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Clinical Darwinism in glaucoma care

About the author

Craig McArthur has extensive clinical experience using optical coherence tomography in conjunction with advanced visual field analysis and has presented on this subject area at numerous conferences in the UK. He is a visiting lecturer and clinical tutor to undergraduates at Glasgow Caledonian University where he also teaches the glaucoma module for the independent prescribing course.

Clinical Darwinism in glaucoma care – Part 1

Craig McArthur MCOptom

Optometrist Craig McArthur considers the advances in technology that have occurred in recent years to aid the diagnosis, monitoring and management of glaucoma. In the first part of this series he explores the use of visual fields for functional assessment and explains the use of progression analysis to monitor and predict change.

General Optical Council — Approved CET For Optometrists

Learning objectives

To be able to explain to patients about the outcome from visual field assessment (Group 1.2.4)
To be able to interpret changes to visual field results by comparing to existing records (Group 2.2.5)
To be able to determine the appropriate visual field program for any given patient and interpret the results (Group 3.1.5)
To be able to identify cases of suspect glaucoma (Group 6.1.5)

General Optical Council — Approved CET For Dispensing Opticians

Learning objectives

To be able to explain to patients about the implications of glaucoma (Group 1.2.4)
To be able to understand the methods used for visual field analysis (Group 3.1.5))
To be able to understand the manifestations of glaucoma (Group 8.1.5)

General Optical Council — Approved CET For Therapeutic Optometrists

Learning objectives

To be able to understand the natural progress of glaucoma (Group 1.1.1)
To be able to assess cases of glaucoma using appropriate techniques (Group 2.1.2)

Introduction

Glaucoma is a leading cause of visual morbidity worldwide and the second most frequent cause of legal blindness in industrialised countries.[1-3] Continual advances in science, technology and modern medicine have resulted in a demographic shift towards an elderly population as a result of improved life expectancy.[4] Multivariate research and numerous prevalence studies have shown a significantly increased risk of open-angle glaucoma (OAG) after 60 years of age, and a heightened risk with each subsequent decade of life.[5-10] This increased life expectancy coincides with a projected epidemic rise in diagnosed glaucoma cases and glaucoma induced visual impairment. By 2020 it is estimated that over 60 million people will suffer from glaucoma worldwide; 58 million from OAG, with 10% bilaterally blind.[11] In 2000, the prevalence of glaucoma in the UK was estimated to be as high as 3.3% in people over 40 years of age and up to 5% in those aged 80 and over.[12]

Perimetric blindness is the most feared outcome from the patient and practitioner viewpoint, however, there is evidence that even mild visual field loss may have a significantly adverse effect on quality of life.[13] Furthermore, approximately 10% of glaucoma patients with early visual field damage will still develop visual impairment or blindness during their lifetime despite medical and surgical interventions.[14] As glaucomatous damage is irreversible and in its early stages largely asymptomatic, it is crucial that the disease is detected at an early stage before significant loss of visual function has developed. Cost-effectiveness analysis estimates that the average annual cost for standard therapy in treatment of glaucoma at £380 per patient in the UK.[15] A further study has demonstrated an increased linear trend in resource consumption and total direct cost with worsening of the disease.[16] As gatekeepers to vision care, optometrists are ideally situated to help reduce not only the socioeconomic burden, but also the impact of glaucoma on the quality of life for the individual by improving our screening methodologies and diagnosing the condition at the earliest stage possible.

Evolving definition of glaucoma

In etymological lexicons, one finds entries from 1643 defining glaucoma as 'cataract, opacity of the lens' as cataracts and glaucoma were not distinguished as separate conditions until around 1705.[17] The definition of glaucoma has changed drastically since its introduction around the time of Hippocrates in approximately 400BC. OAG, the most common form of glaucoma in the Western world[11] is currently defined as a neurodegenerative progressive optic neuropathy that is multifactorial in origin[18-19] and in which a functional deficit – measured as a visual field loss – is associated with morphological or structural changes that occur at the optic nerve head (ONH),[20] the retinal nerve fiber layer (RNFL) and loss of retinal ganglion cells associated frequently but not invariably with raised intraocular pressure (IOP).[21-23] The study of scientometrics in medicine states that roughly half of our knowledge decays within 45 years; this is known as the half-life of facts.[24] As a profession have our screening methods evolved and adapted sufficiently with our understanding of the disease?

Glaucoma screening

The most widespread and commonly used screening methodologies in standard optometric practices rely on the clinical triad of psychophysical testing via visual field analysis; the gold standard of which is standard automated perimetry (SAP),[25] IOP measurement and ONH assessment. Increased IOP remains an important primary and prognostic risk factor for OAG.[26-29] However, IOP measurement, particularly with non-contact tonometry, is neither specific nor sensitive enough in isolation to be an effective screening tool unless combined with other examination techniques, as glaucoma can present with or without increased IOP.[30-31] Despite the exact pathogenesis of OAG not yet being fully understood,[32] the demographic risk factors (increased age,[5-10] family history of glaucoma,[33-36] African ancestry[37]), systemic risk factors (diabetes mellitus,[38-39] use of α-blockers,[40] systolic or diastolic hypertension,[41-43] perfusion pressure – systolic or diastolic blood pressure minus IOP or hypotension[44]) and clinical characteristics (increased IOP,[26-29] cup-to-disc ratio (CDR) >0.7,[34] thin central corneal thickness (CCT),[45] presence of age-related maculopathy (AMD),[10] presence of pseudoexfoliation,[46] high myopia[47]) associated with glaucoma are well known, and in cases of moderate-to-advanced glaucoma, the diagnosis is usually straightforward. A major challenge, however, is how best to detect early glaucoma.

