

Assessment of the Retinal Nerve Fiber Layer in Clinical Trials of Glaucoma Neuroprotection

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Abstract. Assessment of the retinal nerve fiber layer (RNFL) is appealing for use in clinical trials of glaucoma neuroprotection, as it is directly correlated with loss of ganglion cells, which is assumed to be a primary event in glaucomatous damage. Qualitative assessment of the RNFL includes ophthalmoscopy, color stereophotography, and red-free monochromatic photography. In contrast, confocal scanning laser ophthalmoscopy (CSLO), scanning laser polarimetry (GDx), optical coherence tomography (OCT), and retinal thickness analysis (RTA) objectively and quantitatively measure the RNFL thickness. These latter techniques are still in evolution. Continuing meticulous objective validation is necessary to assess the usefulness and limitations of these powerful tools. Nevertheless, there are excellent prospects for using longitudinal assessment of the RNFL in clinical trials of glaucoma neuroprotection. (*Surv Ophthalmol* 45(Suppl 3):S305–S312, 2001. © 2001 by Elsevier Science Inc. All rights reserved.)

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Glaucomatous optic neuropathy is a group of diseases characterized by accelerated loss of retinal ganglion cells. Normal individuals lose ganglion cells in an age-dependent manner, at an estimated rate as high as 5000 axons per year,^{3,16} which may translate to considerable axon loss during a 70-year life span.³ What makes an individual (or an eye) glaucomatous is the accelerated rate at which these cells are lost and the underlying basis for the loss.

Retinal ganglion cells transmit visual information from the inner retina, via the optic nerve, chiasm and optic tract, to the lateral geniculate nucleus (LGN), which is situated in the thalamus. The ganglion cell, with its long axon, is susceptible to damage by any one of several different mechanisms. Current practice assumes that the major site of damage in glaucoma is at the level of the optic nerve head/lamina cribrosa. Axonal injury at the level of the op-

tic nerve head is subsequently reflected in damage to the retinal ganglion cell body, as well. Recently, it has been demonstrated in a hypertensive monkey model of glaucoma that loss of relay (post-synaptic) neurons also occurs at the LGN.^{27,33} Any sensitive and reproducible retinal nerve fiber layer (RNFL) measure for monitoring change in glaucoma would be an invaluable tool for shortening and simplifying the evaluation period of any therapeutic modality for glaucoma.

As glaucomatous damage progresses, several structural and functional changes occur. Each of these changes can potentially serve as a marker for both diagnosing and following the disease process. Although RNFL assessment is attractive as a clinical endpoint, its usefulness is limited by the variability of measurements and the slow progress of the disease. In this review, we shall outline some available op-

tions for assessing the RNFL in glaucoma and monitoring for progression, highlighting the strengths and limitations of each method.

Diagnosing Glaucoma

Diagnosing glaucoma can be problematic. On the one hand, variability within the population precludes a clear cutoff between normality and glaucoma. Such variability exists in disk size, cup size, the total number of axons per eye (anywhere between 750,000 to 1,500,000^{3,8,16}), variability in visual field thresholds, and the susceptibility to—and tolerance of—elevated intraocular pressure. On the other hand, the great redundancy in the visual system makes it difficult to ascertain damage until a significant proportion of ganglion cells has been lost.^{11,20} In addition, most diagnostic technologies discussed lack an age and race-specific normative database against which individual measurements can be compared.

Monitoring Glaucoma for Progression

When monitoring an individual eye for progression, intersubject variability is no longer a concern. When progression is assessed, the findings in the eye are compared to those of previous examinations of the same eye rather than to normative database values, or even to findings in the fellow eye. It would seem that monitoring progression would prove to be far simpler than diagnosing glaucoma. Unfortunately, this is not the case. All modalities currently in use for following the disease process have inherent variability that undermines their ability to ascertain changes that can serve as markers for progression.

