SWEPT SOURCE OCT & OCT ANGIOGRAPHY

HIGHLIGHTS FROM ISSOCT
QUANTIFICATION OF GEOGRAPHIC ATROPHY ASSOCIATED WITH AMD

Evaluation of automatic quantification using a new software.

BY JOSÉ M. RUIZ-MORENO, MD, PhD

Geographic atrophy (GA) is an advanced form of age-related macular degeneration (AMD) that affects more than 5 million people worldwide.¹ It is a common cause of vision impairment and a leading cause of impaired visual function in the elderly. There is no approved treatment.²,³

The quantification of GA and its evolution is an important clinical task, as it is the only procedure that enables us to verify disease progression, which is closely associated with vision loss. Owing to the time-consuming and subjective nature of manual analysis, there is a need for reliable, objective, automated methods of image segmentation to obtain GA measurements.

In response to this need, Topcon developed new software, which my colleagues and I evaluated in a recent study.⁴

STUDY OVERVIEW

The objective of our study was to determine the accuracy and repeatability of new software designed to automatically quantify the GA area associated with AMD using the Triton Swept Source OCT (Topcon). This was a cross-sectional, noninterventional study of eyes with GA without previous choroidal neovascularization. We analyzed 46 eyes of 33 patients, 20 male and 13 female, whose mean age was 76.3 years (age 54 to 96).

We performed color fundus photography, autofluorescent imaging, and OCT macular cube 7x7 mm with eye tracking three consecutive times.

We classified each case according to lesion morphology automatically determined by the software as regular or irregular and the number of lesions as single or multiple. For example, we could have a single lesion or two or more...
lesions with regular morphology. Similarly, we could have a single lesion or multiple lesions with irregular morphology. Of 46 eyes, 30 had single lesions, 16 had multiple lesions, 18 had regular lesions, and 28 had irregular lesions.

Figure 1 shows an eye with a typical GA lesion in the middle of the posterior pole. We manually measured the GA area by drawing a line around the lesion using autofluorescence. Figure 2 shows the potential of this new software. By clicking the GA point, we automatically see the area and the perimeter of the lesion according to the segmentation performed. We have the fundus autofluorescence as a reference image.

Another example shows the improved segmentation performed by the software (Figure 3). In this case, the software did not detect any part of the lesion. When we clicked on this part of the lesion, the measure was corrected to improve the accuracy of the results.

In every patient, we performed manual and automatic determination of the GA area. Manual determination was performed using one fundus autofluorescent image evaluated by three different investigative masked measures. For automatic or semi-automatic detection, we performed three consecutive cube 7x7 mm and one measure in each of the cubes to determine the mean of the three measures in each group. We compared normal distribution with paired Student T Test. The primary endpoint was the area of the lesion, and the secondary endpoint was the perimeter.

**STUDY RESULTS**

Our overall results showed the area measured automatically was 5.62 sq mm versus 5.59 sq mm measured manually; this difference was not statistically significant. These results were accurate, according to the manual measurements obtained with fundus autofluorescence. The automatic measurement of the perimeter determined by the software was larger, 19 versus 16.7 measured manually, and this difference was statistically significant.

Figure 4 shows the distribution according to the number of lesions. The difference between automatic and manual measurements based on the morphology of the lesions was similar in regular lesions (6.04 vs 6.38) and irregular lesions (5.35 vs 5.09) (Figure 5). The perimeter was also similar, but there were more differences between manual and automatic measurements.

Figure 6 summarizes the differences between the automatic versus manual measurements in single and multiple regular and irregular lesions.

The primary endpoint demonstrated good results...
with no differences in the determination of the area with automatic software versus manual measures. When we analyzed the perimeter, the secondary endpoint, the measurement of single lesions was 14 automatically versus 13 manually. We found statistically significant differences between automatic measurements of the perimeter versus manual measurements of the perimeter in multiple lesions and irregular lesions.

