Chapter 11
Imaging Techniques of the Optic Nerve Head and Retinal Fiber Layer

Akvile Stoskuviene

Since glaucoma is the leading cause of irreversible blindness, early diagnosis and detection of progression takes important place in many clinicians everyday practice. The appearance of optic nerve head is one of the glaucoma diagnostic mainstays. However, it is not always easy to asses and even to document the appearance changes, especially in unusual structure discs: tilted, very small or very large optic nerve discs. Written descriptions seems to be insufficient for careful follow-up. Structural characteristics can be documented by taking photos or more sophisticated scanning imaging devices that are playing an increasing role in glaucoma diagnosis, monitoring of disease progress, and quantification of structural damage [1, 2].

Stereoscopic ONH Photography

European Glaucoma Society and American Academy of Ophthalmology recommend the acquisition of the baseline colour fundus photo, as it can document disc haemorrhages, parapapillary atrophy, changes in colour and vessel position and can be used for follow-up assessment. Stereoscopic photography is preferred than non-stereoscopic one [3, 4].

Stereoscopic ONH photography is a simple, quick and low-cost method providing a three-dimensional full-colour view of the ONH; in practice, it is the most commonly utilized technique to objectively document structural damage in glaucoma suspects [5].

A. Stoskuviene (✉)
Department of Ophthalmology, Lithuanian University of Health Sciences, Kaunas, Lithuania

Department of Neurology, Lithuanian University of Health Sciences, Kaunas, Lithuania
e-mail: akvile.daveckaite@lsmuni.lt

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Method

The first device for stereo fundus photography was described by Dr. W. Thoner, in 1909. However, due to the changes in technological peculiarities, in clinical practice stereo fundus photography was applied since sixth decade [6]. Stereoscopic images can be produced by two photographic techniques: simultaneously (with beam spilling prisms) by capturing instantaneous stereo images at single expose or sequentially (with a spatial shift) by capturing two consecutive images using a manual shift [7]. Several stereoviewers are commercially available.

ONH Photography in Glaucoma Trials

The Ocular Hypertensive Treatment Study (OHTS), the Early Manifest Glaucoma Trial (EMGT), and the European Glaucoma Prevention Study (EGPS) used optic disk damage assessment based on photograph as an endpoint, like the other studies also concerned on standardized assessment methods, have shown that by standardizing evaluation, optic disk photographs can be reproducibly evaluated [5, 8–10].

Interpretation of ONH Photos

Currently, ONH assessment techniques that provide quantitative and reproducible imaging are widely used. However, in a qualitative comprehensive ONH evaluation various parameters are included, such as ONH pallor or hemorrhages. Subjective ONH evaluation allows nonglaucomatous detection of changes that may impact quantitative and functional testings [2].

Focal neureretinal rim loss is evident in ONH photographs, while concentric enlargement can be tricky to detect especially in small ONH. A cup of small diameter ONH is often small as well, and concentric enlargement of it becomes available to detect in comparison with a baseline photo. Lamina cribrosa exposure with the thinning of the neuroretinal rim gives impression of pallor. However, pallor by itself, suggests of non-glaucomatous neuropathy as it can also be expressed due to exposure artefacts or pseudophakia. Wedge-shaped defects are seen easier on colour photograps, while retinal nerve fiber layer (RNFL) defects show better exposure on black-and-white photos. ONH haemorrhages (splincter haemorrhages), vessel position changes, peripapillary atrophy can be detected and followed by photographs as well.

Therefore, photographs allow better evaluation of the patient, when patient has changed the doctor. No normative data bases or software are necessary for ONH photographs evaluation [11].

Confocal Scanning Laser Ophthalmoscopy

Physics

The Heidelberg Retina Tomograph (HRT; Heidelberg Engineering, Heidelberg, Germany) is a confocal laser scanning system providing fast and reproducable 3D topographic measurements of the optic disc and peripapillary retina. A diode laser of 670 nm is used for high contrast layer-by-layer (tomographic) image production.

The topographical image is derived from series of 16–64 optical sections at consecutive focal depth planes. Two images—a topographic and a reflectivity image are displayed. Topographic image consists of 256 × 256 or 384 × 384 pixels, with each pixel corresponding to retinal height at its location [12, 13].

Keratometry values must be entered and astigmatism >1.0 D corrected by cylindrical lenses prior acquisition.

After automated 3D image acquisition, the edges of the ONH are defined manually by drawing the contour line. A reference plane is set automatically 50 μm below the contour line at the temporal disc margin (at the papillo-macular bundle) to allow 3D topographic measurements of the ONH (above the reference plane) and cup (bellow the plane) [11].