As a general guideline, the magnitude of change has to exceed variability in order to denote progression. Thus, it is variability that determines how sensitive (and accurate) the technique is for picking up small increments of progression. A technique with little or no variability would enable detecting glaucomatous change across very short intervals (e.g., from one month to the next). In contrast, a technique with significantly larger variability (e.g., vertical cup-to-disk ratio estimation, for which even experts can differ by as much as 0.2) may prove less valuable for following for progression.

To better understand the strengths and limitations of current methods, let us speculate for a moment on what would be an ideal tool for following glaucomatous eyes for progression. Two options come to mind. First, if the total number of axons (or ganglion cells) in an eye could be reliably counted in situ, one could simply graph this decay and compare it to normative values or, alternatively, extrapolate it against the expected individual's life span for prognosis purposes. Second, if a method existed for identifying and counting compromised, dying (or

dead but not yet phagocytized) ganglion cells or axons in situ, one would get a snapshot of the current disease activity. Unfortunately, neither option is currently available. Currently available options for monitoring the RNFL in glaucoma are described in the following sections.

Clinical Examination of the RNFL

The current standard for evaluating the RNFL during a dilated fundus examination consists of an inverted, stereoscopic image obtained with the slit-lamp biomicroscope and a hand-held auxiliary lens. Commonly used lenses include the bi-convex, non-contact 60, 78, or 90 diopter hand-held lenses. A slightly improved view can be obtained through a contact type lens, but this entails longer examination time, discomfort to the patient, and some temporary clouding of the cornea, which undermines the view for subsequent photography or imaging. While simple and accessible, slit-lamp biomicroscopy of the RNFL is difficult to interpret, the data cannot be quantified, and, just as important, a hard copy is not generated. Focal wedge-shaped defects infrequently occur in glaucoma; however, they are easier to detect. In contrast, diffuse RNFL loss occurs more commonly, but it is rather difficult to ascertain with confidence.²⁶

White light originating from the slit-lamp and reflected back by the RNFL is far from ideal for assessing the RNFL. While the longer wavelengths (red) readily penetrate the RNFL, the shorter ones (blue) are more readily reflected back, enabling detection of RNFL loss. Paradoxically, the human eye is poorly sensitive to blue wavelengths, drastically limiting our ability to view the RNFL via a cobalt blue filter. A reasonable compromise between white and blue light is using the green (red-free) filter, which is readily available for any slit-lamp. However, the superiority of photographic film in capturing the fine details of the RNFL reflectance image is clearly better than what an observer's eye alone can visualize (even with red-free illumination) during a clinical examination. It would be safe to say that a well-exposed fundus color photograph allows RNFL details to be better scrutinized than does any type of real-time fundus examination, even under excellent conditions (e.g., lighting, magnification and lens choice). This is in contrast to the situation with other retinal conditions (such as macular holes or peripheral retinal lesions), in which a photographic image often is no substitute for a thorough dynamic retinal examination.

STEREOSCOPIC FUNDUS COLOR PHOTOGRAPHS

Stereoscopic photographs provide a hard copy snapshot of the RNFL with improved resolution over

a real-time slit-lamp examination. Still, many factors undermine this technique. Often, small undilatable pupils, media opacity, or a lightly pigmented fundus can drastically compromise the ability to observe RNFL details. More so, differences in exposure (lighting, film processing, etc.) and slight changes in camera angle may introduce variability that limits the ability of this technique to ascertain progression.

RED-FREE MONOCHROMATIC RNFL PHOTOGRAPHS

The same principles discussed regarding choice of illuminating light wavelength for dilated clinical examinations holds true also for photography. The longer (blue and green) wavelengths are more readily reflected back from the RNFL, hence, contain more RNFL information. Coupled to a film that is highly sensitive to such wavelengths, photography is able to capture the brightness and texture of the RNFL onto a black and white, high resolution transparency film that can be later viewed under high magnification. Good quality RNFL red-free photographs are difficult to obtain, more so than color stereophotographs. However, when obtained, red-free photographs better highlight the brightness and texture of the RNFL, as well as the degree to which the small retinal vessels are covered by RNFL (an indirect indication of RNFL thickness). Both photographic techniques mentioned are bound by the delay imposed by processing the photographs; thus, a clinical decision based on them cannot be made on the same visit. While digital photography avoids many of the drawbacks of film photography, resolution limitations have so far limited its implementation for assessment of RNFL texture.

