Use of OCT in glaucoma management

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Overview

1. Brief introduction to glaucoma
2. How OCT can aid diagnosis
3. Potential pitfalls
4. A systematic approach to OCT interpretation
5. How OCT can help detect (and quantify) progression

What is glaucoma?

A group of chronic progressive optic neuropathies with characteristic morphological changes to the optic nerve head and retinal nerve fibre layer associated with progressive retinal ganglion cell death and visual field loss

European Glaucoma Society

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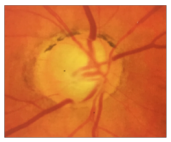

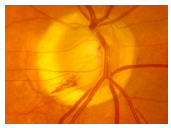

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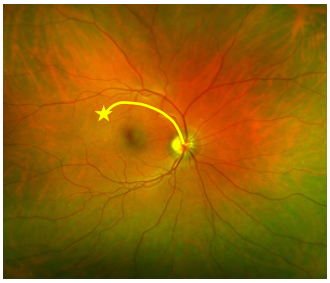

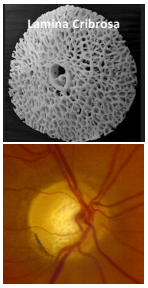

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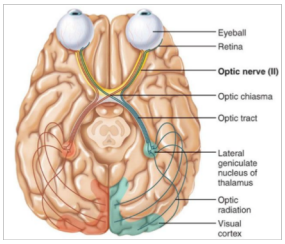

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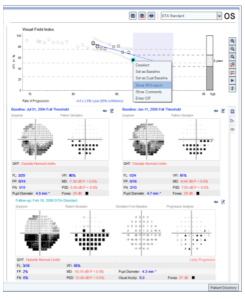
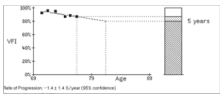
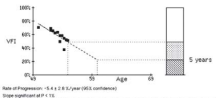


Low lifetime risk



High lifetime risk



What the patient sees

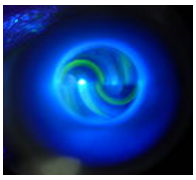
Risk Factors

Modifiable

- Intraocular Pressure
  - But…20% (Baltimore[1]) to 2/3 (Japan[2]) have IOP < 21 mmHg

Non-modifiable

- Thin central corneal thickness[3]
- Low corneal hysteresis[4]
- Myopia
  - 1.9 x higher odds (95% CI 1.5 to 2.4)[5]
  - High myopia (>6D) OR 5.7 (95% CI 3.1 to 11)



1. Sommer A, et al. Arch Ophthalmology 1991; 109: 1090-5.
2. Iwase A, et al. Ophthalmology 2004; 111: 1641-8.
3. Gordon MO, et al. Arch Ophthalmol. 2002;120:714–720.
4. Medeiros F, et al. Ophthalmology 2013; 120:1553-40.
5. Marcus MW, et al. Ophthalmology 2011;118:1989-94.

Risk Factors

Non-ocular risk factors

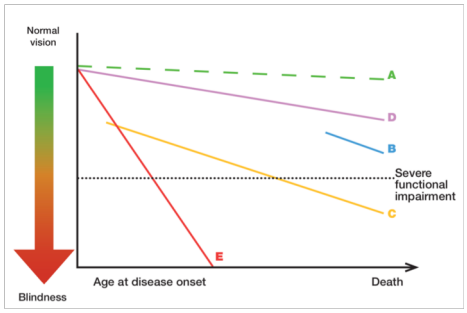
Age	% Prevalence[1]	Age	% Prevalence[13]
≥80	7.8 (5.2–12)		
70–79	5.1 (3.6–7.2)	70	3.3 (2.5–4.0)
60–69	3.7 (2.7–5.0)	60	1.4 (1.0–1.9)
50–59	2.2 (1.6–3.0)	50	0.9 (0.6–1.3)
40–49	1.3 (0.9–1.9)	40	0.3 (0.1–0.5)
30–39	1.6 (0.7–3.8)		
Black ethnicity	Age-adjusted prevalence %[1]	Odds ratio[1]	Relative risk Over 40 years[13]
	7.5 (6.8–8.4)	2.9 (1.4–5.9)	3.8 (2.56–5.64)
Family history in a first-degree relative	Age-adjusted odds ratio[1]		Age-adjusted relative risk[13]
	3.3 (2.0–5.6)		3.14 (2.32–4.25)
Diabetes	Odds ratio[1]		Relative risk[13]
	1.8 (1.4–2.4)		1.93 (1.38–2.69)
Hypertension	Odds ratio[1]		
	1.8 (1.4–2.3)		
Peripheral vascular disease	Odds ratio[1]		
	2.1 (0.83–5.3)		

SIGN 144 - Glaucoma referral and safe discharge

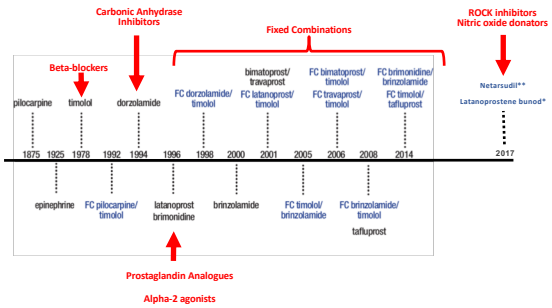
1. Hollands H, et al. JAMA 2013;309:2035-42.

