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Review article

Structural *en face* optical coherence tomography in neovascular and nonneovascularage-related macular degeneration: Use and utility in clinical practice

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ABSTRACT

Age-related macular degeneration (AMD) is a leading cause of blindness and visual impairment worldwide. Structural *en face* optical coherence tomography (OCT) is an innovative imaging technology that has recently attracted interest because of its potential for assessing AMD features. We conducted a comprehensive review of its application in AMD. In neovascular AMD, structural *en face* OCT can detect exudative activity, monitor the neovascularization area, study the choroid in polypoidal choroidal vasculopathy, and visualize neovascular membranes in pigment epithelial detachments. Moreover, in nonneovascular AMD, this study provides details on geographic atrophy and drusen, the identification of intraretinal retinal pigment epithelium migration, and the detection of different patterns of outer retinal tubulations. Our study revealed that structural *en face* OCT can provide relevant information on patients with AMD.

1. Introduction

En face optical coherence tomography (OCT) is a noninvasive imaging technique that has recently attracted increasing interest due to its potential for analyzing pathological findings. It was first introduced by Podoleanu and coworkers in 1997, but the limited resolution of instruments delayed the broad adaptation of this modality.[54]

En face OCT produces coronal scans (C-scans) of individual retinal and choroidal layers at a preferred depth. *En face* OCT images can be captured using different types of OCT, such as time-domain (TD),[39] spectral-domain (SD),[11] or swept-source (SS).[39] Compared with other modalities, SS-OCT can provide finer resolution of the deeper layers of the eye (choroid and sclera) by utilizing a longer wavelength [2] and allows faster image capture. Moreover, TD-OCT has the ability to capture live images and achieve better dynamic focusing on the axial plane [53] than SD-OCT, resulting in faster image capture.

The introduction of OCT angiography (OCTA) represents a landmark in the reappraisal of *en face* OCT. Angiographic *en face* images are captured through the projection of motion signals in a selected depth region of the tissue.[39] Through segmentation, details of multiple layers of the retinal and choroidal vasculatures can be identified, revealing key features of major eye disease.[63]

En face OCT offers many additional clinical advantages over conventional longitudinal OCT scan images. In fact, the *en face* approach has the ability to localize lesions within specific retinal and choroidal layers, allowing for the monitoring of OCT B-scan findings through accurate measurement. This type of OCT permits more precise mapping of pathological and structural changes.[37] Furthermore, it provides the possibility of visualizing multiple pathological findings in a single image. Finally, as a noninvasive technique, *en face* OCT may also be utilized as an adjunct to other imaging modalities for diagnostic pathways.

Herein, we focus on structural *en face* OCT, a technique that identifies the structure of various retinal layers and that has been helpful in the diagnosis of several ophthalmologic diseases. We highlight the clinical application of structural *en face* OCT in neovascular and

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nonneovascular AMD.

2. Structural *en face* OCT of neovascular AMD

En face OCT has been used to study neovascular AMD (nAMD), an advanced form of AMD characterized by the presence of macular neovascularization (MNV).[22] MNVs are divided into 3 subtypes according to their localization. Type 1 MNVs are characterized by vessels that grow from the choriocapillaris into the sub-retinal pigment epithelium (RPE) space. Type 2 MNVs also originate from the choriocapillaris, but their vessels penetrate the RPE and spread subretinally. Moreover, type 3 MNVs include proliferative vessels that extend from the deep capillary plexus of the retina toward the outer retina. Polypoidal choroidal vasculopathy (PCV) is considered a subtype of type 1 nAMD, characterized by a branching neovascular network and polypoidal lesions. [19,86] In the nAMD category, we will include exudative MNVs and quiescent MNVs, a peculiar form of nAMD without exudation or hemorrhage, detected via OCTA.

2.1. Detection of neovascularization and exudative activity in nAMD

One of the most important applications of *en face* OCTA has been the detection of neovascularization in nAMD.[3] While *en face* OCTA images have primarily been used to visualize vascularized networks and describe the different morphologies of various types of MNVs,[72] structural OCT *en face* images could be utilized for assessing the exudative activity of the MNV.[45]

The observation of intraretinal fluid (IRF) and subretinal fluid (SRF) via OCT is recognized as criteria for disease activity and as efficacy outcomes in clinical trials.[17,29,68] On *en face* images, the assessment of the exudative activity of MNVs can be monitored through the visualization of the SRF.[6,70] Additionally, evaluation the changes in the SRF, displayed in its full extension on a single slab, may provide information on the treatment response. [45]

In 2008, Stopa and coworkers evaluated the ability of *en face* OCT to detect the location and extent of the MNV, macular edema, and SRF in AMD patients. In 4 of the 12 eyes, *en face* OCT revealed SRF that was not detected via fluorescein angiography (FA).[70]

Mohammad and coworkers [45] reported a method of *en face* OCT imaging for visualizing and monitoring the spatial extent of the SRF in nAMD. To detect the largest SRF area and assess the effect of fluid accumulation on photoreceptor function, *en face* imaging was performed at the anatomical depth of the photoreceptor inner segment ellipsoid layer, a retinal depth that is in close proximity to the photoreceptor cells.

