# Peripheral retinal lesions in diabetic retinopathy on ultra-widefield imaging

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## Abstract:

Peripheral retinal imaging plays a crucial role in the diagnosis, management, and prognosis of diabetic retinopathy (DR). Traditional fundus imaging techniques have limited coverage of the retina, resulting in missed peripheral lesions. The advent of ultra-widefield (UWF) imaging has revolutionized the assessment of the peripheral retina. UWF imaging modalities provide comprehensive visualization of the retina, enabling the detection of peripheral lesions without the need for mydriasis. Integration of UWF imaging with other modalities, including fluorescein angiography (FA), indocyanine green angiography, pseudocolor imaging, and fundus autofluorescence, further enhances our understanding of peripheral retinal lesions. UWF imaging has demonstrated improved detection of DR lesions and presumably more accurate management of DR compared to traditional fundus photography and dilated fundus examination. UWF-FA and UWF-optical coherence tomography angiography have emerged as valuable tools for assessing retinal and choroidal vascular abnormalities, nonperfusion areas, neovascularization, and microvascular abnormalities. The presence and increasing extent of predominantly peripheral lesions detected using UWF FA are associated with a higher risk of DR progression and proliferative DR. UWF imaging provides a comprehensive evaluation of DR severity, aiding in more accurate risk stratification and treatment decision-making. Overall, UWF imaging modalities have significantly advanced our understanding of peripheral retinal lesions in DR, facilitating early detection and targeted management for better visual outcomes.

**Keywords:**

Diabetic retinopathy, imaging, peripheral lesions, ultra-widefield

## Introduction

Retinal imaging plays a critical role in diagnosing, managing, and monitoring retinal and choroidal diseases.[1]

The origin of retinal photography can be traced back to at least 1886 with Jackman and Webster's publication of the first retinal photographs. Over the years, significant advances have been achieved, including the introduction of the first commercial fundus camera in 1926, the invention of the electronic flash tube in 1953, the emergence of a revolutionary 148° field of view (FOV) camera in 1960, the shift from analog to digital cameras in 1975, and the recent emergence of confocal scanning laser ophthalmoscopy for high-quality imaging and expanded the FOV, along with the introduction of nonmydriatic imaging options.[2]

The term "widefield" is used to describe images that displayretinal features beyond the posterior pole but posterior to the vortex vein ampulla in all four quadrants. On the other hand, fundus imaging that covers a field of retina equal to 100° or more, capturing retinal features anterior to the vortex vein ampulla in all four quadrants, is referred to as ultra-wide field (UWF).[3,4]

Historically, the Early Treatment of Diabetic Retinopathy Study (ETDRS) established a standardized protocol for fundus imaging in clinical trials and clinical research consisting of seven overlapping stereoscopic pairs of 30° fields to map the posterior pole and portions of the mid-peripheral retina. However, many digital cameras offered a wider range of FOV

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options with a 45° to 60° wide-angle capture in addition to the standard 30° to 35° FOV. This widefield approach enabled mapping an equivalent area of seven fields with fewer images. Although it was possible to manually overlap multiple images to create a montage, like combining the seven standard 30° fundus images for a 75° FOV, there were still significant areas of the fundus left uncovered with single-field images. Up to 82% of the retina can be captured in a single UWF image, which is a significant improvement from the 30% to 35% of the retinal surface captured by the ETDRS 7-standard field protocol.[5] Thus, UWF imaging can visualize 3.2 times more retinal surface compared to the traditional seven standard fields.[6] Moreover, a variety of fundus lesions occurring in the peripheral region remained undetectable using traditional seven standard fields.[1,7]

In the last few years, the advent of UWF imaging has improved our understanding of lesions in the peripheral retina and their importance in diagnosing and prognosing the condition.[8]

Diabetic retinopathy (DR) is a major cause of blindness before the age of 50 years worldwide,[9] with approximately one in 12 diabetic patients in the United States experiencing advanced vision-threatening retinopathy.[10] Early detection and treatment of DR are crucial for preventing vision impairment and blindness. Research has indicated that the presence and increasing extent of lesions detected using UWF imaging, which are not visible within the FOV of conventional photography (i.e., ETDRS 7 standard fields), are associated with a higher risk of disease progression.[6,11-15]