Structure and function

Although a substantial proportion of patients who develop glaucoma acquire structural changes before detectable functional changes, this is not always the case, meaning both structural and functional assessments are necessary.[48] Over the last 25 years, ancillary examination techniques have been introduced that can supplement the clinical examination and aid the clinician in determining the probability of disease. Optical coherence tomography (OCT), scanning laser polarimetry (SLP) and confocal scanning laser ophthalmoscopy (cSLO) can be used to provide objective and quantitative measurements of parameters such as RNFL thickness, ganglion cell layer (GCL) thickness and neuroretinal rim area. Such imaging devices include normative databases that allow eyes to be categorised as normal, borderline or outside normal limits. These imaging devices have the ability to distinguish between glaucomatous and healthy eyes.[49] Additional examination techniques such as pachymetry, gonioscopy and stereo fundus photography further supplement the optometrists' already burgeoning diagnostic armamentarium. However, despite the availability of tests that yield quantitative structural and functional measures relevant to glaucoma, there is currently no 'gold standard' for diagnosis. In fact, even for a particular diagnostic test, there is usually no universal consensus on what constitutes an abnormal result. For example, a wide variety of criteria are

used when interpreting the results from visual field data obtained from SAP, ranging from simple global metrics, such as mean deviation (MD), to more local analyses, such as the glaucoma hemifield test (GHT).[50] Furthermore, the initial prospect of integrating this vast array of additional examinations into an eye examination at a busy optometric practice seems daunting. However, with the technology available to combine structural, functional, qualitative and quantitative test data from SAP, fundus photography and OCT in a single integrated report this offers an efficient patient workflow with the potential for earlier diagnosis and referral of glaucoma suspects.

Detection and monitoring of glaucoma with functional testing

Choosing a visual field testing strategy

The 24–2 test pattern using a program designed to shorten test time, such as the Swedish Interactive Thresholding Algorithm (SITA), is preferable in most glaucoma suspects. This examination evaluates 54 locations and offers high accuracy and relatively short test times of three–to–seven minutes per eye.

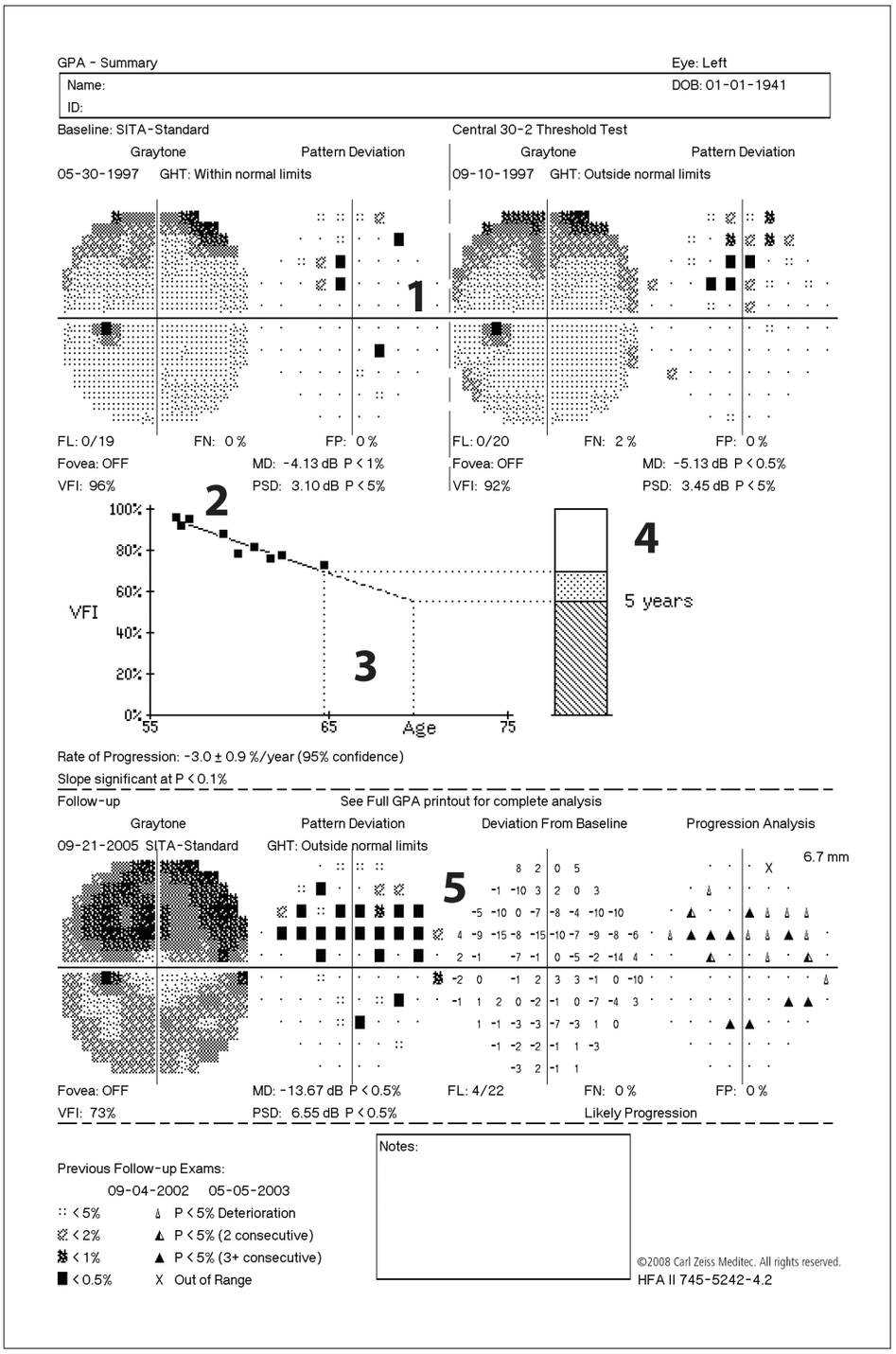

Figure 1 Guided progression analysis detailing patient with a progressive superior arcuate scotoma showing (1) At baseline (2) VFI rate of progression analysis (3) VFI plot (4) VFI bar (5) Follow-up visual field plot. The VFI plot and VFI bar predict a significant reduction in visual function in 3 and 5 years if the current trend continues. *Image courtesy of Zeiss*

