I. **OCT in glaucoma: interpretation, diagnosis, and progression**

A. **Goals**
   1. Discuss analysis of optic nerve OCTs
   2. Review strengths and weaknesses of OCT for glaucoma
   3. Review research about OCT related to diagnosis and progression
   4. Provide tips for better OCT analysis in clinical practice

II. **OCT Overview**

A. **Available OCTs**
   1. Zeiss Cirrus, Heidelberg Spectralis, Topcon, RTVue, Zeiss Stratus, etc

B. **Spectral domain (SD) vs. time domain (TD)**
   1. Spectral also known as Fourier Domain
   2. Similarities/differences in databases
      a) Can’t directly compare progression between instruments
   3. SD-OCT advantages:
      a) Higher resolution, decreased scanning time
      b) Better repeatability of RNFL measurements
      c) More data – peripapillary scans with RNFL thickness maps, macular GC analysis, etc
      d) Better for diagnosis and progression vs TD, HRT, GDx

III. **Interpretation and Influential Factors**

A. **Guide to Interpreting Spectral Domain Optical Coherence Tomography** by Bruno Lumbroso, MD and Marco Rispoli, MD

B. **Normative databases**
   1. Stratus
      a) 328 subjects
      b) 48% male, 52% female
      c) Mean age 47.4 +/- 15.8 yrs, range 18-85
      d) Rx: -11.75 to +6.75, mean -0.54
      e) 63% Caucasian, 24% Hispanic, 8% African American, 11% Asian
      f) No eye surgery except cataract (9 pts), no ocular disease, IOP <22, normal and reliable VF, normal ONH, BCVA >20/32
   2. Cirrus
      a) 284 subjects
      b) 47% male, 53% female
      c) Age range 19-84
      d) Rx: -12 to +8
      e) 43% Caucasian, 18% African American, 12% Hispanic, 1% Indian, 6% mixed
      f) All normal subjects
   3. Spectralis
a) 201 subjects, all Caucasian  
b) 55% male, 45% female  
c) Mean age 48.2 +/- 14.5 yrs, Range 18-78  
d) Only 1 pt <20 and only 13 pts >70  
e) Rx: -7 to +5  
f) No glaucoma, normal IOP, normal VF, normal optic nerve, etc  

4. RTVue  
a) 861 subjects (largest of SD-OCT), various ethnicities  
b) Mean age 50 +/- 15.5 yrs, Range 19-82  
c) Rx: -8 to +8 sphere, -2 to +2 cylinder  
d) No glaucoma, normal IOP, normal VF, normal optic nerve, etc  

C. Average RNFL Thickness measurements  
1. Stratus  
a) Average 94-100um in Caucasian/Japanese  
b) Up to 132.7um in Hispanics  
2. Spectralis  
a) Thicker ppRNFL vs. Cirrus in same eyes  
b) Average 89-97.3um +/- 9.6-15.87um  
c) African American 99.2um, Caucasian 96um  
3. Cirrus  
a) Average 84-94um +/- 13.68  
b) Superior quad up to 122um, inferior quad up to 127um  
4. RTVue  
a) Average 107.9 +/- 10um  
b) African American 107um, Caucasian 102um  
5. Topcon  
a) Average 102um  

D. Red-Green disease  
1. Color code determined by the database of the instrument  
a) Based on probability of that population only  
2. 15-36% of OCTs for glaucoma may contain artifacts that influence red-green analysis  

E. Media/PVD effect scan quality  
1. Can significantly reduce quality of scans  
2. PCIOLs do not seem to have significant effect (Kim 2013)  

F. ONH size/Disc area  
1. Larger ONH means OCT scan is closer to ONH  
a) RNFL thickness decreases as measurement diameter increases  
b) Overestimates RNFL in some studies but not others  
2. Thicker RNFL measurements in larger ONH  
a) 3.3um per 1mm² (Budenz 2007)  
3. RNFL Thickness correlates with disc area (Hirasawa 2010, Japanese)  
4. No association between ONH size and RNFL thickness (AIGS 2012)  
5. Disc area measurements  
a) Cirrus  
   (1) Small: <1.66mm²  
   (2) Medium: 1.63-1.97mm²  
   (3) Large: >1.97mm²
(4) Only 5% of eyes in normal database were <1.33mm$^2$ or >2.5mm$^2$ with Cirrus
b) Stratus
   (1) 2.26mm$^2$ mean disc area
c) RTVUE
   (1) Range 1.86-2.1