## Ultra-wide Field Imaging Modalities

The EIDON confocal scanner (Centervue) is a widefield platform that can capture high-resolution fundus photographs with a true color using white light illumination. It has a FOV of 60° horizontally and 50° vertically. Although it is not considered as an UWF modality, it can provide detailed visualization of high-risk DR features beyond the standard photographs used for screening.[16]

The Optos® (Optos Carfornia®, Optos PLC, Dunfermline, United Kingdom), Clarus™ (CLARUS 500™, Carl Zeiss Meditec Inc., California, USA), Spectralis (Heidelberg Engineering, Heidelberg, Germany), and Nidek Mirante (Nidek Co. Ltd., Gamagori, Japan) are widely used noncontact imaging systems known for their ability to provide widefield views of the retina, although some may require montage imaging or special widefield adapted lenses to achieve UWF coverage[17-20] These systems are highly valuable for assessing the peripheral retina without the need for mydriasis, making them convenient and efficient tools for evaluation [Figure 1].[17,18]

The integration of UWF imaging systems with well-established modalities, such as fluorescein angiography (FA), indocyanine green angiography, pseudocolor imaging, and fundus autofluorescence, has significantly advanced our understanding of the peripheral retina.[21] More recently, UWF imaging systems have been equipped with optical coherence tomography (OCT) and OCT angiography (OCTA), allowing for three-dimensional assessment of peripheral retinal lesions.[22,23]

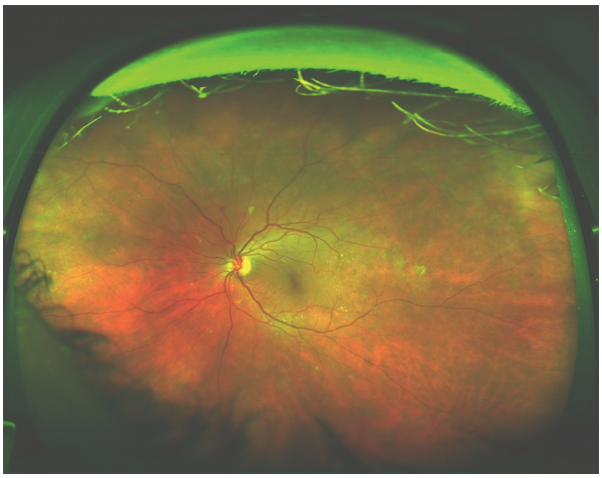

**Figure 1:** Ultra-widefield pseudocolor image (Optos California) of the left eye of a patient with diabetic retinopathy. Intraretinal hemorrhages, cotton wool spots, and lipid exudates are evident

## Ultra-wide Field Fundus Image

The ETDRS severity scale has been the gold standard for DR grading and determining the risk of vision-threatening retinopathy over the years, based on the presence and extent of lesions in the seven standard photographic fields.[24]

A comparative analysis was conducted wherein the grading of DR was compared using two distinct imaging modalities: Mydriatic Optomap UWF scanning laser ophthalmoscope (UWFSLO) full 200° view images and a smaller region within the same image that corresponded to the retinal coverage of the ETDRS 7-standard fields. The results revealed a disparity in the severity level of DR between the ETDRS seven-field and Optomap UWFSLO 200° views in 19% of the examined images. Notably, in 15% of the cases, the Optomap images exhibited a higher severity of DR when compared to the ETDRS seven-standard field image.[12]

Optos 200Tx fundus camera UWF pseudocolor images were graded for the severity of DR considering only the regions within the ETDRS seven-field, as well as the entire UWF image, using two different protocols: The simple International Classification of DR (ICDR) scale and the more complex DRCR.net Protocol AA grading scale. There was a discrepancy in severity level between the ETDRS seven-field region and the entire UWF image in 2.4% of images using the ICDR classification system and in 5.6% of images using the DRCR.net Protocol AA grading scale system. The discrepancies were due to the presence of intraretinal hemorrhage, neovascularization (NV), preretinal hemorrhage, and scatter laser scars in the peripheral fields that were not identified in the ETDRS seven-field region.[25]

UWF images also show a higher agreement with dilated fundus examination findings than the ETDRS 7-fields. Overall, the use of UWF images has the potential to improve the detection and management of DR.[26,27]

