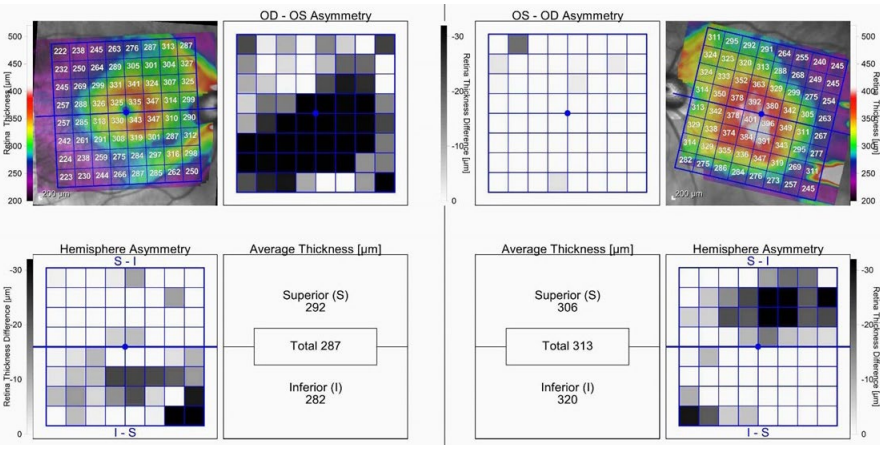
Is It Glaucoma or Not? Watch for RNFL OCT Artifacts

By measuring thinning in the retinal nerve fiber layer (RNFL), OCT has proved to be effective in helping to diagnose glaucoma. However, OCT can give misleading measurements, known as artifacts. "An artifact is an error where the machine provides inaccurate information," said Teresa C. Chen, MD, Associate Professor of Ophthalmology at Harvard Medical School in Boston. Artifacts can arise from multiple sources—the technician administering the exam, other diseases, and glaucoma itself. Because artifacts may lead to misdiagnosis and unnecessary treatments, it's important to understand the various types of artifacts, what causes them, and how to distinguish between retinal thinning caused by glaucoma and other causes of an abnormal OCT, Dr. Chen said.



ARTIFACT. *This patient was screened but was found not to have glaucoma of either eye. Why? There is an artifact in the left macular region caused by past retinal detachment repair and by an epiretinal membrane. In the asymmetry analysis, there appears to be relative superior retinal "thinning" of the left eye due to inferior retinal thickening caused by the epiretinal membrane.*

Types of Artifacts

Dr. Chen enumerated three types of artifacts: inaccurate measurements, such as those due to segmentation errors; inaccurate color coding, which can lead to a false positive glaucoma diagnosis (i.e., "red disease") or a false negative (i.e., "green disease"); and interpretation errors that result from comparing values from different machines.

Segmentation. Segmentation errors are misidentifications of the RNFL's boundaries, which can cause inaccurate measurements. "The segmentation algorithm sees an interface at one tissue and calls that the border of another tissue," said Joel S. Schuman, MD, FACS, Professor of Ophthalmology and Vice Chair for Research Innovation at Wills Eye Hospital, Philadelphia. "For instance, RNFL wouldn't be thinner with epiretinal membrane [ERM] unless the anterior segmentation line is erroneously below the internal limiting membrane [ILM] or the posterior segmentation is anterior to the posterior border of the RNFL. Typically, ERM causes the anterior segmentation line to be anterior to the ILM—at the level of the ERM—and also typically the posterior RNFL border segmentation is unaffected by ERM."

Poor signal strength can cause the opposite problem, said Dr. Schuman. "If the signal is low, the segmentation algorithm could give you a thinner measurement for the RNFL—up until a certain point where the segmentation isn't actually measuring the nerve fiber layer at all because it can't tell where the borders are."

David Huang, MD, PhD, Associate Director and Director of Research, Casey Eye Institute, in Portland, Oregon, said that segmentation artifacts can be detected by looking at the OCT cross-sectional images as well as the thickness map.