One piece of evidence in favor of the use of red-free photographs is a study by Sommer et al²⁴ in which over 1300 ocular hypertensives were followed over a 6-year time period. Of the eyes that converted to glaucoma based on appearance of visual field defects, 50% and 85% (depending on the grader) had RNFL defects as evidenced on red-free photographs at the time of field loss. In 60% of these cases, defects were present 6 years before the appearance of visual field loss.

Several grading systems for interpretation of RNFL red-free photographs in a more standardized approach have been developed. Airaksinen proposed a semi-quantitative score documenting either localized or diffuse RNFL loss.¹ Quigley devised a four-point system grading RNFL brightness, texture, and vessel visibility, as well as the presence of any focal defects,²¹ while Niessen proposed a scoring system based on comparison to a reference set of 25 standardized RNFL photographs.^{17,18}

Imaging Modalities for Measurement of the RNFL Thickness

At the current time, four distinct technologies are available for estimating RNFL thickness measurements in real-time in situ. These instruments are available commercially, but are, at present, at different stages of development and maturation. When analyzing RNFL thickness as an indicator for glaucoma diagnosis and progression, one should not forget that RNFL thickness is only a very crude approximation of the number of axons at any given retinal location.

One should also not forget that our current understanding of the RNFL might not be entirely complete. Consider the following dilemma. From actual ganglion cell counts performed on young normal human retinas, it was concluded that approximately 50% of all ganglion cells are located within 4.5 mm (16°) of the foveal center,⁸ roughly the area bound by the major temporal vascular arcades. More so, ganglion cell density was highest within 2 mm of the foveal center. Considering this, what is the explanation for the fact that the nasal and temporal parapapillary RNFL are roughly similar in thickness (and both considerably less than the superior and inferior quadrant thickness)? Whereas the nasal quadrant RNFL conveys very little visual information originating from the nasal retina, the temporal quadrant is assumed to convey macular fibers that by themselves subsume about one half of the total ganglion cells in the eye.

CONFOCAL SCANNING LASER OPHTHALMOSCOPY

Confocal scanning laser ophthalmoscopy (CSLO)^{22,29,31} provides a three-dimensional topographic representation of the optic disk and peripapillary retina, which is constructed from a series of two-dimensional slices. This three-dimensional representation consists of 256×256 (65,536) pixel elements, each of which is a measurement of retinal height at its corresponding location. Three topography images are usually acquired in a single session and thereafter are automatically aligned and averaged to obtain a single mean topography image. Although the CSLO is similar, in many respects, to a CT scan, the light rays used for CSLO cannot penetrate tissue; this limits this modality to depicting the surface topography of the optic disk and parapapillary retina. CSLO does not measure RNFL thickness directly. Instead, the image is aligned for any tilt (whether anatomical or due to the scanning angle), the parapapillary retinal surface height is subtracted from an imaginary plane running 50 microns below the surface of the temporal parapapillary retina along the disk margin. By assuming that this plane separates the RNFL from the un-

derlying remainder of the retina, a RNFL thickness map is then constructed. Two Heidelberg Retina Tomograph (HRT, Heidelberg Engineering, Heidelberg, Germany) parameters summarize this data: RNFL thickness and RNFL cross-sectional area. In addition to quantitative RNFL thickness data, the CSLO can present the acquired data in the form of optical slices. Some of these slices, particularly those at the plane of the RNFL, may show qualitative focal RNFL defects (Fig. 1).

