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I. OCT in glaucoma: interpretation, progression, and management

  A. Goals

      1. Discuss glaucoma diagnosis and progression in terms of OCT
      2. Review strengths and weaknesses of OCT for glaucoma
      3. Summarize 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 and ganglion cell (GC) analysis, etc
         d) Better for diagnosis and progression vs TD, HRT, GDx

  C. Measurement Boundaries

      1. Retina

         a) Inner boundary – ILM for all

         b) Outer boundary varies: Stratus – photoreceptor inner/outer segment interface, Topcon/Copernicus – inner RPE, Cirrus – outer RPE, RTVue – external RPE, Spectralis – **Bruch's (Giani, Grover 2010)**

      2. Disc margin

         a) Stratus reference – RPE/choriocapillaris plus 150 um above RPE
         b) SD-OCT – **Bruch's membrane is reference**

  D. Properties of selected OCTs

      1. Zeiss Stratus (Time Domain)

         a) 3.46 mm scan around ONH
         b) 400 axial scans/second
         c) 7-8um axial resolution
         d) Motion artifact/centration are difficult
         e) Widely used worldwide
         f) Many clinical trials

      2. Zeiss Cirrus (Spectral Domain or SD)

         a) $6 \times 6mm^2$ cube over ONH
         b) 200 B-Scans with 200 A-Scans each
         c) 27,000 axial scans/second
         d) 3.46mm circle over ONH for clock hour positions
         e) 5 micron axial resolution
         f) Cup/disc dimension measurements

g) Vert and horiz c/d, disc area, cup volume, etc

h) Thickness deviation maps: 50x50 superpixels

i) 92.1-98.3% sensitive for glaucoma detection (Leung 2010)

3. Heidelberg Spectralis (SD)

    a) 6 consecutive circular B-Scans

    b) 40,000 axial scans/second

    c) 12mm scan diameter

    d) 3.45-3.6mm scan around ONH

    e) Scan circle varies with axial length

    f) 3.9 micron axial resolution

4. Optovue RTVue-100 (SD)

    a) 5 micron axial resolution

    b) 26,000 axial scans/second

    c) 13 circular scans of 1.3-4.9mm diameter

    d) Eye tracking

E. Additional features of some SD-OCT

    1. FastTrack (Cirrus), FoDi (Spectralis), GPA – help follow over time

    2. Ability to manually adjust scans

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. 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

D. Average RNFL Thickness measurements
1. Stratus
a) Average 94-100um in Caucasian/Japanese
b) Up to 132.7um in Hispanics
c) OCT1 and OCT2: 86-153um
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

E. ISNT Rule
1. RNFL thickness on OCT usually matches neuroretinal rim appearance, but:
a) Only 42% of normals follow RNFL ISNT with Spectralis
b) Only 79% of normals with HRT
c) Only 28% of glaucoma pts with HRT
2. IST rule
a) 47.1% of normals follow ISNT, but 58.7% follow IST with Stratus
b) 25.9% of normals follow ISNT, but 70.4% follow IST with HRT
(1) Neither is very useful clinically

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

G. 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 1mm^2 (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: $<1.66mm^2$
              (2) Medium: $1.63\text{-}1.97mm^2$
              (3) Large: $>1.97mm^2$
              (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 $1.86\text{-}2.1mm^2$

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. ERM
1. Most common cause of artifact in RNFL determination

J. Peripapillary retinoschisis
1. Can cause false impression of thick RNFL
2. After resolution, can simulate glaucomatous thinning

K. 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)

L. 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
3. Spectralis FoDi example

M. 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)

N. 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 RNFL global average had high sensitivity and specificity to detect POAG
    b) Use absolute RNFL thickness and RNFL asymmetry analyses

(1) **Asymmetry differences aren't col**or coded (yet)

4. Macular asymmetry has also proven sensitive and specific (Sullivan-Mee)

O. Case examples to illustrate points throughout the presentation

IV. Glaucoma Diagnosis and Progression

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) 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 oclock (inf-temp, OD reference)
        (1) 3,4,9 are most variable
    c) RNFL thickness inferior quadrant
    d) Global, sup-temporal and inf-temporal (Spectralis)
5. ONH parameters:
    a) Vertical rim thickness (VRT)
    b) Rim area
    c) Vertical C/D (VCDR)
6. 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
7. Case Examples

C. 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) Dr. George Spaeth and others prefer disc photos 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

D. 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
b) -2.22um to -7.60um/year for Stratus

3. >1 clock hr at the <5% level?
4. **1 clock hr at <5% and overall 'borderline' or 'outside normal'?**

E. 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?
5. Test vs. re-test fluctuations

a) Stratus: ~4-10um per quadrant

(1) Longitudinal changes up to 11.7um occur
(2) Be suspicious of changes over 10um

b) Cirrus: >4-6um between visits is suspicious

(1) 2 superpixels could show progression

c) Spectralis: 5-14um intra- and inter-visit variation

(1) Clinically appears to have very low fluctuation
(2) -2.12um/yr in progressing pts vs. -1.18um/yr in stable pts

d) RTVue: 100% of RNFLT of normals remained normal over 4 years

F. Case examples to illustrate inter-test variation

G. 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. Patterns of RNFL loss on OCT

1. Diagnostic criteria: More than 1 clock hr at <5% level (yellow)

a) 90.5-96.6% sensitive on Cirrus
b) 85.7-91.4% sensitive on Stratus

2. Diagnostic criteria: Average RNFL thickness at <1% (red)

a) 44.4-72.4% sensitive on Cirrus
b) 33.3-60.3% sensitive on Stratus

3. RNFL deviation map was better than peripapillary RNFL measurements

B. Types of RNFL changes (Leung 2012 – Cirrus with GPA)

1. Widening of RNFL defect (85.7%)

a) Angular width of defects can be a useful alternative for RNFL average thickness

