Optical Coherence Tomography – Emerging Role in the Assessment of MS

PD Dr. Konstantin Gugleta

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Retinal Nerve Fiber Layer

1,200,000 fibers
82% Axons,
18% Glia,
no Myelin

Iester M et al. ONH and RNFL Analysis. EGS 2005
Non-(pre)-OCT nerve fiber layer evaluation

Fundoscopy

Red-free fundus photography

Polarimetry – Nerve Fiber Analyzer GDx

Retinal Thickness Analysis – Talia RTA

Scanning Laser Ophthalmoscopy – Heidelberg Retina Tomograph
Optical Coherence Tomography - OCT

Reports

Optical Coherence Tomography

David Huang, Eric A. Swanson, Charles P. Lin, Joel S. Schuman, William G. Stinson, Warren Chang, Michael R. HEE, Thomas Flotte, Kenton Gregory, Carmen A. Puliafito, James G. Fujimoto*

A technique called optical coherence tomography (OCT) has been developed for noninvasive cross-sectional imaging in biological systems. OCT uses low-coherence interferometry to produce a two-dimensional image of optical scattering from internal tissue microstructures in a way that is analogous to ultrasonic pulse-echo imaging. OCT has longitudinal and lateral spatial resolutions of a few micrometers and can detect reflected signals as small as $\sim 10^{-10}$ of the incident optical power. Tomographic imaging is demonstrated in vitro in the peripapillary area of the retina and in the coronary artery, two clinically relevant examples that are representative of transparent and turbid media, respectively.

Tomographic imaging techniques such as x-ray computed tomography (1), magnetic resonance imaging (2), and ultrasound imaging (3) have found widespread applications in medical imaging. OCT has been applied to a variety of medical imaging problems in vivo and in vitro. OCT can provide images of high resolution and high contrast. OCT images can be obtained at micrometer spatial resolutions and high detection sensitivities (12).

We have extended the technique of low-coherence reflectometry to tomographic imaging in biological systems. In low-coherence reflectometry, the coherence property of light reflected from a sample provides information on the time-of-flight delay from the reflective boundaries and backscattering sites in the sample. The delay information is then used to determine the longitudinal location of the reflection sites. The OCT system performs multiple longitudinal scans at a series of lateral locations to provide a two-dimensional map of reflection sites in the sample. This mode of operation is analogous to ultrasonic pulse-echo imaging (ultrasound B-mode).

The optical sectioning capability of OCT is akin to that of confocal microscopic systems (13, 14). However, although the longitudinal resolution of confocal microscopy depends on the available numerical aperture (15), OCT's resolution is limited only by the coherence length of the light source. Thus, OCT can maintain high depth resolution even when the available aperture is small. This feature will be particularly useful for in vivo measurement of deep tissues, for example, in transpapillary imaging of the posterior eye and in endoscopic imaging.

*Optical Coherence Tomography - OCT

Time-domain  

Frequency (spectral)-domain

interference signals in TD vs. FD-OCT
SD-OCT is superior to TD-OCT, not only due to higher resolution, but due to more delivered data.
Ganglion cell complex, for example RTVue

Figure 1 Vertical optical coherence tomography (OCT) cross-section of the macula

The ganglion cell complex (GCC) consists of three layers: the nerve fiber layer (NFL), ganglion cell layer (GCL), and inner plexiform layer (IPL). The three boundaries on the image are the inner limiting membrane (ILM), outer IPL boundary and inner segment/outer segment (IS/OS) junction. The GCC thickness is measured from the ILM to the outer IPL boundary. The retinal thickness is measured from the ILM to the IS/OS junction. Reproduced with permission from: Tan O, Chopra V, Lu AT, et al. Detection of macular ganglion cell loss in glaucoma by Fourier-domain optical coherence tomography. Ophthalmology 2009; 116:2305–2314.