Threshold testing can detect the earliest visual field changes and is also the standard of care for monitoring patients who have established field loss, and, therefore, is preferable over supra-threshold screening tests. Standardising a preferred test pattern and testing strategy is advisable as it facilitates test-to-test comparability. Fast test patterns combined with an interactive algorithm shortens the test time further to around two–to–five minutes per eye and can be very effective in experienced and younger patients, but is less accurate and not so tolerant of patient mistakes. In late stage glaucoma, when significant visual field loss is apparent leaving only a central island of vision, one can switch to a 10–2 test which evaluates only the area within 10° of fixation using test points spaced at 2° intervals as opposed to 6° spacing in the 24–2 test.

Single field analysis (SFA)

In short, the output from the examination offers a variety of options in appraising a visual field including numerical threshold sensitivities, greyscale printouts, total deviation probability plots, pattern deviation (PD) map, glaucoma hemifield Test (GHT) and visual field indices. The single most useful diagnostic analysis on an SFA printout is the PD probability plot. The PD analysis shows localised losses in sensitivity after adjustment has been made to remove any generalised elevation or depression of the overall hill of vision such as that caused by cataract. The GHT is also useful and provides a plain language interpretation of 24–2 test results based upon patterns of loss commonly seen in glaucoma.[50]

What are we looking for?

Glaucomatous visual field loss frequently occurs first in the Bjerrum areas, which follow an arcuate course from the blind spot, radiating above and below the macula, and ending at the temporal raphe. Early glaucomatous field defects most often take the form of localised relative paracentral scotomas. Defects in the nasal field are particularly common, and sensitivity differences across the nasal horizontal meridian are often diagnostically useful. Only a small percentage of glaucomatous defects occur in the peripheral field alone, therefore, testing is normally confined to the central 25°–30° field. Considerable test-retest variability is a hallmark of areas of the visual field affected by glaucomatous visual field loss; variable sensitivity reductions occurring in the same area, but not always at the same test point locations, commonly precede clear-cut glaucomatous field defects. This variability in glaucomatous defects coupled with the variability of subjective psychophysical testing and the patient learning effect result in the need for repeat examination over time and observing for change.

Guided progression analysis: Visual field index

Guided progression analysis (GPA) allows the facility to store, recall and compare multiple visual field plots by allowing electronic paperless archiving and remote terminal viewing *via* review software on multiple computer terminals or even an iPad, but also offers new and novel methods of serial analysis thus allowing better comparison of field defects over time (see Figure 1 page 54). The GPA summary report can help to estimate the current stage of visual loss and rate of progression to support the assessment of a patient's risk of future vision loss.

GPA uses the visual field index (VFI), a summary measurement of a patient's visual field status expressed as a percentage of a normal adjusted visual field. VFI is centre-weighted to better correlate with ganglion cell density and visual function and is less affected by media changes compared with other indices such as mean deviation and pattern standard deviation. VFI is used to quantify the rate of progression on the GPA summary screen and provides an overview of the patient's available visual field history. The VFI is plotted relative to patient age and calculates the rate of functional change over time. The VFI bar indicates the patient's current VFI value. In addition, when the results of the regression analysis are displayed, the VFI bar will also graphically indicate a three- to five-year projection of the linear regression line into the future, shown as a broken line (see Figure 1). Normal vision is associated with VFI values near 100%, while perimetric blindness produces VFI values approaching 0%. This technique can be useful in detecting progressive functional vision loss in early glaucoma and is particularly useful when monitoring diagnosed glaucoma patients overtime.

Conclusion

The present article has demonstrated the importance of careful visual field assessment and highlights the value of progression analysis both for monitoring change and as an important tool to predict potential loss of visual function in the future. Part 2 in the series will consider the clinical approach for structural investigation in glaucoma and how these data may be combined with functional assessment to aid diagnosis and monitoring of the condition.

1 CET POINT

Clinical Darwinism in glaucoma care – Part 2

Craig McArthur MCOptom

Optometrist, Craig McArthur continues to discuss the evolution in technology used for glaucoma diagnosis and monitoring. In the second part of the series he explores the methods used for structural analysis and how this information can be combined with the functional assessment discussed in Part 1.

Course code: C-37948 | Deadline: October 31, 2014

General Optical Council — Approved CET For Optometrists

Learning objectives

To be able to explain to patients about the outcome from structural assessment in glaucoma screening (Group 1.2.4)
To be able to interpret changes to structural assessment reports by comparing to existing records (Group 2.2.5)
To be able to identify cases of suspect glaucoma (Group 6.1.5)

COMMUNICATION · OCULAR DISEASE · PROFESSIONAL CONDUCT

General Optical Council — Approved CET For Dispensing Opticians

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To be able to explain to patients about the implications of glaucoma (Group 1.2.4)
To be able to understand the methods used for structural assessment in glaucoma screening (Group 3.1.5)
(To be able to understand the manifestations of glaucoma (Group 8.1.5)

COMMUNICATION · OCULAR ABNORMALITIES · OCULAR EXAMINATION

General Optical Council — Approved CET For Therapeutic Optometrists

Learning objectives

To be able to understand the natural progress of glaucoma (Group 1.1.1)
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About the author

Craig McArthur has extensive clinical experience using optical coherence tomography in conjunction with advanced visual field analysis and has presented on this subject area at numerous conferences in the UK. He is a visiting lecturer and clinical tutor to undergraduates at Glasgow Caledonian University where he also teaches the glaucoma module for the independent prescribing course.