Treatment

The goal of glaucoma treatment is to minimise the lifetime risk of visual impairment balanced with need to minimise harm from treatment



Eye Drops



*FDA Approved – 2nd November 2017
**FDA Approved – 18th December 2017

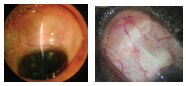
Selective Laser Trabeculoplasty (SLT)

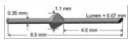
Surgical Options

Subconjunctival

Ab externo

Trabeculectomy, NPGS
Big tubes (Ahmed, Baerveldt)
InnFocus MicroShunt (Santen)





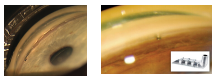
Ab interno

Xen (Allergan)

Canal based

Trabecular bypass

iStent (Glaukos), iStent inject (Glaukos)
Hydrus Microstent (Ivantis)



Trabecular ablation

Trabectome (NeoMedix)

Trabecular removal

Kahook Dual Blade (New World Medical)

Ab interno trabeculotomy

GATT, Trab 360

Dilation of Schlemm canal

Ab interno canaloplasty (ABiC)

Supraciliary

Ab interno

Cypass (Alcon)
iStent Supra (Glaukos)

Cyclodestructive

Ab interno

ECP

Ab externo

CPC

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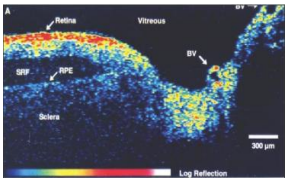
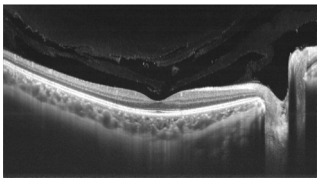
5. How OCT can help detect (and quantify) progression

Optical coherence tomography

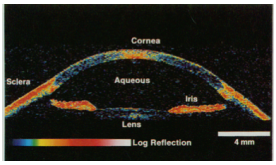
1991 **2018**





Huang D, Swanson EA, Lin CP, et al. Science 1991.

1994 2018

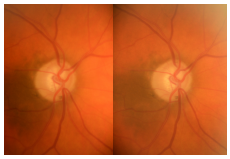


First anterior segment OCT

Anterior segment Swept Source OCT

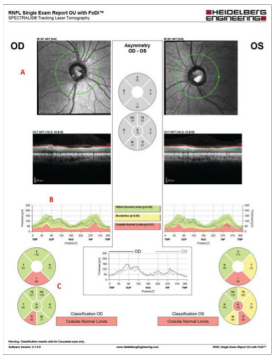
Izatt et al. 1994

Structural assessment before OCT

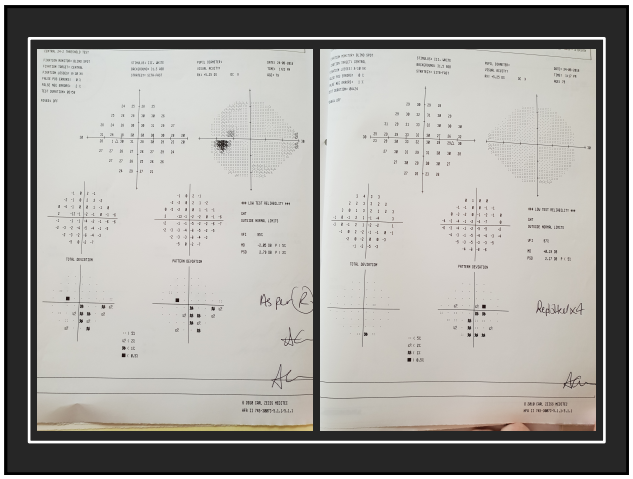


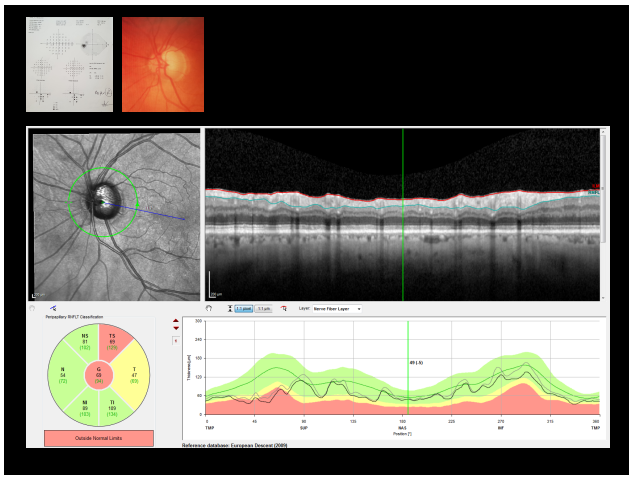
Diagnosis (Classification)