Analysis Strategies

- Moorfield's regression analysis (MRA): the mean topographic image is created from three averaged scans and compared to normative database. This classification algorithm dissociates glaucomatous ONHs based on the stereometric parameter "rim area" adjusted for "disc area", and provide classification as "within normal limits", "borderline" or "outside normal limits" in whole ONH and in six sectors; diagnosis is in the responsibility of clinician [12, 14].
- Glaucoma probability score (GPS): analysis is made independently from contour line drawn by operator manually. Compared to stereometric parameters the diagnostic accuracy remains similar or lower [12, 15]. This strategy is influenced by disc size more than MRA, as larger ONH may be associated with false-positive results (healthy eyes classified as "outside normal limits") and smaller glaucomatous discs classified as "within normal limit" (false-negative) [15].
- Topographic change analysis (TCA): algorithm independent from the disc margin contour line that provides progression analysis in topographic image. It is variable in at any given location and is able to detect even small changes in the ONH and parapapillary retinal topography. However, there is a slipping between the statistically significant changes estimated automatically and the clinical significance [11].

Advantages

- HRT can be widely in used glaucoma management as the data from older versions are almost full matched-up with the current version, HRT III [11].
- HRT measurements has good intra and inter-observer reproducibility [16].
- Image acquisition is fully automated and algorithms that are independent from the manually drawn disc margin contour line are installed. Measurements independent from the reference plane are: cup shape, cup volume below the surface, mean cup depth, maximum cup depth and disc area [11, 12].
- No pupil dilation is necessary. Pupil dilation improves image quality in patients with small pupils and cataracts, however data reproducibility is better in eyes with undilated pupils [14, 16].

Limitations

- Stereometric parameters and diagnostic accuracy become investigator-depended as the contour line, denoting the edges of the ONH has to be circumscribed manually. ONH measurements requiring a reference plane are: cup area, cup-to-disc ratio, cup volume, rim area, rim volume, RNFL thickness, RNFL cross-sectional area [11, 12].
- Inaccurate measurements of stereometric parameters can occur as the reference plane set arbitrary from the contour line may shift over the time especially in patients with glaucoma who may suffer RNFL loss at the temporal ONH margin or simply due to artefacts [11, 17].
- ONH size have influence on diagnostic accuracy in MRA analysis strategy of HRT (as large optic discs are classified as “outside normal limits” while being healthy (false-positive mistake) whereas glaucomatous but small ONHs are classified as “within normal limits” (false-negative mistake).
- Significant variability may be triggered due to misalignment between patient and the scanner in the horizontal plane [11].

HRT Reliability in Studies

- The HRT vertical cup/disc ratio, the MRA and rim area were reported as the most accurate in glaucomatous ONHs ascertaining from healthy ones [18].
- HRT TCA analysis is valuable tool in glaucoma progression disclose as it significance was compared with ONH evaluation in photography’s by glaucoma experts [19, 20].
- HRT MRA whole or sectoral classification as “outside normal limits” was significantly associated with the development of POAG with the hazard ratio from 2.5 to 5.8 [21].

Scanning Laser Polarimetry (GDx–VCC; GDx–ECC)

Physics

The GDx instrument (Carl Zeiss Meditech Inc., Dublin, CA, USA) consists of confocal scanning laser ophthalmoscope with a 780 nm near-infrared diode polarized light laser beam to measure RNFL thickness around the optic nerve head on the basis of retardation of the illuminating laser light. All polarizing structures in the eye cause retardation, especially the cornea. Polarization artefacts arising both from the anterior segment and behind the retina are reduced, and usability of data improved with Variable Corneal Compensation (VCC) and Enhanced Corneal Compensation (ECC) algorithms. Scanning laser polarimetry (SLO) collects data of RNFL retardation obtained from circular band of 1.5–2.5 disc diameters concentric to the disc. Each image consist of 256 × 256 pixels (or 65.536 individual retinal locations covering 15° and corresponding to the retardation value at its location) and is qualitatively illustrated: high retardation is coloured yellow or white, low retardation is presented as dark blue [12, 22–24].

Displayed Measurements

In the GDx printout fully automated measuments are presented: fundus images (or "reflectance" images), retardation (or thickness) maps, deviation maps and TSNIT plots.