Introduction

The relationship of the physiology and structural integrity of the optic nerve head (ONH) and the resultant functional status of the visual system has been actively investigated since Hermann von Helmholtz's invention of the Augenspiegel (direct ophthalmoscope) in 1851.[1] Our ability, as a profession, to assess both the structure and function of the ONH has evolved enormously over the last 160 years, becoming cumulatively more efficient and clinically practical, with ever increasing specificity and sensitivity for the detection of glaucomatous disease. However, the evolution of structural and function diagnostics did not occur in parallel. The last century and a half has seen many advances in functional detection of visual field defects from Von Graefe's confrontation examination and tangent screens in 1856,[2] Aubert and Förster's simple arc perimetry in 1869,[3] Scherk's bowl perimeter in 1872,[4] Bjerrum's campimeter in 1889,[5] Goldmann's projection bowl perimeter in 1945,[6] The Tübinger Perimeter of Harms and Aulhorn in 1959,[7] to the age of automation in the 1980's in the form of the Humphrey Visual Field Analyser, the first computer controlled automated static threshold perimeter,[8] which have led to standard automated perimetry (SAP), our current gold standard.[9]

Advancements continue with the proliferation and development of new methodologies such as frequency-doubling technology (FDT), short-wavelength automated perimetry (SWAP) and flicker-defined form (FDF) perimetry which aim to target specific aspects of visual function, such as movement perception, contrast sensitivity and colour vision in an attempt to improve test sensitivity and retest variability.[10] As clinicians, we rely on the most efficient, sensitive and specific diagnostic test methodologies available to us at any given time. Diagnostic technology enabling detailed functional examination of the visual field has developed quicker than our ability to objectively evaluate structural changes in the ONH and has, therefore, led to its widespread integration into the glaucoma screening procedures of routine optometric practice. Imaging techniques allowing better visualisation of the posterior pole have improved since the days of Helmholtz, from Gullstrand's slit-lamp in 1911 to spectral domain OCT in 2006. Despite this, SAP, intraocular pressure measurement (IOP) and subjective evaluation of the ONH using monocular direct ophthalmoscopy, and more recently, dilated binocular funduscopy and fundus photography have become the mainstay of glaucoma screening and diagnosis within our profession. However, this no longer represents the most efficient, sensitive and specific diagnostic test protocol available at this present point in time.

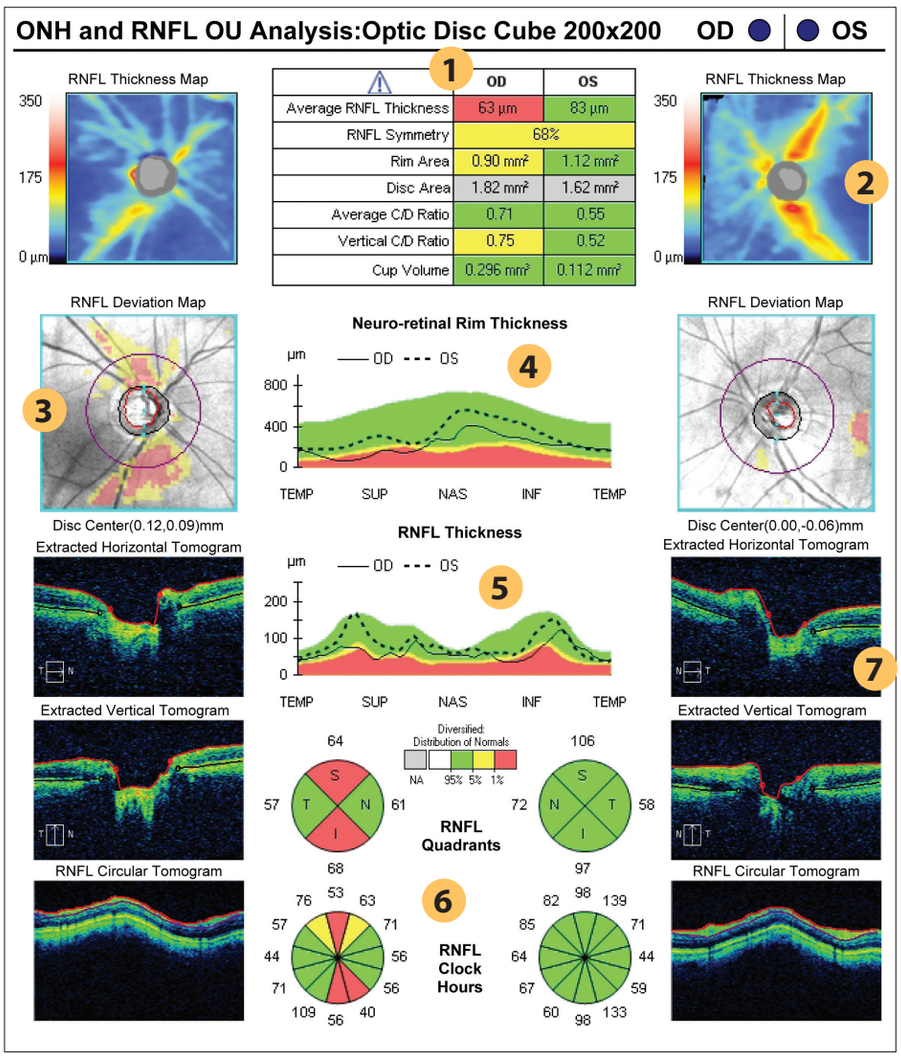


Figure 1 Structural change on OCT showing superior and inferior loss of the RNFL in the right eye. Reduced NRR area, increased vertical CDR and cup volume when compared to the left eye are also noted. The left eye shows a healthy ONH and RNFL. (1) ONH and RNFL parameters compared to normative data (2) Topographical RNFL thickness map (3) RNFL deviation map (4) NRR thickness (5) RNFL TSNIT graph (6) RNFL quadrant and clock hour (7) Horizontal and vertical B-scans

