ABOUT THE AUTHORS

HADY SAHEB, MD, MPH, FRCSC: Dr. Hady Saheb is currently Director of the Glaucoma Fellowship Program at McGill University. He is also a board member of the Canadian Ophthalmology Society (COS), Chair of the Continuing Professional Development (CPD) Council of the COS, and Treasurer for the Canadian Glaucoma Society (CGS).

Dr. Saheb earned his medical degree and completed his residency at McGill University. He was a glaucoma fellow at the Bascom Palmer Eye Institute in Miami and subsequently completed a second fellowship in Novel Glaucoma Surgical Devices and Complex Anterior Segment Surgery with Dr. Ike Ahmed at the University of Toronto. He also completed a Masters in Public Health at the Johns Hopkins University Bloomberg School of Public Health in Baltimore, with an interest in Clinical Trials and Health Leadership. Dr. Saheb is passionate about innovation and education and has received several awards, published peer-reviewed publications and book chapters, and spoken at multiple national and international meetings.

ALI SALIMI, MD, MSc: Dr. Ali Salimi is currently an ophthalmology resident at McGill University. He has published numerous peer-reviewed articles, presented his research internationally, and received various research awards. Dr. Salimi envisions becoming an Ophthalmologist-Scientist practicing at an academic center where he can combine his passion for education, research, and innovation in ophthalmology.

Clinical applications of optical coherence tomography (OCT) in glaucoma

Hady Saheb, MD, MPH, FRCSC and Ali Salimi, MD, MSc

Visual field (VF) testing has been the mainstay for diagnosing and monitoring glaucoma. However, relying solely on VF can delay the patient's diagnosis in the early stages of the disease, as the structural changes are known to precede the functional changes and VF defects may not be clinically detectable until at least 25-35% of retinal ganglion cells (RGCs) are lost. This concept highlights the importance of alternative diagnostic modalities such as optical coherence tomography (OCT). OCT's ability to reliably segregate and quantify the thickness of retinal layers has allowed earlier detection of glaucoma, up to 6 years before the onset of any detectable VF loss.[1] Compared to VF, OCT is less time-consuming and is less dependent on the patient's cooperation and test-taking ability. There are a few commercially available spectral domain OCT (SD-OCT) machines that are routinely used in glaucoma clinics. These devices are fundamentally similar with comparable performance, but their scanning protocols and segmentation algorithms are not analogous; thus, the measured parameters may not necessarily be interchangeable between devices and the values should be interpreted relative to the normative databases specific to each machine (**Table 1**). In this review, we present the clinical applications of OCT imaging in glaucoma and share some clinical pearls and pitfalls.

OCT circumpapillary retinal nerve fiber layer (cpRNFL, commonly referred to as RNFL) and ganglion cell analysis (GCA) are the two most commonly used OCT-derived markers for the detection and monitoring of glaucoma. The clinical implications of each marker in different disease stages remain a topic of research, as the RNFL or GCA thinning may not necessarily occur simultaneously during the course of RGC degeneration. GCA is shown to outperform RNFL in the detection of glaucoma in the very early stages,[2] in keeping with the theory that RGC anomalies precede axonal loss.[3] However, some researchers have published evidence of a comparable diagnostic ability for both measures. With disease progression toward more advanced stages, it has been suggested that the diagnostic value of RNFL is superior to that of GCA, likely because only 50% of the RGCs occupy the macular region compared to nearly all of the RGCs assessed in peripapillary RNFL analysis.[3,4]