Red/green disease. OCT manufacturers use color codes to indicate how a patient compares to a normative database, but this coding can be misleading. For example, myopia is a

BY JUDY GELMAN MYERS, INTERVIEWING **TERESA C. CHEN, MD; DAVID HUANG, MD, PHD;** AND **JOEL S. SCHUMAN, MD, FACS.**

Teresa C. Chen, MD

common cause of red disease, a false positive color coding that could lead to an inaccurate diagnosis of glaucoma. "In red disease, certain quadrants of the retinal nerve fiber layer thickness map, particularly the nasal RNFL, are classified as thinner than normal limits. That can happen in highly myopic eyes, or if the person was born with a thinner nerve fiber layer," said Dr. Schuman.

In contrast, a patient who has severe glaucoma can be misdiagnosed as normal due to segmentation errors, said Dr. Chen. "The RNFL printout can show green when the patient may have very advanced RNFL thinning simply because the posterior RNFL border is incorrectly segmented too posteriorly, making it look like the patient has a really thick RNFL," she said. This is called "green disease," where the RNFL printout shows a green color coding, or normal classification, even though the patient has glaucoma.

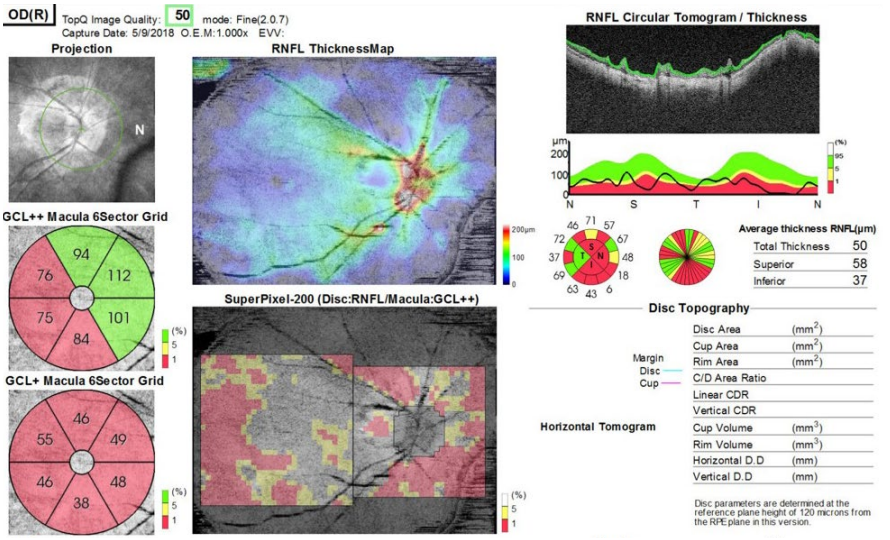
Dr. Huang said there are ways of circumventing these errors. "If you look at overall global nerve fiber layer thickness or quadrant values, you'll miss small nerve fiber bundle loss that occurs in early glaucoma. Maps that give you thickness analysis in narrower sectors will help you detect focal loss better. Many systems give you a map with even higher transverse resolution so you can appreciate arcuate-shaped nerve fiber defects. That is useful to look at as well."

Comparing values from different machines. Measurements from different OCT devices are not interchangeable. As Dr. Schuman put it, "A micron is not a micron where OCT comes into play. One machine will say it's 90 microns and another machine will say it's 95 microns, depending on how the device manufacturers set the calculations for thickness measures."

How to Read an OCT

Glaucoma can be recognized by the characteristic type of optic neuropathy it shows on an OCT.

Check the location and shape. "In order for an abnormality to indicate glaucoma, it should be in the location that you expect and in the shape that you would expect for glaucoma," said Dr. Schuman. "In general, that's going to be inferior, inferior temporal, superior, or superior temporal. It will appear to extend out from the disc in an arcuate pattern that widens."



3D OCT PRINTOUT. *Image quality is borderline at the lower end of nominal threshold, which can cause errors in segmentation and thickness measurements. The circumpapillary RNFL on the upper right of the image shows irregular RNFL borders, related to segmentation errors due to image quality and peripapillary atrophy, which is seen in the projection image. Given these artifacts, all measurements should be interpreted cautiously, said Dr. Schuman.*

Look for structure-function correspondence. Dr. Schuman also said that a glaucomatous OCT should show structure-function correspondence. "If the OCT and the visual field match up, that's pretty good evidence for glaucoma. In early disease, the OCT often gets worse before the defect appears in the visual field. In moderate disease, we tend to see abnormalities and progression in both the OCT and the visual field."