The recent technological leap in automated, non-invasive, objective quantification of the structural parameters of the ONH coupled with visualisation and analysis of the retinal nerve fibre layer (RNFL) and ganglion cell layer (GCL) using techniques such as optical coherence tomography (OCT), scanning laser polarimetry (SLP) and confocal scanning laser ophthalmoscopy (cSLO) combined with studies suggesting that overreliance on SAP in early glaucoma may lead to underestimation of the amount of glaucomatous damage, has led to renewed interest in the structure-function relationship in glaucoma. Although functional defects may be detected before structural changes, in many cases the earliest manifestation of glaucoma is a structural abnormality of the ONH and RNFL.[11,12] Structural changes are traditionally assessed by clinical examination and optic disc stereophotographs.[13] However, diagnostic

difficulties may occur, due to the large variations in normal disc appearance. The understanding that, in early disease structural optic nerve alterations may be more easily observed, has led to the suggestion that use of newer diagnostic techniques, such as OCT, potentially offers an opportunity for the timely detection of glaucoma,[14-16] and furthermore may help determine the probability of disease and estimate the risk of future visual loss.[17-19]

Stereo fundus photography (SFP)

Estimation of the status of the ONH is a complex clinical skill, particularly in early glaucoma, requiring judgement about the shape and structure of the cup, subtle thinning and pallor of the neuro-retinal rim, presence of disc haemorrhages and longitudinal approximation of the horizontal and vertical cup-to-disc ratios (CDR), all of which suffer from intra- and inter-observer variation. Agreement can be improved beyond that gleaned from traditional clinical examination by exploiting SFP. Optic disc stereo-photographs are useful, however, their interpretation is subjective and the improvement in inter-observer agreement in assessing progressive changes is slight.[20]

Optical coherence tomography (OCT)

With greatly enhanced resolution (between 1–5µm) and reduced scan acquisition times compared with older versions of this technology, spectral domain OCT has improved the measurement reproducibility[21] and the ability to detect small changes in RNFL thickness. The technique uses a super-luminescent diode laser with a wavelength of approximately 840nm and an acquisition rate of 27,000 A-scans per second (70 times faster than time-domain OCT). The optic disc

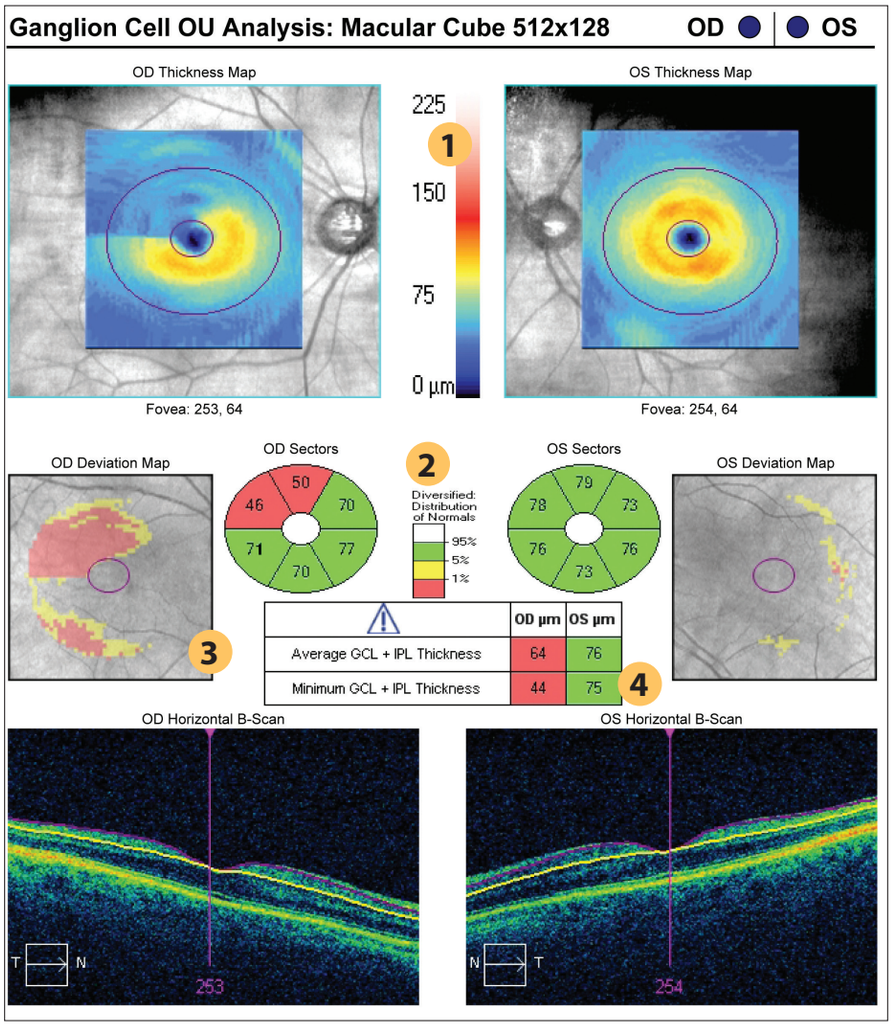


Figure 2 Localised structural loss in the superior ganglion cell layer thickness corresponding to the superior RNFL loss. The left eye appears healthy and within normal limits and well correlated with the ONH and RNFL results in Figure 1. (1) GCL thickness map (2) GCL parameters with normative data comparison (3) GCL deviation map (4) Legend of normal distribution

cube protocol used in Figures 1 to 5 is based on a tri-dimensional scan of a 6x6mm^2 area centred on the optic disc and information from a 1024 (depth) x 200 x 200-point parallelepiped is collected. A 3.46mm circular scan is placed automatically around the optic disc and the information about peripapillary RNFL thickness is obtained. OCT provides a fast (90 seconds per eye for a full battery of examinations) non-invasive, *in vivo* and objective means to quantify structural characteristics of the ONH topography, RNFL thickness and macular GCL thickness, thereby potentially offering an opportunity to detect glaucoma at an earlier

stage.[19] Measurements can also be compared to a normative database to determine the probability of disease and estimate the risk of future visual loss.[22] For a particular age and disc size the patient is expected to have rim volume, CDR, RNFL thickness and GCL thickness within a certain range. Those parameters will be shaded red, yellow or green and white based on how they compare to normal ranges. In a single visit the ONH and RNFL analysis report allows the practitioner to assess the patient's risk of glaucoma development based on structural data (see Figure 1).