On the *en face* OCT images, the SRF corresponded to irregularly shaped dark regions. The area of the dark region diminished after treatment, indicating a reduction in the SRF. With their study, they demonstrated that, on *en face* OCT images, the spatial extent of SRF can be clearly visualized and easily measured quantitatively at each visit. In accordance with the findings of Mohammad and coworkers, Elkhoìy and coworkers described a MNV at the outer retina level with adjacent neurosensory detachment, denoting activity.[18]

Fujiwara and coworkers instead demonstrated the potential of structural *en face* OCT for visualizing the SRF.[24] In their study, the fluid itself was clearly visualized on the *en face* images as a well-demarcated, low-intensity circular region that was easily monitorable.(Fig. 1)

2.2. Monitoring of the neovascularization area in nAMD

En face OCT could also be used to monitor the neovascular complex area, as it provides excellent reproducibility of lesion area measurement.[4] A decrease in the visible dimension has also been described [43] in the very early phases in the active neovascular complex after anti-vascular endothelial factor (VEGF) injections. Over time, however,

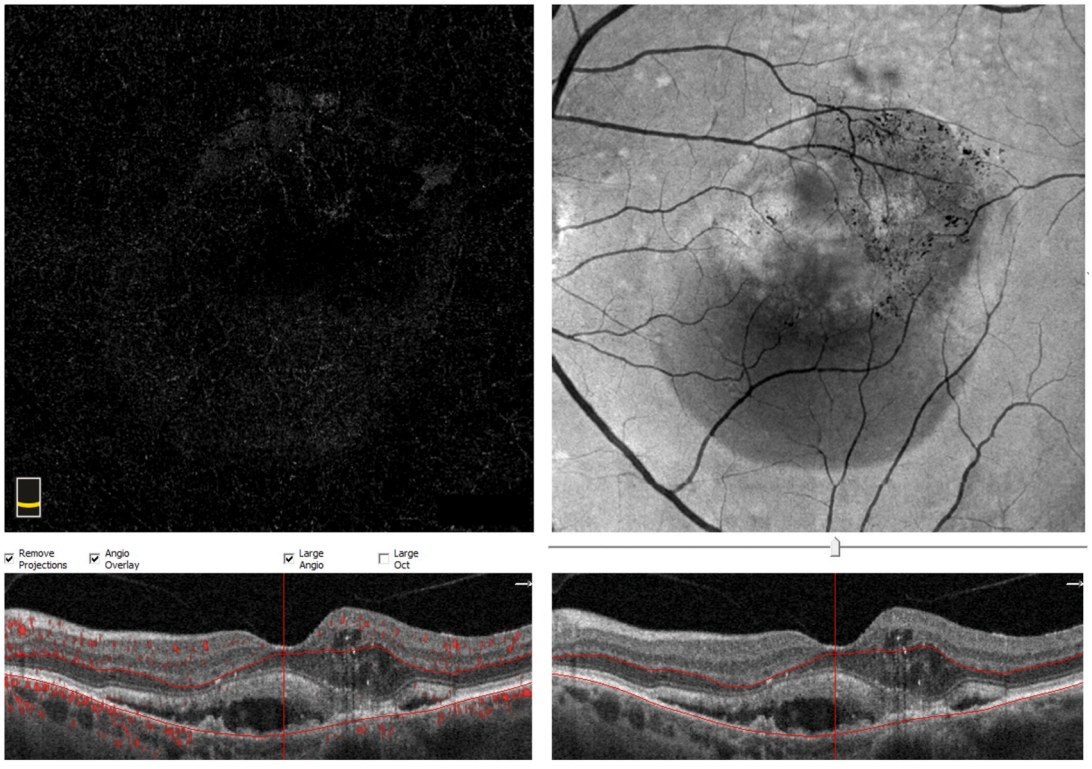

Fig. 1. *En face* OCT of an exudative type 1 MNV. The *en face* OCT angiography slab (upper and left) along the outer nuclear layers did not clearly show defined flow, though mild flow was observed in the upper foveal region. Structural OCT (down on B-Scan) revealed the outline of the slab, which was acquired between the red lines. *En face* OCT (upper and right) delineating a hyperreflective area surrounding the neovascolar membrane in the iuxta-foveal region. A rounded hyporeflective area, corresponding to serous neuroepithelial detachment, can be observed in the iuxta-foveal region on structural OCT (down and right).

and even following consecutive monthly injections, the MNV area reportedly increased an average of 19 %.[71]

In a study by Told and coworkers,[71] the neovascular complex displayed an immediate size reduction of approximately 25 % of the entire extension following one intravitreal injection. This was most likely due to vascular constriction rather than true anatomical shrinkage of the lesion. Within 2 weeks, however, neovascular growth restarts following the underlying VEGF stimulation. An increase in MNV lesion size was also previously shown for treatment-naïve quiescent nAMD MNV lesions by Querques and coworkers.[58] Quiescent MNVs are clinically inactive, but biologically active, showing MNV growth and an increased MNV area over time. Significant growth may help in predicting clinical activation. [12]

Ahmed and coworkers [3] noted that the average lesion area in inactive neovascular complexes was larger than that in active lesions. In the same study, type 1 lesions were reported to have a larger area than type 2 lesions. Unclassified fibrotic lesions had the largest mean area. The previously mentioned studies describe MNV growth as a natural biological behavior and highlight its role as an indicator of disease onset. Nonetheless, the assessment of this parameter and its relevance remain subjects of debate.(Figs. 2–6)

2.3. Identifying pathognomonic features in MNV subtypes in nAMD

En face OCT has also been reported to provide suggestive and peculiar findings of specific types of MNVs.[20] Falavarjani and coworkers described a novel feature, with segmentation at the level of the outer retina, consisting of radial hyperreflective lesions in a spiked wreath pattern called the 'pitchfork sign' surrounding a type 2 neovascular membrane. [20] The pathogenesis of this new sign is still unknown. Dragging of the overlying outer retinal tissue, resulting from traction associated with the type 2 neovascular complex, has been regarded as a possible causal mechanism. In the study by Falavarjani and coworkers, type 2 MNV regressed to a type 1 pattern in all eyes after intravitreal anti-VEGF injections, with resolution of the radial spikes and good improvement in VA. Radial spikes may represent a favorable prognostic outcome after anti-VEGF therapy.