Several limitations of CSLO have been identified. Correct measurement of the disk topography and associated summary indices is dependent upon correct placement of the contour line (optic disk margin) by the operator, as well as upon intraocular pressure^{5,15} and cardiac pulsations.⁶ As with other technologies reviewed here, short and long-term fluctuations exist and confidence intervals need to be validated. Finally, a uniform consensus regarding the most appropriate summary measures remains to be established. One could argue that such an indirect measure, relying on assumptions that seem crude, undermines the validity of CSLO data on RNFL thickness. At this point, it is important to highlight that all available clinical methods for measuring RNFL are based on assumptions and approxima-

tions that introduce at least some error into the RNFL thickness measurement.

NERVE FIBER LAYER ANALYZER (NFA/GDX)

The Nerve Fiber Analyzer (NFA/GDx, Laser Diagnostic Technology, San Diego, CA) is a scanning laser ophthalmoscope coupled to a retinal polarimeter that measures changes in polarization (retardation).^{25,30,32} The laser light generated by the NFA is uniformly polarized (all rays possessing a single polarization axis). This instrument utilizes the fact that polarized light travelling through a medium that contains multiple, parallel, closely spaced structures undergoes a shift in the polarization axis. Laser light travelling through the RNFL and back (reflecting off the retinal pigment epithelium or inner retina) will assume a different change in polarization (retardation) proportional to the amount of parallel birefringent structures (microtubules) it traverses.¹⁴ One could argue that it is, in fact, the number of axons (in relation to their thickness) traversed by the laser beam that is actually what this technique measures. Thus, based solely on theoretical reasoning, this approach seems convincing in depicting what we would really like to know: how many axons are there at any given point in time and at any given retinal lo-

