Imaging Glaucoma

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Proprietary Interest Slide

In the past three years, the speaker has received research funding, research equipment, honoraria and/or payment of travel expenses from Alcon, Inc.; Allergan, Inc.; Carl Zeiss Meditec, Inc.; Heidelberg Engineering GmbH; Lumenis; Merck & Company, Inc.; Optovue, Inc.; and Pfizer, Inc.

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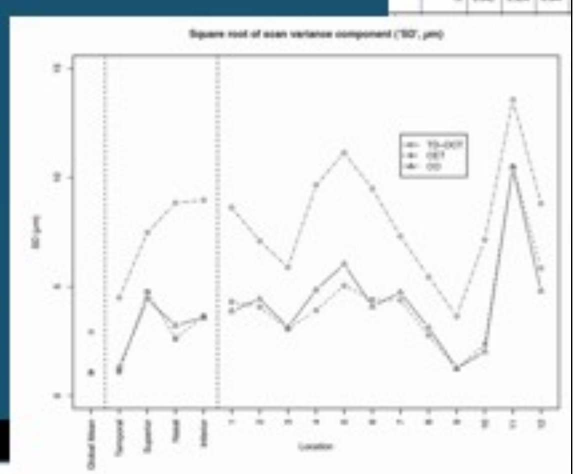
OCT in Glaucoma

- Imaging, in particular Optical Coherence Tomography (OCT), is a useful tool for the assessment of glaucoma
  - Structure – function correlates
    - Diagnosis of glaucoma and its progression
  - Identify areas of abnormality
  - Reassurance or confirmation of glaucoma in Suspects
- What advances are underway in OCT?

Reproducibility

- SD-OCT showed statistically significantly better RNFL thickness measurement reproducibility than TD-OCT
- Re-sampling circle location variation on the SD-OCT was relatively small from scan to scan
- No statistically significant difference was detected between Center Each Time and Center Once methods

Kim JS, Ishikawa H, Sung KR, Xu JA, Wollstein G, Bilonick RA, Gabriele ML, Kagemann L, Duker JS, Fujimoto JG, Schuman JS. Retinal Nerve Fiber Layer Thickness Measurement Reproducibility Improved with Spectral Domain Optical Coherence Tomography. Br J Ophthalmol. Published Online First: 7 May 2009. doi:10.1136/bjo.2009.157875



Reproducibility of RTVue Retinal Nerve Fiber Layer Thickness and Optic Disc Measurements and Agreement with Stratus Optical Coherence Tomography Measurements

ALBERTO O. GONZÁLEZ-GARCÍA, GIANMARCO VIZZERI, CHRISTOPHER BOWD, FELIPE A. MEDEIROS, LINDA M. ZANGWILL, AND ROBERT N. WEINREB

(Am J Ophthalmol 2009;147:1067–1074.)

TABLE 2. Reproducibility of RTVue Retinal Nerve Fiber Layer Thickness Measurements in Healthy Participants and Glaucoma Patients

RNFL Parameters	Healthy Participants				Glaucoma Patients			
	Mean (95% CI)	Sw ± 1.96 se	CV %	ICC (95% CI)	Mean (95% CI)	Sw ± 1.96 se	CV %	ICC (95% CI)
TEMP (μm)	80.6 (77.4 to 83.8)	2.82 ± 0.52	3.54	0.92 (0.88 to 0.95)	71.2 (68.7 to 73.8)	3.36 ± 0.7	4.72	0.86 (0.81 to 0.91)
SUP (μm)	120.6 (117 to 124.3)	3.8 ± 0.57	3.16	0.91 (0.86 to 0.94)	103.2 (99.6 to 106.8)	3.67 ± 0.59	3.53	0.93 (0.89 to 0.95)
NAS (μm)	75.8 (72.9 to 78.7)	2.94 ± 0.44	3.88	0.91 (0.86 to 0.94)	68.6 (66.2 to 71.1)	3.22 ± 0.52	4.6	0.88 (0.83 to 0.92)
INF (μm)	134.3 (129.7 to 138.9)	3.53 ± 0.55	2.65	0.95 (0.92 to 0.97)	113.2 (108.9 to 117.4)	3.21 ± 0.48	2.87	0.96 (0.94 to 0.97)
AVG (μm)	102.8 (100.1 to 105.6)	1.57 ± 0.27	1.54	0.97 (0.95 to 0.98)	89.1 (86.5 to 91.7)	1.69 ± 0.23	1.9	0.97 (0.96 to 0.98)

AVG = average quadrant; CI = confidence interval; CV = coefficient of variation; ICC = intraclass correlation coefficient; INF = inferior quadrant; NAS = nasal quadrant; SUP = superior quadrant; Sw = within-subjects standard deviation; RNFL = retinal nerve fiber layer; TEMP = temporal quadrant.

Reproducibility is expressed as the Sw, the ICC, and the CV. Sw is defined as the square root of the within-subject variance (defined as the within-subjects sum of squares divided by its degrees of freedom). CV is calculated as the square root of the residual mean squared values of 3 measures, divided by mean.

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Diagnostic Ability of Fourier-Domain vs Time-Domain Optical Coherence Tomography for Glaucoma Detection

MITRA SEHI, DILRAJ S. GREWAL, CLINTON W. SHEETS, AND DAVID S. GREENFIELD

Am J Ophthalmol 2009;xx

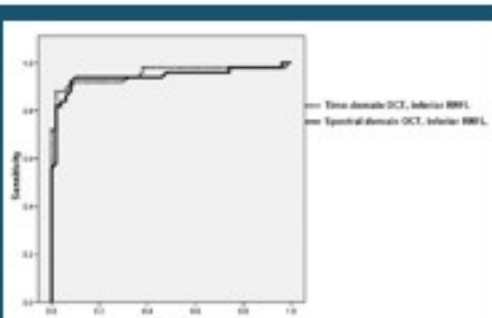

FIGURE 2. Graph showing the area under the receiver operator characteristic curves (AUROCs) for the best parameter obtained using TD-OCT (inferior RNFL thickness; AUROC = 0.95) and FD-OCT (inferior RNFL thickness; AUROC = 0.94; P = .45).

Comparison of Retinal Nerve Fiber Layer Thickness Measured by Cirrus HD and Stratus Optical Coherence Tomography

Kyung Rim Sung, MD, Dong Yoon Kim, MD, Sung Bae Park, MD, Michael S. Kook, MD

Ophthalmology 2009;116:1264–1270

Table 1. Clinical Characteristics of the Study Population

	Glaucoma (n = 55)	GS (n = 48)	Healthy (n = 60)	P Value (ANOVA)
Age (yrs) ± SD	53.7±12.9	53.3±11.3	51.3±12.6	0.11
MD (dB) ± SD	−5.91±5.68	−2.85±1.48	−2.67±1.48	<0.001
PSD (dB) ± SD	5.53±3.26	1.59±0.34	1.49±0.24	<0.001
Average RNFL Thickness by Stratus OCT (μm) ± SD	82.2±18.0	100.3±10.1	110.6±10.5	<0.001 <0.001* <0.001†
Average RNFL thickness by Cirrus HD-OCT (μm) ± SD	72.2±12.7	86.4±7.81	97.3±8.8	<0.001 <0.001* <0.001†

ANOVA = analysis of variance; GS = glaucoma suspect; MD = mean deviation; OCT = optical coherence tomography; PSD = pattern standard deviation; RNFL = retinal nerve fiber layer; SD = standard deviation.
*Comparative P value between glaucoma and GS.
†Comparative P value between GS and healthy by post hoc Tukey test.

Table 4. Sensitivity and Specificity (%) of Stratus Optical Coherence Tomography (OCT) and Cirrus HD-OCT

Parameter	OCT	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Average RNFL	Stratus OCT	40.0 (27.3–54.1)	96.7 (87.5–99.4)
	Cirrus HD-OCT	63.6 (49.5–75.9)	100.0 (92.5–100)
≥1 quadrants	Stratus OCT	58.2 (44.1–71.1)	95.0 (85.2–98.7)
	Cirrus HD-OCT	76.4 (62.7–86.3)	96.7 (87.5–99.4)
≥1 clock hours	Stratus OCT	72.7 (58.8–83.5)	90.0 (78.8–95.9)
	Cirrus HD-OCT	81.8 (68.6–90.5)	83.3 (71.0–91.3)

RNFL = retinal nerve fiber layer.

Conclusions: There were significant differences in RNFL thickness and normative classification as determined by Stratus OCT and Cirrus HD-OCT despite an excellent correlation of RNFL thickness measurement. Overall sensitivity and specificity were higher with Cirrus OCT. These findings are particularly relevant when an individual undergoes longitudinal follow-up with different OCTs.

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Assessment of Artifacts and Reproducibility across Spectral- and Time-Domain Optical Coherence Tomography Devices

Joseph Ho, BS, BA,[1,2] Alan C. Sull, BA,[1,3] Laurel N. Vuong, BS,[1] Yueli Chen, PhD,[4] Jonathan Liu, MS,[4] James G. Fujimoto, PhD,[4] Joel S. Schuman, MD,[5] Jay S. Duker, MD[1]

Oct;116(10):1960-70. Epub 2009 Jul 9.

Ophthalmology 2009;xx:xxx

- Stratus (software version 4.0; Carl Zeiss Meditec, Inc., Dublin, CA)
- Cirrus (software version 3.0; Carl Zeiss Meditec, Inc., Dublin, CA)
- Topcon 3D (software version 2.12; Topcon, Inc., Paramus, NJ)
- RTVue (software version 3.5; Optovue, Inc., Fremont, CA)

Conclusions: Out of all OCT devices analyzed cirrus HD-OCT scans exhibited the lowest occurrence of any artifacts (68.5%), IFT (40.7%), and clinically significant IFT (11.1%), whereas Stratus OCT scans exhibited the highest occurrence of clinically significant IFT. Further work on improving segmentation algorithm to decrease artifacts is warranted.

