Imaging Glaucoma

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PITTSBURGH, PA USA

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.

As an inventor of Optical Coherence Tomography (OCT), Dr. Schuman receives royalties for intellectual property owned by MIT and licensed to Carl Zeiss Meditec, Inc., and has intellectual property owned by University of Pittsburgh and licensed to Bioptigen
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

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

<table>
<thead>
<tr>
<th>RNFL Parameters</th>
<th>Healthy Participants</th>
<th></th>
<th></th>
<th></th>
<th>Glaucoma Patients</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (95% CI)</td>
<td>Sw × 1.96 se CV %</td>
<td>ICC (95% CI)</td>
<td>Mean (95% CI)</td>
<td>Sw × 1.96 se CV %</td>
<td>ICC (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEMP (µm)</td>
<td>80.8 (77.4 to 83.8)</td>
<td>2.82 ± 0.52 3.54 0.02 (0.68 to 0.86)</td>
<td>71.2 (68.7 to 73.6)</td>
<td>3.36 ± 0.7 4.72 0.86 (0.61 to 0.91)</td>
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</tr>
<tr>
<td>SUP (µm)</td>
<td>120.6 (117 to 124.3)</td>
<td>3.8 ± 0.57 3.16 0.01 (0.66 to 0.84)</td>
<td>103.2 (99.6 to 106.8)</td>
<td>3.67 ± 0.59 4.53 0.93 (0.89 to 0.95)</td>
<td></td>
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</tr>
<tr>
<td>NAS (µm)</td>
<td>75.8 (72.9 to 78.7)</td>
<td>2.94 ± 0.44 3.88 0.01 (0.66 to 0.84)</td>
<td>68.6 (66.2 to 71.1)</td>
<td>3.22 ± 0.52 4.6 0.68 (0.63 to 0.92)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INF (µm)</td>
<td>134.3 (129.7 to 138.8)</td>
<td>3.53 ± 0.55 2.85 0.95 (0.92 to 0.97)</td>
<td>113.2 (108.9 to 117.4)</td>
<td>3.21 ± 0.48 2.87 0.96 (0.94 to 0.97)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>AVG (µm)</td>
<td>102.8 (100.1 to 105.6)</td>
<td>1.57 ± 0.27 1.54 0.97 (0.95 to 0.98)</td>
<td>89.1 (86.5 to 91.7)</td>
<td>1.69 ± 0.23 1.9 0.37 (0.36 to 0.96)</td>
<td></td>
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</tr>
</tbody>
</table>

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-subject 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.

**ARTICLE IN PRESS**

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 operating characteristic curves (AUROC) 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

<table>
<thead>
<tr>
<th>Glaucoma (n = 530)</th>
<th>GS (n = 480)</th>
<th>Healthy (n = 80)</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) ± SD</td>
<td>53.7 ± 12.9</td>
<td>53.3 ± 13.5</td>
<td>53.3 ± 12.6</td>
</tr>
<tr>
<td>MD (dB) ± SD</td>
<td>3.3 ± 5.66</td>
<td>2.9 ± 4.45</td>
<td>2.6 ± 5.48</td>
</tr>
<tr>
<td>PSD (dB) ± SD</td>
<td>5.5 ± 3.36</td>
<td>1.3 ± 2.24</td>
<td>1.4 ± 2.44</td>
</tr>
<tr>
<td>Average RNFL</td>
<td>102.3 ± 12.1</td>
<td>110.6 ± 13.5</td>
<td></td>
</tr>
<tr>
<td>Thickness by Stratus OCT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(µm) ± SD</td>
<td>72.2 ± 12.7</td>
<td>88.4 ± 17.8</td>
<td>95.3 ± 8.6</td>
</tr>
<tr>
<td>Average RNFL</td>
<td>102.3 ± 12.1</td>
<td>110.6 ± 13.5</td>
<td></td>
</tr>
<tr>
<td>thickness by Cirrus HD'OCT (µm) ± SD</td>
<td>81.8 ± 18.0</td>
<td>100.3 ± 12.1</td>
<td>110.6 ± 13.5</td>
</tr>
</tbody>
</table>

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.