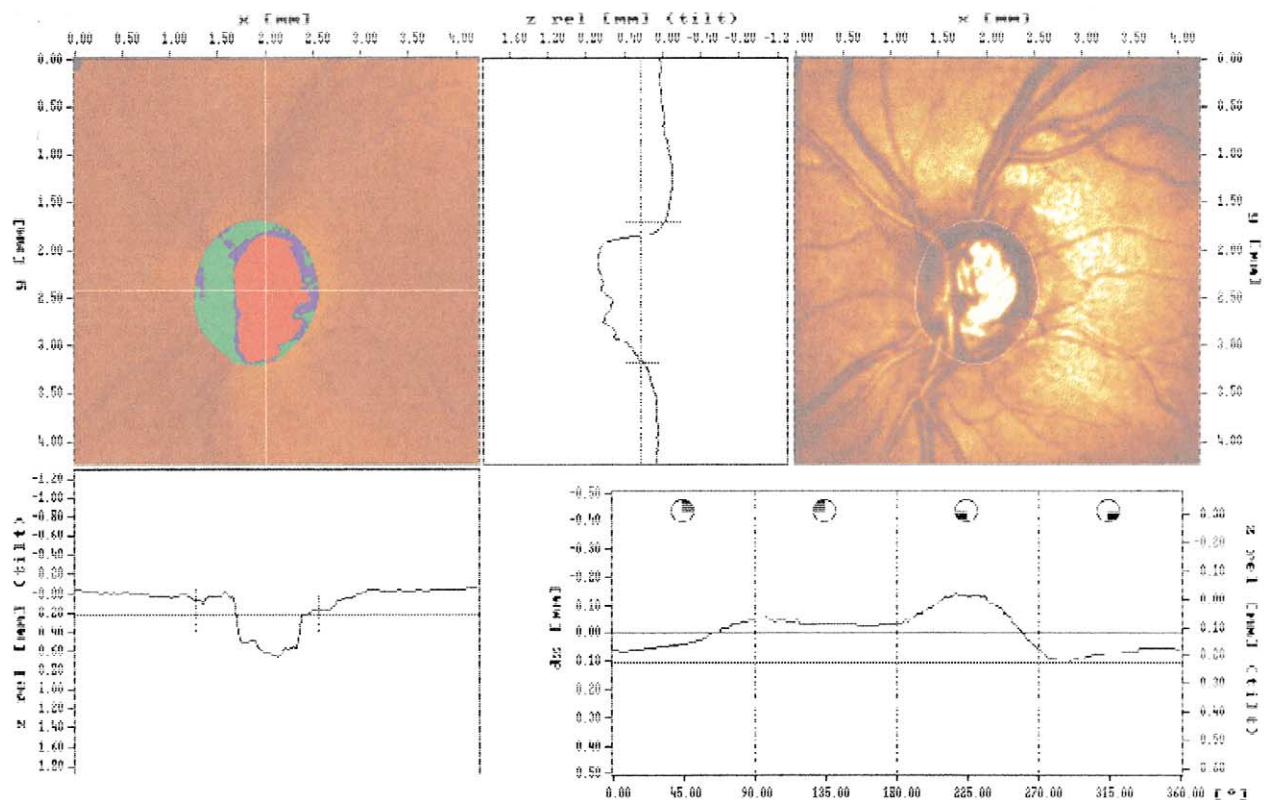


Fig. 1. A confocal scanning laser ophthalmoscope printout of a glaucoma eye showing rim thinning more pronounced inferiorly (Heidelberg Retinal Tomograph).