Clinical Application of SD-OCT in Glaucoma

- Structure before function?
  - OHTS data show conversion by 55% by ONH first, 35% by VF first, 10% by both simultaneously
    - But...OHTS used ONH photos
    - HRT ancillary study showed positive predictive value of CSLO ONH examination at baseline
    - Similar findings with SLP and OCT on different datasets

Gordon MO, Beiser JA, Brandt JD, et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. Arch Ophthalmol 2002;120:714 –720.

Zangwill LM, Weinreb RN, Beiser JA, et al. Baseline topographic optic disc measurements are associated with the development of primary open-angle glaucoma: the Confocal Scanning Laser Ophthalmoscopy Ancillary Study to the Ocular Hypertension Treatment Study. Arch Ophthalmol 2005;123:1188-1197.

Mohammadi K, Bowd C, Weinreb RN, et al.. Retinal nerve fiber layer thickness measurements with scanning laser polarimetry predict glaucomatous visual field loss. Am J Ophthalmol 2004;138:592-601.

Lalezary , Medeiros F,A, Weinreb RN, et al. Baseline Optical Coherence Tomography Predicts the Development of Glaucomatous Change in Glaucoma Suspects. Am J Ophthalmol 2006; 142:576-582

Clinical Application of SD-OCT in Glaucoma

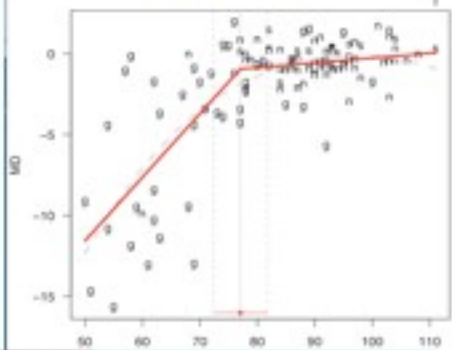
- Structure before function?
  - RNFL thickness “tipping point”

Characteristics of the study participants

	Healthy n=64	Glaucoma n=54	p
F/M	32/32	38/16	0.03[1]
Age (yrs)	48.3 ± 16.2	64.6 ± 11.0	<0.001[2]
VF MD (dB)	-0.58 ± 1.50	-3.56 ± 4.72	<0.001[3]
VF PSD (dB)	1.79 ± 1.29	4.67 ± 4.03	<0.001[3]
OCT mean RNFL (µm)	90.1 ± 9.1	75.6 ± 14.6	<0.001[2]

VF: visual field, MD: mean deviation, PSD: pattern standard deviation, RNFL: retinal nerve fiber layer [1] Chi Square, [2] Wilcoxon, [3] t-test

The Tipping Point



RNFL	Tipping Point (µm)	95% CI (µm)	Normative Value (µm)	% Loss
Mean	77.1 ± 2.4	72.4 - 81.8	90	14.4
Temporal	46.1 ± 0.9	44.3 - 48.0	61	24.3
Superior	96.1 ± 4.2	87.8 - 104.5	113	14.9
Nasal	60.5 ± 7.7	45.3 - 75.6	69	12.4
Inferior	98.5 ± 6.0	86.7 - 110.3	117	15.8

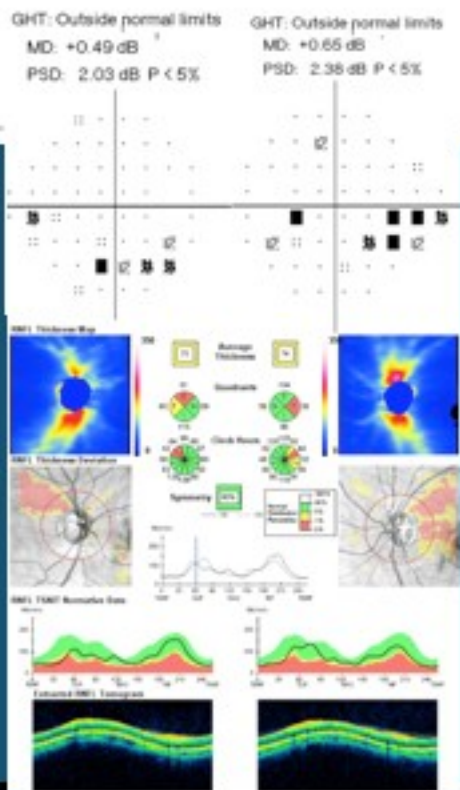
CI: confidence interval

Wollstein, et al. ARVO 200

OCT in Glaucoma

- Three-dimensional OCT imaging
  - More reproducible measurements
  - Exact correspondence with the fundus image
  - Promise of greater sensitivity to abnormality and change over time
- OCT statistical software for the measurement of glaucoma progression is still in the development and testing stage

Clinical Utility of OCT



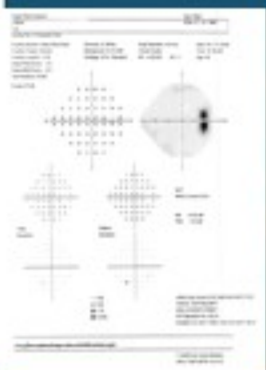
- Structure and Function
  - Good structural and functional correlation in normal and glaucomatous eyes evaluated with OCT
  - Significant difference in RNFL thickness between healthy and glaucomatous eyes
  - Differences between the patient and the healthy population are highlighted on clinical OCT assessment as deviation from the normative database

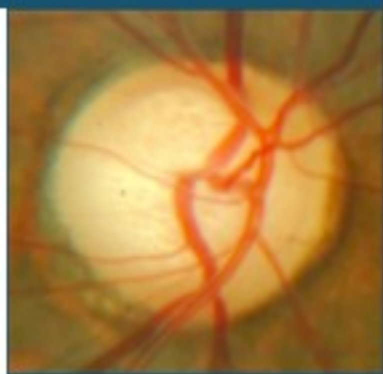
OCT in Glaucoma

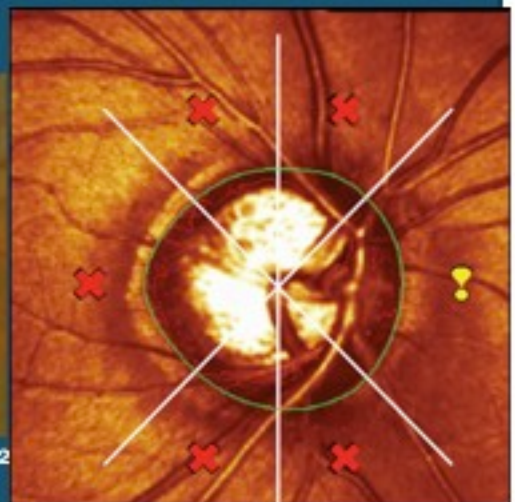
- OCT assessment of the RNFL status of the patient is particularly helpful in glaucoma suspects
  - Suspicious appearing ONH
  - Family history of glaucoma
  - Normal visual fields
  - IOP in the normal or even borderline range
- Thinner OCT RNFL measurements are an independent predictor of the glaucomatous change.

Lalezary , Medeiros F,A, Weinreb RN, et al. Baseline Optical Coherence Tomography Predicts the Development of Glaucomatous Change in Glaucoma Suspects. Am J Ophthalmol 2006; 142:576-582

Glaucoma Suspect: 40 YO AA Man, IOP 23, CCT 555







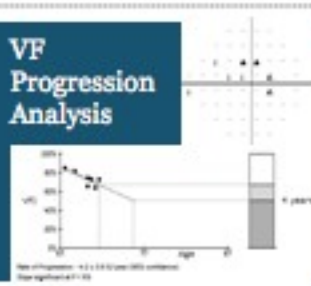
disc area = 3.95 mm^2

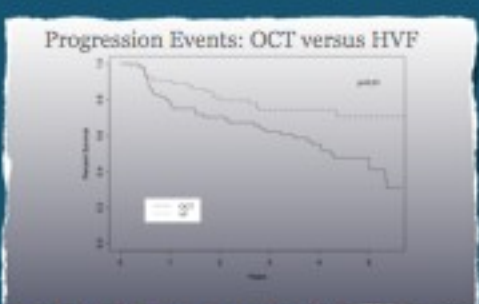
Consider disc size

OCT in Glaucoma

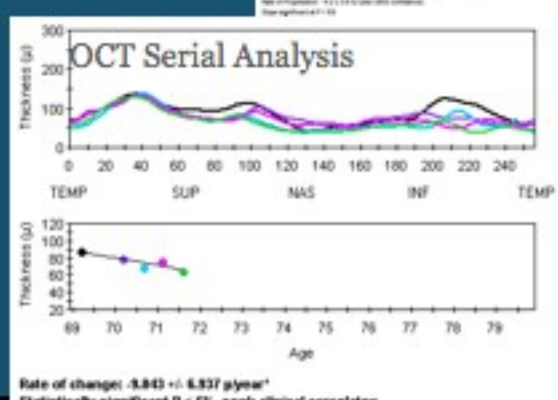
- Retinal nerve fiber layer thickness may be followed for change over time to track glaucoma progression, but validated, robust software for this purpose is not commercially available.