CONCLUSION

This new software enables us to automatically quantify the GA area and the perimeter associated with AMD. The image analysis is fast and objective, with a lower coefficient of variation than with manual procedures. The software is accurate in single, regular, and atrophic lesions, but segmentation should be improved for irregular cases and cases with multiple lesions.


JOSE M. RUIZ-MORENO, MD, PhD

- President, Spanish Retina and Vitreous Society, Spain
- Professor, Department of Ophthalmology, Castilla La Mancha University, Albacete, Spain
- Head of Ophthalmology Department, Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain
- Medical Director, Vissum Corporation, Madrid, Spain
- JoseMaria.Ruiz@uclm.es
- Financial disclosures: Advisory Board (Alimera, Allergan, Bayer, Novartis, Quark Pharmaceuticals); Grant Support (Spanish Ministry of Health); Research Funding (Topcon)

This study has been supported in part by a grant from the Spanish Ministry of Health, Instituto de Salud Carlos III, Red Temática de Investigación Cooperativa en Salud: "Prevención, detección precoz y tratamiento de la patología ocular prevalente, degenerativa, crónica" (RD16/0008/0021). Dr. José M. Ruiz-Moreno receives research support from Topcon.

OCT-A FINDINGS OF MYOPIC CNV

Where does myopic CNV originate?

BY KYOKO OHNO-MATSUI, MD, PhD

Myopic choroidal neovascularization (CNV) develops in 10% of pathologic myopia and is the most common cause of visual impairment in people with high myopia.1 In the natural course and the treated course, myopic CNV goes through three phases: active, scar, and atrophic (also known as CNV-related macular atrophy).2

OCT angiography (OCT-A) of the three phases shows that myopic CNV maintains blood flow in the atrophic phase long after the onset of CNV (Figure 1). In the active phase, a clear vascular network is visible, but in the scar phase, the CNV is shrunken and irregularly shaped. In the atrophic phase, we...
still detect CNV with blood flow. This is strange because myopic CNV almost never recurs at the atrophic phase.

CNV-related macular atrophy is not simply a chorioretinal atrophy but a Bruch’s membrane hole. The eyes shown in Figure 2 developed CNV around 10 years ago. In the OCT image, the arrows show a retinal pigment epithelium (RPE) end. We can also see the remnants of Bruch’s membrane shown by arrows near the RPE end, and there is an area without Bruch’s membrane around the CNV. In the area without Bruch’s membrane, the choroid also disappears. What is the source of the blood flow within the atrophic CNV?

**ROLE OF SCLERAL PERFORATING VESSELS**

The purpose of our recent study was to examine the scleral perforating vessels of myopic CNV using Swept Source OCT (SS-OCT) to determine whether these vessels are arteries or veins by using indocyanine green (ICG) angiography.

Giuffré and colleagues reported that perforating scleral vessels were found in 71% of eyes at the site of myopic CNV. As a mechanism of this association, they focused on lacquer cracks. The scleral discontinuity at the site of perforating vessels may lead to increased stretch forces on Bruch’s membrane, causing lacquer cracks. The authors thought that CNV occurred subsequent to lacquer crack formation. This is an important study, but not all myopic CNV has lacquer cracks. The role of perforating scleral vessels for myopic CNV is not fully clarified.

Louzada and colleagues reported a case in which CNV was connected to an intrascleral blood vessel. This report, for the first time, suggested a possibility that CNVs can originate directly from scleral vessels. The authors observed scleral perforating vessels at or around myopic CNV in 93 (75%) of the 124 eyes. Perforating vessels were seen in all phases from active through atrophic. In 10 eyes (11%), the authors observed a direct communication between the scleral vessels and CNV through a Bruch’s membrane defect.

