium reflective band associated with visible choroidal vessels within the tumor.^[62] In addition, choroidal nevi show smooth moderate dome-shape with overlying retinal pigment epithelial alterations, subretinal cleft, and photoreceptor loss.^[63] Choroidal melanomas have a highly reflective band in the anterior choroid with lack of visibility of either the choroidal vessels or inner sclera,^[62] and they are smooth, moderately dome-shaped, and with overlying shaggy photoreceptors.^[63] Choroidal hemangiomas appear as a medium-to-low reflective band with a homogeneous signal and intrinsic spaces [Fig. 5],^[62] as well as smooth, acutely dome-shaped, and with subretinal fluid and/or cystoid retinal edema.^[63] Differently from all other choroidal masses, which show inward compression of the choroidal vasculature, in hemangiomas the choroidal vessels are expanded.^[63] In addition, ICG angiography is the most accurate tool to demonstrate the intrinsic vascular pattern of circumscribed choroidal hemangioma; on late-phase angiography, hemangiomas have a peculiar aspect with a relative decrease in fluorescence and possible washout of the dye.^[64] Choroidal metastasis show a hyporeflective band in the deeper choroid causing enlargement of the suprachoroidal space,^[62] as well as “lumpy, bumpy” irregular surface topography, subretinal fluid, and shaggy photoreceptors.^[63] Choroidal osteoma have a smooth undulating surface with intralaminar lamellar lines and tubules, representing bone lamellae or vessels.^[63]

Choroidal Lymphoma

Intraocular lymphoma is one of the most challenging masquerade syndromes because frequently resembles a chronic posterior uveitis with the most common ocular complaints being floaters and blurred vision. Intraocular lymphoma has primarily a vitreo-retinal involvement, but choroidal

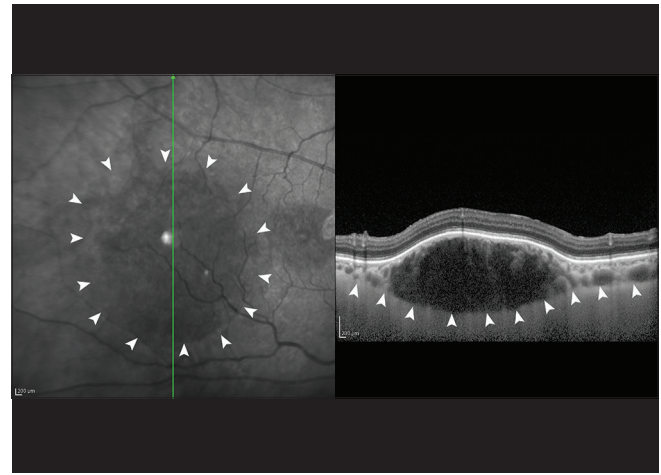


Figure 5: Choroidal scan, obtained using enhanced depth imaging mode with spectral domain optical coherence tomography shows the homogeneous intrinsic spaces (arrow-heads showing outer boundary of choroid on right panel) in an eye with choroidal hemangioma (arrow-head on left panel on infrared image)

lymphoma also occurs. EDI-OCT can be helpful to visualize and measure lymphomatous collections. Shields *et al.* have reported EDI-OCT characteristics of a series of choroidal lymphomas; they have been described as having “placid, rippled, or seasick” surface. In addition, greater tumor thickness correlated with increasing tumor surface fluctuation as placid was mean 1.7 mm, rippled was 2.8 mm, and seasick pattern was 4.1 mm in ultrasonographic thickness.^[65]

Uveal Effusion Syndrome

Uveal effusion syndrome is an idiopathic condition where a transudative fluid escapes from the choriocapillaris into the surrounding potential space, causing engorgement and thickening of the choroid, choroidal detachment, and consequent fluid in the subretinal space resulting in a secondary serous retinal detachment. This extremely rare disease seems to be related to impaired scleral permeability to proteins and compression of the vortex veins.^[66] Beside multiple abnormalities on fluorescein angiography and ICG angiography,^[67] EDI-OCT can easily demonstrate extremely thick choroid in such condition,^[68] and it also represents a useful tool to manage patients following surgical treatments for uveal effusion syndrome such as full-thickness sclerectomy.

Conclusions

Choroidal imaging using deep-penetration OCT systems is a noninvasive reproducible technique that allows *in-vivo* quantitative and qualitative assessment of the choroid, including each layer. Choroidal imaging could be used to explain the vision loss, disease activity, and monitor the treatment response for a large variety of chorioretinal disorders. Also, many choroidal diseases possess unique clinical features that are discernable on a thorough ophthalmic examination. The distinct fundoscopic appearance of each entity is generally enough to establish the diagnosis. In more challenging cases, ancillary studies including deep-penetration OCT, ICG angiography, or other imaging modalities can be helpful in confirming the diagnosis. Further advancement

in choroidal imaging including measurement of blood flow and morphological changes during follow-up would help to improve the understanding and utility of this information in daily clinical practice.

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Cite this article as: Chhablani J, Barteselli G. Clinical applications of choroidal imaging technologies. *Indian J Ophthalmol* 2015;63:384-90.

Source of Support: Nil. **Conflict of Interest:** None declared.