VF Progression Analysis





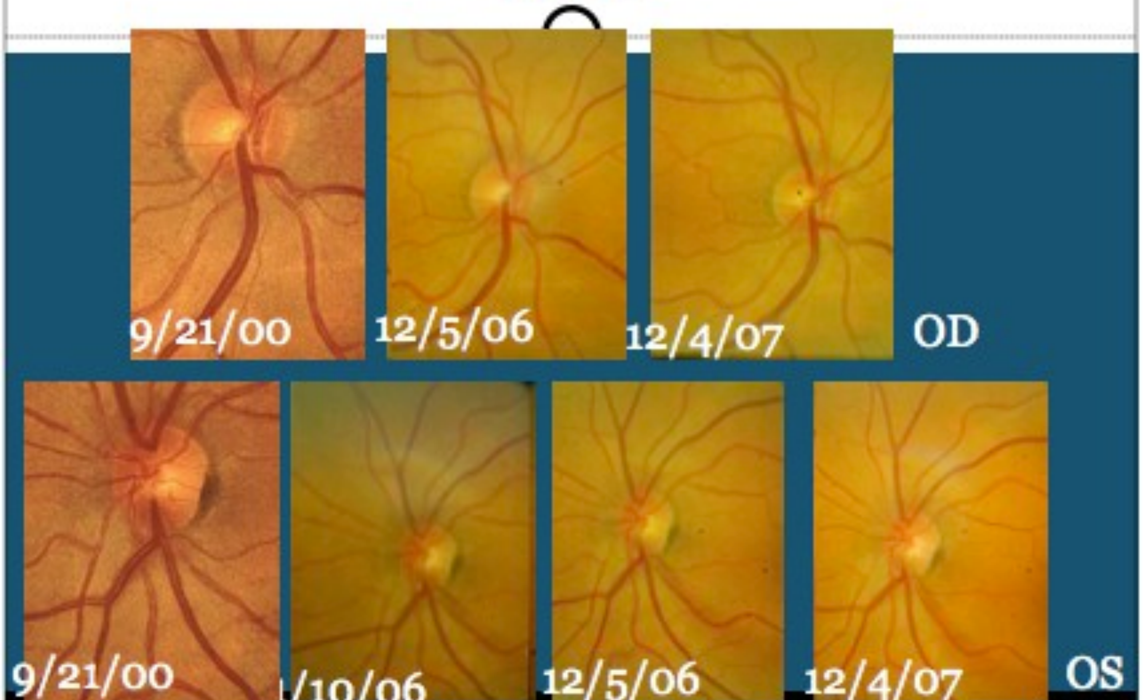
Wollstein G, Schuman JS, Price LL et. al.: Optical Coherence Tomography Longitudinal Evaluation of Retinal Nerve Fiber Layer Thickness in Glaucoma. Arch Ophthalmol 2005; 123:464-470



Case 6

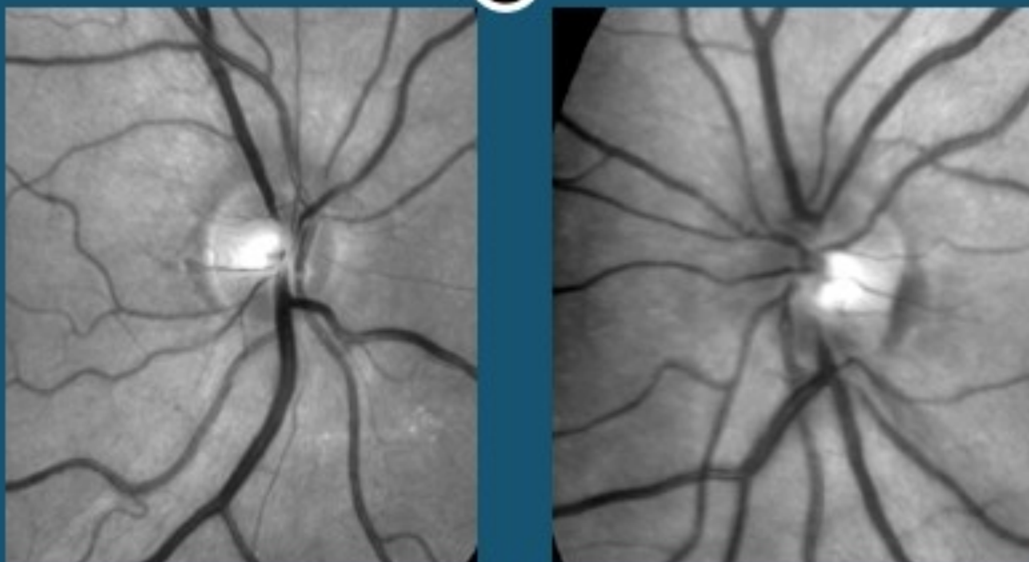
- 63 year old woman with PMH:
  - Normal Tension Glaucoma OS s/p SLT (OS, 2006)
  - s/p conductive keratoplasty (OU, 2004)
  - NS cataracts OU – NVS
  - Rosacea with dry eye
- Allergies: PCN
- Ocular Rx: Restasis
- Systemic Rx: ASA, Vitamins C, D, FA, B12
- FHx: Non-contributory; SHx: Non-smoker, No EtOH
- Best Corrected VA: 20/25-1 (OD), 20/25-2 (OS); plano
- Pachymetry: 544(OD), 538(OS); Tonometry: 13(OD), 12(OS)
- External Exam: Normal (OU)
- Slit Lamp Exam:
  - OD: 1+ NS
  - OS: CK scars on cornea, 1+ NS, 1+ Anterior cortical changes
- Fundus:
  - **OD:** Nl disc, C/D = 0.5x.0.4; macula, vessels, and periphery nl
  - **OS:** Disc with IT RNFL wedge defect , C/D = 0.8x0.7; macula, vessels, and periphery nl