G. ERM
1. Most common cause of artifact in RNFL determination
2. Improper segmentation on tomograms

H. PPA
1. Present in 15% of normals but 62-84% of glaucoma patients
2. Disc size variations between instruments
   a) Stratus overestimates disc size in glaucoma patients and controls
   b) Cirrus performs well compared to clinical disc evaluation

I. Axial length
1. Some studies found no correlation with axial length and RNFL thickness
   (Hirasawa 2010)
2. Others show total RNFL thickness decreases with increased axial length
   (2.2 um/1mm in Stratus)
3. If temporal quadrant is thick, superior and inferior thinning could be due to
   refractive error (Alasil 2012)
   a) 60.3% supernormal sectors in Japanese myopes, mostly temporal,
      indicating false positive (Yamashita 2014)
4. Be cautious of thinning in myopic Caucasians
5. Stratus database may be inaccurate (Vernon 2008)

J. ONH distance to foveola
1. High myopia: RNFL bundles converge causing abnormalities (Leung 2012)
2. Temporal or nasal deviated RNFL plot can over diagnose glaucoma
   a) Longer foveola to ONH distance – increased false positives

K. Other Factors
1. Rx: RNFL thinner by 1.2um/diopter of myopia
2. Race: RNFL decreases from Hispanics>Asians> African Americans>Caucasians
3. Patients with FOHx of glaucoma have thinner RNFL and GCC than normals
   (Rolle 2014)

L. Case examples to illustrate points throughout the presentation

IV. Glaucoma Diagnosis

A. Utility
1. RNFL loss precedes VF loss by 6 years in 60% of eyes (Sommer 1991)
2. In OHTS, HRT showed glaucomatous change 8 years before VF defects
3. 17% RNFL loss before VF detection (Wollstein 2012)
4. Progressive optic disc changes may not correspond to RNFL thinning in the
   same eyes with glaucoma progression

B. Glaucoma Detection
1. Both TD and SD have high sensitivity and specificity for glaucoma when
   >1 clock hour is <5% level (red)
2. Both TD and SD may be inadequate in detecting preperimetric RNFL defects
   a) Worse when defects <10 degrees
   b) Stratus has difficulty determining severity of glaucoma (Smith 2014)
3. Cirrus can discriminate mild glaucoma from normal based on ONH parameters
4. RNFL parameters:
   a) Average RNFL thickness*
   b) RNFL thickness at 7 o'clock* (3,4,9 are most variable)
   c) RNFL thickness inferior quadrant
   d) Global, sup-temporal and inf-temporal (Spectralis)
5. Additional helpful information:
   a) Cirrus – RNFL thickness map and deviation-from-normal map
      (1) Yellow if exceeds test-retest variability once
      (2) Red if exceeds on consecutive visits
   b) Stratus – TSNIT
   c) Asymmetry
6. Case Examples
C. Interocular symmetry
   1. Increasing age is not associated with increased RNFL asymmetry
   2. Cirrus: >9 um difference may be indicative of early glaucoma
   3. Spectralis: 6.6x greater asymmetry in glaucoma vs. normal
      a) Difference of 6um for RNGL global average had high sensitivity and specificity to detect POAG
      b) Use absolute RNFL thickness and RNFL asymmetry analyses
         (1) Asymmetry differences aren’t color coded (yet)
   4. Macular asymmetry has also proven sensitive and specific (Sullivan-Mee)
D. Progression considerations
   1. Variable nature of glaucoma
   2. Event-based vs. trend-based analyses
      a) Event: difference between baseline and follow-up measurements exceeds test-retest variability limit
      b) Trend: linear regression analysis of a parameter (i.e. average RNFL) over time showing negative slope
   3. Changing technology – longitudinal follow-up difficulties
      a) Spaeth prefers disc photo as gold standard
   4. Instrument variability
   5. No consensus on limit of RNFL thinning that equals progression; no reference standard
      a) In patients without VF loss, it is hard to determine if OCT structural changes are false positives or if they are structural change before functional change
E. Progression: Various methods
   1. Average RNFL thickness may be better than sector analysis with lower inter-test variation
   2. Significant negative trend in average RNFL thickness with time?
      a) -1.52um to -5.03um/year for Cirrus
   3. >1 clock hr at the <5% level?
   4. 1 clock hr at <5% and overall ‘borderline’ or ‘outside normal’?
F. Reliability and reproducibility
   1. Inter-visit repeatability is good for most SD-OCT
   2. Signal strength – 7 or greater desired
   3. Dilation – may not effect repeatability
   4. Variability vs. progression?