- Fundus images are presented for image quality evaluation (central circle location marks proper fixation; consequently, as they are made with monochromatic scanning laser, the rim and cup differ from their real appearance).
- Retardation maps graphically represent RNFL thickness in colours from bright and warm (representing thicker areas) to dark and cool shades of blue (for a thinner ones). Black colour usually represent the lack of data.
- *Usually retardation pattern presents higher values superiorly and inferiorly in healthy eyes. The glaucomatous RNFL reduction cause disturbances in this pattern as well as may the distance to the eye. Atypical retardation patterns, as irregular splotchy patches of elevated retardation, can be presented and falsified measurements of RNFL presented.
- The deviation maps compare the retardation value (RNFL thickness) to the age and ancestry database and express it in colour coded map.
- The TSNIT plots presents peripapillary RNFL thickness along the circular measurement band around the ONH. From this annulus 6 parameters are derived (TSNIT average, superior and inferior averages, TSNIT standard deviation, inter-eye symmetry and nerve fiber indicator (NFI)).
- The NFI is the main parameter to distinguish healthy subjects from glaucomatous patients. It values varies from 0 (completely normal) to 100 (advanced glaucoma)

whereas value between >35 and ≤45 is regarded as borderline, therefore other parameters may be significant for diagnosis. However, NFI may not reflect localized RNFL defects [11].

Advantages and Reliability

- GDx-ECC provides significantly reduced atypical birefringence patterns (ABPs) manifestation and improved correlation between RNFL thickness and visual function compared to GDx-VVC [22, 25].
- GDx VCC had a good diagnostic accuracy and was more accurate than ONH photographs [26, 27].
- GDx VVC may be useful in preperimetric glaucoma cases as it was able to detect early structural changes in such eyes compared to controls [28].

Limitations

- Even with VVC and ECC compensators embedded into SLP devices, unreliable RNFL thickness values have been reported in patients with a history of refractive surgery, ocular surface and media opacities, peripapillary atrophy, posterior staphyloma and high axial myopia [29].
- Atypical birefringence patterns (ABPs) occurs in nearly one quarter of healthy eyes and can reach half of glaucomatous patients as a device induced artefact in attempt to compensate poor noise-to-signal ratio reached with GDx-VCC [24].
- GDx analysis hardware must be upgraded with each advancement and images acquired with current generation of instrument to be included in progression [2].

Optical Coherence Tomography (OCT)

Optical Coherence Tomography (OCT) is a non-invasive, non-contact low-coherence interferometry based technique, providing high-resolution cross-sectional 2D and 3D images of the retina and optic nerve. OCT is analogous to B-sacn ultrasonography, however near-infrared light interferometry is used; while third-generation OCT uses a swept wavelength tunable laser. The differentiations in retinal layers are composed due to unique time delay of reflections from various tissue components. The more reflective a structure is, the more intensively red it appears in color-coded examination, or white in black-and-white report. The most reflective structures in the retina are RNFL, the pigment epithelium and the interplexiform layers. As the outer part of retinal pigment epithelium is highly absorbent, whilst basal region is highly absorbent due to the presence of melanin, a

combination of absorbtion and expotential reduction of the power of the beam, structures below the retinal pigment epithelium were unestimated with previous generation OCT devices.

Since the first application of OCT in ophthalmology, this method continuously been improved and current instruments, Fourier-domain (FD) or Spectral domain (SD) and swept-source OCT systems, provide faster image acquisition, higher resolution and better image segmentation than previous time-domain (TD) OCT. Comparison of SD-OCT and SS-OCT parameters is presented in Table 11.1 [30].

OCT is highly reproducible and operator independent device, therefore is widely used as a supplementary technique in routine glaucoma patients management [32–34].

Even OCT instruments are produced by several various manufacturers, main parameters measured and analyzed for classification and detection of progression are the same. Three currently used OCT markers in glaucoma are: (1) the optic nerve head (ONH) topography; (2) the peripapillary nerve fiber layer (RNFL) thickness; (3) the complex of ganglion cell layer (GCL) and innex plexiform layer (IPL) thickness in the macula [10, 32–34].

Analysis Protocols

- **Peripapillary RNFL analysis** is the most commonly used scanning protocol for glaucoma diagnosis. The image is acquired from circular scans with 3.4 mm diameter centered on the ONH. Registered changes in reflectivity between inner and outer retinal boundaries are automatically converted to quantative RNFL thickness values by a special computer algorithm. The TSNIT curve provides comparison between patients RNFL thickness and age-related normative database. In the circular diagram of 12 clock-hour section patients RNFL thickness is matched to normative database. A color coded values of the significance intervals are provided. Normal values are indicated in green, those between 1st and 5th percentile in yellow and those below 1st percentile in red. According to the software, glaucoma trend analysis can be provided.
- **ONH analysis** enables assessment of the ONH. Depending on the device, radial scans or, more common, 6 × 6 mm cubed area are centered on the ONH. Changes in reflectivity are registered between anterior surface of the RNFL and the retinal