**REPRESENTATIVE CASES**

A patient developed CNV 12 years prior, and the fundus showed CNV-related macular atrophy (Figure 3). OCT-A of the outer retina slab and the choriocapillaris slab show CNV with detectable blood flow. SS-OCT shows subretinal CNV. Two cross-sections of blood vessels within the sclera can be seen. In a serial section, a vessel appears to penetrate the outer surface of the sclera and run toward the choroid and through a Bruch’s membrane defect.

What is the vessel that is penetrating the sclera? There are two types of perforating vessels around the macula: short posterior ciliary arteries (SPCAs) and macular vortex veins. In normal eyes, SPCAs penetrate around the optic nerve and the macula. In eyes with pathologic myopia, however, the penetration sites are dislocated toward the periphery because of globe expansion.

Macular vortex veins exist in one-fourth of myopic eyes. They exit the eye in and around the macula, sometimes forming ampulla.
Which type of penetrating vessel does this patient have? In the arterial phase of the ICG angiogram, we can see the retrobulbar part of the SPCAs (Figure 4). They penetrate the eye somewhat distant from the fovea, but some are still visible just around the CNV.

In a magnified image (Figure 5), the oblique vessel is already seen at 8 seconds in the arterial phase of ICG angiography. No macular vortex vein was identified in the venous phase. This perforating vessel is probably SPCA.

A second patient developed CNV 13 years prior and now has CNV-related macular atrophy. OCT-A shows the detectable blood flow within the CNV (Figure 6). SS-OCT shows subretinal CNV, and we can see that a large vessel penetrates the sclera and courses toward the choroid. We can also observe some branches coming from this large vessel toward the CNV. In a serial section, this vessel originates from the large vessel and is continuous to the CNV through a defect of Bruch’s membrane.

**CONCLUSION**

In these eyes, some of the myopic CNVs had penetrating scleral vessels that directly communicated with the CNV. This communication indicates that at least some of the myopic CNVs can be called SPCA-derived CNVs, or in some cases, intrascleral vessel-derived CNVs.

Although no histological studies show direct communication between scleral vessels and CNV, this communication could be possible in eyes with pathologic myopia with almost absent choroid. If they do not have enough choroid nearby, they might seek another route, perhaps somewhere deeper.

Myopic CNV maintains its blood flow even in the atrophic phase surrounded by absent choroid because it has a special route of supply. It is like the Persian Qanat, the water supply system under the desert.


KYOKO OHNO-MATSUI, MD, PhD

- Department of Ophthalmology and Visual Science, Tokyo Medical and Dental University, Japan
- kohno.oph@tmd.ac.jp

Financial disclosures: None acknowledged
QUALITATIVE AND QUANTITATIVE ASSESSMENT WITH OCT-A IN EXUDATIVE AMD

Two new studies underscore the utility of OCT-A for managing AMD.

BY FLORENCE COSCAS, MD

Previous qualitative studies of choroidal neovascularization (CNV) showed good reproducibility for CNV detection and activity using OCT angiography (OCT-A) versus multimodal imaging.1 In a unique multicenter study, combined OCT-A and structural OCT had a sensitivity of 85.7% for detecting type 1 CNV.2

The following are summaries of recent studies underscoring the utility of OCT-A for managing exudative age-related macular degeneration (AMD).

QUALITATIVE RETREATMENT CRITERIA FOR AMD

This study describes OCT-A findings based on qualitative activity criteria in treating exudative AMD versus structural OCT signs ultimately leading to the decision to perform an intravitreal injection (IVI).3 A total of 126 eyes were included: 84.8% had active type 1 CNV; 15.2% had type 2 CNV. Type 3 CNV and polyps were excluded from this study.

We evaluated four OCT-A criteria (tiny branching, loops, dark halo, and peripheral arcade) versus structural OCT criteria (intraretinal fluid, subretinal fluid, and central macular thickness).

The mean follow-up was 22.97 (+/−13.47) months. The mean number of IVIs was 10.39 +/−6.45; and the mean interval between two injections was 2.35 +/−1.42 months (eyes that were + 6 months without IVI were excluded).