G. Variability vs. Progression
   1. Stratus: ~4-10um per quadrant
      a) Longitudinal changes up to 11.7um occur
      b) Be suspicious of changes over 10um
   2. Cirrus: >4-6um average RNFL between visits is suspicious
      a) 2 superpixels could show progression
   3. Spectralis: 5-14um intra- and inter-visit variation
      a) Clinically appears to have very low fluctuation
      b) -2.12um/yr in progressing pts vs. -1.18um/yr in stable pts

H. Suspected progression
   1. Variability:
      a) Average RNFL: ~5um
      b) By quadrant: ~8um
      c) By clock hour: ~10-12um
   2. Thinning of >10um (or maybe 20um) are more concerning, especially I/T and S/T
   3. Suspicious OCTs should be repeated

I. Case examples to illustrate inter-test variation

J. Recommendations
   1. Repeat OCTs before making treatment decisions
      a) 41-56% of abnormal scans were not duplicated on f/u exams
   2. Consider abnormal if 2 of 3 RNFL or GCIPL scans are borderline or ONL

V. Types of RNFL loss and analysis

A. Types of RNFL changes (Leung 2012 – Cirrus with GPA)
   1. Inferotemporal meridian is most common in glaucoma
      a) Widening of RNFL defect (85.7%)
      b) Development of new RNFL defect (17.9%)
   2. Other optic neuropathies can cause RNFL thinning, but patterns are different
   3. Age related thinning is most common superior and inferior

B. Rates of Change and Age-Related RNFL Loss
   1. Average rate: -0.10 to -0.52um /yr (1.5-2mm/decade)
   2. Greater baseline thickness = faster rate of change
   3. No significant change in nasal and temporal quadrants with age
   4. Rate in glaucoma is faster:
      a) -2.54 um/yr is significant (outside 95% confidence)

C. GPA for OCT
   1. Cirrus: GPA available for OCT or HVF or combined analysis for both
   2. Pros: OCT GPA on Cirrus is useful to judge progression when VF defect is mild
3. Cons: Agreement between OCT GPA and disc photos or VF analysis can be poor, subject to artifacts in scans, not yet fully validated
4. Example cases

VI. Macular OCT analyses for glaucoma

A. Macular OCT
   1. Utility in advanced glaucoma due to papillomacular bundle preservation
   2. Early glaucoma detection
      a) High discriminating power
      b) High reproducibility

B. Evidence of various patterns of macular damage

C. Macular vulnerability zone

D. Ganglion cell analysis (GCA)
   1. Macular RGC complex is 1-7 cells thick: RNFL, GCL and IPL
      a) GCIPL is less variable than RNFL and ONH
      b) Contains 50% of retinal RGCs
      c) Average RGC count is lower in eyes with early VF defects: 652K vs 911K (Medeiros 2013)
      d) RGC loss of 7877 per year (Medeiros 2012)
   2. Macular RGC counts can be affected by drusen and AMD
   3. GCIPL thinning with thinner RNFL, older age, longer axial length, and males
   4. GCIPL and total macular thickness (TMT) have similar sensitivity in detecting glaucoma progression
   5. Average RNFL was better in diagnosis
   6. Minimum GCIPL is best parameter for early perimetric glaucoma detection and is similar to best RNFL or ONH parameters (Mwanza, Jeoung)

E. Macular asymmetry analysis - Spectralis
   1. Glaucoma is likely when:
      a) Intereye macular thickness asymmetry >5 um
      b) Intraeye macular thickness asymmetry >9 um
      c) Intereye RNFL thickness asymmetry >9 um
      d) Global RNFL thickness <78 um

F. Ganglion cell asymmetry shows good diagnostic ability in early glaucoma (Cirrus)

VII. Conclusions

A. OCT is great technology but it isn't perfect
   1. Correlate HVF and OCT findings
   2. Currently there is no set standard for OCT progression

B. Evaluate scan data and not just colors
   1. Remember artifacts, instrument capabilities, etc

C. No set standard for OCT progression
   1. Research studies vs. clinical care

D. Repeat OCTs and correlate with other findings before making treatment decisions
VIII. References