2.4. Study of the choriocapillaris and choroid and its application in polypoidal choroidal vaculopathy (PCV)

The choriocapillaris and choroid are known to play important roles in the etiology and physiopathology of nAMD[23,46,57]; therefore, their study via *en face* OCT may increase our ability to diagnose and treat patients.

Flores-Moreno and coworkers [22] demonstrated that *en face* OCT slabs of the RPE and choriocapillaris layers, including type 3 MNVs, exhibited pathological alterations early in the disease process in nAMD. Hyporeflective changes were predominant at the RPE level and hyperreflective at the choriocapillaris. Similarly, Siu-Chun Ng and coworkers [47] attempted to identify, through structural *en face* OCT scans, exudative PCV, based on the presence or absence of pachyvessels, as the presence of pachyvessels has been reported in PCV patients. Pachyvessels were characterized by focal or diffuse dilatation of the outer choroidal vessels, sometimes with evidence of club-shaped posterior termination.

Kameda [31] was the first to demonstrate the utility of *en face* OCT as a screening examination for PCV in 2007. En face OCT identified polypoidal lesions in 84 % of the eyes examined in this study as small round protrusions of the RPE and identified branch vascular networks (BVNs) in 52.6 % of the eyes as smaller elevations of the RPE. Later, Kokame and coworkers [34] described PCV on *en face* SD-OCT as a subretinal vascular structure with hyperreflective borders and polypoidal dilations, with or without a BVN.

2.5. Visualization of neovascular membranes in pigment epithelial detachments (PEDs)

En face imaging may also be used to visualize MNVs in PEDs related to nAMD.[44] A retinal PED is defined as the separation of the RPE from the inner collagenous layer of Bruch membrane.[32] PEDs are a common feature of AMD (including idiopathic PCV) and develop in more than 80 % of eyes with nAMD.[7,51,56,80]

In their study, Semoun and coworkers [66] evaluated the identification of polyps inside a PED associated with dilated choroidal vessels using *en face* OCT. The dilated choroidal vessels were visible as hyporeflective tubes interconnecting with each other. The polyps presented as dome-shaped or round structures visible with heterogeneous reflectivity deeper than the pigment epithelium layer and attached to its posterior face under the dome of the PED. These polyps were detected in all

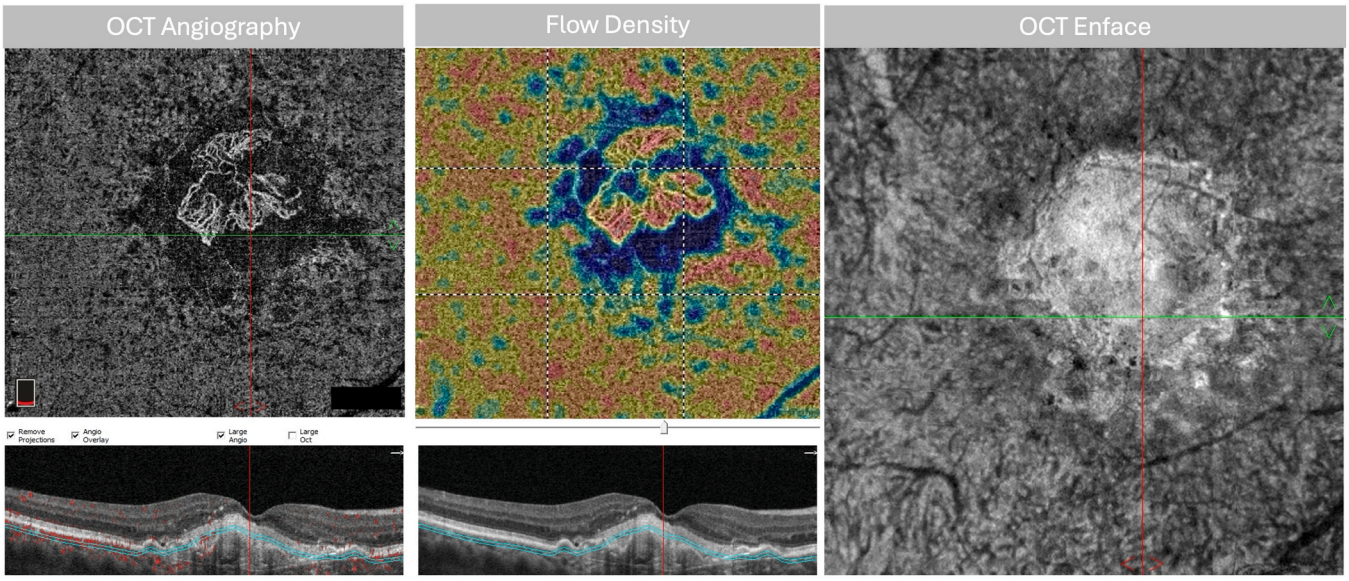

Fig. 2. *En face* OCT image of a fibrotic MNV scar. On the left, *en face* OCT angiography (upper image) and structural OCT (lower) images are shown. On the right, structural *en face* OCT reveals a hyperreflective central area corresponding to subfoveal fibrosis.