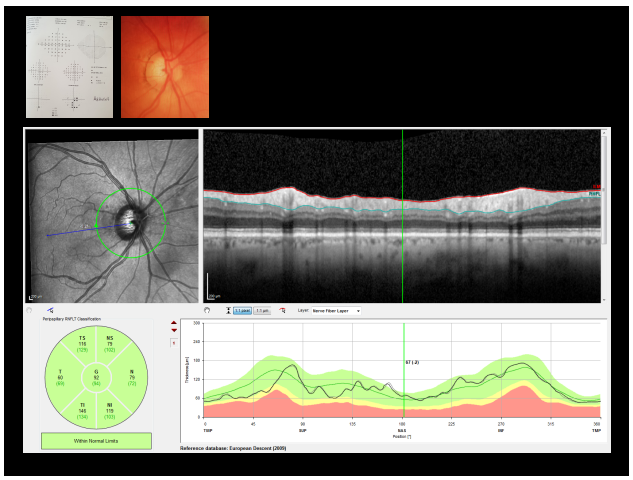
1. Retinal nerve fibre layer (RNFL)



Is this glaucoma?



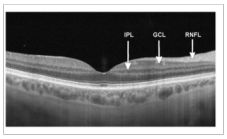




Diagnosis (Classification)

2. Macula

- Central 8 degrees
- <2% of retinal area but >30% of RGCs
- Less inter-individual variability than ONH
- Often involved early in disease[1,2]

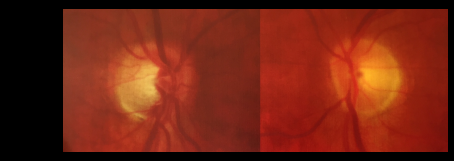


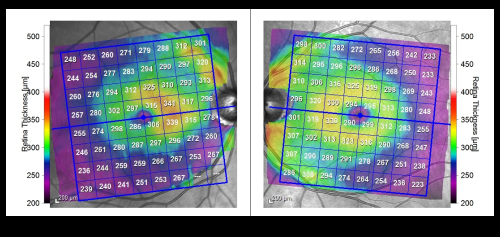
	Cirrus HD-OCT	Spectralis OCT	RTVue FD-OCT	Topcon 3D-OCT	Swept-source DRI OCT	RS-3000 OCT
Manufacturer	Carl Zeiss Meditec, Dublin, California	Heidelberg Engineering, Hildelberg, Germany	Optovue, Fremont, California, USA	Topcon, Tokyo, Japan	Topcon, Tokyo, Japan	Nidek, Gamagori, Japan
Scan speed (A-scans/s)	27 000	27 000	26 000	27 000	100 000	53 000
Axial resolution (µm)	5	3.9	5	5–6	20	7
Transverse resolution (µm)	15	14	15	20	8	20
Grid dimensions (mm)	6×6	8×8	7×7	6×6	12×9 (wide scan)	9×9
Centre	Fovea	Fovea	1 mm temporal to the fovea	Fovea	Fovea	Fovea
Measurement layer	GCL+IPL	Separate measurement of entire retinal layers	GCL+IPL+RNFL	RNFL/GCL+IPL/GCL+IPL+RNFL	RNFL/GCL+IPL/GCL+IPL+RNFL	GCL+IPL+RNFL

Ganglion cell analysis (GCA) — **Ganglion cell complex (GCC)**

1. Traynis I, et al. JAMA Ophthalmology 2014; 132:3:291-7.
2. Kim KE, Park KH, Macular Imaging by OCT in the diagnosis and management of glaucoma. BJO 2017, in press.

Is this glaucoma?





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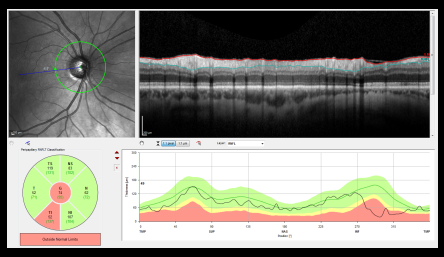
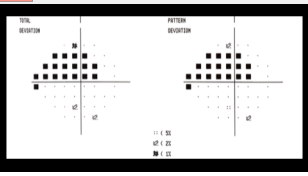