The floor effect can hide worsening glaucoma. The floor effect is the point at which no further structural loss can be detected using OCT global measures. It can mislead ophthalmologists into thinking that their patients' glaucoma is not getting worse. Said Dr. Schuman, "In late glaucoma, you have abnormalities in both OCT and visual field but can't track progression with OCT global structural measures because you hit a measurement floor. The OCT doesn't change so you think your patient is stable, when in fact they may be getting worse, and even much worse." He suggested consulting the volumetric analysis on the OCT to identify local areas of progression that might otherwise go undetected due to the floor effect.

Glaucoma can cause loss of reflectivity. Glaucoma itself can cause OCT artifacts. "RNFL thickness is the most commonly used parameter for assessing glaucoma, but in some ways, it can be the worst parameter because the disease itself causes loss of RNFL reflectivity," said Dr. Chen. "As the RNFL loses reflectivity, it becomes harder for the machine to segment the posterior border of the RNFL, which means that RNFL measurements are potentially more inaccurate as the disease gets worse."

Variation between patients is normal. Dr. Chen advised doctors to not necessarily assume that the color classification is correct. The color-coding classification can be incorrect because there is a wide range of normal RNFL thickness values, she said. Different patients may have different normal baseline RNFL thickness measurements, and progression from baseline is more suggestive of glaucoma than stable values from baseline.

Look at trends. To truly diagnose glaucoma, Dr. Huang recommended looking at trends rather than a single change. "Having linear regression based

Joel S. Schuman, MD, FACS

Advances in the Field

On Oct. 24, 2023, President Biden awarded Dr. Huang the National Medal of Technology and Innovation for coinventing OCT technology in 1990, along with James Fujimoto, PhD, and Eric Swanson, MS. The coinventors also received the prestigious Lasker-DeBakey Clinical Medical Research Award in September 2023. Dr. Schuman, also a coinventor of OCT, collaborated on the research, contributing crucial retinal experiments and samples.[1]

Later iterations of the technology, such as spectral domain and swept-source OCT, enhanced its speed, gathered more data, and improved image resolution, which enabled ophthalmologists to recognize critical pathologies missed at slower speeds.

Today physician-scientists are developing OCT even further and taking the technology in different directions.

Dr. Huang's research team uses AI to refine function and signal processing, image enhancement, image segmentation, and disease classification. His goal is to reduce artifacts in OCT angiography, making it more readable and quantifiable.

Dr. Schuman developed the circumpapillary nerve fiber layer scan, which became the standard method for evaluating glaucoma, during his collaboration with Dr. Huang, Dr. Fujimoto, Mr. Swanson, Carmen Puliafito, MD, and Charles Lin, PhD. Today, Dr. Schuman's research group focuses on using AI to improve the quality and analysis of the OCT image so that ophthalmologists are better able to predict disease trajectory and adapt their management strategies according to disease progression. He's also part of a consortium that is working on harmonizing the thickness measurements between machines so that a micron is a micron no matter which machine one is using.

Dr. Chen's research group, in collaboration with Johannes de Boer, PhD, was the first to image the human eye in vivo with video rate spectral domain OCT, producing ultra-high-resolution 3D video imaging of the optic nerve and the retina. She's currently exploring the potential for 3D OCT algorithms to improve in vivo imaging in glaucoma.[2]

Two other recent studies report using deep learning to correct artifacts in RNFL thickness maps, improving their usability in the clinic for diagnostic and prediction purposes.[3,4]

1 Huang D et al. *Science*. 1991;254(5035):1178-1181.

2 Celebi ARC et al. *Transl Vis Sci Technol.* 2021;10(6):28.

3 Shi M et al. *Transl Vis Sci Technol.* 2023;12(11):12.

4 Shi M et al. *Med Image Anal.* 2024;94:103110.

on four or more time points is more reliable in assessing the speed of progression and more able to catch change with higher sensitivity than comparing two scans is," he said.

Artifacts From Other Diseases

Other diseases can masquerade as glaucoma on an OCT.

Myopia. "In myopia, the retina thins because it covers a larger area. That will give you a nerve fiber layer outside the normal limits," said Dr. Schuman. "The normative data on most OCT devices goes up to about –6 diopters of myopia, so you're going to be outside the normative database pretty quickly for moderate to high myopes."