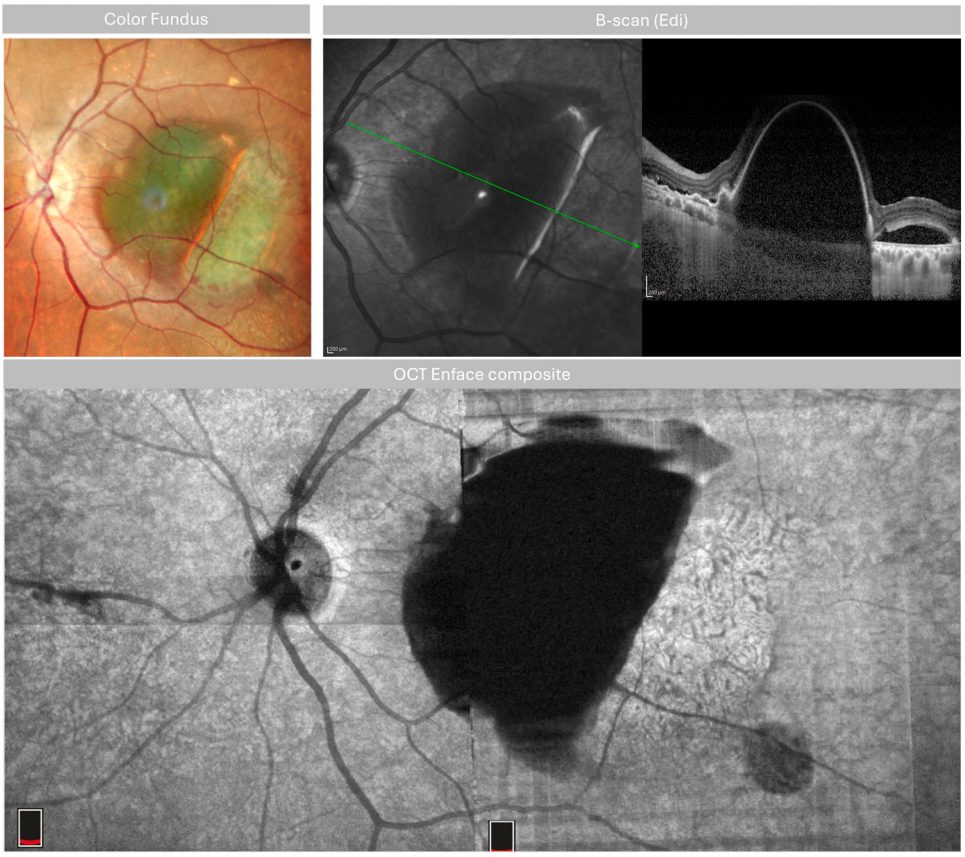

Fig. 3. Multimodal imaging of a PVC in a PED. The upper left image shows a color fundus of a PED with an RPE tears temporally to the fovea. The oblique outline of the tear is clearly recognizable. On the right, the B-Scan infrared and OCT B-scan EDI of the PED, which contains a clear content, are shown. Nasally to the PED, neuroepithelial microdetachments and ondulation of the RPE with corpuscular content, typical of polypoidal lesions, are visible. Temporally, the presence of SRF in the PED suggests the activity of the polypoidal lesion. The inferior OCT *en face* composite displays the area occupied by the PED, involving almost the entire macular region. The RPE tear is well distinguished temporally to the fovea through visualization of the choroid under the area of the retina stripped from the RPE.

patients. The PEDs were visualized as hyporeflective areas, predominantly circular with well-defined hyperreflective margins. Ninety percent of the polyps were surrounded by a hyporeflective area, corresponding to the SRF on *en face* OCT, and were located above the pigment epithelium layer.

Coscas and coworkers [14] proved that *en face* enhanced depth imaging (EDI) SD-OCT was able to demonstrate type 1 MNVs as a hyperreflective network within the fibrovascular PED in 79 % of eyes with nAMD, with an adjacent area of homogeneous hyporeflectivity consistent with serous exudation. Moreover, Van Velthoven and coworkers [73] demonstrated the use of *en face* OCT in identifying type 3 MNV when combined with fluorescein angiography (FA) to study PEDs. FA alone has limitations in defining the extent of type 3 MNV involvement due to blocked fluorescence.

3. Structural *en face* OCT of nonneovascular AMD

En face OCT has been applied to the study of the numerous features of nonneovascular AMD.

3.1. Study of geographic atrophy in nonneovascular AMD

One of the most sought after areas of interest has been geographic atrophy (GA), a late-stage form of nonneovascular AMD that leads to gradual and irreversible loss of central visual function.[10] GA is characterized by the loss of photoreceptor cells and the RPE, leading to atrophic patches in the macula, which tend to enlarge with time. [59] These lesions have well-defined borders and can be seen as areas of reduced or absent pigmentation on color fundus photography. Overall, GA progression rates have been reported in the literature for total study populations range from 0.53 to 2.6 mm2/year, with a median of ~1.78 mm2/year.[21] As new therapies recently approved by the FDA have demonstrated statistically significant reductions in the growth of GA lesions,[69] it is crucial to promptly identify GA patients who could benefit the most from treatment.