Case 6



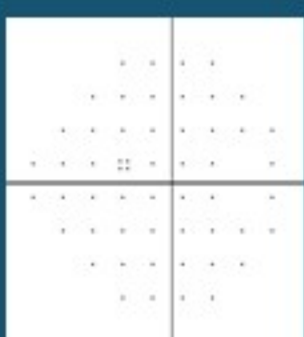
RED FREE PHOTOGRAPHS

OD OS

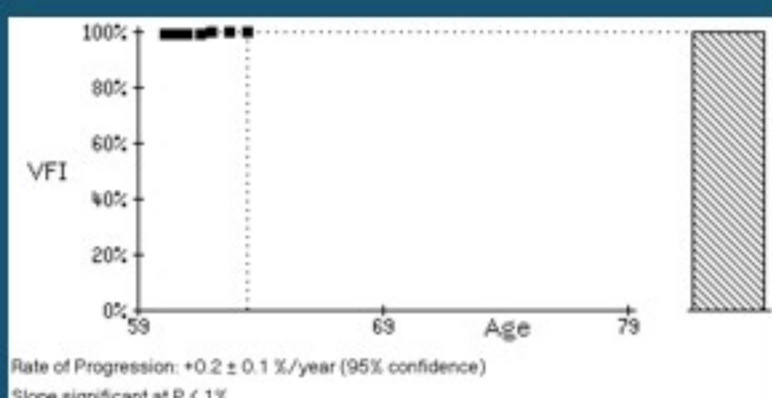


Case 6 – Humphrey Visual Fields GPA: OD

- No Progression

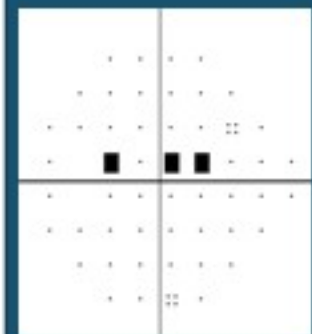


2009

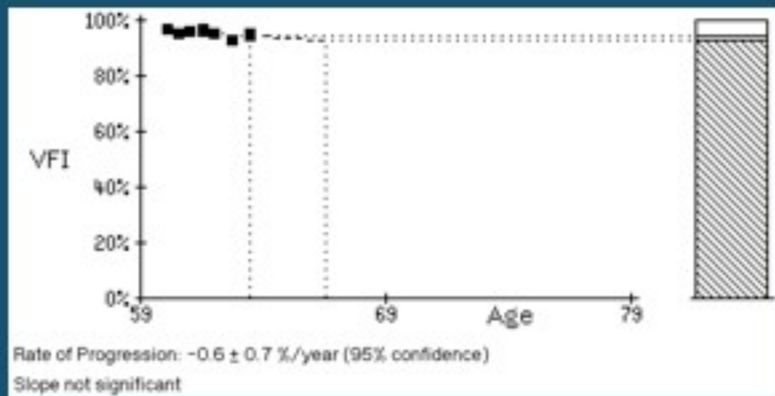


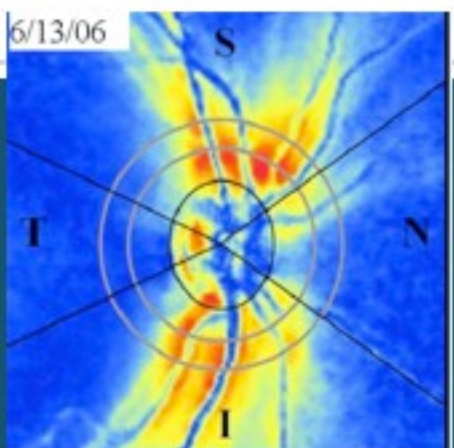
Case 6 – Humphrey Visual Fields GPA: OS

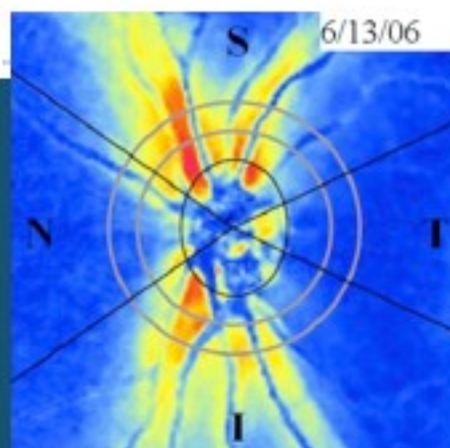
- No Progression



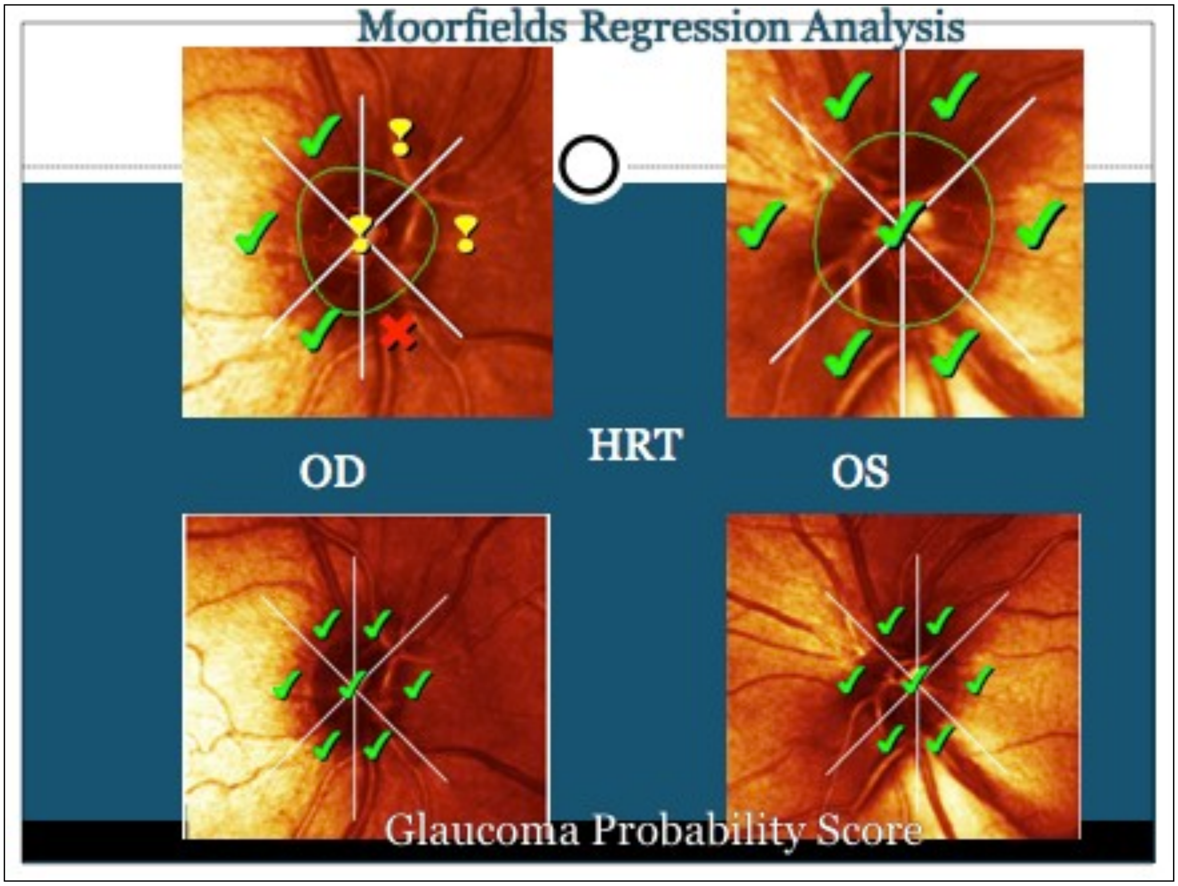
2009

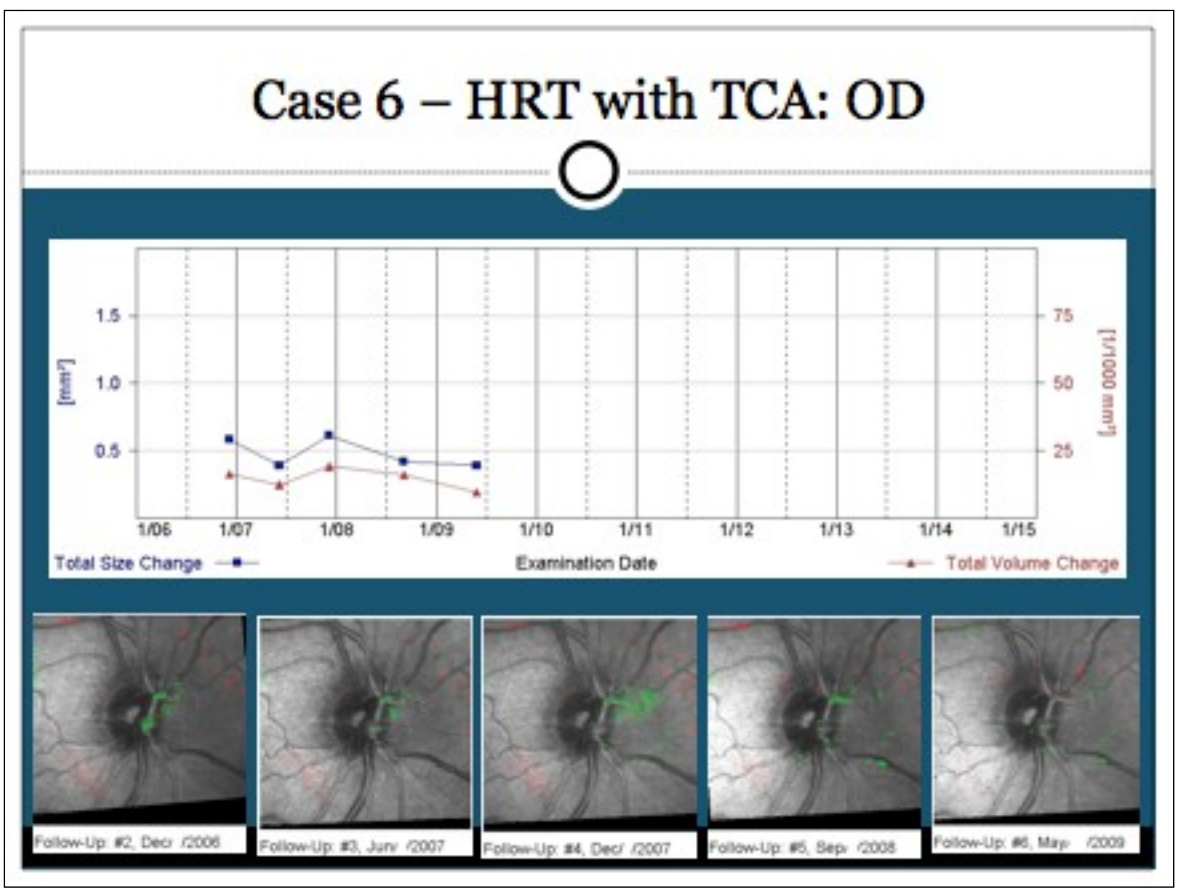




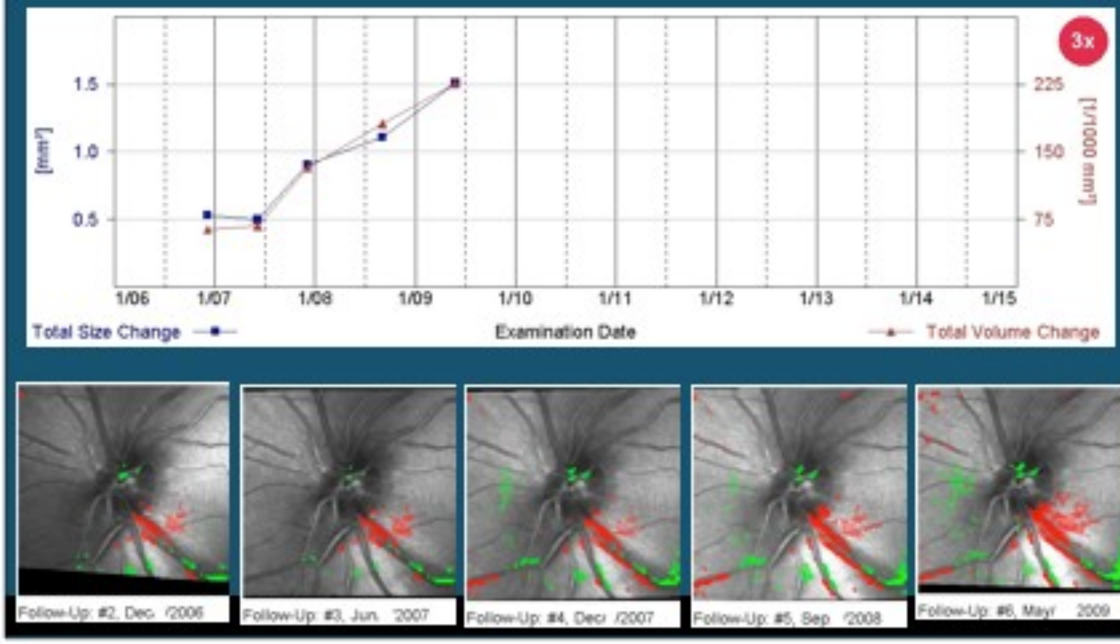


Date of GDx	6/13/06	12/5/06	6/5/07	12/4/07	9/2/08
NFI OD	8	10	10		
NFI OS	18	20	20		

