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Role of Optic Nerve Imaging in Glaucoma Clinical Practice and Clinical Trials

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Abstract

Purpose—To provide an update on the role of optic nerve and peripapillary retinal nerve fiber layer imaging in glaucoma clinical practice and clinical trials.

Design—Perspective.

Methods—Review of recent literature and authors' clinical and laboratory studies.

Results—Imaging technologies such as confocal scanning laser ophthalmoscopy, scanning laser polarimetry, and optical coherence tomography provide objective and quantitative measurements that are highly reproducible and show very good agreement with clinical estimates of optic nerve head structure and visual function. Structural assessments provided by imaging complement optic disc photography in clinical care, and have the potential to identify relevant structural efficacy endpoints in glaucoma randomized clinical trials. As with other technologies, imaging may produce false identification of glaucoma and its progression, thus clinicians should not make management decisions based solely on the results of one single test or technology.

Conclusion—Although optic disc stereophotography represents the standard for documentation of glaucomatous structural damage in practice and research trials, advances in computerized imaging technology provide useful measures that assist the clinician in glaucoma diagnosis and monitoring, and offer considerable opportunity for use as efficacy endpoints in clinical trials.

Introduction

Almost two decades have elapsed since the introduction of computerized imaging technology for assessment of the optic nerve and peripapillary retinal nerve fiber layer (RNFL). Imaging

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Design and conduct of the study (DSG, RNW); Collection and management of the data (DSG, RNW); Analysis and interpretation of the data (DSG, RNW); Preparation, review, and approval of the manuscript (DSG, RNW).

This study was performed with adherence to the Declaration of Helsinki and all federal and state laws.

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technologies such as confocal scanning laser ophthalmoscopy (Heidelberg Retina Tomograph, HRT, Heidelberg Engineering, Germany), scanning laser polarimetry (GDxVCC, Carl Zeiss Meditec, Dublin, CA), and optical coherence tomography, (OCT, Carl Zeiss Meditec, Dublin, CA) provide objective and quantitative measurements that are highly reproducible and show very good agreement with clinical estimates of optic nerve head structure and visual function. Yet, many unanswered questions exist regarding how to integrate such measurements in glaucoma clinical practice and clinical trials. Does imaging enhance clinical care? How should imaging technology best be integrated into clinical practice for glaucoma diagnosis and monitoring? Is there a role for imaging in glaucoma clinical trials? It is time to critically assess what we know, as well as what we still need to learn, about the use of imaging in glaucoma clinical care and research.

Clinical assessment of the optic nerve and retinal nerve fiber layer

Examination and documentation of the optic disc and retinal nerve fiber layer (RNFL) is essential for diagnosis and monitoring of glaucoma. With a high-power convex lens and stereoscopic slit lamp biomicroscopy, a clinician can observe and document the salient characteristics of glaucomatous optic neuropathy and identify subtle structural changes consistent with progression. Clinical features including focal or diffuse narrowing of the neuroretinal rim width and loss of peripapillary RNFL, increased vertical excavation of the optic cup, presence of beta-zone parapapillary atrophy, and optic disc hemorrhage must be identified. Annotated detailed drawings of the optic nerve are useful for documentation but are often inaccurate, incomplete and poorly reproducible. Stereoscopic optic disc photography allows such features to be permanently recorded for future reference. Simultaneous stereoscopic photography is the preferred method for documenting disc appearance given the fixed stereobase which provides stable depth scaling; sequential stereoscopic photography is an acceptable alternative.

Recommendations for imaging of the optic disc and RNFL in glaucoma have emerged during the past few years. Digital imaging is recommended to facilitate assessment of the optic nerve and RNFL in the Consensus Initiative of the World Glaucoma Association. Moreover, it is recognized in this consensus report that different technologies may be complementary, and may detect different abnormal features in the same patient.¹ More recently, a comprehensive review by the Ophthalmic Technology Assessment Committee Glaucoma Panel of the American Academy of Ophthalmology² also concludes that “ongoing advances in imaging and related software as well as impracticalities associated with obtaining and assessing optic nerve stereophotographs have made imaging increasingly important in many practice settings”. The panel also posits that the information obtained from imaging devices is useful in clinical practice when analyzed in conjunction with other relevant clinical parameters that define glaucoma diagnosis and progression. Not only is there strong support for the use of glaucoma imaging, but the use of imaging devices has disseminated widely.

Does Imaging Add to Clinical Care?

1. Documentation

There is evidence that physician behavior may deviate from the recommendations of established guidelines. A chart review³ of almost 400 patients with glaucoma reported that 47% of patients did not have an optic disc drawing or photograph at the time of the initial examination. Other studies have shown that 66% of patients do not undergo optic disc photography after the initial visit,⁴ and only 6% undergo disc photography or imaging every 18 months⁵. In order to identify change in any progressive disease, it paramount that baseline images be obtained and periodically compared with subsequent images. Imaging provides an

effective means of establishing baseline documentation and quantifying structural damage in glaucoma.