In a study comparing a nonmydriatic 200° UWF SLO to onsite mydriatic ophthalmologic examination for DR. Neubauer *et al*. found that the Optomap achieved a sensitivity of 94% and a specificity of 100% for detecting more than mild DR. They concluded that Optomap images are of sufficient quality for valid DR and clinically significant macular edema assessment, making them suitable for telescreening programs.[28]

According to a study by Silva *et al*., DR severity assessment in UWF images and ETDRS photographs matched in 80% of cases and was within one level in 94.5% of cases. However, UWF and dilated fundus examination matched in 58.8% of cases and were within one level of severity in 91.2% of cases.[26]

In 10% of cases, UWF imaging revealed peripheral retinal pathology that was not observed with traditional fundus photography.[29]

Friberg *et al*. used a noncontact scanning laser-based retinal imaging system to generate a wide-field panoramic image of the fundus over a 200° area of the retina. DR was identified as a general diagnosis with a sensitivity of 94%, and follow-up recommendations matched the clinical recommendations in 82% of cases.[30]

In 20% of eyes, UWF images and ETDRS film photographs showed discrepancies in DR severity: 52% of discrepancies were caused by hemorrhage or microaneurysms (MAs), 26% by intraretinal microvascular abnormalities (IRMAs), 17% by new vessels elsewhere (NVE), and 4% by venous beading. Approximately one-third of hemorrhages, MAs, IRMAs, and NVEs occurred outside the ETDRS. According to the UWF images but not the ETDRS film photographs, 10% of the eyes had more DR severity based on the lesions identified on the UWF images.[26]

In a study conducted by Silva *et al*., predominantly peripheral lesions (PPLs) were defined as specific retinal abnormalities located outside the standard ETDRS fields, including MAs, hemorrhages, venous beading, IRMAs, and NVE; with the designation of PPL assigned as long as at least one peripheral field showed more extensive lesions compared to its corresponding EDTRS field. The findings demonstrated that the presence and increasing extent of PPLs were associated with a 3.2-fold increased risk of two-step or more progression of DR and a 4.7-fold increased risk of progression to proliferative DR (PDR) over a 4-year period, compared to eyes without PPLs.[11]

As a screening referral threshold, wide-field fundus imaging in conjunction with regular OCT demonstrated increased detection of advanced stages of DR in comparison to clinical examination alone.[14]

## Ultra-wide Field Fluorescein Angiography

UWF-FA allows imaging of up to 200° of the retinal surface in a single image, compared to 30° to 50° in a traditional angiogram [Figure 2].[31]

In addition to macular edema, UWF-FA can detect retinal vascular occlusions, NV, capillary nonperfusion (NP),[32] and retinal vascular staining and leakage.[33] It has been shown that UWF-FA imaged 3.9 times more NP and 1.9 times more NV. Around 70% of NP in diabetic eyes is found outside the posterior pole.[34] In order to determine NP, UWF-FA has been used to measure the ischemic index (ISI).[35] To calculate this index, the area of capillary NP observed in the arteriovenous phase image is outlined using the area measurement function and divided by the total image area in pixels.[32]

The correlation between the ISI in UWF-FA and diabetic macular edema (DME) has been evaluated in a few studies. Patel *et al*.,[32] observed that a higher ISI, indicating more severe DR, was correlated with recalcitrant DME. Eyes with higher ISI showed less reduction in central macular thickness (CMT) and required more macular photocoagulation treatments. Sim *et al*.[36] found moderate correlations between the foveal avascular zone area and peripheral ISI, as well as between the peripheral leakage index and foveal avascular zone area, but they did not find a significant correlation between macular thickness and peripheral ischemia in DR. Similarly, Silva *et al*.[37] did not find an association between the NPV area and ISI and clinically significant DME. To summarize, studies have yielded mixed results regarding the correlation between the ISI and DME, with some indicating a positive association with recalcitrant DME and the severity of DR, while others failing to demonstrate significant correlations. In addition, Wessel *et al*.[6] found a significant correlation between peripheral retinal ischemia and DME while, Oliver and Schwartz[33] observed that peripheral NP was associated with NV but not with macular edema. They also found a relationship between