2. Deepening of RNFL defect

a) RNFL defect depth percentage index (RDPI) (Suh 2014)
  (1) New parameter on Cirrus RNFL thickness deviation map
  (2) Better discrimination than cpRNFL between mild and moderate RNFL defects, but not moderate and severe
3. Development of new RNFL defect (17.9%)
4. Inferotemporal meridian is most common in glaucoma
  a) ONH parameters, RNFL thickness and GCIPL thickness vary according to optic disc morphology and initial area of glaucomatous damage (Shin 2014)
5. Other optic neuropathies can cause RNFL thinning, but patterns are different
  a) Compressive optic neuropathy has nasal and temporal thinning

C. Rates of Change and Age-Related RNFL Loss
1. Average rate: -0.10 to -0.52um /yr (1.5-2mm/decade)
2. Influenced by baseline thickness
  a) Greater baseline thickness = faster rate of change
3. No significant change in nasal and temporal quadrants with age
4. Rates between normal and glaucoma pts vary:
  a) -0.17 to-0.86 um/yr is normal
  b) -2.54 um/yr is significant (outside 95% confidence)
5. **Highest progression rates in 6 o'clock sector of cRNFL (**-2.35 um/yr) and inferior outer sector of macula (-2.879 um/yr) (Na 2014)
  a) Perimetric glaucoma had higher rates than pre-perimetric
6. Rate of global RNFL loss was more than 2x as fast in those who developed VF defects (Miki 2014) (-2.02 um/yr vs. -0.82 um/yr)
  a) 1 um/yr faster RNFL loss = 2.05x risk of developing VF defect

D. Correlation between RNFL changes and VF defects
1. Low agreement for progression on both VF and OCT; 0.9 to 46.4% (Leung 2011, 2012)
2. OCT accuracy is effected by severity
  a) Better in more severe glaucoma (Leite 2010)
3. Faster rate of RNFL thinning by OCT than VF loss (Wollstein 2005)
4. Eyes that progress on VF have faster rate of RNFL loss on OCT (Grewal 2012)

E. Progression analysis software for OCT (GPA)
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
4. Example cases

VI.   Macular OCT analyses for glaucoma

A. Macular OCT
1. Utility in advanced glaucoma due to papillomacular bundle preservation
2. Macular OCT may be better for progression in moderate and severe glaucoma
  a) Other studies show RNFL average thickness is still better (Grewal 2013)

b) Macular thickness rate of change was higher than RNFL thickness change

                        (1) -2.43um/yr to -0.98um/yr, foveal rate highest

   B. 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. RGC counts performed better than average RNFL thickness for separating glaucomatous eyes with early/minimal VF loss from healthy eyes

        a) GCIP and GCC measurements are able to diagnose pre-perimetric glaucoma (Topcon)

        b) Pattern deviation on SAP may underdiagnose glaucoma cases that have diffuse loss of sensitivity

        c) However, macular RGC counts can be affected by drusen and AMD

      3. GCIPL and total macular thickness (TMT) have similar sensitivity in detecting glaucoma progression, but average RNFL was better in diagnosis (Na 2012)

      4. GCIPL thinning with thinner RNFL, older age, longer axial length, and males (Mwanza 2011)

      5. Minimum GCIPL is best parameter for early perimetric glaucoma detection and is similar to best RNFL or ONH parameters (Mwanza 2014)

      6. Macular GCA maps were useful in early glaucoma detection, but missed abnormal findings when angular distance from fovea to RNFL defect was large (Hwang 2014)

      7. Macular mean sensitivity on HVF and GCIPLT showed stronger correlation with worsening of glaucoma compared to pRNFLT (Kim KE 2014)

        a) Relationship was not established in preperimetric cases

VII. Considerations

   A. Problems with progression

      1. V**F testing isn't as good in early stages**

      2. OCT **isn't as good in late stages**

      3. Clinical trials show structural or functional changes can occur first

      4. Discrepancies in literature

        a) Only a moderate association between VF regions and RNFL thickness in glaucoma patients (Ferreras 2008)

        b) Agreement in progression detection between OCT of RNFL and ONH rim with VF is poor and rates vary considerably (Leung 2011)

        c) Linear relationship exists between VF and RNFL loss (Grewal 2009)

      5. Combining structural and functional tests may be the best technique (Medeiros 2012)

   B. Adjunct and future technology

      1. Enhanced depth imaging (EDI) – inverted image by moving SD-OCT closer to eye, can be used for choroid or lamina

      2. Swept source OCT (SS-OCT) – longer wavelength (150nm) and tunable laser can image retina and choroid together

      3. SD-OCT integrated with adaptive optics (AO-OCT) – corrects optical aberrations for better resolution

4. Polarization-sensitive SD-OCT – intrinsic tissue properties measured along with structure

5. Micro-OCT and ultra-high resolution OCT are coming with 1um resolution

6. These techniques are now allowing for excellent visualization of lamina cribrosa to see pores, displacement, etc.

VIII. Summary points

A. OCT is great technology but it isn't perfect

   1. OCT is validated for glaucoma diagnosis/screening and has been shown to be highly repeatable

B. Need to evaluate scan data and not just color codes

   1. Confounding factors, artifacts, instrument capabilities, etc

   2. Repeat OCTs before making treatment decisions

C. Progression can be judged many ways and they do not always agree

   1. Limitations due to slow, variable nature of glaucoma

   2. Currently there is no set standard for glaucoma progression on OCT

      a) Limited long-term follow-up data

   3. **OCT can't detect disc hemes, pall**or, etc so need to combine that information with clinical exam, disc evaluation and HVF

   4. Keep in mind limitations of normal database vs. monitoring changes in individual patients

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