I. What’s your GPA?: Glaucoma Progression using Visual Fields and OCT

A. Today’s Goals
   1. Discuss glaucoma progression without optic nerve evaluation
   2. Visual field use for staging glaucoma and determining progression
   3. Discuss strengths and weaknesses of OCT for glaucoma
   4. Review research on VF and OCT related to progression
   5. Provide tips for better VF and OCT analysis in clinical practice

B. Initial diagnosis of glaucoma
   1. Methods to determine glaucomatous damage
      a) Disc photos, visual fields, OCT, etc
   2. Definitions of glaucoma according to visual fields alone
      a) Hodapp-Parrish-Anderson (HPA) - Only need 1 of the following:
         - GHT: Outside normal limits on 2 VFs
         - Cluster of 3+ contiguous non-edge points p<5% and 1 point p<1%
      b) Clinical Trials - Both of the following required:
         - GHT: Outside normal limits
         - Cluster of 3+ contiguous non-edge points at 5% on pattern deviation
      c) Other authors have slight variations
   3. OHTS patient examples

II. Progression and Visual Field

A. Common glaucoma visual field patterns
   1. VF case examples
   2. Learning curve; age-matched normative database does not include first time test takers

B. Staging glaucoma based on visual field results
   1. Hodapp-Parrish-Anderson
      a) Baseline = 2 VFs
      b) Early defect – Must meet all 3:
         (1) MD > -6 dB
         (2) Less than 25% (18 pts) below 5% level and <10 pts below 1% on pattern deviation
         (3) No point in central 5° can be <15dB
      c) Moderate defect – Must meet all 4 below:
         (1) MD > -12 dB
         (2) Less than 50% (37 pts) below 5% level and <20 pts below 1% on pattern deviation
         (3) No point in central 5° is 0 dB
         (4) Only 1 hemifield has a point of <15dB within central 5°
      d) Severe defect – Only 1 necessary:
         (1) MD < -12 dB
         (2) More than 50% (37 pts) below 5% level and 20 pts below 1% on pattern deviation
         (3) Any point in central 5° is 0 dB
         (4) Both hemifields have points <15dB within central 5°
   2. Glaucoma staging system (GSS)
a) Adapted from HPA scale, Stage 0 to Stage 5  
b) More for research than clinical practice

3. AGIS, CIGTS, other trials, etc  
a) Not standardized  
4. Placing patients into stages can help assess for progression

C. Judging visual field progression
1. NO WIDELY ACCEPTED STANDARD!  
2. Most authors agree:  
a) Deepening or expansion of an existing scotoma  
b) New defect in a previously normal area  
3. 20% progress even with 30% ↓ in IOP  
4. 50% have no VF progression without tx  
5. Risk factor analysis

D. Major challenges  
1. Variations between clinical trials  
2. Individual patient fluctuations  
3. Need to differentiate progression from fluctuations in order to accurately treat

E. VF Progression HPA  
1. New defects  
a) 3 or more nonedge points ↓ >5dB or p<5%  
b) 1 nonedge point ↓ >10dB  
2. Deeping defects  
a) 3 or more nonedge points ↓ >10dB  
b) May be different if contiguous  
3. Expanding scotomas  
a) 2 points within central 15 deg or 3 points outside central 15deg ↓  
>10dB or p<5%

F. VF Progression in Clinical Trials  
1. AGIS – depth of defects  
a) Threshold total deviations ↓ 5-9dB  
b) Scored from 0-20  
c) Progression = 4+ increase from baseline  
d) 3 consecutive 6-month visits  
e) Worsening of 2+ locations in a GHT cluster  
f) 30% progressed  
2. CIGTS – probability  
a) Clusters of 3+ points within lowest 5%  
b) Scored from 0-20  
c) Better for earlier defects  
d) Progression = 3+ increase from baseline  
e) Baseline = 2 VFs  
f) Must confirm with 2 additional VFs  
g) CIGTS identifies progression 2x over AGIS  
3. EMGTS  
a) 3+ noncontiguous locations worsened on pattern deviation of GCP  
on 3 consecutive VF  
4. CNTGS
a) 2+ locations contiguous with existing defect worsened by 10+ dB (or 3x baseline STF)
b) New local defect = suspect progression
c) Confirm in 1-4 weeks and again at 3 months

5. Other definitions
   a) 1 point with >1dB loss per year (p<.01)
   b) Nasal edge points >2dB per year (p<.01)
       (1) Need 2 adjacent points in same hemi-field
   c) MD reduction of 2 dB from baseline on 2 of 3 consecutive visits
d)

G. Determining Progression
   1. Clinical judgment
   2. Defect classification systems - HPA, AGIS, CIGTS
   3. Event analysis - Greater change from baseline than expected
   4. Trend analysis - Rate over time
   5. MD change, VFI, GPA
   6. All have pros and cons!