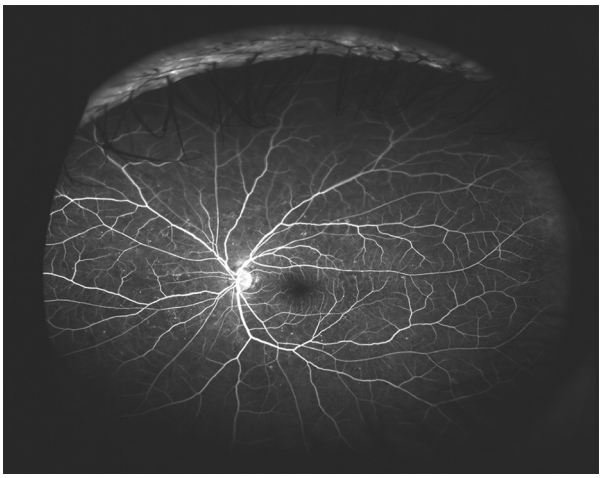

**Figure 2:** Ultra-widefield fluorescein angiography of the left eye of a patient with nonproliferative diabetic retinopathy. Numerous microaneurysms are evident

peripheral vascular leakage, peripheral NP, and posterior NV, while no significant association was detected between peripheral vascular leakage and DME. Interestingly, they did find a strong association between peripheral vascular leakage and focal macular edema in eyes without peripheral NP.

Oliver and Schwartz also utilized UWF-FA to investigate the correlation between peripheral diabetic changes, including capillary NP and peripheral vessel leakage (PVL) and NV. They found that PVL occurred as frequently as NV (41% of eyes) and less often than peripheral NP (54%) or macular edema (57%).[33]

DRCR.net Protocol AA utilizes a comparison between UWF fundus imaging (UWF-color photograph [CP] and UWF-FA) and the standard ETDRS seven-field imaging to assess DR and predict its progression. The findings indicate that FA-based PPLs exhibits predictive value for the progression of non-PDR (NPDR), while color-image PPL did not demonstrate the same predictive capacity. However, at more severe levels of DR (mod-sev NDPR or greater), PPLs were associated with a higher risk of DR progression. While the study overall highlighted the importance of PPLs, it did not suggest that peripheral lesions outweighed those in the posterior pole in terms of importance.[5]

A recent study has confirmed that increased NP is correlated with the presence of FA-PPL, supporting findings consistent with the DRCR.net Protocol. This study suggests that UWF-FA may offer improved predictive capabilities for the future progression of DR compared to UWF-color imaging alone.[34]

Identifying more posterior variables that correlate with peripheral capillary NP is of great significance, especially considering the invasive nature of FA. A recent study by Decker *et al*. demonstrated that there is a correlation between 3 mm × 3 mm OCTA parameters, particularly geometric perfusion deficit and UWF-FA NP. The accuracy of these OCTA and UWF-FA parameters was found to be comparable in detecting eyes with referable DR.[38]

Although UWF-FA has the advantage of capturing more peripheral lesions compared to conventional imaging techniques, evidence suggests that widefield OCTA is a promising alternative to UWF-FA in this regard as it is noninvasive and capable of detecting peripheral lesions.

Compared to FA, wide-field OCTA (WF-OCTA) was found to have a specificity of 99% and a sensitivity of 92% in distinguishing between IRMA and NV. OCTA demonstrated distinct features for differentiating these lesions, such as the presence of supraretinal flow breaching the internal limiting membrane and posterior hyaloid for NV and the outpouching of the internal limiting membrane for IRMA. WF-OCTA has the potential to provide detailed characterization and differentiation of these retinal lesions, offering a noninvasive approach for evaluating peripheral ischemia and flow abnormalities in DR. Further longitudinal studies are warranted to explore the evolution of IRMA into NV and to quantify the flow characteristics.[39,40]

## Ultra-widefield Optical Coherence Tomography Angiography

Conventionally, spectral domain OCTA has common FOVs of 3 × 3 and 6 mm × 6 mm, but larger FOVs of up to 9 × 9 and 12 mm × 12 mm can be more readily achieved using faster swept source (SS) OCTA systems. However, larger scan areas result in decreased resolution, which can be addressed by using a montage protocol to merge multiple individual scans, allowing for a larger FOV with maintained vascular resolution.[41]