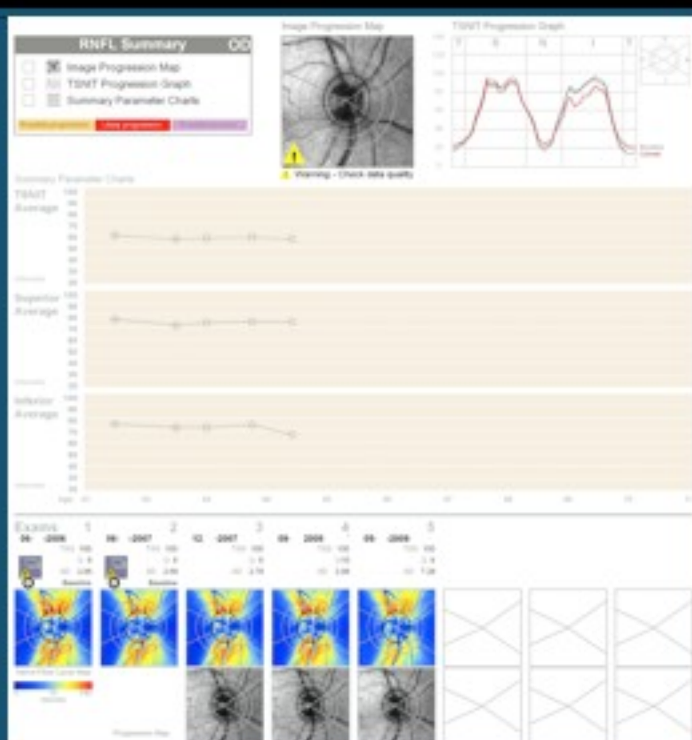

Moorfields Regression Analysis
OD
HRT
OS
Glaucoma Probability Score


Case 6 – HRT with TCA: OD
1.5
1.0
0.5
[mm²]
75
50
25
[1/1000 mm³]
1/06
1/07
1/08
1/09
1/10
1/11
1/12
1/13
1/14
1/15
Total Size Change
Examination Date
Total Volume Change
Follow-Up: #2, Dec/ /2006
Follow-Up: #3, Jun/ /2007
Follow-Up: #4, Dec/ /2007
Follow-Up: #5, Sep/ /2008
Follow-Up: #6, May/ /2009