GCC (Ganglienzell-Komplex) aus
  NFL = Axone
  GCL = Zellkörper
  IPL = Dendriten

GCC jedoch **nicht** der RNFL Messung überlegen.
...do not only read the number...observe, look for **patterns**...
Diagnostic difficulties and roles of OCT in MS

* Patterns of OCT-RNFL loss & OCT - Artefacts

* ON – Relapse

* ON atrophy (post-ON & ON-independent)

* Varia (Macula etc.)
Patterns of RNFL loss, measurement artefacts, diagnostic difficulties
Diagnostic difficulties: **patterns**

Neuro-ophthalmic disease and optical coherence tomography: glaucoma look-alikes
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**Key points**

- Retinal nerve fiber layer (RNFL) optical coherence tomography (OCT) shows thinning in glaucomatous and nonglaucomatous optic neuropathies and should be used in conjunction with the clinical examination.
- RNFL OCT in anterior ischemic optic neuropathy and optic nerve drusen may mimic glaucomatous RNFL loss due to predilection for superior and inferior quadrants.
- Many nonglaucomatous optic neuropathies cause loss of the temporal RNFL.
- One should be aware when evaluating patients with glaucoma that degenerative diseases such as Alzheimer’s and Parkinson’s disease can also cause RNFL loss; thus, the clinical examination is of outmost importance.

**Purpose of review**

The use of optical coherence tomography (OCT)-measured retinal nerve fiber layer (RNFL) thickness in neuro-ophthalmic disease has grown since its first use in glaucoma and retinal diseases. OCT-measured RNFL in nonglaucomatous optic neuropathies shows thinning, which may mimic those seen in glaucoma. This article aims to provide insight regarding the use of OCT in nonglaucomatous optic neuropathies and sheds light on common patterns of RNFL loss in different nonglaucomatous optic neuropathies.

**Recent findings**

RNFL thinning is most likely to occur in the temporal peripapillary quadrant than in other quadrants in nonglaucomatous optic neuropathies. The pattern of RNFL thinning in ischemic optic neuropathy and optic nerve head drusen is more likely to mimic the pattern found in glaucoma due to the superior and inferior quadrant predilection. OCT-measured RNFL thickness in Alzheimer’s disease reveals thinning superiorly and inferiorly, whereas superior and temporal thinning is seen in Parkinson’s disease. The thinning observed in neurodegenerative diseases is believed to be multifactorial including causes such as axonal degeneration and retrograde degeneration. However, more studies are needed to further study these changes.

**Summary**

OCT is a valuable tool in evaluating the peripapillary RNFL in both glaucomatous and nonglaucomatous optic neuropathies. This technology may be used for both research and clinical purposes to assess disease progression in optic neuropathies and diseases that affect the central nervous system. OCT-measured RNFL thickness remains complimentary to the clinical examination skills in the evaluation of nonglaucomatous optic neuropathies.
Artefacts: decentration
other difficulties in new generation devices...

**Figure 2** Relationship between the angle of the arcuate nerve fibers and the distance between the foveola and the optic nerve head

(a) When the distance between the macular center and the optic nerve head center is large, the angle of the arcuate nerve fibers is narrow. (b) When the distance between the macular center and the optic nerve head center is small, the angle of the arcuate nerve fibers is wide. Reproduced with permission from: Hong SW, Ahn MD, Kang SH, Im SK. Analysis of peripapillary retinal nerve fiber distribution in normal young adult. Invest Ophthalmol Vis Sci 2010; 51:3515–3523.
Artefacts & diagnostic difficulties: **age**

= normal RNFL loss varies between 0.15 und 0.5 micrometers per year.
Normative database

The Disc Area values of patients in the Cirrus ethnically diverse normative database (see User Manual for details on the study) fell within these ranges: one third of patients had Disc Area values less than 1.58 mm², one third of patients had Disc Area values between 1.58 and 1.88 mm², and one third of patients had Disc Area values larger than 1.88 mm².

In the table of values, Rim Area, Average C/D Ratio, Vertical C/D Ratio and Cup Volume have a grey background color when the Disc Area is less than 1.3 mm² or greater than 2.5 mm². The normative data is not applicable because the database has insufficient number of subjects with the disc areas of these sizes.