What's the evidence? - RNFL

Study	Eyes	Mean deviation (dB)	Device	Area under the curve
Leung et al 2009	83 Glaucoma 97 Healthy	-10.36	Cirrus	0.962
Leung et al 2010	79 Glaucoma 76 Healthy	-10.36	Spectralis	0.978
Mwanza et al 2011	73 Glaucoma 146 Healthy	-10.4	Cirrus	0.95
Leite et al 2011	126 Glaucoma 107 Healthy	-5.85	Cirrus Spectralis RTVue	0.88 0.88 0.87
Mwanza et al 2012	58 Glaucoma 99 Healthy	-3.2	Cirrus	0.94
Sung et al 2012	144 Glaucoma. 109 Healthy	-2.54	Cirrus	0.943
Takayama et al 2012	38 Glaucoma 48 Healthy	-2.33	Cirrus	0.89
Lisboa et al 2012	48 PPG 86 Healthy	-0.63	Spectralis	0.86
Lisboa et al 2013b	48 PPG 94 Healthy			
Jeoung et al 2014	164 Glaucoma 119 Healthy			
Begum et al 2014	21 PPG 53 Healthy			

Limitations

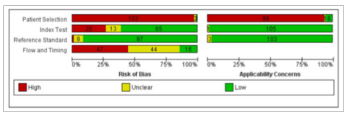
- Case-control design over-estimates accuracy
- Strict inclusion criteria and case definitions
- Did not evaluate normative databases
- Different reference standards
- Excluded poor quality OCT

Cochrane Database of Systematic Reviews

Optic nerve head and fibre layer imaging for diagnosing glaucoma

Cochrane Library

- 63 (9390 participants)
- All studies had high risk of bias due to case-control design



Conclusion

- Further case-control studies are not useful
- Future studies should evaluate OCT within a specific care pathway

Glaucoma Automated Tests Evaluation (GATE)

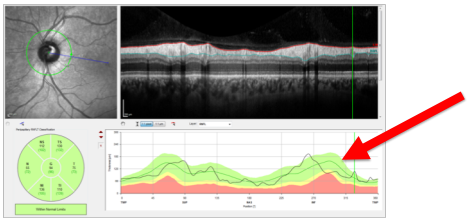
Automated imaging technologies for the diagnosis of glaucoma: a comparative diagnostic study for the evaluation of the diagnostic accuracy, performance as triage tests and cost-effectiveness (GATE study)

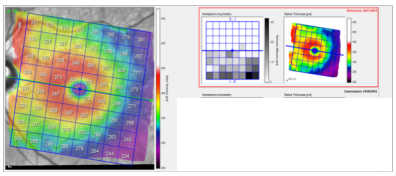
Augusto Azuara-Blanco, Katie Banister, Charles Boachie, Peter McMeekin, Joanne Gray, Jennifer Burr, Rupert Bourne, David Garway-Heath, Mark Batterbury, Rodolfo Hernández, Gladys McPherson, Craig Ramsay and Jonathan Cook

- 966 patients referred due to suspected glaucoma or OHT
- Reference standard = diagnosis by glaucoma expert (without imaging)
- RNFL global classification `outside normal limits' AUC = 0.83

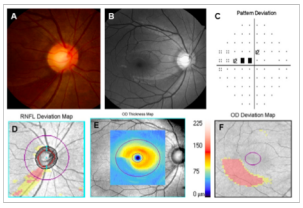
77% sensitivity for 79% specificity

1. Azuara-Blanco A, et al. Health Technology Assessment 2016; 8:1-168.
2. Virgili G, et al. BJO 2017; in press.

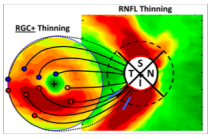




Glaucoma typically affects the inferotemporal and superotemporal RNFL first…



…and the inferotemporal macula (macular vulnerability zone)



1. Hood DC, et al. Glaucomatous damage of the macula. Prog Ret Eye Res. 2013; 32C: 1-21.

What's the evidence? - Macula

Study	Eyes	Mean deviation (dB)	Device	Parameter	AUC
Mwanza et al 2012	58 Glaucoma 99 Healthy	-3.2	Cirrus	Rim area cpRNFL thickness mGCIPL thickness	0.91 0.94 0.94
Takayama et al 2012	38 Early Glaucoma 48 Healthy	-2.33	Cirrus	RNFL thickness mGCIPL thickness Minimum mGCIPL	0.89 0.82 0.90
Lisboa et al 2013b	48 Preperimetric Glaucoma 94 Healthy	-0.81	RTVue	Rim area RNFL thickness mGCC thickness	0.72 0.89 0.79
Jeoung et al 2014	164 Early Glaucoma 119 Healthy	-2.68	Cirrus	Rim area RNFL thickness mGCIPL thickness Minimum mGCIPL	0.86 0.90 0.82 0.90
Begum et al 2014	21 Preperimetric Glaucoma 53 Healthy	-1.9	Cirrus	Rim area RNFL thickness mGCIPL thickness	0.85 0.79 0.59