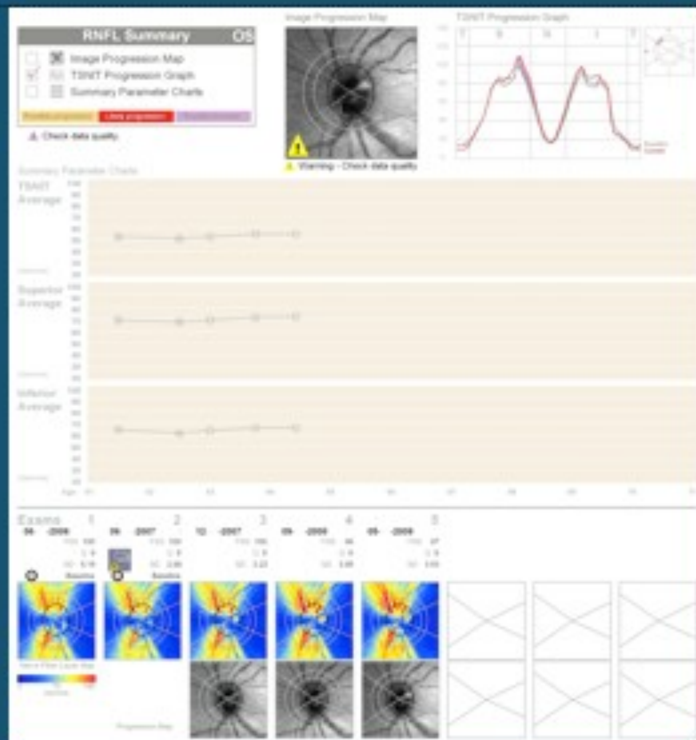
Case 6 – HRT with TCA: OS



Case 6 – GDx GPA: OD

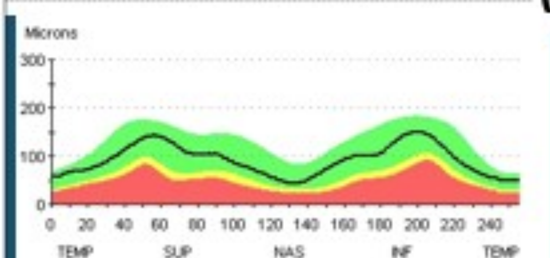


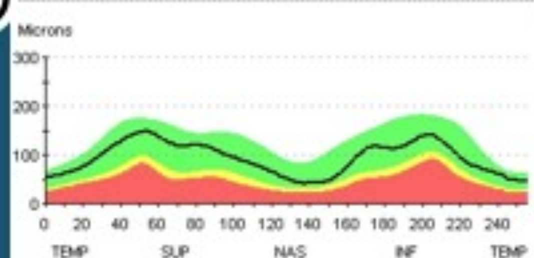
Case 6 – GDx GPA: OS



STRATUS OCT 9/2/08

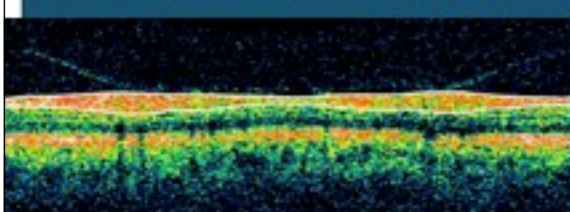
OD | **OS**

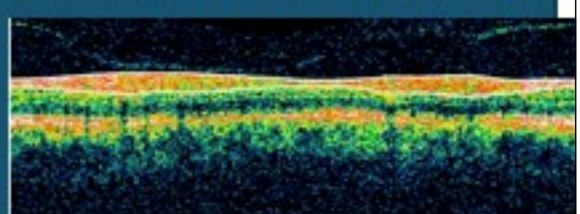




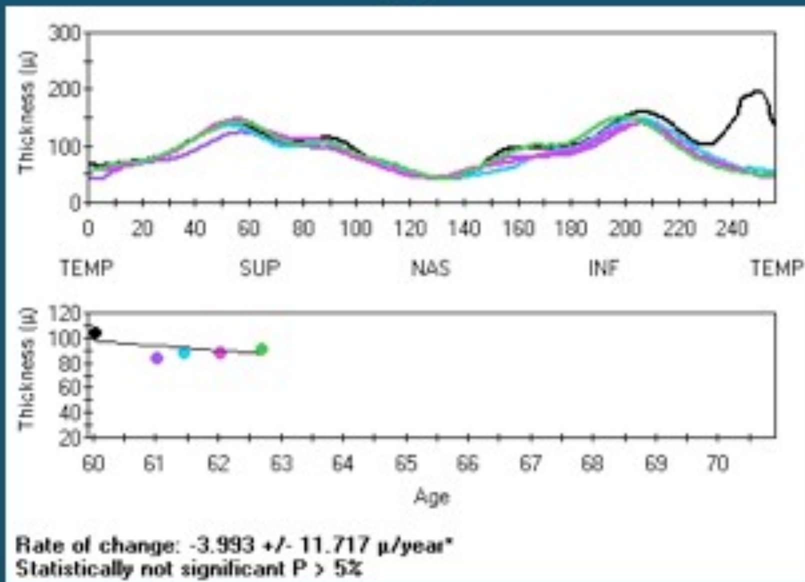
RNFL Thickness=52

RNFL Thickness=50

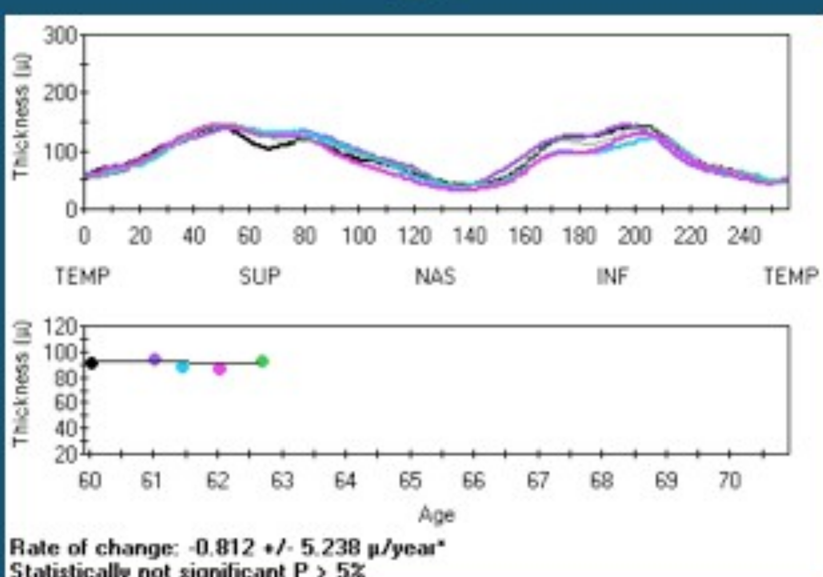


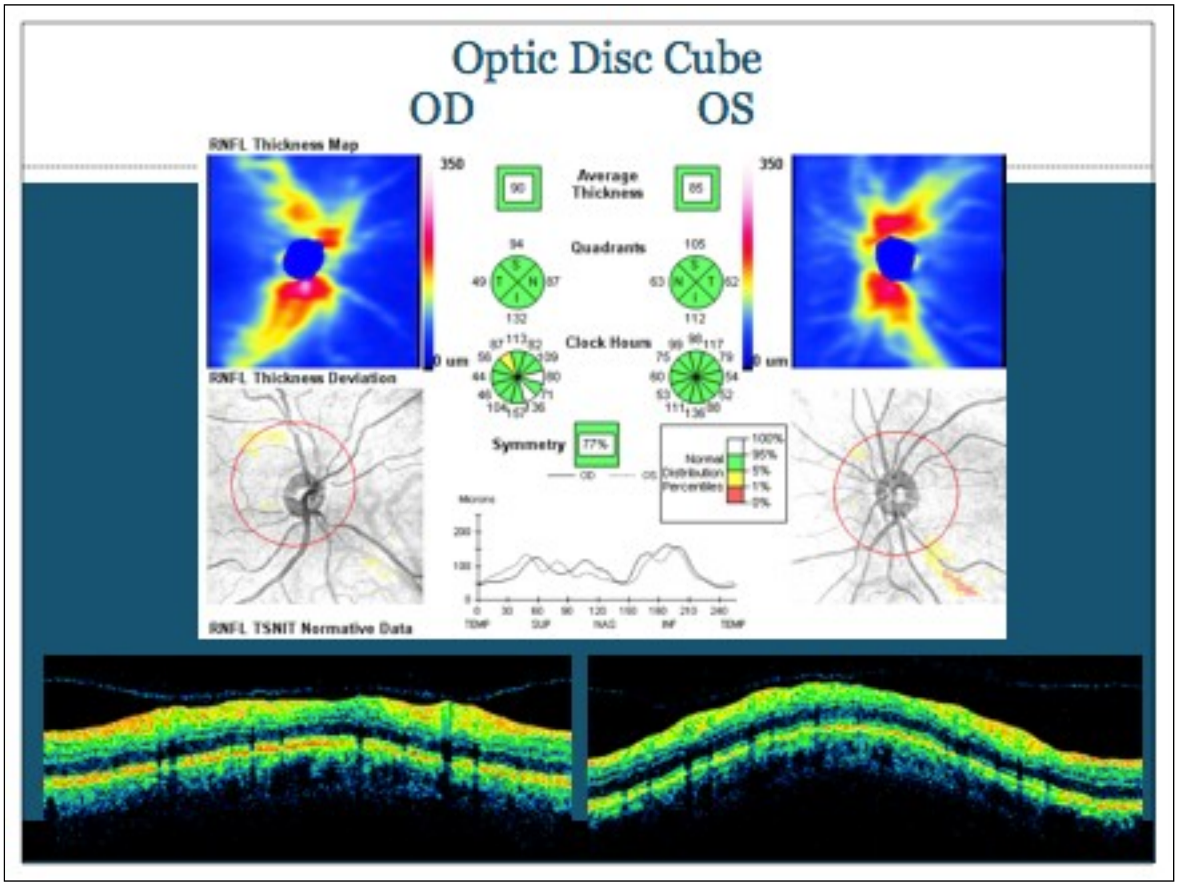


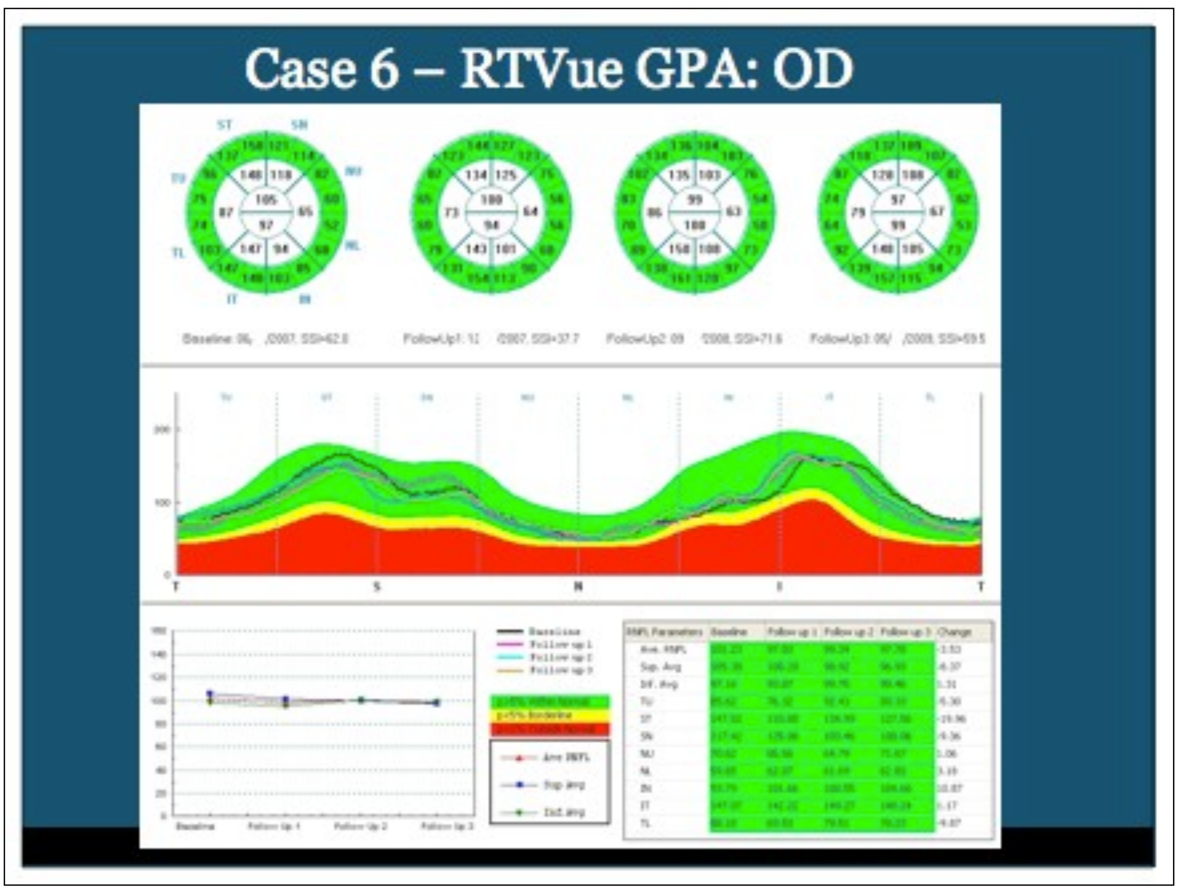
Case 6 – Stratus OCT GPA: OD



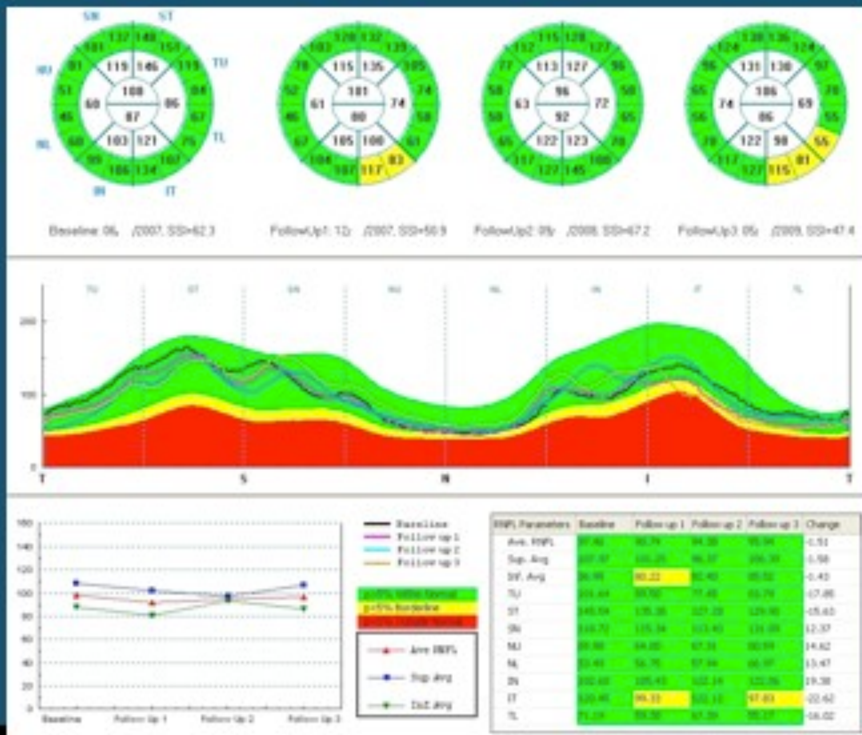
Case 6 – Stratus OCT GPA: OS




Optic Disc Cube
OD
OS
RNFL Thickness Map
350
0 um
Average Thickness
90
85
Quadrants
Clock Hours
RNFL Thickness Deviation
Symmetry
77%
Normal Distribution Percentiles
100%
95%
5%
1%
0%
Microns
TEMP
SUP
NAS
INF
TEMP
RNFL TSNIT Normative Data


Case 6 – RTVue GPA: OD
ST
SN
TU
NU
TL
NL
IT
IN
T
S
N
I
T
Baseline
Follow up 1
Follow up 2
Follow up 3
RNFL Parameters
Change