The 12 mm × 12 mm FOV corresponds to approximately 50°, offering a restricted view for assessing retinal microvasculature in DR.[42]

Even though the extent of wide-field SS-OCTA is limited in comparison to UWF-FA, studies have demonstrated that wide-field SS-OCTA is comparable in terms of its significance in the assessment of retinal microvasculature to UWF-FA. The results suggest that wide-field SS-OCTA has the potential to serve as a single imaging technique for the diagnosis and ongoing monitoring of PDR.[43-46]

Sawada *et al*. conducted a study using the Optos® panoramic 200Tx imaging system for UWFFA and the PLEX Elite 9000® for OCTA with 12 mm × 12 mm FOV. Their findings demonstrated that wide-angle OCTA (12 mm × 12 mm) showed clinical utility in detecting NP areas (NPAs) and retinal NV in eyes with DR, even though the coverage area of widefield OCTA was smaller compared to UWF-FA images.[47]

By montaging consecutive images acquired at different retinal regions, OCTA images can have an expanded FOV.[48]

Approximately 70 (2 mm × 15 mm × 9 mm)-90 (5 mm × 12 mm × 12 mm) degrees of the posterior pole can be covered by five 12 mm × 12 mm scans or two 15 mm × 9 mm scans. This wider coverage exceeds what can be achieved with a single 12 mm × 12 mm or 15 mm × 9 mm scan [Figures 3 and 4].[49]

In a cross-sectional study, the clinical utility of WF-OCTA was compared to UWF FA (UWF-FA) and UWF-CPs for detecting NV in PDR. WF-OCTA utilizing 12 mm × 12 mm fields of five partially-overlapping locations demonstrated a noninferior detection rate compared to UWF-FA for NVEs and achieved a sensitivity and specificity of 100% for detecting NV at the discs. With a wider FOV, WF-OCTA enabled visualization of retinal vessels in different layers. The study concluded that WF-OCTA detected subtle retinal NV that was not visible on UWF-CP and confirmed the presence of NV through combined visualization of the vessel pattern and demonstration of vessels above the ILM by flow overlay on OCT B-scans. While UWF-FA had a broader FOV, the majority of NVs in PDR cases were observed within the mid-periphery covered by WF-OCTA

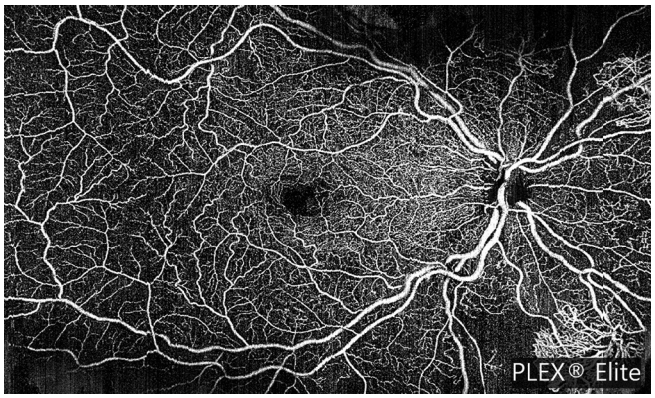


**Figure 3:** Enface swept source optical coherence tomographic angiography; Zeiss Plex Elite 9000 of the right eye of patient with proliferative diabetic retinopathy. Large areas on neovascularization are evident in the superonasal and inferonasal corners of the image with some surrounding areas of nonperfusion

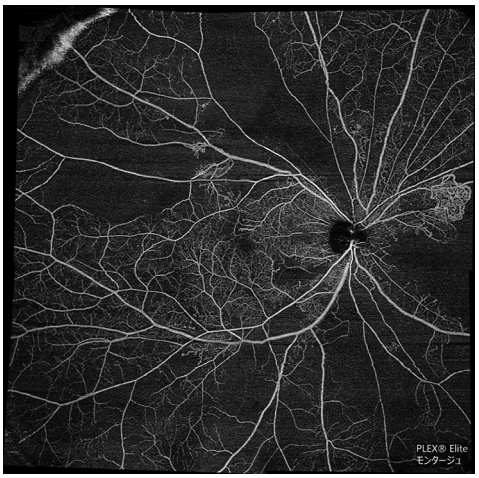


**Figure 4:** Montage or composite swept source optical coherence tomographic angiography (OCTA; Zeiss Plex Elite 9000) image of a right eye with proliferative diabetic retinopathy, created by combining five partially overlapping 12 mm × 12 mm OCTA scans. Multiple areas of neovascularization (including most notably superonasally OS), intaretinal microvascular abnormalities, and extensive peripheral nonperfusion are evident