Macular retinal ganglion cell layer analysis

Macular thickness changes and thinning of the retinal ganglion cell layer are well correlated with changes in visual function and RNFL structure in glaucoma and may be a surrogate indicator of retinal ganglion cell loss.[23] As such, evaluation of the GCL may be of diagnostic merit in early and progressing glaucoma. GCL analysis allows us to compare a patient's GCL thickness to age-matched normative data to highlight abnormalities, which may further aid early diagnosis (see Figure 2).

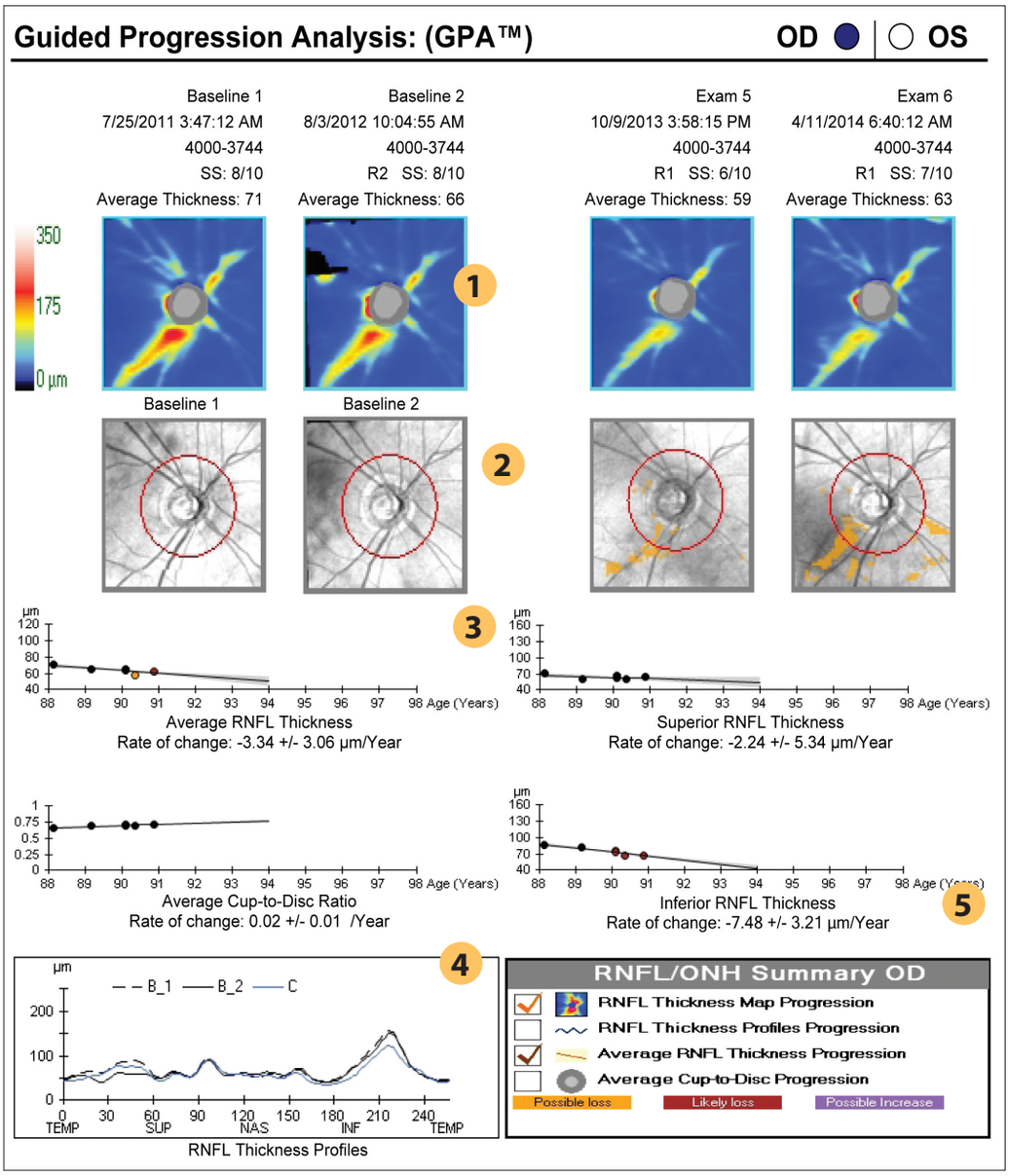


Figure 3 OCT GPA showing progressive thinning of the average RNFL thickness particularly inferiorly and an increase in the average CDR over time. (1) RNFL thickness maps (2) RNFL thickness change maps (3) Average RNFL thickness (4) RNFL thickness profiles (5) RNFL summary

Guided progression analysis (GPA)

GPA can help in the identification of glaucoma progression through RNFL thickness trend analysis and event analysis over time with repeated measurements. Trend analysis looks at the rate of change over time, using linear regression analysis to determine the rate of change. Event analysis assesses change from baseline compared to expected variability. If the change is outside the range of expected variability, it is identified as a progression. In a similar manner to the GPA analysis employed in visual field analysis, the OCT GPA allows serial analysis of repeat longitudinal measurements of structural data, a change in which may lead to functional loss and thus glaucoma diagnosis (see Figure 3).