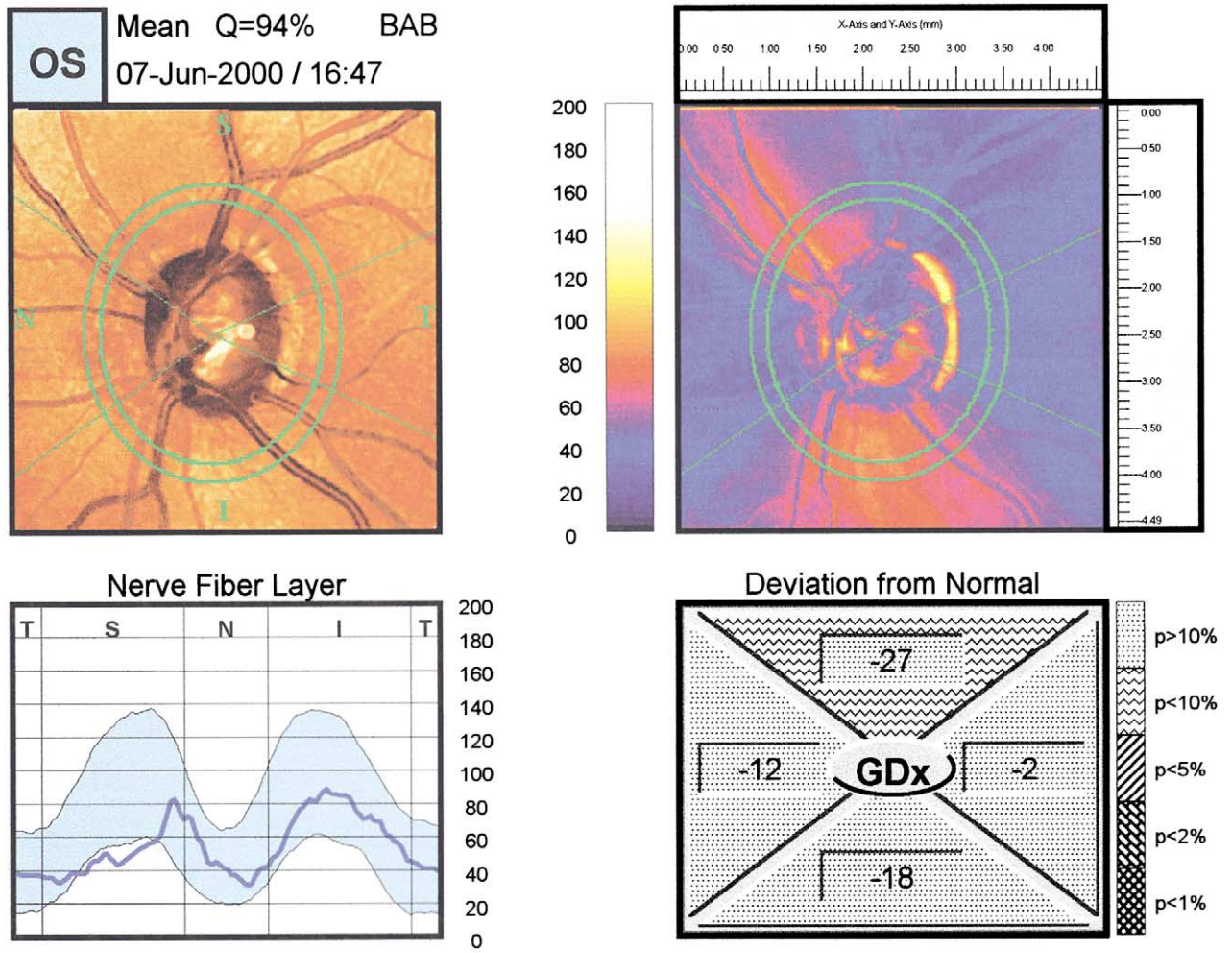


Fig. 2. A scanning laser polarimeter printout of a glaucoma patient showing marked RNFL loss superiorly (GDx).

cation (Fig. 2). However, while appealing on theoretical grounds, this technology has not yet reached its potential. In fact, in a recent study of a group of 94 normals and glaucoma patients, GDx parameters were found to be the least predictive, as compared to other structural (OCT) and functional (SWAP, FDT) techniques,⁴ for diagnosing early to moderate glaucoma.

One reason why GDx data may not be as informative is related to the design of the corneal polarization compensator, a built-in component in this device. In short, the cornea and lens, which the laser light ray must penetrate twice in order to reach the RNFL and return to the detector, are significant sources of polarization, because their structure is composed of regularly spaced parallel elements.²⁸ The cornea is far more influential in magnitude, so we shall ignore the lens for the remainder of this discussion.¹² The polarization effect exerted by the cornea has both an axis and a power component. This is, in many respects, similar to the concept of the astigmatic component of a refraction prescription.

The corneal polarization compensator measures the magnitude (power) of the corneal polarization component. Rather than also measuring its axis, it assumes a standard axis of around 15° nasally downward for all eyes.⁹ In reality, the corneal polarization axis differs among individuals.⁹ This standard axis assumption introduces bias into measurements of a subset of individuals whose axis deviates significantly. Research is currently conducted on ways to compensate for this bias. One solution would be to incorporate an axis-measuring device that will enable refinement of the corneal polarization compensator algorithm.

OPTICAL COHERENCE TOMOGRAPHY

Optical coherence tomography (OCT 2000, Humphrey-Zeiss Instruments, San Leandro, CA) utilizes near infrared superluminescent diode light in a fashion similar to the way B-mode ultrasound uses sound to generate two-dimensional images. Although sound has the advantage of penetrating tissue (for example, scanning a fetus in utero), light, with its much

shorter wavelength, has the advantage of obtaining significantly higher resolution. OCT can thus produce high resolution cross-sectional images of the retina, the upper portion of these images being the RNFL (Fig. 3). Because of the relatively long acquisition time, OCT currently obtains only 100 data points at each scan acquisition, compared to over 65,000 data points routinely acquired during a single HRT or GDx scan. Accurate measurements on the OCT are largely dependent upon edge-detection algorithms that accurately pinpoint the RNFL edges, a difficult task, considering the fact that the retina is uniformly transparent. Recall that the distinct retinal layers, as we often envision (and observe in histology slides), are the result of post-mortem staining techniques. A newer generation high resolution OCT holds promise in delivering higher resolution than is currently available.²³

The OCT, as we currently know it, is still in its infancy. A normative database is not commercially available, and, perhaps more important, complex parameters have not been defined yet for the OCT. Although crude parameters, such as RNFL thickness in the inferior quadrant based on around 25 data

points, have shown good sensitivity-specificity in distinguishing normals from early/moderate glaucoma,^{4,34} it is likely that this technology still can be improved. One potential problem with the current OCT model is the small number of data points sampled. Increasing the sampling density has been shown to improve reproducibility in glaucoma eyes.¹⁰ Another issue for concern has to do with the accuracy with which the OCT is able to define the boundaries of the RNFL.⁷

Using the OCT in its current mode is rather cumbersome and at times difficult. Dilation is required and a relatively long learning curve compared to that required for other imaging instruments exists for examiners in order to obtain good quality images. Even for the most trained technicians, obtaining images on the OCT is probably more difficult than for either the HRT or GDx, which also do not require pupil dilation.