Dr. Huang suggested looking at the pattern of neuropathy on the OCT to distinguish between myopia and glaucoma. "Myopic eyes are longer, so an OCT scan of fixed angular extent covers a greater millimeter width, creating OCT images with lower transverse magnification. Nerve fibers spread out and arc temporally as they radiate outward from the optic disc. So, myopia leads to an apparent thinning of the nerve fiber layer that is more severe nasally and less so temporally. Myopic eyes tend to have greater nerve fiber layer thinning in the nasal quadrant, whereas glaucomatous eyes typically have defects in the inferior and/or superior quadrants."

He suggested looking at the ganglion cell complex thickness on macular OCT scans because this is less affected by myopia. He also recommended OCT angiography because "vessel density evaluation on OCT angiography is less affected by myopia," he said.

Epiretinal membranes. ERMs can cause artifact in two different ways, said Dr. Schuman. "If it's causing traction on the retina, you may get retinal thickening, so the RNFL would actually appear to be thicker than it really is. It also may appear to be thicker than it really is if the epiretinal membrane causes a segmentation error so that the machine is reading the top of the epiretinal membrane as the inner limiting membrane as opposed to the inner limiting membrane in its true location."

Peripapillary atrophy. "Peripapillary atrophy can cause high reflectance in the more posterior part of the eye, so you get more choroidal or scleral reflectance," said Dr. Schuman. "That will throw off the algorithm, and you'll get an error that may make the RNFL appear to be thicker or thinner, depending on what the algorithm error is."

Macular edema. "If we're looking at macular thickness or the ganglion cell complex, changes in the macular region may not be from glaucoma. For example, cystoid macular edema will cause the macula to be thicker, unrelated to the glaucoma," said Dr. Chen.

This can cause problems in the long run, said Dr. Schuman. "If you're following a patient longitudinally who develops macular edema, they may appear to be doing well or even getting better—but they're probably not getting better if it's glaucoma."

Chorioretinal scar. "On a macular OCT you may pick up an abnormality that corresponds to a visual field defect, but it may be the result of a chorioretinal scar, not glaucoma," said Dr. Schuman.

Progression vs. Testing Fluctuation

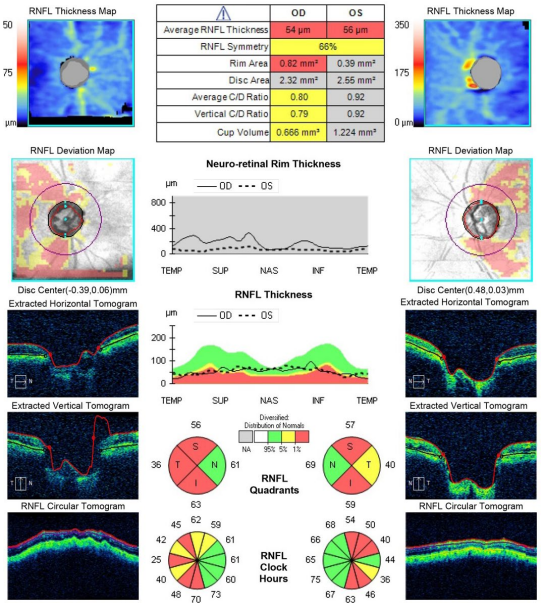
The "rule of five," which is used by some physicians, says that a change of 5 µm or more in global RNFL thickness more likely indicates glaucoma progression and less likely indicates normal testing variability or noise. Like most rules, this one has caveats, too.

More testing noise in the quadrants. "The rule of five applies to global RNFL thinning, but in OCT, there's actually more testing noise in the quadrants and sectors, so normal inter-test variability may be more than 4 or 5 microns there," said Dr. Chen. "Unfortunately, there's more variability in the superior and inferior quadrants, where glaucoma preferentially occurs."

Dr. Huang concurred, "RNFL thickness measurements are quite repeatable on an overall level. So, if you're looking at overall global nerve fiber layer thickness, an interval loss of 5 microns or so would be pretty definitive. On a sector and quadrant level, though, the repeatability is lower, so you would need a greater number of micron loss to be considered statistically significant."