Macular versus Retinal Nerve Fiber Layer Parameters for Diagnosing Manifest Glaucoma

A Systematic Review of Diagnostic Accuracy Studies

Francesco Oddone, MD,[1] Evelin Lucenteforte, ScD, PhD,[2] Manuele Michelessi, MD,[2] Stanislao Rizzo, MD,[3] Simone Donati, MD,[4] Mariacristina Parravano, MD,[5] Gianni Virgili, MD[6]

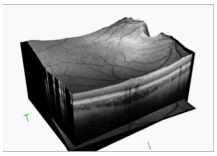
Conclusion

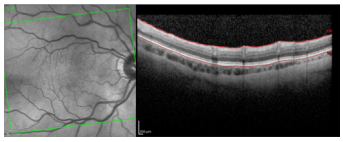
- RNFL parameters are still preferable to macular parameters but the differences are small
- Macular scans will detect damage in some eyes missed on RNFL (and vice versa)

OCT Device	Parameter	No. of Direct Studies (No. of Patients)	Sensitivity (95% CI)	Specificity (95% CI)	Relative DOR (95% CI)	*P* Value
RTVue	RNFL average	17 (2704)	0.66 (0.57–0.74)	0.95 (0.92–0.96)	Reference	Reference
	GCC average		0.60 (0.50–0.69)	0.94 (0.92–0.96)	34.06 (22.14–52.39)	0.0451
3D Topcon	RNFL average	4 (520)	0.64 (0.56–0.71)	0.93 (0.87–0.97)	0.69 (0.47–0.99)	Reference
	GCC average		0.66 (0.58–0.73)	0.90 (0.82–0.95)	Reference 24.71 (11.03–55.35)	0.3802
Cirrus	RNFL average	9(1454)	0.69 (0.60–0.77)	0.94 (0.91–0.96)	0.73 (0.36–1.48)	Reference
	GCIPL average		0.62 (053–0.71)	0.92 (0.89–0.94)	Reference 32.29 (19.85–59.24)	0.0068
					0.54 (0.35–0.84)	

Limitations of macular imaging

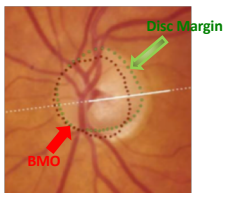
- Doesn't capture information about state of whole retina
- Affected by age, axial length, comorbidities[1]
- Difficult to confirm by clinical examination

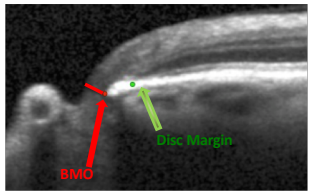




1. Mwanza JC, et all. Profile and predictors of normal ganglion cell-inner plexiform layer thickness measurement with cirrus HD-OCT in normal, hypertensive and glaucomatous eyes. BJO 2014;98:322-8.

Bruch's membrane opening (BMO)





- BMO-MRW = Minimum distance between BMO and ILM
- Smallest area through which nerve fibers must pass from the retina to the optic nerve

1. Reis A, et al. IOVS 2012; 1852-1860.
2. Chauhan B, et al. Ophthalmology 2013; 535-543.

Learning Points

1. OCT is useful for aiding diagnosis but cannot be relied on alone
2. RNFL is preferred but performing RNFL alone will miss some patients with macular damage…but performing more tests will lead to more false positives
3. Don't rely on average measurements as this will lead to localized changes being missed – need to look at the whole scan
4. The location of damage can provide important clues as to whether changes are due to glaucoma or not

Overview

1. Brief introduction to glaucoma
2. How OCT can aid diagnosis
3. Potential pitfalls
4. A systematic approach to OCT interpretation
5. How OCT can help detect (and quantify) progression

