Point-Counterpoint

# Do you make treatment decisions on optical coherence tomography (OCT) changes alone?

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## Decide Based on OCT Changes Alone: "A Yes Perspective"
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Optical coherence tomography (OCT) measurement of the retinal nerve fiber layer (RNFL) may be considered the best among the currently available digital imaging instruments for detecting and tracking optic nerve damage in glaucoma. RNFL analysis with the OCT provides an alternative to visual inspection of the optic nerve neuroretinal rim as well as quantitative examination of retinal ganglion cell loss. In addition to diagnosis, the quantitative and reproducible nature of spectral-domain OCT (SD-OCT) thickness measurements are useful for monitoring disease progression.[1] However, a number of factors may affect the quality and accuracy of the SD-OCT (Cirrus® HD-OCT, Carl Zeiss Meditec, Inc.). Signal quality should be at least 7/10. Scans should be aligned at the visual axis and have a correct scan depth. Media opacities and improper segmentation of the RNFL are also important points to be considered when interpreting OCT results.

Another important question to ask is, "What quantity of change is significant?". Not all changes in OCT means glaucoma progression. Therefore, it is imperative to distinguish between progression from glaucoma versus normal age-related structural loss or intertest variability. Evidence shows excellent intravisit and intervisit measurement reproducibility of SD-OCT, superior to time-domain OCT (TD-OCT), indicating the potential utility of the former in monitoring glaucoma progression.[2] The mean rate of change of average RNFL thickness measured by Spectralis® SD-OCT (Heidelberg Engineering GmbH, Heidelberg, Germany) due to aging in normal healthy eyes is 0.52 µm/year. Whereas, a 5-µm intertest change in average RNFL thickness or 8-µm in sectoral RNFL thickness is considered significant. Ways to increase confidence in detecting progression is by having 2 or more baseline measurements and confirming change on subsequent exams.[3,4]

SD-OCT allows progression analysis. Event analysis is able to detect progression if a follow-up measurement exceeds a preestablished threshold for change from baseline. It identifies gradual change over time that crosses a threshold or an acute event that exceeds a threshold. Confirmatory test is always recommended.[5] Trend analysis measures the rate of progression by monitoring the behavior of a number of parameters over time. It is less sensitive to intertest variability.[5] In glaucoma patients, progressive RNFL thinning determined by both event- and trend-based progression analysis of serial RNFL thickness maps obtained with the SD-OCT is associated with a more than 5-fold and 8-fold increase in risk of subsequent development of visual field loss, respectively.[6] Thus, it

is better to monitor progression using both event and trend analysis.

Preperimetric glaucoma is defined as having structural evidence of glaucomatous optic neuropathy with normal visual field results. I use OCT to monitor these cases because OCT detects more changes in early disease.[7,8] I would make treatment changes based on significant RNFL thinning on OCT because I would not want to wait for the irreversible visual field defect of glaucoma to occur before escalating treatment.[9]

Patients who cannot reliably take the visual field examinations are very good candidates for monitoring using OCT alone. Specifically, pediatric patients who cannot follow instructions properly and patients with coexisting medical conditions such as Alzheimer disease, tremors, or arthritis. It may be best in these instances to follow the patient's disease with structural rather than functional tests.

On the other hand, late in the disease, OCT is less useful because of the "floor effect". When the RNFL thickness reaches about 45 to 50 μm, it bottoms out and doesn't decrease any further—even if there is continuing damage. Once you reach this level, using OCT to detect progression would just give you a false sense of security that your patient is stable. It is better to use visual field or other functional tests to monitor these cases.[10,11]

Although visual function is what matters most to our patients, progressive structural changes often precede functional loss. Evidence shows that patients with faster changes on OCT are at increased risk of worsening visual losses. Therefore, I strongly agree that offering the possibility of escalating treatment at an earlier stage in certain cases may preserve vision better by stopping irreversible visual field loss from glaucoma.

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## Decide Based on OCT Changes Alone: "A No Perspective"

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Technological devices such as the optical coherence tomography (OCT) have their own inherent challenges and shortcomings that it may be difficult to rely on one device alone in monitoring glaucoma progression and making treatment decisions.