2. Disc size

Measurement of optic disc size is critical in order to interpret clinical estimates of cup-disc ratio and neural rim integrity.^{6, 7} Large optic discs have physiologic increased cupping that may be confused with glaucoma; small glaucomatous discs may not manifest any appreciable cupping or neural rim atrophy.⁸ Optic disc size may be clinically estimated using a slit lamp reticule. Such measurements have limited reproducibility and can be affected (particularly at the extremes) by axial length, refractive error, and magnification. Quantitative imaging provides a useful means of quantifying optic disc size. Although the measurements may differ across technologies⁹, such measurements are highly reproducible and facilitate the interpretation of the optic disc in common clinical situations such as a glaucoma suspect with enlargement of cup-disc ratio due to a physiologically large macrodisc, or cup-disc asymmetry between fellow eyes due to asymmetry in disc area.

3. Risk Assessment

Established risk factors for the progression of ocular hypertension to glaucoma include increased age, intraocular pressure, cup-disc ratio, optic disc hemorrhage, and reduced central corneal thickness.^{10–12} The Confocal Scanning Laser Ophthalmoscopy (CSLO) ancillary study to the Ocular Hypertension Treatment Study (OHTS) adds to this list demonstrating that even when the optic disc is not classified by expert review of stereoscopic photographs as glaucomatous and the standard visual field is normal, certain optic disc features obtained using baseline HRT imaging are associated with development of primary open-angle glaucoma. In contrast, optic discs that were classified as being within normal limits at baseline with the Moorfields regression analysis were unlikely to develop a glaucoma endpoint during the 5-years duration of analysis. This study provided the first evidenced-based validation for a glaucoma imaging technology. Similar studies demonstrating that certain structural changes can precede the observation of a glaucoma endpoint have also been performed with scanning laser polarimetry¹³ and OCT¹⁴. Undoubtedly, models of global risk assessment will evolve that incorporate topographic assessments of optic disc in conjunction with clinical parameters.

4. Early Diagnosis

The significant advances in hardware and software platforms for glaucoma imaging should not mislead a clinician to think that glaucoma diagnosis can be solely machine-based at the current time. Rather, the imaging information should be considered as being complementary to other clinical measures. Yet, there are some data suggest that imaging and expert assessment of optic disc photographs are similar in their ability to identify early glaucoma,^{15, 16} and it is clear that imaging does offer some very attractive advantages. Given the variability of clinician drawings and recordings of optic disc measures, imaging may elevate the assessment of the optic nerve by the general clinician, perhaps to the level of a fellowship-trained expert. Imaging enables the clinician to objectively evaluate the peripapillary RNFL which unlike the optic nerve cannot be easily visualized or measured, and has been demonstrated to change early in the course of the disease.^{17–20} RNFL abnormalities often exist in eyes with early glaucoma with normal standard automated perimetry.^{21, 22} Finally, imaging enables the clinician to compare a patient to a population of age-matched “normals” facilitating one’s ability to identify abnormal structural features. The inability to reliably detect optic disc hemorrhage with any of the available imaging technologies is a definite liability of their use, and highlights the need for clinical examination to provide complementary information.

5. Progression

There are few studies involving the role of imaging in human glaucoma progression detection, hampered in part by rapidly evolving changes in technology that disrupt longitudinal studies. Progressive RNFL thinning measured with OCT²³ and optic nerve cupping measured with CSLO^{24, 25} have been reported in experimental models involving non-human primates. At present there is limited evidence to support that imaging may assist the clinician in identifying progression of established glaucoma. Many studies have identified greater change in imaging derived measures than standard automated perimetry^{26–29} but the specificity of such changes remains to be validated. Longer follow-up intervals are required in order to determine if the changes identified only using structural technologies predict the subsequent development of visual field progression.

Standard Structural Endpoints in Glaucoma Clinical Trials

The standard structural efficacy endpoint in randomized and population-based glaucoma clinical trials is a reproducible change in optic disc appearance using stereoscopic optic disc photography^{12, 30–34}. With careful inspection, glaucomatous structural progression may be identified by noting diffuse or focal neural rim thinning with expansion of the optic cup, and progressive RNFL atrophy. Non-quantitative changes such as optic disc pallor, parapapillary atrophy, and optic disc hemorrhage may be identified with photography and cannot be measured with imaging technology. In the OHTS, inspection of disc photographs identified significantly more frequent disc hemorrhage events than recorded by the examiner.³⁵