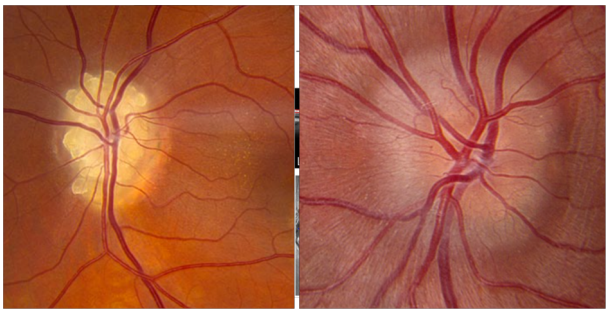
Potential Pitfalls

1. Other diseases can cause OCT abnormalities
2. Artefact
3. Limitations of the normative databases

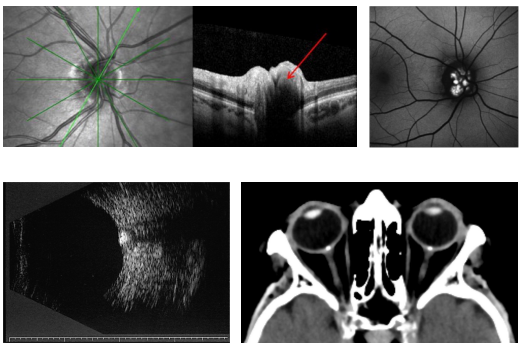
Potential Pitfalls

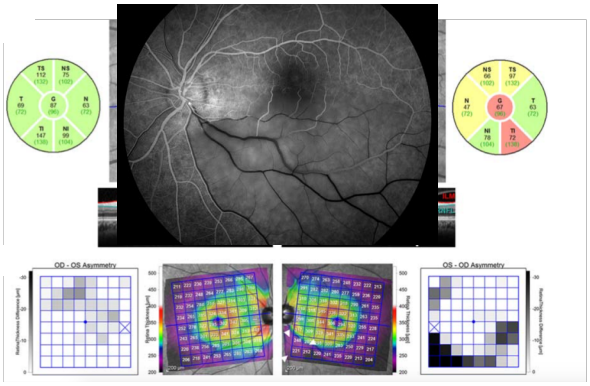
1. Other diseases can cause OCT abnormalities

- **Non-glaucomatous optic neuropathies**
  - Congenital
  - Compressive
  - Inflammatory
  - Anterior ischaemic optic neuropathy (AION)
  - Traumatic
  - Toxic
- **Other ocular diseases**
  - Epiretinal membrane
  - Vitreo-retinal traction
  - Retinal vascular disease – BRAO, BRVO
  - Optic disc drusen
- **Neurological diseases**
  - Stroke
  - Alzheimer's disease
  - Multiple sclerosis
  - Tumour



Optic Disc Drusen





Don't interpret OCT in isolation…always start with history and examination

Examination findings suggesting a non-glaucomatous optic neuropathy

- RAPD
- Impaired colour vision
- Pallor > Cupping
- Visual field loss respecting the vertical midline
- Symmetry
- Progressing despite low IOP
- Poor agreement between structural and functional changes

Potential Pitfalls

1. Other diseases can cause OCT abnormalities
2. Artefact
   - Spectralis OCT RNFL scans (software version 4.0)
   - Artefact in 46% (of 2,313 eyes)

     1. De-centration (28%)
     2. Error associated with posterior vitreous detachment (14%)
     3. Posterior RNFL misidentification (8%)
     4. Poor signal (5%)
     5. Anterior RNFL misidentification (3%)
     6. Missing parts (2%)
     7. Peripapillary atrophy associated error (1%)
     8. Incomplete segmentation (1%)
     9. Motion artefact (<1%)
     10. Cut-edge (<1%)

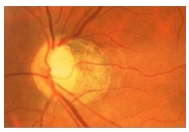
Liu Y, et al. Patient characteristics associated with artifacts in Spectralis optical coherence tomography imaging of the RNFL in glaucoma. AJO 2015;159:565-76.

Potential Pitfalls

1. Other diseases can cause OCT abnormalities
2. Artefact
3. Limitations of the normative databases

Myopia

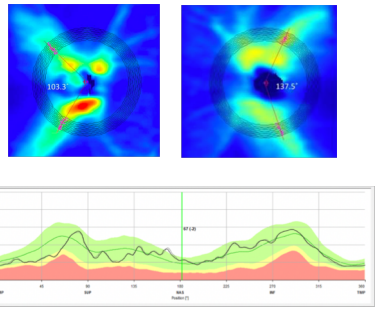
- Cirrus normative database has mean error of -0.82 D (271 subjects)
- Atypical disc appearance common[1]
  - Peripapillary atrophy (81%)
  - Optic nerve head tilt (57%)
- **High rate of false positives on OCT (red disease)[2]**



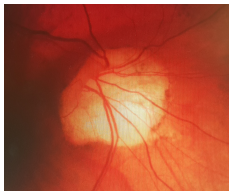
1. Chang L, et al. Myopia-related fundus changes in Singapore adults with high myopia. AJO 2013;155:991-999.
2. Vernon SA, et al. Peripapillary retinal nerve fibre layer thickness in highly myopic Caucasians as measured by Stratus optical coherence tomography. BJO 2008;92:1076-80.