images. Limitations of the study included instrument-related factors and the time-consuming process of WF-OCTA image acquisition and processing. Nonetheless, the study suggested that WF-OCTA could serve as a valuable noninvasive imaging modality for the detection and monitoring of NV in PDR, offering a safer and potentially cost-effective alternative to invasive fluorescein dye testing.[50]

In another investigation, authors conducted a study using wide-field SS OCTA with a Zeiss PLEX Elite 9000 device and the montage feature of the Advanced Retinal Imaging network image analysis software using 12 mm × 12 mm images. The objective was to compare the accuracy of identifying NV through en face and cross-sectional OCTA scans in comparison to UWF-FA, which is considered the standard method. The results indicated that graders achieved a high level of precision in identifying retinal NV when provided with both en face and cross-sectional OCTA scans, comparable to the accuracy achieved with UWF-FA. However, when presented with only en face OCTA images, the graders showed lower accuracy in identifying retinal NV, particularly for NV locations near the optic nerve head and NV originating from areas with normal capillary density. The combination of en face and cross-sectional OCTA images facilitated clear delineation of NV extending beyond the vitreo-retinal interface, resulting in a high level of sensitivity and specificity for detecting retinal NV. In addition, the study measured the percentage change in retinal NV size after 6 months of anti-vascular endothelial growth factor (VEGF) injections and observed an overall reduction of 69.8% compared to the baseline measurements.[51]

While the study conducted by Yang *et al*. did not meet the consensus criteria for UWF imaging, they employed the term "UWF SS OCTA" to investigate the changes in the retinal microvasculature in individuals with preclinical DR. To confirm the absence of clinical signs, the Optos 200Tx system was used for UWF imaging. For OCTA imaging, a commercially available SS OCTA system with a scanning speed of 20k A-scans per second was utilized to capture volumetric data of 12 mm × 12 mm. Multiple fixation points were employed during OCTA scanning to obtain and montage multiple fields to achieve a wider FOV, and composite UWF OCTA images were generated by overlaying OCTA data onto UWF color images. By analyzing OCTA images, retinal microvascular lesions, such as NPAs, capillary dilation and tortuosity, and NV, were categorized and identified. The study successfully demonstrated the ability to detect microvascular impairments in diabetic eyes without clinical signs, particularly in peripheral regions. This highlights the potential of UWF SS OCTA as a screening tool for the early detection of DR.[52]

In an observational case series, researchers utilized SS wide-field (SS-WF) OCTA to assess retinal NP in DME patients undergoing anti-VEGF therapy. Considering the higher lateral resolution of 15-mm × 9 mm images compared to 12 mm × 12 mm images, 15 mm × 9 mm images were preferred (24 vs. 18 m, respectively). They obtained five images of 15 mm × 9 mm areas using PLEX Elite OCTA and created a montage using i2kRetina software. UWF color fundus photographs (CFPs), UWF FA, and SS-WF OCTA were performed at baseline and after treatment. The analysis revealed improved DR severity, decreased MAs and retinal hemorrhages on UWF CFP, and no reperfusion of vessels or capillary networks in NPAs on FA or OCTA. The detection rate of NPAs was higher with SS-WF OCTA, indicating its potential as a valuable imaging modality for assessing retinal NP in DR.[53]

You *et al*. analyzed WF-OCTA obtained using the RTVue-XR device (Optovue in Fremont, CA). By combining multiple scans from both a prototype and a commercial device, they were able to generate larger montaged images that were

25 mm × 10 mm and 15 mm × 6 mm, respectively. The findings showed that WF-OCTA had the capability to detect small NV that might not be apparent during clinical examination or through CPs, indicating its potential to improve the clinical evaluation of DR.[54]