The values below are based on a 69-year old patient.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Range*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average RNFL Thickness</td>
<td>75.0 - 107.2</td>
</tr>
<tr>
<td>RNFL Symmetry</td>
<td>76% - 95%</td>
</tr>
<tr>
<td>Rim Area</td>
<td>1.015 - 1.615</td>
</tr>
<tr>
<td>Average C/D Ratio</td>
<td>0.618 - 0.169</td>
</tr>
<tr>
<td>Vertical C/D Ratio</td>
<td>0.594 - 0.165</td>
</tr>
<tr>
<td>Cup Volume</td>
<td>0.288 - 0.004</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Range*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal Quadrant</td>
<td>45.1 - 82.2</td>
</tr>
<tr>
<td>Superior Quadrant</td>
<td>88.9 - 136.7</td>
</tr>
<tr>
<td>Nasal Quadrant</td>
<td>50.0 - 86.2</td>
</tr>
<tr>
<td>Inferior Quadrant</td>
<td>89.4 - 138.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clock Hour</th>
<th>Normal Range*</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>36.4 - 67.4</td>
</tr>
<tr>
<td>10</td>
<td>52.7 - 100.5</td>
</tr>
<tr>
<td>11</td>
<td>87.2 - 154.6</td>
</tr>
<tr>
<td>12</td>
<td>70.7 - 155.7</td>
</tr>
<tr>
<td>1</td>
<td>72.6 - 133.9</td>
</tr>
<tr>
<td>2</td>
<td>52.4 - 109.7</td>
</tr>
<tr>
<td>3</td>
<td>41.7 - 70.4</td>
</tr>
<tr>
<td>4</td>
<td>44.8 - 89.0</td>
</tr>
<tr>
<td>5</td>
<td>61.9 - 125</td>
</tr>
<tr>
<td>6</td>
<td>85.7 - 163.2</td>
</tr>
<tr>
<td>7</td>
<td>84.8 - 159.4</td>
</tr>
<tr>
<td>8</td>
<td>42.2 - 90.2</td>
</tr>
</tbody>
</table>
Artefacts & diagnostic difficulties: signal strength and quality
Artefacts & diagnostic difficulties:
bulbus axial length (myopia effect)

= no known and widely accepted correction – still, do not forget...
Artefacts & diagnostic difficulties: optic disc size

= no known and widely accepted correction – still, do not forget…

Ophthalmology, 2009
Case example: female patient, age 49

No therapy. Varying VF in course of time. Ophthalmological findings, including the IOP, within the normal limits, except the VF and OCT.

Concentric VF-defect = „functional“?

OCT – artefacts?
= inflammatory-demyelinating CNS disease

OCT RNFL pattern loss not typical (sup./inf., instead of temporal – perhaps an additional form of optic atrophy, NTG?); Plaques in visual pathway explain homonymy of the VF defects (BMW sign, bilateral posterior / occip./ lesions).
RBN (relapse), yes or no, to treat or not to treat, that is (are) the question(s)…
Case example: female patient, age 41
MS diagnosis since 2.5 years, DMT (Avonex).
Visual disturbance in the left eye since couple of days, slightly blurred vision, diplopia (not constant). VA 1.0 OD, 0.7 OS. No RAPD. RBN (relapse) LA?
No RAPD on the left side.

No (OCT/fundus) sign of RNFL swelling in the left eye whatsoever, compared to the right eye.

VF – not exactly typical for RBN.

…known intermittent esophoria/esotropia (OS) decompensation with known amblyopia…

P.S. …already had high dose i.v. steroids…
Seven consecutive patients with multiple sclerosis (MS) were prospectively imaged from the onset of ON for 6 to 12 months.

**RNFL measured with FD-OCT initially increased in all eyes with diffuse optic disc edema. Inner macula thickness and polarimetric RNFLT decreased already in the acute phase, in all eyes. Poor image quality with polarimetry occurred in 2 eyes in the acute phase of ON.**

**Conclusions.** Change of RNFLT and macular thickness during the course of acute ON in MS strongly depends on the method used for the measurement.

*Inner macula thickness, measured with FD-OCT, was especially useful for the follow-up, since it was not influenced by initial disc edema and had consistently high image quality.*
Longitudinal OCT RNFL readings in MS, useful as a parameter of disease activity?
Reproducibility of peripapillary retinal nerve fiber layer thickness and optic nerve head parameters measured with cirrus HD-OCT in glaucomatous eyes.

Mwanza JC, Chang RT, Budenz DL, Durbin MK, Gandy MG, Shi W, Feuer WJ.
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Abstract
PURPOSE: To assess the reproducibility of peripapillary retinal nerve fiber layer (RNFL) thickness and optic nerve head (ONH) parameters measured with Cirrus HD-OCT in glaucomatous eyes.

METHODS: Fifty-five glaucomatous eyes were included in the study. The optic disc cube 200 × 200 protocol was used to obtain three scans during the same visit to evaluate the intravisit reproducibility. One scan on 4 additional days within a 2-month period of the first session was obtained to assess intervisit reproducibility. Intraclass correlation coefficient (ICC), coefficient of variation (CV), and test-retest SD (TRT SD) were calculated for each RNFL and ONH parameter. The formula 1.645 × √2 × intervisit TRT SD provides an upper tolerance limit to variability beyond which nonphysiologic change should be considered.