Anterior segment OCT (AS-OCT)

AS-OCT can be utilised in the non-invasive measurement of central corneal thickness (CCT) and has been shown to compare well with full-contact ultrasound pachymetry, the gold standard method.[24] AS-OCT can also be used to rapidly and non-invasively visualise the anatomical structures of the iridocorneal angle and anterior chamber. It has been shown to be highly sensitive and beneficial in detecting angle

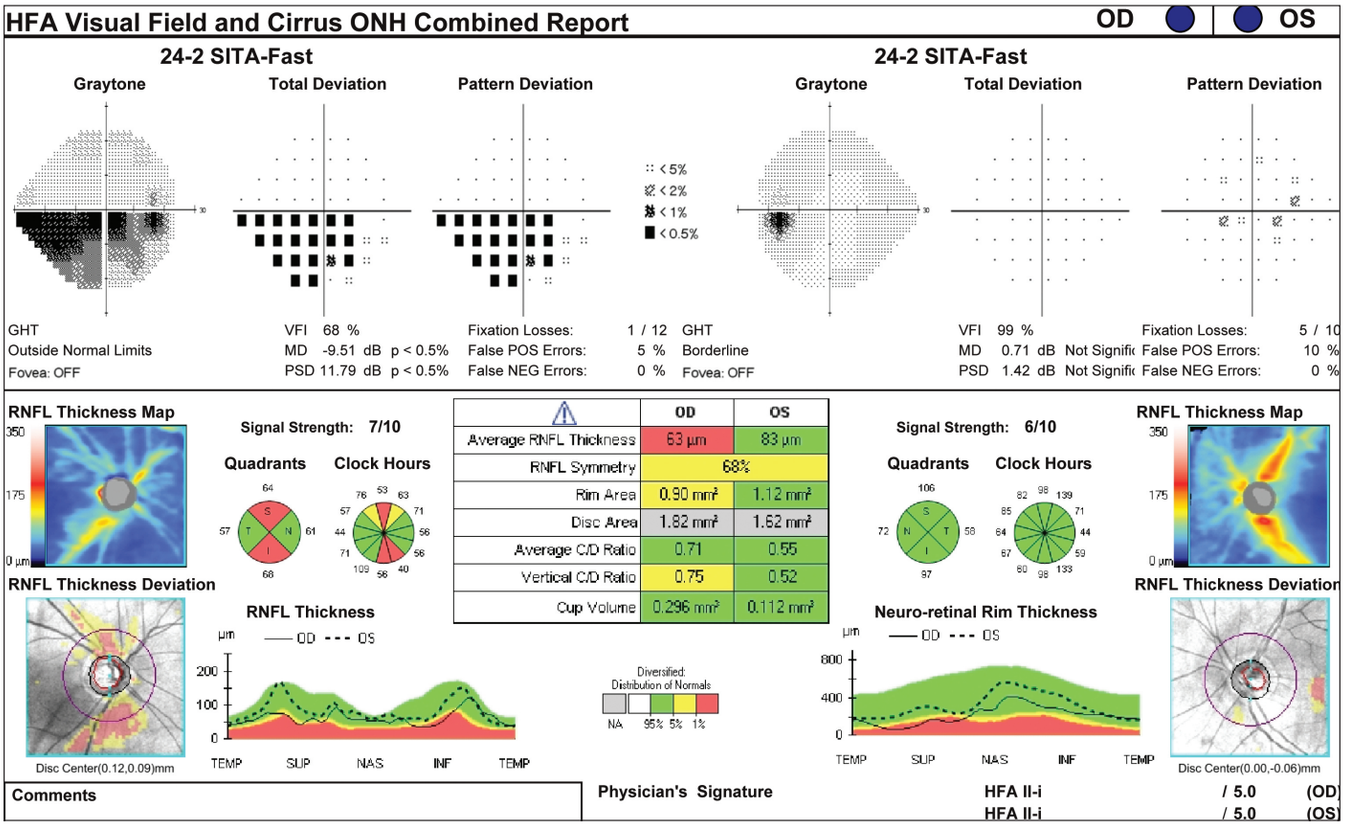


Figure 4 Combined visual field and OCT results showing the correlation of structural changes with functional loss. The structural loss of superior RNFL corresponds with the inferior arcuate scotoma in the right eye. The MD, PSD, VFI and GHT all depict results outside of normal limits and highly suggestive of glaucomatous loss. The left eye reveals a healthy ONH, RNFL and a normal and intact visual field

closure when compared to gonioscopy.[25]

OCT thus enables capture of subtle progressive structural changes by clinicians who are not experts. The reproducibility of images is excellent due to sophisticated retinal tracking systems and acquisition is relatively easy and as such can be undertaken by trained ancillary staff. Remote viewing software allows the practitioner to view and manipulate the data electronically and eases the integration of such techniques into the patient journey in a busy optometric practice.