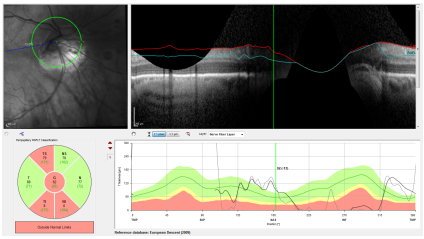
Temporal displacement of the arcuate bundles

-6.75D -2.00D



1. Leung CK, et al. IOVS 2012; 53:7194-7200.
2. Kang S H, et al. IOVS 2010; 51: 4075-4083.





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A systematic approach

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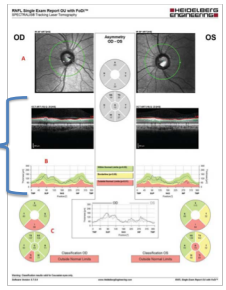
8. Look at the TSNIT plot for localised thinning
9. Look at the position of the arcuate bundles (myopia)
10. Compare to the other eye
11. Compare to visual field – is there agreement between structure and function?
12. Look at the pattern of changes – MVZ, IT and ST RNFL

The most important part of the report



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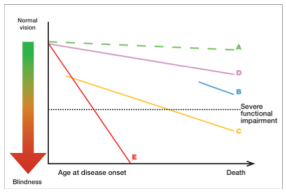
What is glaucoma?

A group of chronic progressive optic neuropathies with characteristic morphological changes to the optic nerve head and retinal nerve fibre layer associated with progressive retinal ganglion cell death and visual field loss

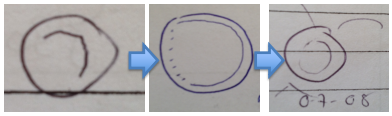
European Glaucoma Society

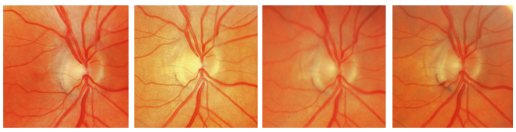
Reasons to detect (and quantify) progression

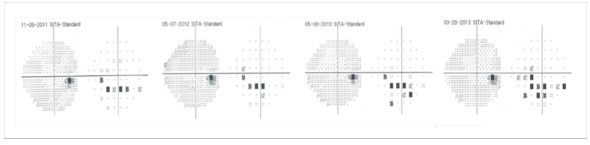
1. To estimate lifetime risk of visual impairment
2. To determine if treatment is effective
3. To aid diagnosis in early disease



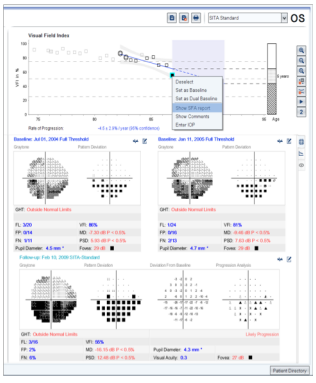
Detecting Progression



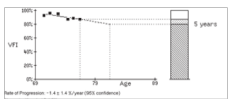




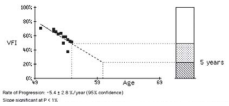
Trend and event based progression analysis



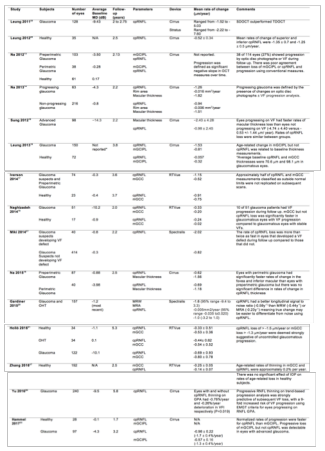
Low lifetime risk



High lifetime risk



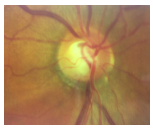
There are a large number of longitudinal OCT studies examining progression in glaucoma

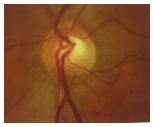


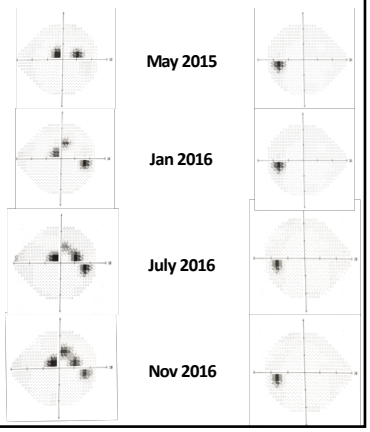
Tatham AJ, et al. Detecting structural progression in glaucoma using OCT. Ophthalmology 2017.

Case

- 57 year old GP
- Diagnosed POAG May 2015
- Presenting IOP 23/21 mmHg
- CCT – 560 OD / 558 OS
- Medical treatment → IOP 15 mmHg OU







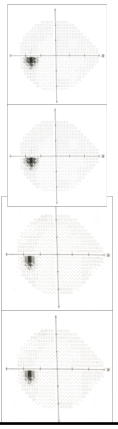
May 2015

Jan 2016

July 2016

Nov 2016

Case



Questions about progression

1. How much change on OCT is needed to be confident it is genuine?
2. If this is genuine change why is the visual field not changing?
3. Given that the visual field is normal does change on OCT matter?