RESULTS: All ICCs were excellent, ranging from 83.9% to 99.2% for intravisit measurements and from 80.8% to 99.1% for intervisit measurements. Cup/disc area ratio had the lowest CV (1.1%) in either type of measurement, followed by average RNFL thickness (1.9% and 2.7%). Nasal clock hours and quadrants showed the poorest reproducibility as did the clock hour directly temporally. The intervisit tolerance limit for average RNFL thickness was 3.89 μm.

CONCLUSIONS: Intravisit and intervisit measurements of peripapillary RNFL thickness and ONH parameters with Cirrus HD-OCT showed excellent reproducibility, indicating that this instrument may be useful in monitoring glaucoma progression. When comparing two measurements from the same eye on two different visits, a reproducible decrease in average RNFL thickness of approximately 4 μm or more may be considered a statistically significant change from baseline.
Acute ON excluded; 92.6% of patients were RRMS; EDSS 2.5 at baseline; 36% no treatment, the rest Betaferone Rebif, Copaxone (two had Mitoxantrone).
Retinal damage in multiple sclerosis disease subtypes measured by high-resolution optical coherence tomography.


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Abstract

Background. Optical coherence tomography (OCT) has facilitated characterisation of retinal alterations in MS patients. Only scarce and in part conflicting data exists on different MS subtypes. Objective. To analyse patterns of retinal changes in different subtypes of MS with latest spectral-domain technology. Methods. In a three-centre cross-sectional study 414 MS patients and 94 healthy controls underwent spectral-domain OCT examination. Results. Eyes of MS patients without a previous optic neuritis showed a significant reduction of both retinal nerve fibre layer (RNFL) thickness and total macular volume (TMV) compared to healthy controls independent of the MS subtype (P < 0.001 for all subtypes). RNFL thickness was lower in secondary progressive MS (SPMS) eyes compared to relapsing-remitting MS (RRMS) eyes (P = 0.007), and TMV was reduced in SPMS and primary progressive MS (PPMS) eyes compared to RRMS eyes (SPMS: P = 0.039, PPMS: P = 0.005). Independent of the subtype a more pronounced RNFL thinning and TMV reduction were found in eyes with a previous optic neuritis compared to unaffected eyes. Conclusion. Analysis of this large-scale cross-sectional dataset of MS patients studied with spectral-domain OCT confirmed and allows to generalize previous findings. Furthermore it carves out distinct patterns in different MS subtypes.
Study:
“Pattern of retinal thickness changes measured by ocular coherence tomography in patients with multiple sclerosis,”

Retinal ganglion cells are concentrated (50%) in an area between 0.4-2.0 mm from the center.

-Wallerian degeneration leads to 1:1 Axon-Soma loss, producing an above affect.
Miscellaneous
Case example: male patient, age 47

MS since 23 years. Referral question: ophthalmologic contraindication for Gilenya-Th?

BCVA (best corrected VA) OD 0.6, OS 0.7
No RAPD.

Both optic discs cupped glaucoma-like. Still, IOP within normal range (well, borderline), no clear risk profile for NTG, and cave – large discs = relatively large cupping.

Superior/inferior OCT RNFL loss corresponds to VF defects (OD>OS). In a longstanding MS, such pattern not typical, but not impossible. Still, other etiologies (NTG?) not excluded…

Temporal pallor in both discs present – speaks for St. p. RBN, positive history for RBN bilaterally, but OCT RNFL temporal thinned only OS.
**Macula OD** shows a lamellar defect / hole, due to (idiopathic?) epiretinal fibroplasia. It explains the thickening of all the retinal layers OD, and hence masking of RNFL atrophy due to St. p. RNB OD. VA is affected by the ERF / lamellar hole due to Style-Crawford effect.

Referral question: green light for fingolimod, as far as eyes are concerned. Close follow-up nevertheless necessary.
Take-home messages:

OCT is a promising and precise technique of visualising and quantifying ocular tissues at a „histology in vivo“ micrometer level.

It can be used as an adjunct diagnostic method in unclear cases of optic neuropathies.

In MS patients, it can be used for the precise objective diagnosis of RBN (provided previous scans are available), and for the follow-up of optic nerve atrophy in MS, with or without history of ON (in latter case, unclear whether reproducibility / measurement sensitivity is high enough for studies shorter than several years).
Thank you for your attention!