H. Long-term fluctuations
   1. Examples of VF changes with time

I. Rate of progression
   1. "Disease progression rates in glaucoma vary very much among patients – and cannot be predicted even taking risk factors into account.” – Anders Heijl, 2011
   2. VF Progression – MD
      a) CNGTS: -0.41dB/yr
      b) EMGT: -0.36 to -1.08dB/yr
      c) OHTS: -0.08 dB/yr (-0.26 dB/yr in POAG pts)
      d) Low Pressure Glaucoma Study: -1 to -2dB/yr
      e) No association between rate of VF loss in dB and baseline VF mean deviation
      f) Important to determine a rate that is acceptable for a given patient
   3. Progression – Rates
      a) CNTGS: Untreated patients had a mean survival time to detectable progression of 1,695 days (4.6 years)
      b) EMGT: Untreated controls had a median time to progression of 4 years
         (1) 60% progress in 6 years
      c) Even in patients that end up legally blind, the rate of progression is 1 VF score every 3 to 4 years
d)
   4. Progression - OHTS
      a) At 5 years, 90.5% of untreated patients showed no ONH or VF progression
         (1) IOPs of 24-32mmHg
      b) Faster progression if VF endpoint was met
      c) 85.9% of eyes with initial VF defects had normal repeat VF
d)
   5. Confirming Progression
      a) AGIS – 12,746 VFs over 10-13 years
         (1) Sustained decreased VFs (SDVF)
         (2) VF can temporarily recover
(3) 55% with SDVF on 2 visits, 40% on 3 visits showed recovery 

b) Repeat VF at least once!
   (1) If VF score ↑ 2 or MD ↓ 2dB, confirmed by 1 VF in 6 months = glaucoma progression 
   (2) 1 retest = 72%, 2 retests = 84%

6. Visual Field Index (VFI)
   a) Summary index on 24-2 and 30-2 tests 
   b) Calculated by all test points in pattern dev’n 
      (1) Normal points (p>5%) = 100% 
      (2) Absolute defects (0 dB) = 0% 
   c) Reduced points = scored by depth and age norms 
   d) Eccentricity-weighted mean of scores 
   e) Expresses visual function as % of normal age VF 
   f) Resistant to cataract 
   g) Used to judge rate of progression 
      (1) VFI values of first 5 VFs can predict loss 
      (2) Median VFI progression = -1.5% per year

7. Guided (or Glaucoma) Progression Analysis (GPA)
   a) Calculates rate of progression from VFI 
      (1) 1-2 page summary report 
   b) Baseline exams at top 
   c) VF trends in middle 
   d) Current exam at bottom 
   e) Uses oldest 2 exams as baseline 
      (1) Can and should be changed*

J. How many VFs are needed? 
   1. OHTS: 3 consecutive, abnormal, reliable 
      a) Originally 2 VFs, but 66% then were WNL 
   2. HPA: 2 reliable for baseline 
   3. WGA: 2 reliable baseline in 6 months, then 2 more within 18 months 
   4. CIGTS: 2+ for confirmation 
   5. CNTGS: 2-3 in 1st month & 2-3 at 3 months 
   6. HVF algorithms: 2 to 6 for analysis

III. Progression on OCT

A. Utility
   1. RNFL loss precedes VF loss by 6 years in 60% of eyes (Sommer 1991) 
   2. 17% RNFL loss before VF detection (Wollstein 2012) 
   3. “It should be obvious that the presence of visual field loss by itself would obviate the need for using an imaging instrument to diagnose a disease in clinical practice.” - Lisboa, 2012

B. Available OCTs
   1. Zeiss Cirrus 
   2. Heidelberg Spectralis 
   3. Nidex 3000 
   4. Canon Copernicus 
   5. RTVue
6. Opko/OTI Spectral OCT/SLO
7. Topcon 3D-OCT
8. Zeiss Stratus (Time Domain)
9. HRT I-III
10. 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. Zeiss Stratus (Time Domain)
1. Time domain
2. 3.46 mm scan around ONH
3. 400 axial scans/second
4. 7-8um resolution
5. Motion artifact/centration are difficult
6. Widely used worldwide
7. Many clinical trials