The fundus autofluorescence (FAF) imaging technique allows for accurate and reproducible quantification of GA lesions, but it has limitations, such as more challenging acquisition, limited availability in clinics, and discomfort for patients during the exam. Furthermore, Borrelli and coworkers [9] demonstrated that, on FAF images, borders of the atrophic area may not appear as hypofluorescent, generating difficulty in precise mapping of the GA. Previous studies [50] have shown that this phenomenon could be related to the presence of subretinal hyperreflective material located within the bed of atrophy, whereas Borrelli and colleagues [8] hypothesized that this phenomenon could be caused by green-emitting fluorophores in the material, which may alter the definition of borders.

In 2013, Nunes and coworkers demonstrated the possible use of *en face* OCT in predicting the area of progression of GA in nonneovascular AMD patients. [48] *En face* SD-OCT imaging can identify areas of inner segment/outer segment (IS/OS) retinal disruption, which appear as darker regions extending beyond the borders of the GA. These regions accurately predicted GA progression over one year in approximately 43.3 % of the examined eyes.

In the same year, Kim and coworkers introduced phase-variance OCT (pvOCT) to produce *en face* images of the vasculature in different layers

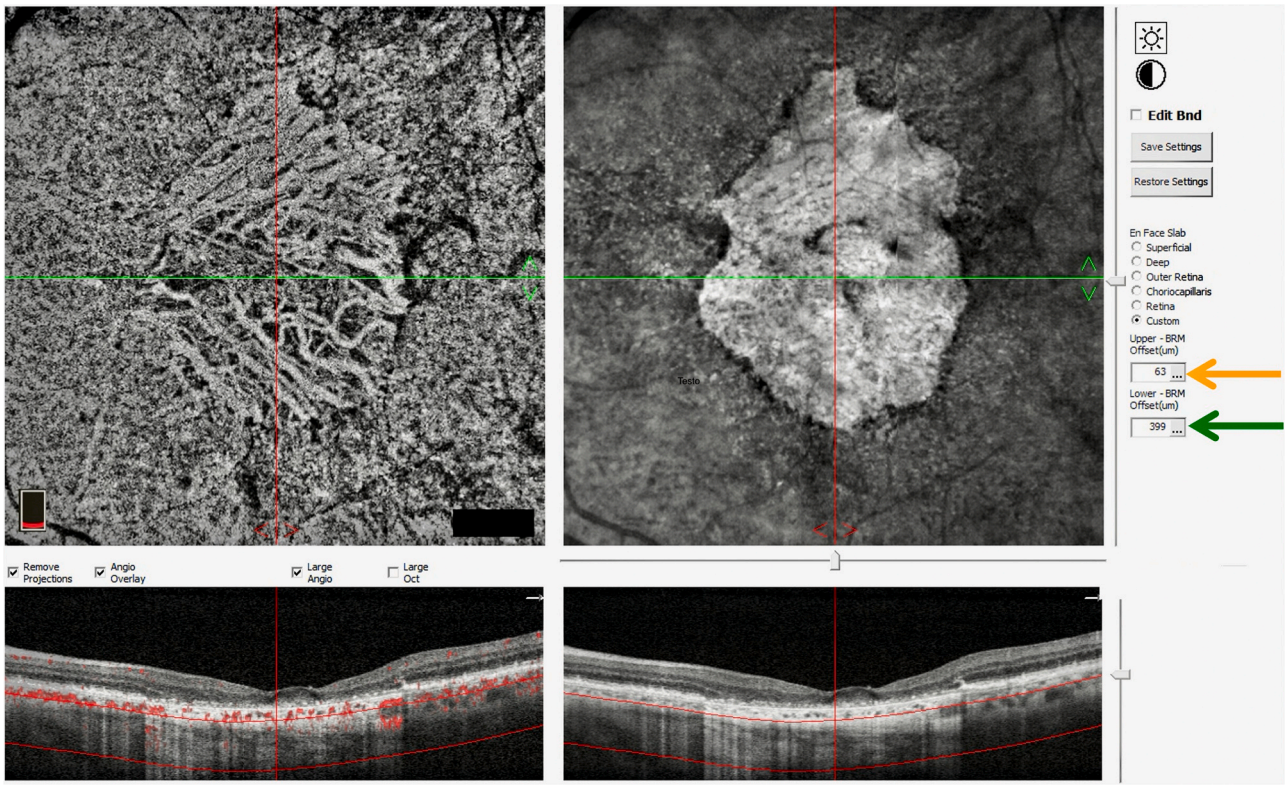

Fig. 4. *En face* OCT image of an atrophic area. On the left, *en face* OCT angiography (upper image) and OCT (lower image) are shown. On the right, structural *en face* OCT delineates a hyperreflective central area corresponding to atrophy (superiorly). The green and yellow arrows indicate the values of the sub-RPE segmentation slab (approximately 65–400 μm).

of the retina and choroid.[33] This technique uses a different scanning protocol that includes the acquisition of several B-scans over the same location (M-scans). Phase variance processing allows the identification of regions of motion by visualizing blood cell movement and identifying the retina vasculature. *En face* projection images created from three-dimensional datasets provide clear vascular visualization, comparable to that of currently used invasive angiographic imaging. [65,85] Accordingly, *en face* OCT has proven to be effective in generating high-quality microvascular images, particularly of the anterior choroidal vasculature and choriocapillaris, allowing early diagnosis of GA by detecting subtle morphological changes in the choriocapillaris. In patients with GA secondary to nonneovascular AMD, small focal areas of choriocapillaris dropout within the region the GA region were revealed on *en face* pvOCT.