Table 11.1 Feature comparison of SD-OCT vs. SS-OCT

	SD-OCT	SS-OCT
Light source	SLD	Swept laser
A-scan wavelength, nm	840	1.050
A-sacn rate, Hz	50.000	100.000
Resolution (x), μm	20	20
B-sacn measurement time, s	1.0 (50×)	1.0 (96×)
Imaging depth, mm	2.3	2.6

Adapted from [31]

pigment epithelium (RPE) and converted to an anatomical quantified ONH parameters. These ONH parameters are not compared with normative database.

- **The macular thickness analysis** uses scans that also detect reflectivity between the RNFL and RPE. 50% of RGCs are found in the macula, and RGC bodies are thicker than their axons, thus are potentially easier to detect. A color coded map is created, illustrating the thickness for specific regions of macula. The TD-OCT devices, such as Zeiss Stratus, were able to evaluate only the total macular thickness, which had been shown to have poorer glaucoma diagnostic accuracy than RNFL thickness [35–37]. SD-OCT (Zeiss Cirrus, Heidelberg Spectralis, Optovue RTVue, Topcon 3D-OCT) allows measurements of specific retinal layers implicated in the pathogenesis of glaucoma, namely: macular nerve fiber layer (mNFL), ganglion cell layer with inner plexiform layer (GCIPL), and ganglion cell complex (GCC) (composed of mNFL and GCIPL). Segmented analysis is reported to have better diagnostic ability for glaucoma than total retinal thickness [37, 38], and may be comparable to RNFL thickness [38–40].
- **Wide scan analysis**, is novel analysis protocol, presented by TopCon. This 12 × 9 mm wide scan protocol includes ONH and macula in single scan. This mode provides analysis of total macula, GCL+, GCL++ and peripapillary RNFL thickness. The results are compared with a normative reference database, and are automatically color-coded classified as 'within normal limits' (green), 'borderline' (yellow), and 'outside normal limits' (red) [41].
- **Glaucoma Module Premium Edition (GMPE)**, presented by the Spektralis (Heidelberg Engineering) provides assessment of the optic nerve head, the retinal nerve fiber layer, and the ganglion cell layer in a precisely matched scan pattern. With the proprietary Anatomic Positioning System (APS) all scan protocols are automatically orientated according patient's anatomic map, by foveal – Bruch's membrane opening (FoBMO) axis. Precise examinations are performed and compared with reference data [42].

OCT has shown good diagnostic accuracy in detecting glaucomatous optic neuropathy, with overall sensitivity and specificity ranging from 61 to 84% and 85 to 100% consequently [43].

Advantages

OCT provides various quantative analysis protocols that supplements clinical interpretation.

Progression analysis allows automatically registration and follow-up to baseline scans.

The refractive state and the axial length of the eye does not affect axial OCT measurements.

OCT measurements of RNFL thickness are not depended on tissue birefringence [12, 43].

Limitations

With the wide spread of this technique, OCT devices are manufactured with different technical parameters, as well as separate software and normative database characteristics; thus the values measured with different OCT systems are not interchangeable.

Media opacities may limit the ability to perform valuable OCT analysis [12, 43].

Additional OCT Applications in Glaucoma

While being non-invasive, non-contact imaging modality that provides high-resolution cross-sectional imaging of various ocular tissues (retina, optic nerve, and anterior segment), OCT technology has a wide spectrum of application in glaucoma; it can be applied for anterior segment structural assessment OCT (AS-OCT), evaluate choroid thickness and assess its impact of glaucomatous damage, and estimate lamina cribrosa changes using SS-OCT or enhance structural visualization with appliance of EDVI modality [44–46].

Frequency of Imaging

According to European Glaucoma Society recommendations [3] for imaging techniques application in glaucoma management, assessment should be applied as follows:

Frequency of imaging in glaucoma patients

At baseline [II,D]	*For monitoring progression [II,D]*
– Glaucoma suspects with normal or unreliable visual field	Frequency should be similar to that for VF testing
– Glaucoma with early and moderate damage	– Patients should be followed with the same test/method to facilitate estimation of progression [I,D]
	– Baseline, repeated within 3 months after baseline, and then up to 4 more times in the first 2 years in case of high risk of progression [II,D]
	– Baseline, repeated annually, for ocular hypertensives [II,D]

ID strong recommendation with low quality of evidence; *IID* week ("suggestive") recommendation with low quality of evidence

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