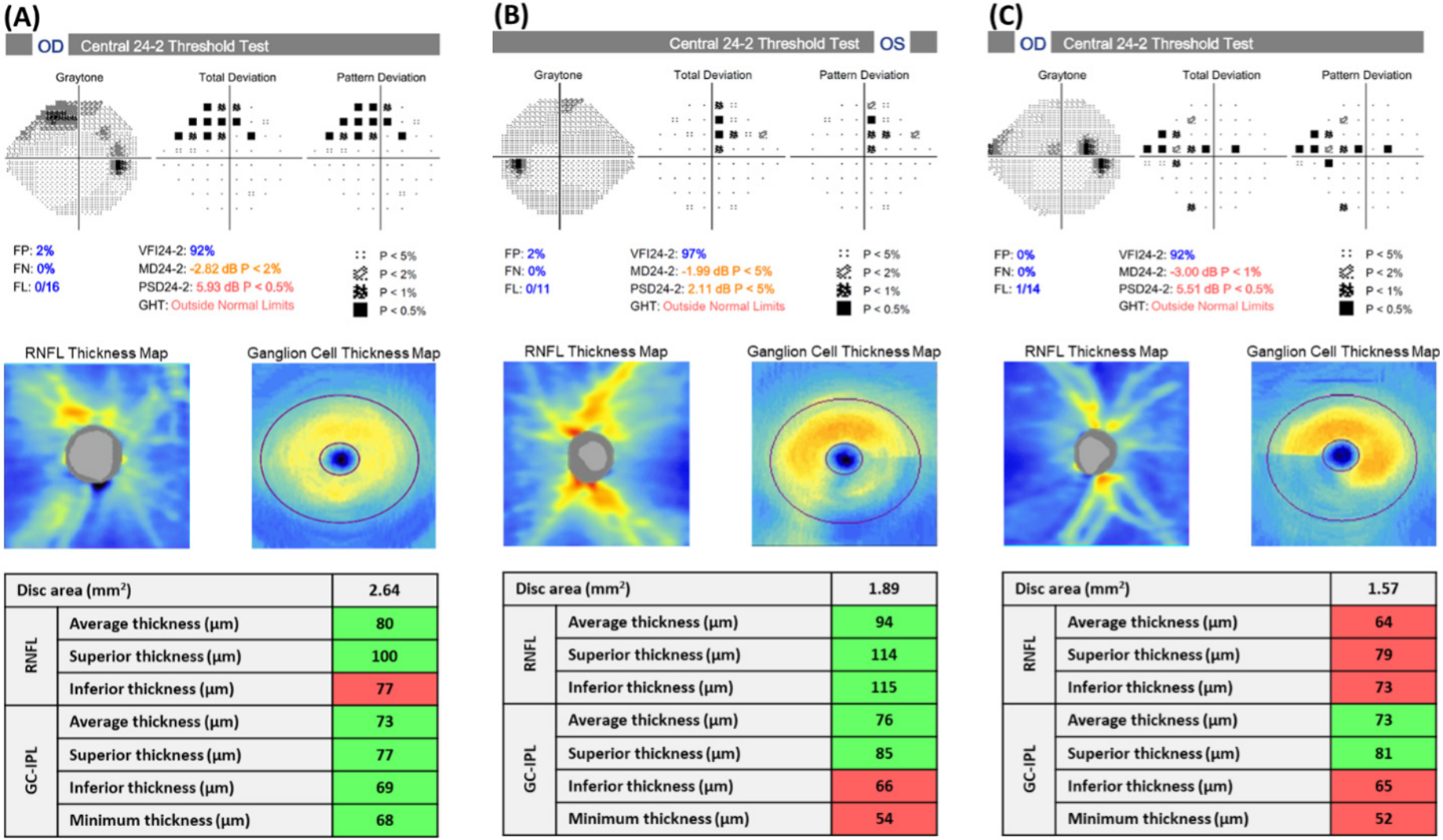
In addition to their diagnostic ability, RNFL and GCA are useful in monitoring disease progression. However, in longitudinal analyses, the pathological change should be discerned from the physiological age-related change. Both parameters exhibit some variation in the age-related rate of thinning, (0.14-0.82 µm/year for RNFL and 0.11-0.32 µm/year for GCA), depending on the patient population being studied and the OCT machine being used. However, the rate of thinning associated with glaucoma is notably greater (0.86-3.30 µm/year for RNFL and 0.49-1.46 µm/year for GCA). Moreover, faster RNFL thinning has been associated with faster disease progression; according to the Duke Glaucoma Registry Study, in those with slow disease progression, RNFL thinning occurred at <1 µm/year compared to >2 µm/year in fast progressors.[5] Currently, there exists no consensus on a cut-off value signifying a clinically significant rate of progression. Nevertheless, in earlier stages of glaucoma, RNFL loss occurs at a faster rate compared to the GCA. As the disease progresses, the RNFL loss slows down and eventually plateaus to a floor, while GCA exhibits a comparatively faster rate of thinning in advanced glaucoma cases. This notion supports the use of RNFL in monitoring disease progression through RNFL at earlier stages of the disease and through GCA in more advanced cases,[6-8] although our clinic still uses both measures throughout the disease spectrum (**Figure 1A–C**).