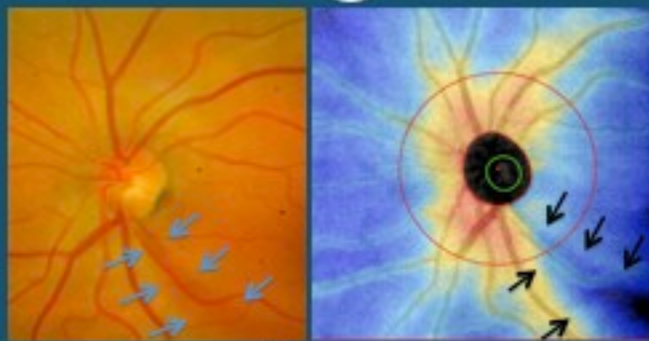
Case 6 – RTVue GPA: OS

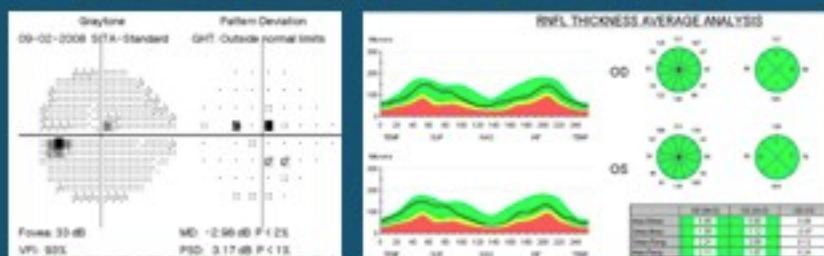


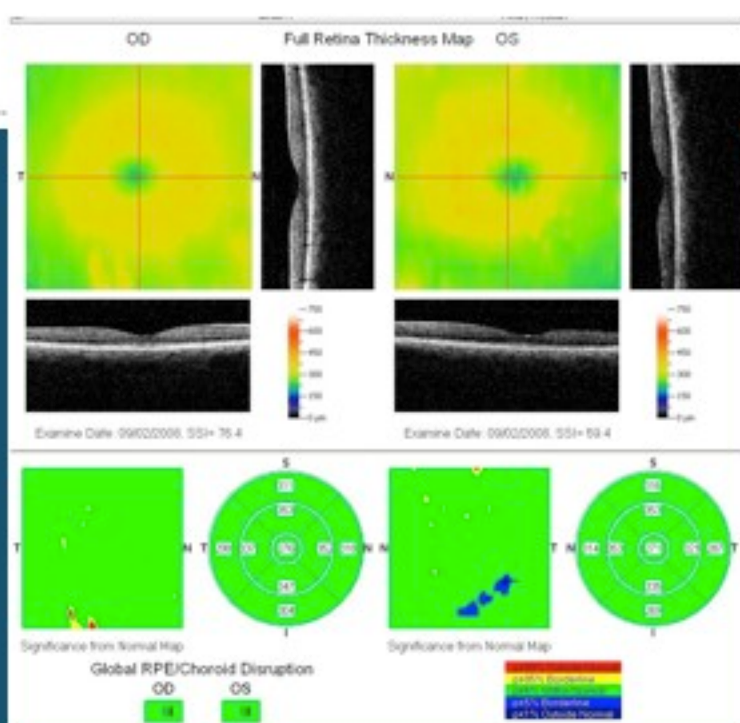
Clinical Application of SD-OCT in Glaucoma

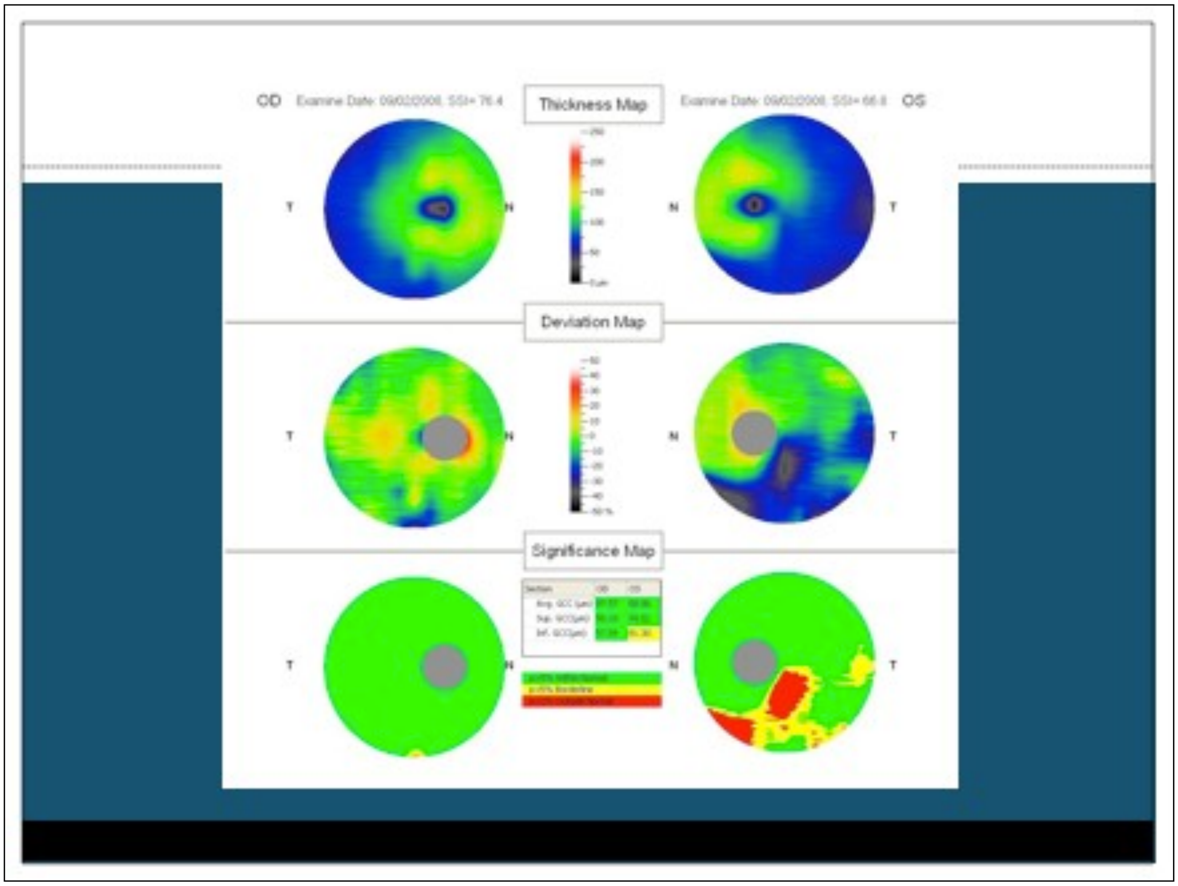
- Where to look?
  - 3D OCT presents new opportunities and challenges
  - Can now evaluate the tissue layer of interest in the macula on a single visit or over time
  - Peripapillary RNFL in 3D ONH cube may provide valuable new diagnostic information for a single visit or for detecting change
    - RNFL thickness may not be "outside normal limits" all the way to the circumpapillary scan region

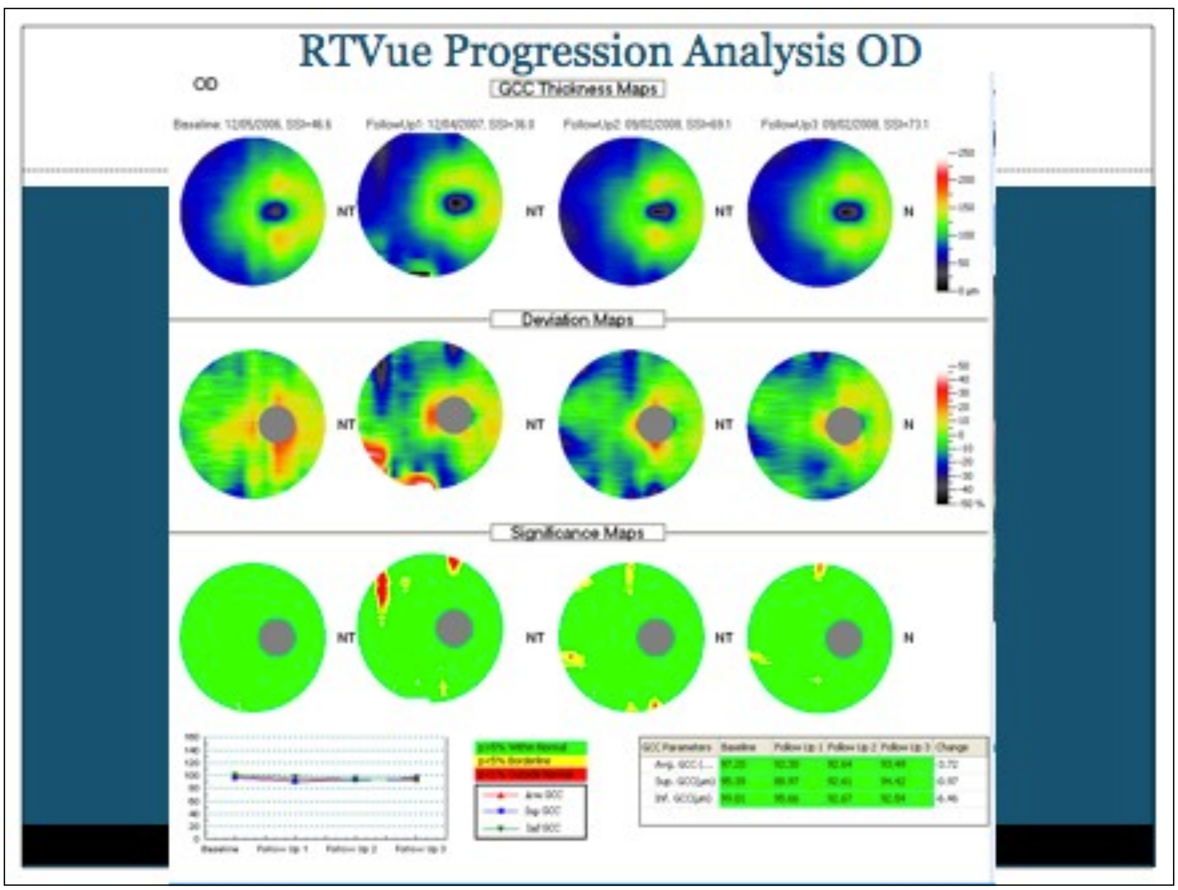
Focal RNFL Defect



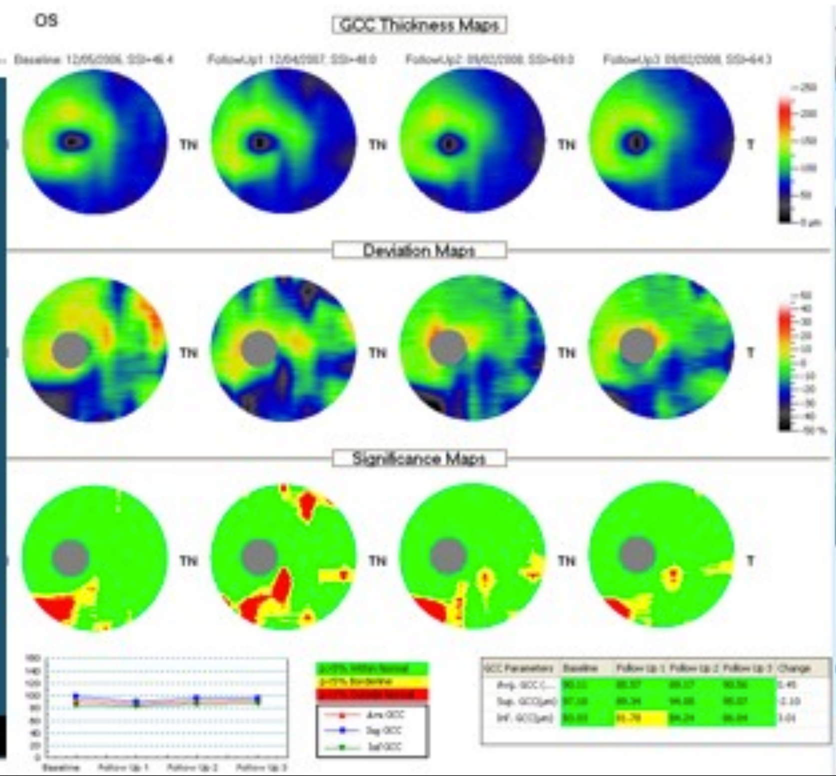





OD
Thickness Map
OS
Deviation Map
Significance Map


RTVue Progression Analysis OD
OD
GCC Thickness Maps
Deviation Maps
Significance Maps

RTVue Progression Analysis OS



The Future of OCT - Where Are We Going?