RETINAL THICKNESS ANALYZER (RTA)

This imaging modality originated from slit-lamp-mounted laser biomicroscopy,^{13,19} a simple device that projects a sharp, crisp, slit-lamp-type beam com-

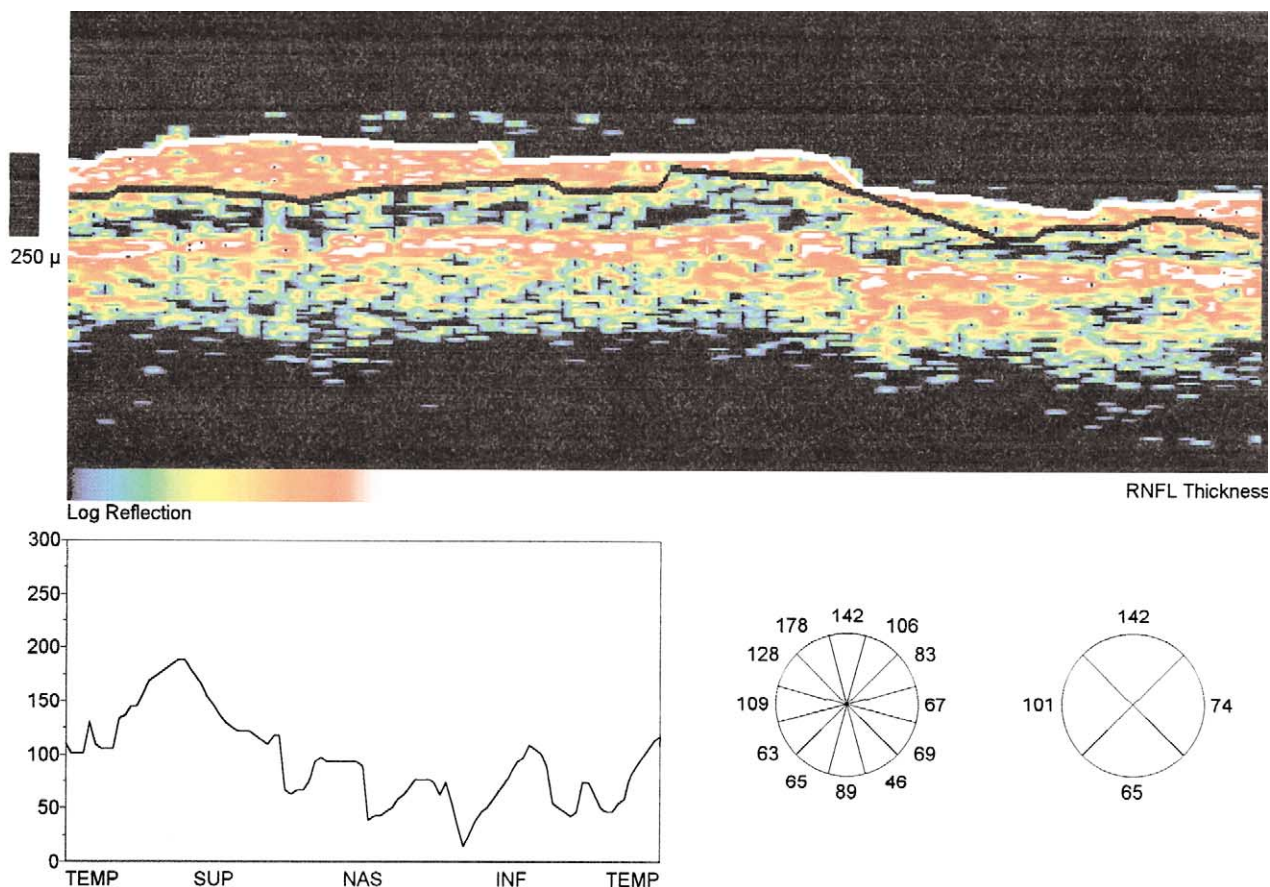


Fig. 3. An optical coherence tomograph printout of a glaucoma patient showing marked RNFL loss inferiorly (mean thickness 65 ▲), (OCT).