High degree of false positives. One research group found that using a loss of at least 5 µm in the global RNFL to diagnose glaucoma led to false positives in nearly a quarter of control participants (n=92) after five years of semiannual testing, but the results were limited by the lack of a gold-standard comparator. The authors concluded that this could lead to unnecessary treatments in patients with stable disease.[1]

Another approach. Recently, the rule of five was found to be inferior to trend-based analysis for global average RNFL OCT assessment over time. A prospective cohort study of 300 eyes, followed for approximately five years, showed that the latter method was significantly ($p < 0.001$) more accurate in identifying progression.[2] Limitations of the study include: the use of global average RNFL rather than sectoral RNFL, and limited severity of disease, with most eyes having mild or moderate disease, which may restrict the generalizability of the findings.



	OD	OS
Average RNFL Thickness	54 µm	56 µm
RNFL Symmetry	66%	
Rim Area	0.82 mm²	0.39 mm²
Disc Area	2.32 mm²	2.55 mm²
Average C/D Ratio	0.80	0.92
Vertical C/D Ratio	0.79	0.92
Cup Volume	0.666 mm³	1.224 mm³

OCT OPTIC NERVE HEAD PRINTOUT. *Signal strength (SS) is not included on this printout, but thumbnail images suggest marginal or poor SS. Segmentation errors are seen in the optic nerve head and circumpapillary B-scans, suggesting that reported measurements of these tissues are likely inaccurate, especially in the right eye, said Dr. Schuman.*

Other Artifacts

RNFL artifacts on OCT can be produced by additional factors.

Dry eye. Glaucoma drops can exacerbate dry eye, which may decrease OCT image quality and can lead to artifacts, such as segmentation errors. Using artificial tears just prior to OCT scanning can be helpful in avoiding this artifact, said Dr. Chen.

Aging. As patients age, the RNFL thins. According to Dr. Huang, glaucomatous change tends to be sectoral, while aging changes tend to be global.

Macular retinal surgery or a macula-off retinal detachment can cause thinning of the retina, including the RNFL, according to Dr. Schuman.

Panretinal photocoagulation (PRP) surgery can destroy areas of the retina, thinning the RNFL, said Dr. Schuman.

Eye Exam Is Still the Gold Standard

Although Dr. Chen was an early adopter of OCT technology, she believes that a clinical eye examination is still the gold standard for evaluating glaucoma.

"The big picture to keep in mind is that the machine is just a machine, and it's just one data point. We have so many other data points—the clinical history, the eye pressure, the visual field test, and the general eye exam. Only when we look at all these data points together can we make the most accurate assessment of whether the patient has glaucoma and whether the glaucoma is stable or getting worse," said Dr. Chen.

1 Thompson A et al. *Ophthalmol Glaucoma.* 2019; 2(5):319-326.

2 Thompson A et al. *Ophthalmol Glaucoma.* 2020; 3(6):414-420.

Dr. Chen is a physician and surgeon at Massachusetts Eye and Ear and Associate Professor of Ophthalmology at Harvard Medical School in Boston. *Financial disclosures: Alcon: S; Fidelity Charitable Fund: S; NIH: S.*

Dr. Huang is Professor of Ophthalmology and Biomedical Engineering at the Oregon Health & Science University School of Medicine, and Wold Family Chair in Ophthalmic Imaging and Associate Director and Director of Research of the Casey Eye Institute. *Financial disclosures: Cylite: S; Genentech: P; GoCheck Kids: PS; Intalight: S; Kugler: P; NEI: S; Research to Prevent Blindness: S; Stroma Medical: C; Visionix: P,S.*

Dr. Schuman is Vice Chair for Research Innovation, Vickie and Jack Farber Vision Research Center; Director, Advanced Center of Ophthalmic Research in Neuroimaging (ACORN) and Codirector, Glaucoma Service, Wills Eye Hospital, Philadelphia. Professor, Department of Ophthalmology, Sidney Kimmel Medical College at Thomas Jefferson University and Professor of Biomedical Engineering, Drexel University School of Biomedical Engineering, Science and Health Systems. *Financial disclosures: AEYE Health: C,PS; Alcon: C; Boehringer Ingelheim: C; BrightFocus Foundation: S; Carl Zeiss Meditec: C,P; NEI: S; NYU School of Medicine: P; Ocugenix: C,SO,PS,P; Ocular Therapeutix: C,US; Opticient: C,SO,PS; Perfuse: C,S; Regeneron: C; Slack: C,P; Tufts University School of Medicine: P; University of Pittsburgh Medical Center: P.*

See disclosure key, page 10.

Joel S. Schuman, MD, FACS