E. Zeiss Cirrus (Spectral Domain or SD)
1. Spectral domain
2. 6x6mm² cube over ONH
3. 200 B-Scans with 200 A-Scans each
4. 27,000 axial scans/second
5. 3.46mm circle over ONH for clock hour positions
6. Cup/disc dimension measurements
7. Vert and horiz c/d, disc area, cup volume, etc
8. Thickness deviation maps: 50x50 superpixels
9. 92.1-98.3% sensitive for glaucoma detection (Leung 2010)

F. Heidelberg Spectralis (SD)
1. 6 consecutive circular B-Scans
2. 40,000 axial scans/second
3. 12mm scan diameter
4. 3.45-3.6mm scan around ONH
   a) Scan circle varies with axial length

G. Spectral domain vs. time domain
1. Similarities/differences in databases
   a) Color codes do not agree well
   b) Progression between instruments?
2. SD-OCT advantages:
a) Better repeatability of RNFL measurements
b) More data – peripapillary scans with RNFL thickness maps, macular GC analysis, etc
c) Better for diagnosis and progression

H. 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
3. Cirrus can discriminate mild glaucoma from normal
4. General:
   a) Cirrus – RNFL deviation-from-normal map
   b) Stratus – TSNIT

5. RNFL parameters:
   a) Average RNFL thickness*
   b) RNFL thickness at 7 oclock* (3,4,9 are most variable)
   c) RNFL thickness inferior quadrant
   d) Global, sup-temporal and inf-temporal (Spectralis)

6. ONH parameters:
   a) Vertical rim thickness (VRT)
   b) Rim area
   c) Vertical C/D (VCDR)

7. Case Example

I. Progression considerations
1. Variable nature of glaucoma
2. Event-based vs. trend-based analyses
3. Changing technology – longitudinal f/u
4. Instrument variability
5. No consensus on limit of RNFL thinning that equals progression; no reference standard

J. 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’?

K. 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. Stratus
   a) Test-retest variability of ~4-10um per quadrant
   b) Longitudinal changes up to 11.7um occur
   c) Be suspicious of changes over 10um
6. Cirrus
a) Thinning of >4-6μm between visits is suspicious  
b) 2 superpixels could show progression  

7. Spectralis  
a) Clinically appears to have very low fluctuation  
b) 5-14μm intra- and inter-visit variation  
c) -2.12μm/yr in progressing pts vs. -1.18μm/yr in stable pts  

IV. Influential Factors  
A. 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  

B. Average RNFL Thickness  
   1. Stratus  
      a) Average 99-100μm in Caucasian/Japanese  
      b) Up to 132.7μm in Hispanics  
      c) OCT1 and OCT2: 86-153μm  
   2. Spectralis  
      a) Average 97.3μm +/- 9.6μm  
      b) African American 99.2μm, Caucasian 96μm  
   3. Cirrus  
      a) Average 94μm  
      b) Superior quad up to 122μm, inferior quad up to 127μm  
   4. Topcon  
      a) Average 102μm  

C. ISNT Rule  
   1. RNFL thickness on OCT usually matches neuroretinal rim appearance, but:
a) 42% of normals with Spectralis
b) 79% of normals with HRT
c) 28% of glaucoma pts with HRT

D. Media/PVD
1. Can significantly reduce quality of scans

E. 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 <1.33mm² or >2.5mm² with Cirrus
   b) Stratus
      (1) 2.26mm² mean disc area
   c)

F. PPA
1. Present in 15% of normals but 62-84% of glaucoma patients
2. Stratus overestimates disc size in glaucoma patients and controls
3. Cirrus performs well compared to clinical disc evaluation

G. 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)
4. Be cautious of thinning in myopic Caucasians
5. Stratus database may be inaccurate (Vernon 2008)

H. 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

I. 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:
J. Other Factors
1. Rx: RNFL thinner by 1.2um/diopter of myopia
2. Race: RNFL decreases from Hispanics>Asians>African Americans>Caucasians
   a) Differences in ONH area, ave C/D, vert C/D, cup volume also

K. Interocular symmetry
1. >9 um difference may be indicative of early glaucoma

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
3. Development of new RNFL defect (17.9%)
4. Inferotemporal meridian is most common in glaucoma
5. Age related thinning is most common superior and inferior