Current published guidelines from the American Academy of Ophthalmology and the European Glaucoma Society do not endorse a recommended frequency for OCT imaging of glaucoma patients.[9,10] Nonetheless, evidence from multiple studies suggests that best practice includes semi-annual testing intervals using OCT for following glaucoma patients.[11,12] A more recent study found that increasing the OCT testing frequency from twice yearly to three times per year did not reduce the time to detect glaucoma progression.[11]

The clinical applications of RNFL and GCA may not necessarily be generalizable to all eyes and should be individualized in the context of specific pathologies. For instance, in the case of eyes with pathological myopia and tilted disc, RNFL is more significantly affected than GCA,[13-15] rendering GCA a better diagnostic parameter irrespective of glaucoma severity. Similarly, larger disc diameter has been linked to greater RNFL thickness but not ganglion cell thickness;[14,16] thus, GCA is superior to RNFL, as the latter can lead to false negatives in eyes with larger disc diameters. Conversely, in eyes with macular pathology, ganglion cell measures can be artifactually abnormal, thereby rendering RNFL a more reliable diagnostic tool for these cases.

		Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA, USA)	Spectralis (Heidelberg Engineering, Germany)	3D OCT 1000 (Topcon, Paramus, NJ, USA)	RTVue-100 (Optovue, Fremont, CA, USA)
Pupil size requirement (mm)		≥ 2.0	≥ 2.0	≥ 2.5	≥ 3.0
Scan speed (a-scans/ second)		27,000	40,000	18,000	26,000
Axial resolution (microns)		5	7	5	5
Recommended signal quality		Called "Signal Strength" ≥ 6 [0–10]	Called "Signal Strength Index (SSI)" ≥ 15 [0–40]	Called "Quality factor (Q-factor)" 45 [0–160]	Called "Quality (Q)" 30 for macular [0–100]
RNFL	scanning protocol	Optic Disc cube 200×200 protocol (6×6 mm^2 area)	Peripapillary scan circle spanning 12° of arc	Optic Disc cube 200×200 protocol (6×6 mm^2 area)	combination of radial scans and circular scans
RNFL	thickness measurement	3.46 mm diameter circle centered over ONH	Circle diameter depends on the axial length of the eye	3.4 mm diameter circle centered over ONH	3.45 mm diameter circle centered over ONH
Ganglion cell	scanning protocol	Macular Cube 200×200 protocol or 512×128 protocol	30°×25° volume scan of retinal thickness	Macular Cube 512×128 protocol	7×7 mm square area centered 0.75-1 mm temporal to the fovea (thickness calculated within a 6 mm diameter circular macular area)
Ganglion cell	thickness measurement	GC-IPL = GCL + IPL GCC = RNFL + GCL + IPL	Posterior pole asymmetry analysis	GCL + IPL RNFL + GCL + IPL	6-mm diameter circular macular area GCC = RNFL + GCL + IPL
Thickness measurement reference plane		Reference-plane dependent (200 µm above the RPE)	Reference-plane independent	Reference-plane dependent (120 µm above the RPE)	Reference-plane dependent (150 µm above the RPE)
Normative Database	Sample size (n)	284 individuals (284 eyes) for RNFL 282 individuals (282 eyes) for macular scan	330 individuals (330 eyes)	399 individuals (399 eyes)	480 individuals (640 eyes)
Normative Database	Average age [range] (years)	46.5 [19–84]	49.7 [20–90]	46.3 [18–88]	50.7 [19–82]
Normative Database	Gender (M:F)	134 : 150 for RNFL 133 : 149 for macular scan	146 : 184	173 : 226	N/A
Normative Database	Ethnicity, (%) • White / Caucasian • Hispanic • Black / African American • Asian • Indian • Other / mixed	 43 12 18 24 1 6	 66 14 12 7 - 1	 49 18 20 13 - -	 18 11 10 47 14 -
Normative Database	Scan values are adjusted for	Age	Age, and Bruch's membrane opening area	Age	Age, signal strength, disc area, ethnicity
Normative Database	Scan values are NOT adjusted for	Axial length, refraction, optic disc area, signal strength, ethnicity	Axial length, refraction, optic disc area, signal strength, ethnicity	Axial length, refraction, optic disc area, signal strength, ethnicity	Axial length, refraction

Table 1: *Characteristics of four commercially available spectral domain optical coherence tomography devices.*[28-37]



Disc area (mm²)		2.64
RNFL	Average thickness (µm)	80
	Superior thickness (µm)	100
	Inferior thickness (µm)	77
GC-IPL	Average thickness (µm)	73
	Superior thickness (µm)	77
	Inferior thickness (µm)	69
	Minimum thickness (µm)	68

Disc area (mm²)		1.89
RNFL	Average thickness (µm)	94
	Superior thickness (µm)	114
	Inferior thickness (µm)	115
GC-IPL	Average thickness (µm)	76
	Superior thickness (µm)	85
	Inferior thickness (µm)	66
	Minimum thickness (µm)	54