- What to do with all those visits?
  - HRT has long made use of old data
  - OCT has gone through three iterations (to date) of incompatible data sets
    - It is possible to create “backward compatibility” so that time-domain OCT data can be used in conjunction with spectral domain OCT scans

Reproducibility of RTVue Retinal Nerve Fiber Layer Thickness and Optic Disc Measurements and Agreement with Stratus Optical Coherence Tomography Measurements

ALBERTO O. GONZÁLEZ-GARCÍA, GIANMARCO VIZZERI, CHRISTOPHER BOWD, FELIPE A. MEDEIROS, LINDA M. ZANGWILL, AND ROBERT N. WEINREB

(Am J Ophthalmol 2009;147:1067–1074.)

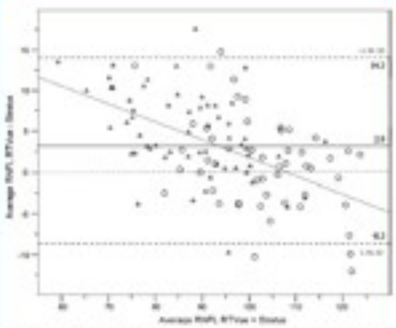


FIGURE 1. Bland-Altman plot showing the average retinal nerve fiber layer thickness (RNFL) agreement between RTVue spectral-domain optical coherence tomography (SD-OCT) and Stratus time-domain optical coherence tomography (TD-OCT) in healthy persons (circle) and glaucoma patients (triangle).

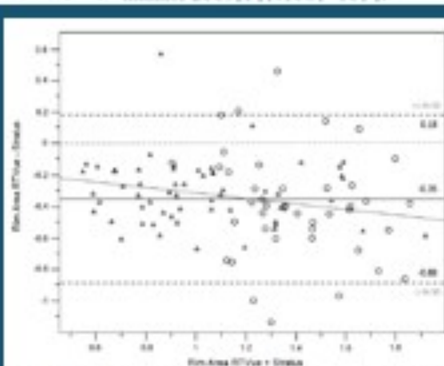


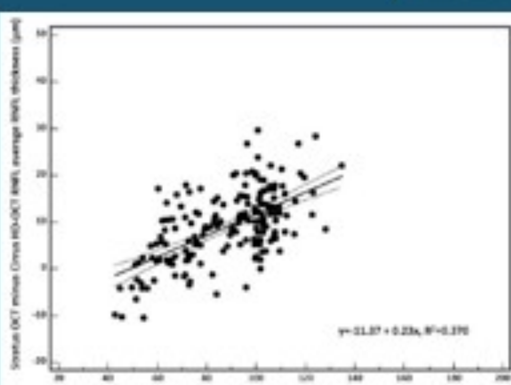
FIGURE 2. Bland-Altman plot showing the rim area agreement between RTVue SD-OCT and Stratus TD-OCT in healthy persons (circle) and glaucoma patients (triangle).

Retinal Nerve Fiber Layer Imaging with Spectral-Domain Optical Coherence Tomography

A Variability and Diagnostic Performance Study

Christopher Kai-shun Leung, MD, MBChB,[1] Carol Yim-lui Cheung, PhD,[1] Robert N. Weinreb, MD,[2] Quanliang Qiu, BM,[1,3] Shu Liu, MSc,[1] Haitao Li, PhD,[1] Guihua Xu, BM,[1,3] Ning Fan, BM,[1,4] Lina Huang, MD,[4] Chi-Pui Pang, DPhil,[1] Dennis Shun Chiu Lam, MD, FRCOphth

Ophthalmology 2009;116:1257–1263 © 2009 by the American Academy of Ophthalmology



A

Conclusions: Although the diagnostic performance and the strength of the structure–function association were comparable between Cirrus HD-OCT and Stratus OCT RNFL measurements, Cirrus HD-OCT demonstrated lower measurement variability compared with Stratus OCT with significant differences at 1, 3, 4, and 8 to 11 o'clock. The poor agreement was likely related to the different inherent characteristics of the 2 OCT systems.

Comparison of Retinal Nerve Fiber Layer Measurements Using Time Domain and Spectral Domain Optical Coherent Tomography

Ophthalmology 2009;116:1271–1277

O'Rese J. Knight, MD, Robert T. Chang, MD, William J. Feuer, MS, Donald L. Budenz, MD, MPH

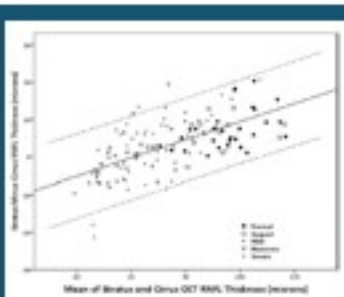


Figure 2. Bland-Altman plot of the agreement of mean retinal nerve fiber layer (RNFL) thickness between Stratus OCT and Cirrus OCT. The difference (Stratus OCT RNFL thickness – Cirrus OCT RNFL thickness) between both measurements is plotted against the average of both measurements (Stratus OCT RNFL thickness + Cirrus OCT RNFL thickness)/2. The line of equality (solid) is plotted with the 95% limits of agreement (dashed). OCT= optical coherence tomography.

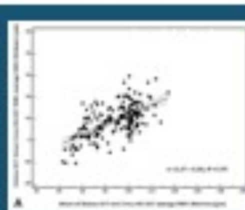


Table 2. Regression Conversions for Stratus to Cirrus

Location	Regression Formula: No Severe Glaucoma	Regression Formula: Severe Glaucoma	r^2	Residual Variance	Stratus Mean (μm)	95% Tolerance Interval Around a Predicted Cirrus Measurement
Mean RNFL	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Temporal	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Inferior	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Superior	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Nasal	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

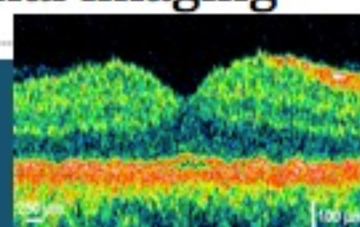
Conclusions: RNFL thickness measurements between Stratus OCT and Cirrus OCT cannot be directly compared. Clinicians should be aware that measurements are generally higher with Stratus than with Cirrus except when the RNFL is very thin, as in severe glaucoma. This difference must be taken into account if comparing Stratus measurements with Cirrus measurements.

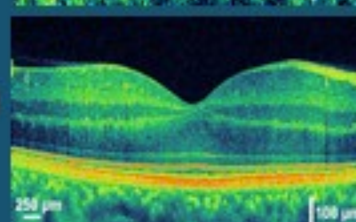
OCT technologies for retinal imaging

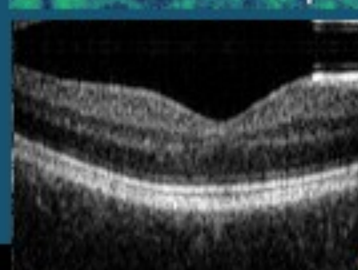
Time-domain OCT
- 400 axial scans per second
- 1 (500 pixel) image per second
- Zeiss StratusOCT

Spectral / Fourier domain OCT
- ~25,000 - 52,000 axial scans per second
- ~100 images per second
- >7 companies marketing instruments

Swept source / Fourier domain OCT
- ~250,000 axial scans per second
- ~500 images per second
- Resolution lower than spectral OCT
- Currently in the research stage







SD-OCT

- Limitations
  - The technology is young, still in evolution.
  - OCT imaging may be difficult in the presence of media opacities such as dense central corneal scarring, severe posterior subcapsular cataract, dense vitreous hemorrhage
  - SD-OCT still requires development of robust alignment and registration algorithms to approach its clinical potential

OCT in Glaucoma

- Optical Coherence Tomography (OCT) is a useful tool for the assessment of the presence or absence of glaucoma
  - Structure – function correlates
  - Identify areas of abnormality
  - Reduce uncertainty in Glaucoma Suspects
- 3D OCT imaging increases reproducibility, and may enhance sensitivity and specificity
- OCT statistical software for the measurement of glaucoma progression is still in the development and testing stage

The Future of OCT - Where Are We Going?

- Novel diagnostics are at hand for assessment of disease and its progression
- Current commercially available technology may be used in new ways to assess disease and progression

The Future of OCT - Where Are We Going?

- It is possible to measure more specifically and in more areas using SD-OCT than using TD-OCT, providing access to more sensitive macular and peripapillary assessment
- It may be possible to make use of legacy TD-OCT data in conjunction with SD-OCT
- The lamina cribrosa may prove a powerful target for glaucoma diagnostics, both in terms of structural imaging and assessment of laminar compliance

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