In the overall analysis, considering all four qualitative OCT-A criteria versus structural OCT, OCT-A was found to have:

• 96.7% sensitivity.
• 66.7% specificity.
• 88.5% intra-grader coefficient.
• 78.4% inter-grader coefficient.

A validation test with a grader from another team on a new sample of 104 patients showed a concordance rate of 90.4%.

A key take-away message regarding OCT-A versus structural OCT is that the probability of having an IVI with only two qualitative criteria (tiny branching and peripheral arcade) is 71.23%. With all four qualitative criteria, the probability is 96.7%. We used Principal Component Analysis to avoid bias of the multicollinearity of these OCT-A signs.

FRACTAL DIMENSION ANALYSIS

Until now, OCT-A qualitative studies described morphological changes in CNV during IVI. Fractal dimension analysis may be useful in quantifying the complexity and homogeneity of different stages of CNV.

Previous methods to quantify CNV are scarce, often restricted to the area and density of CNV, and they are based on manual delineation of CNV. A new automated quantitative technique using fractal analysis enables the quantification of nonperfusion areas and may be helpful in monitoring CNV.4,5

OCT-A may provide quantitative biomarkers of activity and guide monitoring of CNV.6 Other studies suggested that lacunarity could be an objective way of evaluating CNV.7

Fractals are patterns found in nature and biological systems that show self-similarity at different magnifications. The application of fractals and fractal growth processes to the normal human retinal circulation led to an estimate fractal dimension of 1.7 on red-free images.

In experimental studies of tumoral neovascular networks submitted to anti-VEGF therapies, blood vessels reduced their density, lost their random architecture, and returned to a more normal and regular pattern.8,9 Fractal dimension tends to increase to get closer to normal during treatment.

Fractal analysis or organization calculates the complexity of a lesion according to the size of the boxes necessary to cover the image versus the number of boxes necessary to cover the image.

The lacunarity (homo or inhomogeneity) characterizes the distribution of spaces in an object in a given scale and...
describes the texture of this object according to the scale, homogeneity versus inhomogeneity.

The mean fractal dimension of the superficial capillary plexus is 1.63 (mean 68 eyes) using the Topcon OCT-A. The mean lacunarity is 1.49 on the same superficial capillary plexus using the Topcon OCT-A. The lower the fractal dimension is, the more random the architecture is. The lower the lacunarity is, the more homogenous the CNV is.\(^\text{10,11}\)

**FRACTAL ANALYSIS OF CNV**

In this study, we sought to answer the question: can fractal analysis allow us to measure the difference in complexity between naïve CNV and fibrotic treated lesions?

We performed a retrospective review of 61 eyes, mainly type 1 and 2; we excluded type 3 and polypoidal choroidal vasculopathy.

The 26 eyes in group 1 (naïve CNV) had a diagnosis of CNV on fluorescein angiography and indocyanine green (ICG) angiography and fluid on structural OCT. They had at least two active criteria on OCT-A (tiny branching and peripheral arcade). The 35 eyes in group 2 (fibrous CNV) showed absence of fluid. Their last IVI was more than 6 months ago. They had at least two fibrous criteria (no interconnected tiny capillaries and no peripheral arcades).

The OCT-A quantifier software is an original user-friendly interface with automatic speckle noise removal, automatic blood flow delineation, and scale invariance likelihood score. This automatic analysis from the outer retinal slab provides: blood flow area, aspect ratio, vessel density, fractal dimension, and lacunarity in a few seconds.

Figure 1 shows examples of naïve CNV versus fibrous CNV. We detected lower fractal dimension and lacunarity in active CNV versus fibrous treated CNV.

Figure 2 is a case of fibrotic treated CNV. During follow-up, we observed a stable qualitative aspect, but fractal dimension decreased between June and September. The eye was treated with intravitreal anti-VEGF and 2 months later, the CNV became less organized with an increase of fractal dimension.