Combined structure and function reports

What is the probability of disease? This is the fundamental question of the glaucoma diagnostic process. As clinicians we make an intuitive estimate of disease probability based on medical history, demographic risk factors, systemic risk factors and clinical examination findings; this is referred to as the pre-test probability. A high-risk patient, for example, an individual with a first-degree relative with glaucoma, high IOPs and a suspicious disc appearance may only require abnormal results from either a functional or structural test to initiate referral for further investigation in secondary care. Whereas, a low risk patient, for example, an individual with no positive family history, normal IOPs and an abnormal disc appearance may require abnormal results correlated from both functional and structural exams before being considered for referral. The results from functional and structural tests can thus be used to modify the pre-test probability and obtain a new post-test probability of disease, which ultimately leads to a more informed view of whether a patient should be

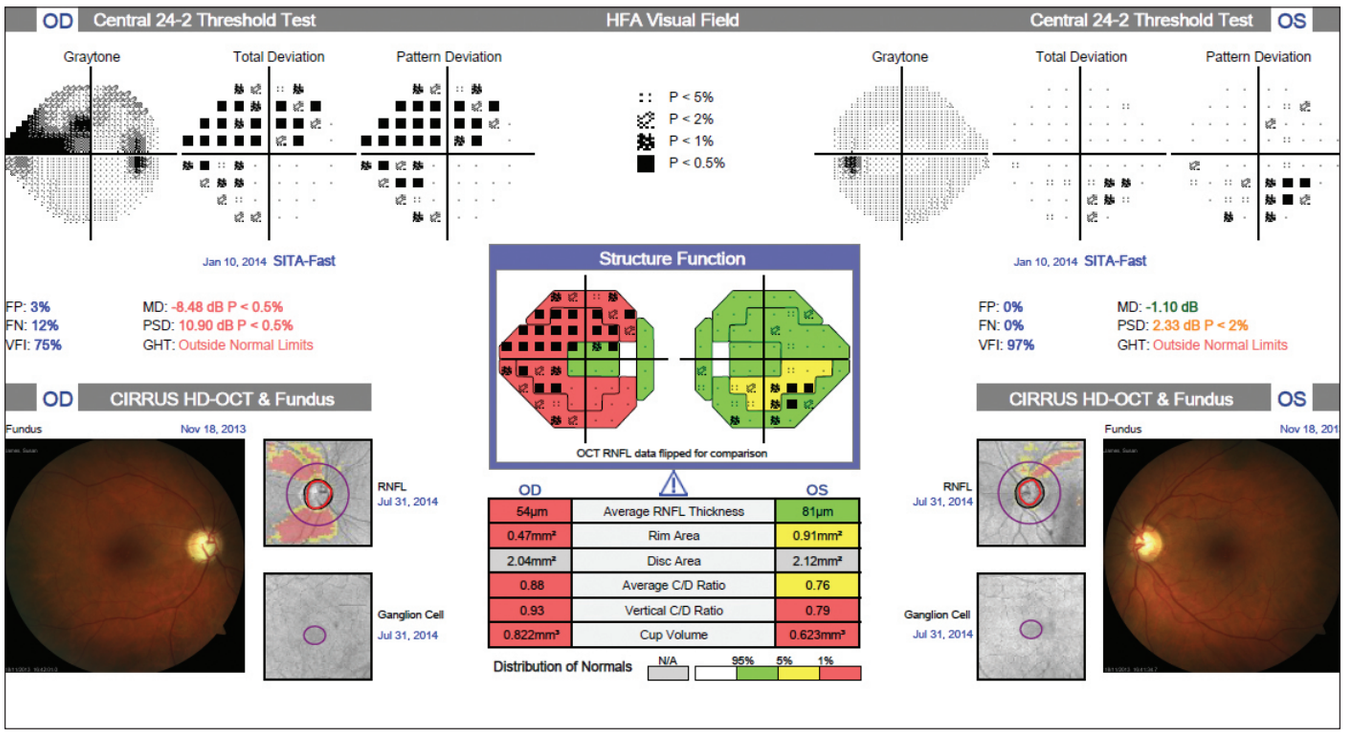


Figure 5 Report showing established structural loss of the superior and inferior RNFL in the right eye with corresponding functional deficit, an inferior and superior arcuate scotoma. Abnormal MD, PSD and VFI values and a GHT outside normal limits are reported in both eyes. Early loss of superior RFNL in the left eye corresponds with an emerging inferior arcuate scotoma

referred to a glaucoma specialist.[22]

The Ocular Hypertension Treatment Study examined 168 patients at risk of developing glaucoma.[26] In this study, 87 were diagnosed on the basis of structural changes using OCT, 40 patients were identified from functional deficits using visual fields and 41 patients were identified on both functional and structural tests. One of the conclusions of the study is that both sets of data are required to detect patients at the earliest stage in the disease process as structural and functional examination may diagnose different patients.

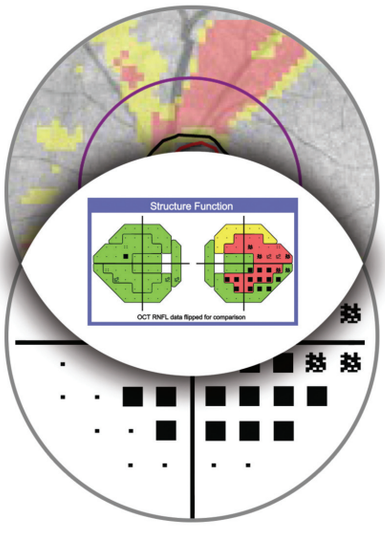
Combined structure and function reports can be used to quickly assess and correlate data from a variety of exams in a single document. The combined visual field and ONH/RNFL OCT report can be used to examine physiological changes associated with a visual field defect, or vice versa (see Figure 4). The full structure/function report compiles data from threshold visual fields, fundus photography, GCL, RFNL analysis and ONH parameters in a single, easy-to-read output comparing the patient with age-related normative data.

Such reports coupled with longitudinal guided progression analysis reports from visual fields and OCT allow us to highlight those with a significant probability of glaucoma at an early stage in the disease process and thus refer more quickly and offer the patient the best possible prognosis (see Figure 5).

Conclusion

It is evident that early detection of glaucoma is vital, particularly as quality of life may be adversely affected with even mild loss of visual function. Both functional and structural tests are necessary for early diagnosis. Recent technological advances in combined SAP and ophthalmic imaging have enhanced our ability to assess both domains and will improve significantly in the coming years enabling us to provide better care for our patients.

The moment you are certain it is glaucoma.
This is the moment we work for.



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