A recent study compared the WF-OCTA Xephilio OCT-S1 (wavelength: 1060 nm, scan speed: 100,000 A-scans/second; Canon Inc., Tokyo, Japan) and UWF FA (Optos California; Optos plc, Dunfermline, United Kingdom). In this study, WF-OCTA images of the superficial capillary plexus consisted of single capture 23 mm × 20 mm scans centered on the fovea. Quantitative analysis was performed using vessel density as a parameter from WF-OCTA and the ISI as a parameter from UWFFA. They found that although the noninvasive WF-OCTA has great potential for the management of patients with DR, in a small percentage of patients, OCTA images could not be reliably graded for the presence of NP and NV. In these cases, conventional FA needs to be performed.[23]

Furthermore, Hirano *et al*. demonstrated that fovea-centered widefield 23-mm × 20-mm SS-OCTA images captured by OCT-S1 can effectively detect NV in eyes with PDR, with a detection rate of 96%. The use of disc-centered OCTA images resulted in a high NV detection rate of 99% [Figure 5].[55]

Some studies have demonstrated that it is possible to achieve the required FOV on OCTA required to meet the criteria for UWF imaging by using a montage of images or even a single frame.

In a previous study conducted by Zhang *et al*., a limited number of PDR cases were examined. The montage approach employed in the study consisted of a 4 × 4 grid, comprising 16 individual scans with a FOV of 6 mm × 6 mm each. This montage approach enabled a high vascular resolution, providing a wide coverage of up to 100°.[41] Such a montage, however, can be extremely time-consuming and impractical for clinical use. To simplify the acquisition of WF OCTA images, Hirano *et al*. obtained SS OCTA imaging with the patient wearing a 20 diopter lens in a trial frame, and demonstrated the FOV could be expanded 1.8 fold for a standard 12 mm × 12 mm acquisition, albeit at the loss of resolution. Depending on the assessment required, however, this loss of resolution may be acceptable and may make widefield OCTA more practical in the context of a busy clinical practice.[45]

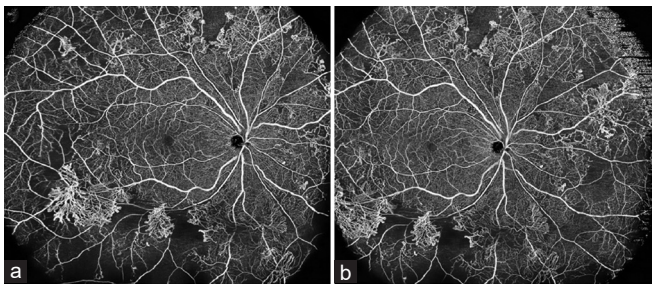


**Figure 5:** Widefield 23-mm × 20-mm swept-source optical coherence tomography angiography (OCTA; Canon Xephilio OCT-S1) images demonstrating multiple areas of neovascularization elsewhere, along and beyond the arcades. Fovea-centered (a) and disk-centered (b) images are shown

Recently, Li *et al*. compared the rates of detection and distributions of DR lesions in single scan UWF SS-OCTA images with FOV measuring 24 mm × 20 mm (FOV 120°) and 12 mm × 12 mm (FOV 50°). The detection rates of MAs, IRMAs, and NV were similar between the 12 mm × 12 mm central and 24 mm × 20 mm images. However, the detection rate of NPAs was significantly higher in the 24 mm × 20 mm image.[42]

## Ultra-widefield Imaging in the Management of Diabetic Retinopathy

UWF imaging has proven to be an effective tool for the detection and screening of DR, even in nonophthalmic settings. The use of UWF imaging in telemedicine applications has been established and is expected to expand, particularly with the growing global prevalence of diabetes.[56]

Several studies have demonstrated the value of UWF imaging in detecting DR. Within an endocrinology department of a multi-specialty private hospital, UWF fundus photography identified DR in 9.3% of 1024 screened patients.[57] In a medical retina virtual clinic, UWF imaging facilitated the assessment of retinal pathology in 274 patients being evaluated for diabetic eye disease, allowing for appropriate triage to follow-up or discharge. A hybrid telemedicine system utilizing both fixed and mobile UWF cameras enabled the screening of 2788 diabetic patients, resulting in the detection of DR in 27% of the patients.[58]