Few studies have compared the use of different segmentation methods of *en face* slabs to establish the most accurate approach for measuring GA. Pilotto and coworkers demonstrated the potential use of *en face* OCT in detecting and measuring the GA.[52] The study revealed that the GA area detected was comparable to that quantified via blue fundus autofluorescence (B-FAF) and to that quantified via near-infrared fundus autofluorescence (NIR-FAF). Two different images were generated: outer retinal (OR) and choroidal (CH) *en face* images.

The GA area measured on *en face* OCT images at the OR level was equivalent to that measured on both the B-FAF and NIR-FAF images. Moreover, the *en face* OCT measurements of the GA at the choroid level were quantitatively inferior to the FAF images. These results support the hypothesis that, in GA, earlier degenerative involvement of the outer retina and RPE photoreceptor atrophy, visualized by *en face* OCT at the OR level, occur before choriocapillaris loss.

Yehoshua and coworkers [82] introduced a new approach for imaging in a GA, known as the sub-RPE slab. The sub-RPE slab is an *en face* visualization formed by axially projecting only the OCT image data from a region below Bruch membrane that extends from 65 μm to 400 μm. This slab utilizes only the light penetrating below the RPE into the choroid and sclera, creating an *en face* image from the light reflected from beneath the RPE. In these images, the GA area appears brighter than the surrounding areas. By using only the light that penetrates into the choroid, the sub-RPE slab was found to possess greater contrast at the borders of the GA than the standard OCT fundus image (OFI). Nevertheless, both the OFI and sub-RPE slab images have been proven valuable in quantifying and monitoring areas of GA.

On another note, the use of boundary-specific segmentation with a choroidal slab under the RPE allows for an *en face* image that specifically highlights the choroidal hypertransmission defects (hyperTDs) that arise when the RPE is absent. In 2016, Schaal et al. [64] published a retrospective observational case series illustrating the role of *en face* OCT imaging in identifying nascent geographic atrophy (nGA) in eyes with intermediate age-related macular degeneration. nGA refers to specific features seen on OCT B-scans that are strongly associated with the future development of geographic atrophy (GA). These features include subsidence of the inner nuclear layer and outer plexiform layer and/or a hyporeflective wedge-shaped band within Henle fiber layer.[81]

A total of 37 eyes were evaluated for at least 1 year using both B-scans and *en face* images. *En face* OCT imaging has shown potential for delineating areas suspicious for nGA identified by detecting the hypertransmission signal into the choroid, a signature indication of RPE degeneration and drusen collapsing into the GA.

HyperTDs into the choroidal layer—seen as bright areas on *en face* OCT images positioned in the sub-RPE segmentation with borders from 65 μm to 400 μm under the Bruch membrane—are a reliable and reproducible feature and a risk factor for GA.[41,67] HyperTDs appear brighter than the surrounding areas on the *en face* images due to increased light transmission into the choroid where the RPE is absent or attenuated. HyperTDs measuring at least 250 μm in the greatest linear dimension have been defined as persistent hyperTDs, as they are likely to persist for at least 3 years. These lesions are strongly correlated with