There are limitations to using optic disc photography as the sole structural outcome measure in glaucoma clinical research. Glaucoma progression occurs slowly and changes are often subtle and easily missed. Further, fewer optic disc endpoints exist in eyes with moderately advanced glaucoma with considerable neural rim atrophy complicating the ability to detect structural change. In ocular hypertensive eyes with normal optic disc appearance enrolled in the European Glaucoma Prevention Study (EGPS) and OHTS, isolated optic disc endpoints were observed in 40%³⁶ and 55%³¹ of progressing eyes respectively. In contrast, 0.8% and 11% of progressing eyes with established glaucomatous optic nerve damage demonstrated detectable structural endpoints in the Early Manifest Glaucoma Trial (EMGT)³² and Collaborative Normal-Tension Glaucoma Study³³, respectively. Unresolved issues exist regarding viewing methods and confirmation of suspected structural progression that may have contributed to these discrepant results. In the OHTS confirmatory optic disc photographs were required to substantiate suspected change and direct stereo-viewing of images by experts was utilized to assess optic disc progression. In EGPS³⁰ confirmatory disc photographs were not obtained, and in the EMGT³⁷ flicker chronoscopy of non-stereo disc images, but not stereoscopic disc photography, was utilized to assess optic disc progression.

Role of Imaging in Clinical Trials

Imaging technologies have the potential to identify relevant structural efficacy endpoints in randomized clinical trials (RCTs). The HRT has been studied in the EGPS³⁶ and in an ancillary study of the OHTS³⁸. Topographic parameters generated with the HRT have been demonstrated to correlate highly with clinical estimates of the optic nerve generated using expert assessment at an independent reading center after correction for optic disc size.³⁹ The CSLO ancillary study to the OHTS³⁸ demonstrated that the HRT may predict conversion to primary open-angle glaucoma with a positive predictive power of up to 40%, and a negative predictive power of 93%. Thus far, glaucoma RCTs have not employed RNFL imaging technologies such as OCT or GDxVCC. It is highly probable, however, that RNFL assessment will play an expanded role in trials to explore both IOP-lowering and non-IOP lowering

therapies such as potential neuroprotective compounds in which the optic disc and RNFL is a more appropriate efficacy endpoint.

Imaging is unlikely to replace optic disc photography in glaucoma RCTs or clinical practice, nor should it. Optic disc photographs are a useful means of judging progression, particularly in glaucoma suspects and eyes with early disc damage, and documentation of optic disc hemorrhage. Yet, imaging may serve as a useful adjunct to disc photography to provide complementary information that may facilitate progression detection using rate-based changes over time since the output data is quantitative, and highly reproducible at all stages of the glaucoma continuum. Imaging in RCTs may also be useful for enrichment of glaucoma cohorts consisting of populations at high risk for glaucoma progression. For example, ocular hypertensive eyes with baseline HRT abnormalities³⁸ and reduced RNFL thickness measured with OCT¹⁴ and GDx¹³ have been demonstrated to be at increased risk for subsequent progression to POAG. Finally, imaging may provide an opportunity for more robust identification of glaucoma endpoints and faster, less costly clinical trials. Regulatory hurdles presently exist that limit the ability to use optic disc and RNFL imaging as endpoints.

Pitfalls With Imaging

Technology undergoes constant evolution and we as physicians, and our patients, have benefited considerably in this regard. The last decade has produced expansion of datasets that enable one to differentiate normal from abnormal, improved precision, increased resolution and image registration; and constant software upgrades. A sacrifice for such change has been the costs associated with replacing technologies that become outdated or are no longer backwards compatible with previously collected data. This has certainly negatively impacted longitudinal studies seeking to validate the use of imaging for detection of glaucoma progression. Other pitfalls exist. Image quality is dependent upon operator skill, patient-related factors such as pupil diameter and media clarity, and instrument-dependent variables. Imaging artifact, such as poorly compensated corneal birefringence using the GDx^{40–44} or the low signal strength using the OCT that is sometimes identified^{45, 46}, continues to exist amongst all technologies prompting questions regarding the precise role of imagers in clinical practice.⁴⁷ Imaging may produce false identification of glaucoma and its progression. Imaging also may fail to detect a glaucomatous optic disc or RNFL. Thus, clinicians should not make clinical decisions based solely on the results of one single test or technology.

The Future of Imaging

The paradigm has shifted from macroscopic to microscopic measurements. Current technologies enable measurement of the optic nerve and RNFL. Higher resolution devices have been developed with shorter acquisition times and three-dimensional imaging of posterior segment structures,⁴⁸ that may subsequently enable direct measurement of the retinal ganglion cells or assessment of retinal ganglion cell dysfunction. Imaging of cellular and sub-cellular structures may soon follow. Improvements in image registration and refinement in software algorithms that differentiate test-retest variability from true biological changes will enhance progression detection.

Conclusions

Computer assisted imaging of the optic disc and RNFL facilitates glaucoma diagnosis and monitoring. The clinician who successfully integrates imaging in practice complements their clinical evaluation with adjunctive diagnostic testing. Some issues have been resolved; others need to be further addressed, particularly progression detection. Longitudinal studies currently underway will undoubtedly provide additional guidance. It is clear that technologies will continue to evolve and new information will emerge.

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Biography

DSG Biography

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