UWF-FA has increasingly been utilized in the management of DR. It has been suggested as a complementary tool for guiding retinal photocoagulation, allowing for targeted treatment of specific areas of NP and potentially reducing complications associated with full panretinal photocoagulation (PRP). This targeted approach, known as targeted laser photocoagulation (TRP),[17] has shown promising results in treating PDR.[59,60]

Compared to PRP, TRP is less destructive and potentially less uncomfortable for patients. Both treatment modalities improved visual acuity and mean visual field defect in the short term (4–12 weeks), with no significant difference between them. The decrease in CMT after TRP treatment was similar to PRP treatment. In terms of safety, TRP demonstrated no serious ocular complications or adverse events, preserving more healthy retinal tissue compared to PRP. Overall, the efficacy of the two methods for DR appears to be comparable, but TRP offers potential advantages in terms of reduced retinal damage and improved patient comfort. Thus, TRP may serve as a future alternative to PRP to some extent.[61-64]

TRP for management of DME, however, has not showed a similar benefit. The DAVE trial was a small randomized

trial that compared ranibizumab + TRP versus ranibizumab monotherapy for patients with center-involved DME. The DAVE study found no significant benefits in visual outcomes or treatment burden reduction between treatment arms.[65] Similarly, the study on wide-field guided PRP demonstrated no significant decrease in the number of required injections in the 1st year of treatment. These results indicate that local VEGF activity in the macula may primarily drive DME, while peripheral ischemia's impact on macular disease may be less prominent.[66]

UWF-FA has also proven useful in monitoring and quantifying treatment response, such as measuring peripheral ischemia after intervention. Studies have observed reductions in peripheral ischemic areas following treatment and even possible reperfusion of previously nonperfused retinal areas.[67-69] OCTA, however, has not corroborated these areas of reperfusion, and thus these may be an artifact due to reduction in contrast following treatment which may make identification of NP regions more challenging.[53] Although reperfusion may occur in retinal vascular diseases such as DR, it is likely quite limited in extent. Therapeutics are in development, however, specifically targeting the improvement of perfusion and these therapies may benefit from UWF FA and OCTA assessment techniques.

## Conclusion

In summary, wide-field and UWF retinal imaging are the promising techniques for detecting peripheral retinal lesions in DR. These techniques have been shown to be superior to standard fundus photography in detecting peripheral retinal lesions, more accurately grading the severity of DR, and monitoring disease progression over time.

The findings of DRCR.net protocol AA suggest that incorporating UWF-FA for evaluating retinal regions peripheral to standard ETDRS fields can enhance the ability to predict disease progression in NPDR, supporting its inclusion in future DR staging systems and clinical care for improved prognosis determination.[5]

UWF-FA is particularly useful in detecting retinal vascular occlusions, NV, capillary NP, and retinal vascular staining and leakage. Studies have shown that UWF-FA images capture significantly more NP and NV compared to traditional fundus photography. The presence and increasing extent of PPLs in UWF images have been associated with a higher risk of DR progression. UWF-FA can also provide valuable insights into the correlation between peripheral changes, such as NP and vascular leakage, and the development of NV and macular edema.

The integration of UWF imaging with OCT and OCTA has further enhanced our understanding of peripheral retinal lesions. Wide-angle OCTA has been shown to detect NPAs and retinal NV in eyes with DR, even though its coverage area is smaller compared to UWF-FA images. OCTA can provide detailed characterization and differentiation of retinal lesions, offering a noninvasive approach to evaluate peripheral ischemia and flow abnormalities. SS-WF OCTA has shown promise in assessing retinal NP in DME patients undergoing anti-VEGF therapy.

Overall, the combination of UWF imaging, UWF-FA, and UWF-OCTA has revolutionized our ability to evaluate the peripheral retina and has the potential to improve the detection, management, and monitoring of DR. Its integration into telemedicine applications holds great promise for improving access to care and facilitating early intervention for patients with diabetes worldwide. Despite the advantages of widefield and UWF retinal imaging, there are some limitations to these techniques. These include the high cost of equipment and the potential need for specialized training in image interpretation. The distortion induced by warping a three-dimensional surface onto a two-dimensional image may also present a challenge, though some devices have developed validated techniques for stereographic projection to achieve accurate measurements.[70]

Incorporation of these UWF technologies into clinical trials will be critical to be define their optimal use in the clinical management of DR.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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