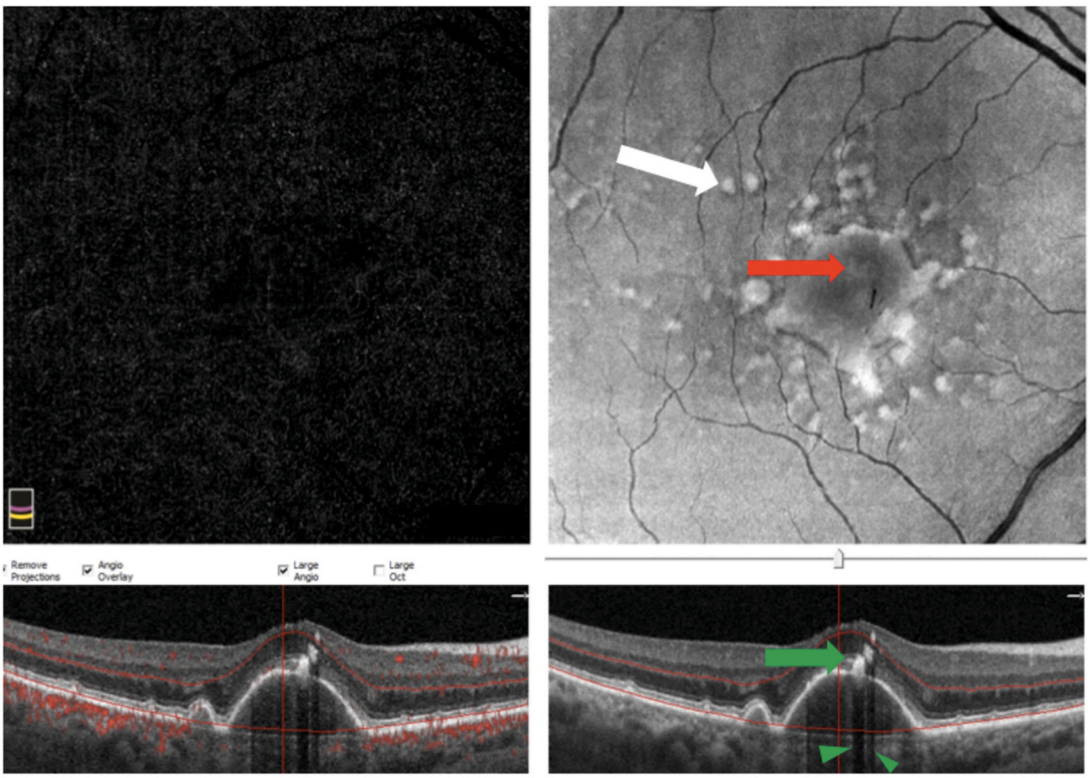

Fig. 5. *En face* OCT of mixed nonneovascular AMD features: drusen and pigment migration. On the left, *en face* OCT angiography (upper and left images) revealed no areas of flow, and the corresponding structural OCT (down and left) did not show any areas of hyporeflectivity (IRF) within the retinal layers above the PED. *En face* OCT (upper and right) revealed drusen as hyperreflective multiple round areas (white arrow) and pigment migration as hyperreflective areas with poorly defined borders (red arrow). Confluent drusen merged into a larger PED of inhomogeneous content in the foveal region. The hyperflective dots superior to the PED correspond to pigment migration (green arrow) on structural OCT (down and right). The pigmentary characteristics of these dots were confirmed via a B-scan via the shadow effect behind the hyperreflective dots (green arrowheads).

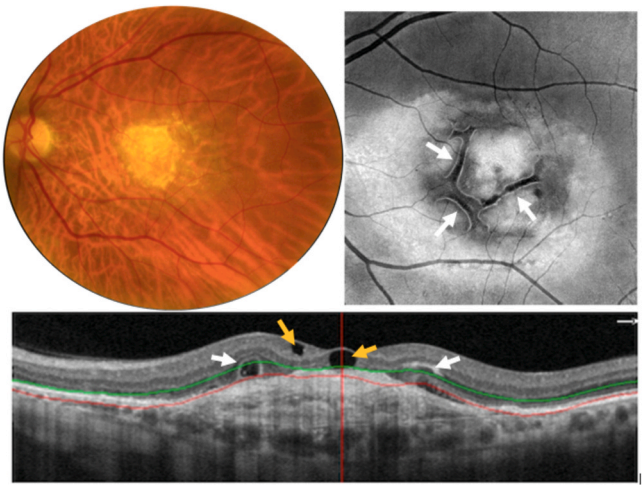

Fig. 6. Upper images: Fundus photography (left) and OCT *en face* image (right) of the ORT in a fibrovascular scar. Fundus photography revealed a yellow inhomogeneous scar occupying the entire foveal region. *En face* OCT image showing the pathognomonic "pseudodentritic" pattern of the ORT (white arrows). Inferior image: structural OCT with ORT (white arrows) and intraretinal degenerative cystic spaces (orange arrows). On structural OCT, the difference between cystoid spaces and ORTs is evident: ORTs present a round morphology with a hyperreflective outline, whereas cystic spaces appear irregular and almost never present a hyperreflective contour.

nGA (79 %) and are associated with an 80-fold increased risk of the formation of complete RPE and outer retinal atrophy (cRORA) within 3 years. HyperTDs of smaller sizes have been found to be transient and not highly correlated with the development of atrophy.[36,67]

3.2. Identification of intraretinal RPE migration in nonneovascular AMD

Additionally, *en face* OCT has been used for the detection of RPE migration. Alterations in the RPE are considered important indicators of AMD development,[83,84] and intraretinal RPE migration into the neurosensory retina has been reported as an important precursor of chorioretinal atrophy.[5,26]

In a study by Ho and coworkers *en face* OCT revealed high-intensity intraretinal RPE migration in 54.5 % of the examined eyes affected by early to intermediate nonneovascular AMD. [26] Intraretinal RPE migration appears on *en face* OCT as a hyperreflective, highly back-scattering lesion within the neurosensory retina. Similarly, Laiginhas and coworkers [35] reported that *en face* OCT imaging in conjunction with OCT B-scans, was able to reliably identify and localize the hyperpigmentation seen in color fundus images.

3.3. Study of drusen in nonneovascular AMD

The study of drusen via *en face* OCT has also shown great promise. Drusen represent one of the most common features of AMD, especially in its early stages. They typically accumulate between the RPE's basal lamina and Bruch membrane and are composed of numerous extracellular accumulations of debris, including lipids, carbohydrates, zinc, and proteins.[1] Measuring drusen volume and assessing their structure are crucial for evaluating the progression from early/intermediate AMD to

GA. For example, calcified drusen have been recognized as clinically significant lesions that are strongly associated with the development of GA.[49,62,74]

Chen and coworkers [13] first developed a novel algorithm enabling quantitative drusen measurements through automated drusen segmentation via SD-OCT, calculated from *en face* projection images of the RPE layer. Quantitative drusen measurements, such as area and volume, along with drusen shape visualization, represent useful tools that could be used to monitor the progression of nonneovascular AMD and predicting patient outcomes.

Jurgens and coworkers [30] analyzed the potential of quantifying early and intermediate AMD through *en face* OCT. The outcomes revealed that the results of the quantitative analysis of *en face* OCT images were comparable to the standardized drusen analysis of fundus photography.

Liu and coworkers [42] showed the use of *en face* OCT imaging in the detection and monitoring of calcified drusen and nonneovascular AMD. On the *en face* SS OCT images, calcified drusen appear as dark focal lesions or choroidal hypotransmission defects (hypoTDs), which are detected in the choroid via a subretinal RPE slab. In most calcified drusen, hyperTDs appear to develop progressively around the periphery of the hypoTDs, giving the appearance of a donut lesion on the en-face SS OCT images. These donut lesions correspond to hypoautofluorescent areas on autofluorescence (FAF) images, aligning with foci of cRORA on B-scan OCT.