True change versus noise

- OCT has high short-term reproducibility[1]
- Average RNFL: ICC = **98.6% intra-visit**
  97.2% inter-visit
- Global RNFL thinning of **at least 4 µm** should be considered as significant change

Age-related change

- Mean rates of change in RNFL[2]
  - **0.52 µm/year** (average) (95% CI 0.86 to 0.17)
  - 1.35 µm/year (superior)
  - 1.25 µm/year (inferior)
- 5% lower limit = -0.92 µm/year[3]

1. Mwanza et al. IOVS 2010; 51: 5724-30.
2. Leung et al. Ophthalmology 2012; 119: 731-7.
3. Wu et al. AJO 2017;181:106-113.

Questions about progression

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- Disagreement is normal[1,2]
- E.g. OHTS

Table 1. One Hundred Sixty-Eight Eyes of 152 Ocular Hypertensive Participants with Primary Open-Angle Glaucoma (POAG) End Points

POAG Study End Point	No. of Eyes	% of Eyes
Optic disc, no visual field	87	52
Visual field, no optic disc	40	24
Both visual field and optic disc at same time	12	7
Visual field initially, then optic disc	17	10
Optic disc initially, then visual field	12	7
Total	168	100

- Relying on only one test will miss progression in some patients

1. Kelmer JL, et al. Ophthalmology 2006;113:1603-1612.
2. Medeiros FA, Tatham AJ. Ophthalmology 2017, in press.

Questions about progression

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That depends….

- Life expectancy
- State of the fellow eye
- Occupation
- Driver or non-driver
- Family history

- **There is an important difference between statistically and clinically significant change!**

1. Miki A, et al. Ophthalmology 2014;121:1350-8.
2. Kamal DS, et al. Br J Ophthalmology 2000;84:993–8.
3. Chauhan BC, et al. Ophthalmology 2009;116:2110–18.

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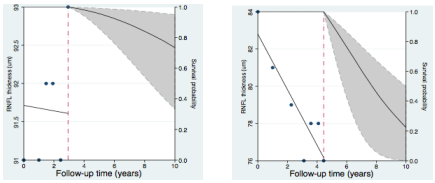
Faster rates of change on OCT are associated with increased risk of visual field loss

- Each 1 um per year faster RNFL loss → 2 x risk of field defect



1. Miki A, et al. Ophthalmology 2014;121:1350-8.
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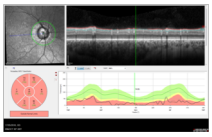
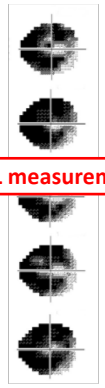
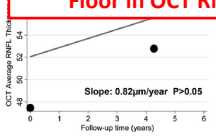
Advanced disease



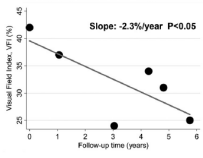


Floor in OCT RNFL measurements at ~40 µm

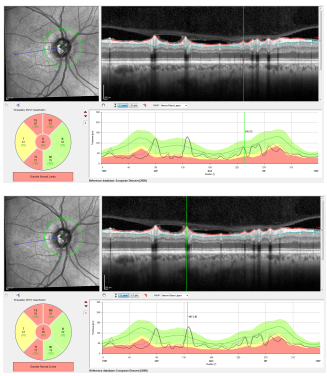


OCT Progression

Visual Field Progression

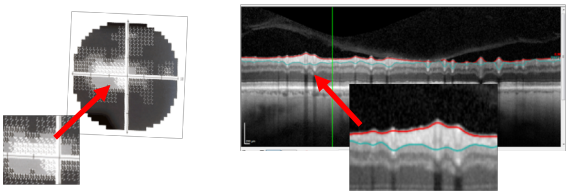


OCT also measures non-neural tissue



Advanced disease

- Although average indices reach a floor e.g. MD, average RNFL thickness
- Looking for localized change is useful
- Need to look at the whole visual field and whole OCT scan



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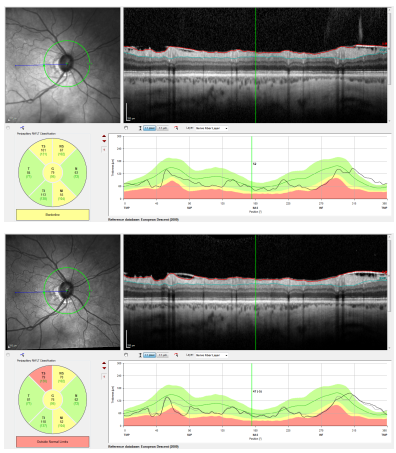

Is this progression?

Learning Points

1. Many patients have progression on OCT prior to change on visual fields (but depends on stage of disease)
2. There is an important difference between statistically and clinically significant change
3. Need to take account of age-related changes
4. For optimal detection of progression we need a combination of tests of structure and function

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- **OCT should not be used in isolation!**