Disc area (mm²)		1.57
RNFL	Average thickness (µm)	64
	Superior thickness (µm)	79
	Inferior thickness (µm)	73
GC-IPL	Average thickness (µm)	73
	Superior thickness (µm)	81
	Inferior thickness (µm)	65
	Minimum thickness (µm)	52

Figure 1: *Clinical examples of glaucomatous eyes with structural abnormalities detected through optical coherence tomography. (A) abnormal retinal nerve fiber layer thickness (RNFL) and normal ganglion cell-inner plexiform layer thickness (GC-IPL); (B) normal RNFL thickness and abnormal GC-IPL thickness; (C) Abnormal RNFL and GC-IPL thickness.*

Automatic color-coding of RNFL and GCA values according to the age-matched normative database can facilitate and expedite data interpretation; however, clinicians should remain cognizant that the current normative databases offered by the OCT machines' glaucoma modules are established in healthy populations with no retinal or neuro-ophthalmic pathologies. In addition, statistically normal tests are not always indicative of clinically normal measurements. Thus, relying solely on automatic color-coding can lead to false-negative or false-positive interpretations. In cases where the values seem to be within the normal limits of the normative database, attention should be paid to any asymmetry between the two eyes. For instance, on scans performed by Cirrus HD-OCT, an asymmetry greater than 9 µm in average RNFL thickness or 5 µm in GCA should raise suspicion of glaucoma.[17-19] Also, the RNFL temporal-superior-nasal-inferior-temporal (TSNIT) graph is a valuable indicator of subtle RNFL abnormalities that can be missed by the averaged global indices–a pitfall known as green disease. In contrast, the RNFL in highly myopic eyes tends to be thinner and can therefore be color-coded in red, even in absence of glaucoma.[13] In such cases, assessing the interocular RNFL symmetry and the GCA parameters as well as looking for focal defects can help avoid the "red disease" pitfall.

OCT imaging remains prone to errors and the absence of clinically significant artifacts should be ensured before any clinical interpretation. Each manufacturer provides a threshold for signal strength below which the automatic segmentation algorithms may not be reliable (**Table 1**). Misalignment of the optic nerve head (ONH) circle can result in measurement variations,[20] as the RNFL thickness is the highest in the circumpapillary area and decreases away from the ONH.[21] Blinking, saccadic eye movements, the presence of media opacity, and optical focus can all lead to erroneous segmentation, limiting the validity and reliability of the scans.[22] Lastly, in the absence of a normative database for longitudinal age-related changes in RNFL and GCA, the trend-based analysis fails to differentiate the glaucomatous changes from the age-related ones. Thus, statistical significance in the slope of trend-based analysis should be interpreted with caution, given its susceptibility to yield high false positive rates.[23]

More recently, swept-source OCT (SS-OCT) has shown clinical utility in glaucoma clinics thanks to its speed, longer wavelength, deeper penetration, and ability to concurrently capture the ONH and the macula in a single scan.[24] By extending the RNFL measurements beyond the circumpapillary region and the GCA beyond the macular region, this new technique allows simultaneous RNFL and GCA analysis as a single layer. SS-OCT has comparable performance to SD-OCT in detecting glaucoma and monitoring progression,[24] yet it outperforms SD-OCT in myopic eyes[25]–a population in which detection and monitoring of glaucoma are particularly challenging. As SS-OCT gains popularity in glaucoma clinics, clinicians should keep in mind that the RNFL and GCA values obtained via SD-OCT and SS-OCT are not interchangeable.[26]

OCT-angiography (OCTA) constitutes another area of innovation in OCT imaging, with a potential role in glaucoma clinics. This non-invasive dye-free imaging modality allows qualitative and quantitative assessment of retinal vasculature. Flow index and vessel density are two of the OCTA parameters that are affected in glaucomatous patients. Although the evidence at this time is limited, the macular vessel density is not limited by the floor effect, which allows OCTA to overcome one of the main limitations of OCT imaging, making it a potentially superior test for eyes with high myopia or advanced glaucoma.[27] OCTA remains a relatively new technique, but has the potential of leading to a paradigm shift in the detection and monitoring of glaucoma. However, until more evidence uncovers its full applications and limitations, clinicians should remain cautious in interpreting the OCTA results.

The future holds much promise for the prompt detection and monitoring of glaucoma. The continuous technological advancements in imaging modalities have led to a surge in the availability of data on glaucoma. Artificial intelligence and machine learning algorithms continue to unlock the mysteries of glaucoma diagnostics by combining the data from a variety of functional and imaging modalities such as VFs, fundus photos, OCT, and OCTA. A validated and widely accepted integrative algorithm capable of combining functional and structural measures to detect glaucoma or monitor its progression is of paramount clinical importance but has yet to be developed and commercialized.

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