C. 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)

D. GPA for OCT
1. Cirrus: GPA available for OCT or HVF or combined analysis for both
2. Faster rate of RNFL loss in patients with thicker baseline RNFL
3. Pros: OCT GPA on Cirrus is useful to judge progression when VF defect is mild
4. Cons: Agreement between OCT GPA and disc photos or VF analysis can be poor
5. Example cases

E. Macular OCT
1. Useful in advanced glaucoma
a) Papillomacular bundle preservation
2. Macular OCT may be better for progression in moderate and severe glaucoma
3. Other studies show RNFL average thickness is still better (Grewal 2013)
4. Macular thickness rate of change was higher than RNFL thickness change
   a) -2.43um/yr to -0.98um/yr, foveal rate highest

F. Ganglion cell analysis
   1. Macular RGC complex is 1-7 cells thick: RNFL, GCL and IPL
      a) Contains 50% of retinal RGCs
      b) Average RGC count is lower in eyes with early VF defects: 652K vs 911K (Medeiros 2013)
      c) 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) Pattern deviation on SAP may underdiagnose glaucoma cases that have diffuse loss of sensitivity
      b) 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)

G. Problems with progression
   1. VF 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)

H. Combining structure and function
   1. Clinical trials show structural or functional changes can occur first
   2. Combining structural and functional tests may be the best technique (Medeiros 2012)

I. Future technology
   1. Swept source OCT
   2. SD-OCT integrated with adaptive optics
   3. Polarization-sensitive SD-OCT

VI. Summary points
   A. Progression can be judged many ways and they do not always agree
      1. Limitations due to slow, variable nature of glaucoma
   B. Visual fields are highly variable
      1. No set standard for VF progression
      2. Need to determine glaucomatous VFs and confirm defects (2x)
   C. OCT is promising but not perfect
1. Currently there is no set standard for OCT progression either
   a) Limited long-term follow-up data
2. Need to evaluate scan quality, instrument variability, etc
3. Keep in mind limitations of normal database vs. monitoring changes in
   individual patients

VII. References

1. Nduaguba C, Lee RK. Glaucoma screening: Current trends, economic
   issues, technology, and challenges. *Curr Opinion in Ophthalmol*
   2006;17:142-152.
   Doyle J. Categorizing the stage of glaucoma from pre-diagnosis to end-stage
3. Caprioli K, Zeyen T. A critical discussion of the rates of progression and
   causes of optic nerve damage in glaucoma: International glaucoma think tank
   Research and Opinions*, 2009;125(9):2167-2177.
6. Bengtsson B, Heijl A. False-negative responses in glaucoma perimetry:
   2000;41:2201-2204.
7. Bengtsson B, Patella VM, Heijl A. Prediction of glaucomatous visual field
   loss by extrapolation of linear trends. *Arch Ophthalmol*, 2009;127(12):1610-
   1615.
8. Brusini P, Johnson CA. Staging functional damage in glaucoma: Review of
9. Foster PJ, Buhrmann R, Quigley HA, Johnson, GJ. The definition and
10. Heijl A. Visual field changes in early glaucoma and how to recognize them.
12. Drance SD, Anderson DR, Schulzer M (For the collaborative normal-tension
    glaucoma study group). Risk factors for progression of visual field
    708.
13. Sample PA. What does functional testing tell us about optic nerve
14. Spry PGD, Johnson CA (Zarbin M, Chu D eds). Identification of
    progressive glaucomatous visual field loss. *Surv Ophthalmol*,
15. Giangiacomio A, Garway-Heath D, Caprioli J. Diagnosing glaucoma
    progression: Current practice and promising technologies. *Curr Opinion in
16. Chauhan BC, Garwaw-Heath DF, Goni FJ, Rossetti L, Bengtsson B,
    Viswanathan AC, Heijl A. Practical recommendations for measuring rates of
    Caprioli J. Predictive factors for glaucomatous visual field progression in the


42. Yim SY, Park HL, Park CK. The effects of peripapillary atrophy on the diagnostic ability of Stratus and Cirrus OCT in the analysis of optic nerve head parameters and disc size. IOVS, 2012;53:4475-4484.
47. Jeoung JW, Park KH. Comparison of Cirrus OCT and Stratus OCT on the ability to detect localized retinal nerve fiber layer defects in preperimetric glaucoma. IOVS, 2010;51:938-945.
54. Huang D, et al. for the Advanced Imaging for Glaucoma Study (AIGS) Group. Does optic nerve head size variation affect circumpapillary retinal
nerve fiber layer thickness measurement by optical coherence tomography? IOVS, 2012;53:4990-4997.