Figure 3 shows an example of quantitative detection of recurrence during a treat-and-extend regimen. At month 4, we observed fractal dimension and lacunarity had increased. No fluid was observed on structural OCT, and visual acuity had increased. At month 6, we saw an increase of fractal dimension and lacunarity, no fluid, and increased visual acuity. At month 8, we observed recurrence. Finally, we detected a decrease of fractal dimension and lacunarity in a more random and more homogenous CNV. In fact, it could have been possible to reduce the treat-and-extend interval earlier owing to the decrease of lacunarity. We observed less increase at month 6 than at month 4.

**PRELIMINARY RESULTS**

We observed higher density and lower area in the eyes with naïve CNV versus those in the fibrotic group. Fractal dimension and lacunarity were lower in the active group versus the remission group. We also found that active CNVs were smaller and denser than fibrotic CNVs in remission. Fractal dimension, lacunarity, and area were lower in the active versus the remission group.

The area of blood flow could be the biomarker with discriminative power. Associating fractal dimension and area could have the best predictive performance. Studies are ongoing.
Note that this is a preliminary study with a small sample. Among the technological limitations were segmentation, motion, and projection artifacts. Some signals were weak because of high pigment epithelial detachments and hemorrhages, as well as poorly perfused or multiple CNVs. In addition, we used 2D analysis of three-dimensional structures.

**CONCLUSION**

OCT-A-based fractal dimension may be useful for assessing the maturation status of a neovascular network. Further studies are needed to evaluate neovascular networks with fractal analysis over the course of treatment. ■


**FLORENCE COSCAS, MD**
- Centre Ophthalmologique de l’Odéon, Paris, France
- coscas.f@gmail.com
- Financial disclosures: Consultant (Allergan, Bayer, Novartis, Topcon)

**MINIMIZING RELIANCE ON PERIMETRY FOR GLAUCOMA DIAGNOSIS AND STAGING**

How SS-OCT may reduce the need for repeated perimetry in clinical practice.

**BY JEFFREY M. LIEBMANN, MD**

We are in the middle of a revolution for glaucoma, and paradigms are changing rapidly. Significant discovery is resulting in advances in translational science with novel interventions, surgeries, and medical therapies. The application of telemedicine and machine learning will change how we interpret these images. All of these advances are leading to individualized disease detection and treatment.

We understand a great deal about glaucoma and the linked structural changes that occur in the retina, optic nerve head, retrobulbar optic nerve, lateral geniculate nucleus, and visual cortex. Among these structures, the optic nerve head—specifically, the lamina cribrosa—is often considered the primary site of retinal ganglion cell axonal injury in glaucoma. Therefore, in addition to clinical optic disc examination, evaluation of the lamina cribrosa structure may improve glaucoma diagnostics and our understanding of glaucoma pathophysiology.

We understand a great deal about the stages and progression of glaucoma from normal through cell death, loss of the ganglion cells, nerve-fiber layer loss, and eventually visual impairment.

**DIAGNOSTIC CHALLENGES**

With all of this knowledge, why is diagnosing glaucoma so difficult? One of the major reasons is the wide variation in the clinical appearance of a healthy optic disc, which may be affected by size, tilt, parapapillary atrophy, and media opacity. These factors may limit our ability to accurately diagnose this disease.

In addition, there is no proven screening methodology for glaucoma. Essentially, people need a complete eye examination, including perimetry, but visual field testing is
highly variable and unreliable for both screening and monitoring progression. In the Ocular Hypertension Treatment Study, if a patient had a normal visual field test and then had an abnormal test, upon the third test, 86% of patients did not have a repeatable visual field abnormality.\(^1\)

In clinical trials, confirmation of an endpoint requires repeated testing using the same modality. While this is an important research tool, it is not useful clinically. Clinically, we corroborate damage. We observe the disc and the visual field individually, and then we evaluate them together to see if there is a match in terms of structure and function. In the past, it was suggested that there is a disconnect between structure and function in glaucoma, but we now know that a precise structure-function relationship exists in virtually all of our patients throughout the glaucoma spectrum, even in very early disease.\(^2\)