3.4. Detection of different patterns of outer retinal tubulations (ORTs) in AMD

En face OCT has been utilized in the study of another feature of AMD, outer retinal tubulations (ORTs). Curcio and coworkers [15] were the first to identify tubulations in a histopathological study of eyes with advanced AMD. They described how surviving photoreceptors reorganized into interconnecting tubes over disciform scars. Zweifel and coworkers [87] subsequently described ORTs on OCT as circular or ovoid structures with hyperreflective borders.

The presence of ORTs in nonneovascular AMD has been associated with slower growth of GA lesions,[25] while the CATT study [38] correlated the presence of ORTs with poor visual acuity in eyes with nAMD. Thus, ORTs can be considered an important prognostic factor.

Wolff and coworkers [77] utilized *en face* SD-OCT to differentiate between ORTs in neovascular and nonneovascular AMD. In fact, ORTs present 2 different patterns depending on the disease. In neovascular AMD, ORTs appear on OCT *en face* images with a branching network emanating from a fibrovascular scar with numerous ramifications (or digitations), creating a “pseudodendritic” pattern.

Meanwhile, ORTs in nonneovascular AMD follow a circular pattern associated with invaginations inside the atrophic zone. These tubulations usually follow the margins of the chorioretinal atrophic area, giving them a “perilesional” appearance.

4. Artificial intelligence (AI) and *en face* OCT

The role of AI-based image analysis is becoming increasingly important in daily clinical practice. A large variety of AI techniques, particularly deep learning-based approaches, have been proven to provide accurate measurements in a variety of ophthalmological diseases,[60,79] including AMD.

In fact, Russakoff and coworkers [61] reported, through the use of a convolutional neural network (CNN), a type of deep learning image analysis network, high accuracy in the prediction of progression from the intermediate form of AMD to the advanced form of the disease. As CNNs are capable of detecting CNVs,[76] deep learning algorithms may be useful in classify the neovascolar form of AMD.

The implementation of AI software in OCT *en face* acquisition may have many advantages in clinical practice. First, it has already shown its usefulness in providing feedback when acquiring images. Wu and coworkers [78] introduced in their study a method to generate quantitative maps that described the quality of an OCTA acquisition at each location. The values were recorded with subjective quality grades, which were alerted if the image needed to be retaken.

Additionally, *en face* scans are frequently subject to artifacts by media opacities or eye movements. AI has been described [27] as capable of identifying or removing specific artifacts, such as bulk motion artifacts. These artifacts may manifest as disruptive bright stripes caused by microsaccades or slower forms of motion, such as ocular pulsation and drift.

Overall, deep learning software enhances the quality of *en face* OCT angiograms as a result of its ability by accessing multiple views.[28] Multiple simultaneous input images enable the deep learning network to extract information from the examined region at a specific retinal layer, providing a better signal response and compensating for regions that are partially eclipsed. The results from AI-based studies show great promise for diagnosis and prognosis; however, several issues have been raised regarding the implementation of this approach in clinical practice. For example, the accuracy of image interpretation, standardization, and transparency must be guaranteed for the correct diagnosis and management of patient care.[75] These aspects will undoubtedly be evaluated and improved in the near future to allow easier application and promote more beneficial AI use in clinical practice.

5. Current limitations of structural *en face* OCT

Despite its potential, structural *en face* OCT still has several limitations, and thus, it currently needs to be combined with other modalities to mitigate its intrinsic shortcomings. [55] One of the main challenges of structural *en face* OCT is the contrast mechanism applied to the visualization of different structures, which is based on backscattering differences without being highly tissue specific. Another issue to be addressed is possible motion distortions during the recording of volumes.[40] Certainly, artifacts could be corrected by correlation with a faster imaging modality or through the use of AI. Another disadvantage to be mentioned is the limited field of view provided by structural *en face* OCT. The montage technique allows for a larger field of view, but in the future, faster scanning speeds would be fundamental to obtain wider fields of view with higher resolution.[16]

6. Conclusion

The ability of multimodal imaging of the retina has improved AMD recognition and is extremely useful for its diagnosis and assessment. OCTA has already established its role as a noninvasive technique to visualize in detail the microvasculature of the retina and the choroid. By overlaying high-resolution structural features, *en face* structural OCT has been shown to enhance the interpretability of OCTA imaging in several chorioretinal diseases.

At present, structural *en face* imaging alone is insufficient and must be supplemented with other imaging modalities for an accurate diagnosis; however, as demonstrated in our study, it can currently supply numerous details and help determine the extent of tissue involvement.

7. Methods of literature search

A thorough literature search was performed on PubMed with the following search terms: *en face* OCT, *en face* OCTA, structural *en face* OCT, and OCT *en face* in AMD, in various combinations to find relevant studies. No timeframe restrictions were applied. Non-English articles were not considered. Papers were selected independently by each author and then discussed by a board. The final selection was approved by all the authors.

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CRediT authorship contribution statement

Clara Rizzo: Writing – original draft, Conceptualization. **Raphael Kilian:** Investigation, Data curation. **Maria Cristina Savastano:** Writing – review & editing, Writing – original draft, Conceptualization. **Stanislao Rizzo:** Writing – review & editing. **Giorgio Marchini:** Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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