posed of laser light. In much the same way, the retinal thickness analyzer (RTA; Talia Technologies, Mevaseret Zion, Israel)^{2,35} projects a slit-shaped illumination beam, from an angle, to optically “dissect” the retina.³⁶ This, in turn, produces multiple cross-sectional slices that can be reconstructed to obtain a three-dimensional thickness map of the retina. RTA was originally developed to enable whole retina thickness measurements for assessment of retinal conditions such as diabetic and cystoid-macular edema. Only later was it realized that this technology might be useful for diagnosing and following glaucoma. This technique cannot differentiate the RNFL from the remaining retina, so RNFL thickness is not a true measure of RNFL, but an extrapolation from the total retinal thickness at any given location. There are few data describing the use of this technology to evaluate the RNFL.

Criteria for Evaluating New Technology

Evaluation of any new technology for diagnosing and following glaucoma is problematic. There is no consensus for precise diagnostic criteria in glaucoma. Staging the disease process and establishing whether progression occurred is even more difficult. Similarly, gold standards in glaucoma are often questionable. Some criteria to which every new imaging technology should be subjected include:

1. *Accuracy (histological correlation)*. Eyes scheduled for enucleation but having clear media and normal posterior segments are rarely seen. Obtaining consent for imaging studies in such cases may be emotionally charged. Hence, initial histological validation of RNFL measurements should best be performed on animal eyes, preferably primates. While relatively simple to perform, insufficient data exists with respect to histological confirmation of RNFL measurements for using the described technologies.
2. *Reproducibility (within a visit, across visits, across examiners)*. When one lacks a gold standard entirely, or if the current gold standard accuracy is questioned, it is often useful to start an evaluation process by establishing reproducibility. Any measurement device that lacks reproducibility cannot possibly prove valid. In glaucoma, one seeks reassurance that if a test were conducted over and over again on the same, or on separate but close, visits, the measurements obtained would remain relatively constant. Similarly, the test should provide identical results regardless of the operator. Establishing whether a learning curve exists for a new operator is another important issue worth resolving. It is important to point out that one

must never assume that high reproducibility necessarily implies accuracy.

3. *Discrimination of normal from glaucoma*. Ultimately, these devices are used to diagnose glaucoma or assess its progression. However, in the face of a mediocre gold standard, even an excellent device might contrast unfavorably. Hence, provided that the diagnosis (glaucoma or normal) attributed to a group of individuals is questionable in the first place, the ability to evaluate any new technology is limited.
4. *Detection of change over time*. Change in glaucoma, as captured by current diagnostic techniques, occurs very slowly. This, in turn, tempers our ability to validate and later select individual therapies based on progression of the disease. The emergence of potential glaucomatous therapies that do not exert their effect via lowering of intraocular pressure has intensified our search for objective means for assessing progression. While it seems very likely that RNFL thickness may be a useful parameter, techniques for studying it are not adequate at the current time.

Conclusion

Several techniques are currently available for estimating the RNFL in clinical practice. Ophthalmoscopy, color stereophotography, and red-free monochromatic photography provide qualitative assessment of the RNFL. In contrast, CSLO, NFA (GDx), OCT, and RTA provide quantitative RNFL thickness values across the posterior pole. These quantitative techniques are currently still in evolution in terms of hardware, defining robust parameters, and improvements in the analysis software. Meticulous objective validation is necessary to assess the usefulness and limitations of these powerful instruments. Despite the current limitations, it would appear that there are excellent prospects for introducing in the future these RNFL measurements into clinical trials of glaucoma neuroprotection.

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