I think we are entering an era of structure-structure assessment, which will greatly change our need for other types of testing for many patients. For example, a suspicious neuroretinal rim can be confirmed or denied by optical OCT assessment of the retinal nerve fiber layer (RNFL) thickness and pattern. A notch can be corroborated by an RNFL defect. In this setting we need no further information to diagnose glaucoma. We can also add in the ganglion cell inner plexiform layer thickness or pattern. In the future, we will be able to incorporate data about the status of the lamina cribrosa. Other factors such as disc hemorrhage also allow us to perform a structure-structure assessment.

Imagine if we could combine all of these parameters into a machine-learning approach, we might be able to reduce or even eliminate the use of visual fields.

**STRUCTURE-STRUCTURE ASSESSMENT**

I will focus on the RNFL and the ganglion cell complex and its pattern, as detailed in the Hood Report, which is exclusive to Topcon’s Swept Source OCT (SS-OCT) Triton.\(^3\) The report includes a circumpapillary RNFL scan to verify the absence of defects and a circumpapillary RNFL plot that focuses on the macula in the center. We can view the en face slab image, the RNFL thickness map, the macula thickness map, the probability maps, and so on, with the visual field points superimposed on the probability plots. That is an important function, because it enables us to determine whether or not a field defect is related to one of these points. Often, we find visual fields that would have been passed as normal actually have subtle defects, particularly on the 10-2 testing.

We can also see that the changes in the macula region are occurring simultaneously with those in the RNFL.\(^4,5\)

**CLINICAL EXAMPLES**

The key to using the Hood Report is to examine all parts of the OCT image and report. For example, we can evaluate a healthy eye with a normal visual field using a step-wise approach (Figure 1). The circumpapillary image shows normal RNFL thickness. The en face slab image, the macula thickness map, and the probability map are normal. The likelihood of glaucoma in that setting is extremely low. On the glaucoma continuum, this is a normal eye (Figure 2).

We should not underestimate the value of a normal scan when we evaluate glaucoma suspects. It enables us to whittle down that nebulous category of glaucoma suspect. For example, many patients who have a large cup/disc ratio and a normal image are normals. Rather than categorize them as glaucoma suspects and see them every 3 to 6 months, we could see them in 2 or 3 years for reassessment if we have some level of suspicion about them. Being able to determine that these eyes are normal means that we can apply our resources to the people who actually have disease.

Figure 3 shows visual field tests from a male patient who has ocular hypertension. After 20 years of essentially normal fields, tested twice a year, he finally may be developing an
abnormality. Imagine if we were obtaining OCT images during that time, and they were all normal. These visual field tests probably would have had very little added value. We probably could have done visual field tests less frequently and monitored the patient with imaging, which is highly reproducible (unlike visual fields) and patient friendly.

Figure 4 shows an example of a patient who has a full visual field with a slight defect. Looking at this nerve, I would say it is glaucomatous, perhaps early disease, but imaging reveals much more loss (Figure 5). Instead of staging this as early disease, we can recast it and say there is central visual field loss and the patient’s disease is much more advanced based upon the accumulation of the data and the testing.

In practical terms, our current approach does not utilize all of the data that is available, and our approach to patient care will become more effective when we do.

CONCLUSION

We have a series of unmet needs in glaucoma, but our diagnostic and monitoring tools are changing the landscape. In summary, OCT reduces the need for repeated perimetry in clinical practice for early glaucoma and glaucoma suspects. Increasing the combination of structural assessments will improve sensitivity and specificity.

JEFFREY M. LIEBMANN, MD

Professor of Ophthalmology, Glaucoma Service Director, and Vice Chair for the Department of Ophthalmology at Columbia University Medical Center, New York, New York

jm1234@cumc.columbia.edu