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 Laura N. Vuong, BS,1 Yaeli Chen, PMD,4 Jonathan Liu, MS,4 James G. Fujimoto, PhD,5 Joel S. Schuman, MD,2 Jay S. Duker, MD2

• 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


Clinical Application of SD-OCT in Glaucoma

- Structure before function?
  - RNFL thickness “tipping point”
Characteristics of the study participants

<table>
<thead>
<tr>
<th></th>
<th>Healthy</th>
<th>Glaucoma</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=64</td>
<td>n=54</td>
<td></td>
</tr>
<tr>
<td>F/M</td>
<td>32/32</td>
<td>38/16</td>
<td>0.03</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>48.3 ± 16.2</td>
<td>64.6 ± 11.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VF MD (dB)</td>
<td>-0.58 ± 1.50</td>
<td>-3.56 ± 4.72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VF PSD (dB)</td>
<td>1.79 ± 1.29</td>
<td>4.67 ± 4.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OCT mean RNFL (µm)</td>
<td>90.1 ± 9.1</td>
<td>75.6 ± 14.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

VF: visual field, MD: mean deviation, PSD: pattern standard deviation, RNFL: retinal nerve fiber layer

The Tipping Point

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

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.

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

disc area = 3.95 mm²
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.

Progression Events: OCT versus HVF

OCT Serial Analysis

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: NI disc, C/D = 0.5x0.4; macula, vessels, and periphery nl
  - OS: Disc with IT RNFL wedge defect, C/D = 0.8x0.7; macula, vessels, and periphery nl
Case 6 – Humphrey Visual Fields GPA: OD

- No Progression

Rate of Progression: +0.2 ± 0.1 %/year (95% confidence)
Slope significant at P < 1%

2009
Case 6 – Humphrey Visual Fields GPA: OS

- No Progression

Rate of Progression: ~0.6 ± 0.7 %/year (95% confidence)
Slope not significant

<table>
<thead>
<tr>
<th>Date of GDx</th>
<th>6/13/06</th>
<th>12/5/06</th>
<th>6/5/07</th>
<th>12/4/07</th>
<th>9/2/08</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFI OD</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NFI OS</td>
<td>18</td>
<td>20</td>
<td>20</td>
<td></td>
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</tbody>
</table>
Moorfields Regression Analysis

Glaucoma Probability Score

Case 6 – HRT with TCA: OD

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 – GDx
GPA: OS

STRATUS OCT 9/2/08
OD OS
RNFL Thickness=52 RNFL Thickness=50
Case 6 – Stratus OCT GPA: OD

Rate of change: -3.993 ± 11.717 μ/year
Statistically not significant P > 5%

Case 6 – Stratus OCT GPA: OS

Rate of change: -0.812 ± 5.238 μ/year
Statistically not significant P > 5%
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
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


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 Ka-shan Lui, MD, MRCOphth,1 Carol Yee-lai Cheung, PhD,1 Robert N. Weinreb, MD,2 Quanping Qiu, BM,2 Shun-Liu, MD,2 Hanne L., PhD,2 Goh Bee, BM,2 Ning Fan, BM,2 Lina Huang, MD,2 Chi Pei Pang, DPht,1 Dennis Shiu Chiu Lam, MD, FRCOphth


Conclusions: Although the diagnostic performance and 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

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

Figures 2 and 3: Scatter plots of the agreement of mean retinal nerve fiber layer (RNFL) thickness between Stratus OCT and Cirrus OCT. The difference Stratus OCT mean thickness – Cirrus OCT mean thickness of both measurements is plotted against the average of both measurements. The line of equality (solid) is plotted with the 95% limits of agreement (shaded). "OCT" = optical coherence tomography.

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