First challenge on the use of the OCT in glaucoma diagnosis is structural variability. Structural measurements may display overlap between early glaucomatous eyes and abnormal-appearing optic discs that do not show evidence of disease progression over time. Normal age-related retinal nerve fiber layer loss can also confound the interpretation of longitudinal glaucoma assessment.[1]

The second challenge involves its use in different stages of the glaucoma disease. At the first stage of the glaucoma continuum which includes glaucoma suspects, recognition of RNFL decline due to age-related loss must be studied against normal ranges of age-related reduction especially if the baseline RNFL measurement is thick.[2] There are also patients where-in glaucoma progresses slowly whilst technological

advancements occur faster than disease progression.[3] Presence of myopia, a known confounder, can cause optical projection artifact which can also complicate glaucoma diagnosis. Difficulty in OCT interpretation may also be encountered among asymptomatic glaucoma patients who are in their "tipping point". In these eyes with very mild disease, correlation between structural and functional changes may not be demonstrated yet.[4] Lastly, among patients with advanced glaucoma, measurement of RNFL thickness below the minimum will not yield any more useful clinical information (also known as the "floor effect").[5]

Third challenge is the presence of artifacts. Artifacts can produce 2 kinds of diseases, called the "green disease" and "red disease". The "green disease" may confer a false sense of security which leads to unrecognition of glaucoma or its progression.[6] The "red disease" is due to the confounders in the normative database.[7] Both add up to the uncertainties of OCT, including difficulty of establishing the most accurate assessment of each instrument due to absence of a clear gold standard demonstrating true RNFL thickness.[8]

Imaging technology should be used as an adjunct in the clinical decision-making process. Clinical decision should still be based on a complete ophthalmic examination and visual field assessment.

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## *Consolidating the Evidence*
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The issue of the relative importance of structure and function in glaucoma diagnosis and treatment has long been debated. At some level, structural damage should precede functional damage. Since it is often irreversible, early detection of progressive structural damage, before functional damage, is the ideal. Since glaucoma is a neuropathy, it stands to reason that the loss of nerve fibers is the incontrovertible proof that damage has occurred.

In theory, structural damage, whether measurable or not, should precede functional loss; and if we can detect and intervene the moment such damage occurs, we can theoretically limit the extent of subsequent functional damage, or prevent it entirely. The question is: "Is progressive thinning of the retinal nerve fiber layer (RNFL) alone, as measured by the optical coherence tomography (OCT), clear evidence that irreversible nerve damage or progression is present, which in turn should be enough basis for the clinician to intervene?".

In reality, as Dr. Quino points out, too many variables are unknown in RNFL thinning and the results generated by current OCT, when used alone, may lead to under- or over-diagnosis; or worse, either under- or over-treatment. In other words, even though the OCT offers an unprecedented capacity to measure RNFL thickness, we still do not know for certain what all the numbers are telling us, or whether it inevitably portends clinically significant functional loss.

There are many reasons for this uncertainty: (1) glaucoma is a complex lifelong disease; (2) early and late glaucoma are two different animals; (3) the decision to start a patient on glaucoma medications is very often a life sentence; (4) glaucoma medications are expensive and have significant side effects; (5) compliance is an issue; and (6) significant change can take months or years to develop. As a consequence of this uncertainty, the overtreatment of glaucoma is a clear and underappreciated possibility in majority of the cases we see in the clinics today, an issue we, in the glaucoma community, must also start to discuss in the open.

Obviously, no single measurement of structural change - whether by the OCT or any other device

- can be the basis for making treatment decisions that could impact our patients' lives. But it is also undeniable, as Dr. Chao-Po has shown, that current and future technologies have given, and will give us remarkably precise measurements that can be stored and objectively reviewed and analyzed using digital technology. If properly understood, these results should be reliable enough to be used to make therapeutic decisions.

Yet, our goal in treating glaucoma is to preserve function. The ultimate measure of our success is the prevention of functional loss, arguably even if we fail to prevent structural progression. Thus, in the absence of visual field changes, progression of RNFL thinning as measured by the OCT should not really be enough to make a clinical decision.

It is highly likely that we will be able to measure structural change to even greater precision as our machines get more and more sophisticated. But, just like intraocular pressure measurements, precision by itself is meaningless if the information gathered cannot be used as a basis for making long-term clinical decisions.

Hopefully as we learn to rely more and more on these increasingly sophisticated machines and the remarkable data they generate, we can come to a clearer understanding of why nerve cells die, and ultimately, how we can stop or even reverse it. But until then, the decision to treat should rest not on the machines but on the abilities of a qualified specialist to gauge their value, using all the information available.