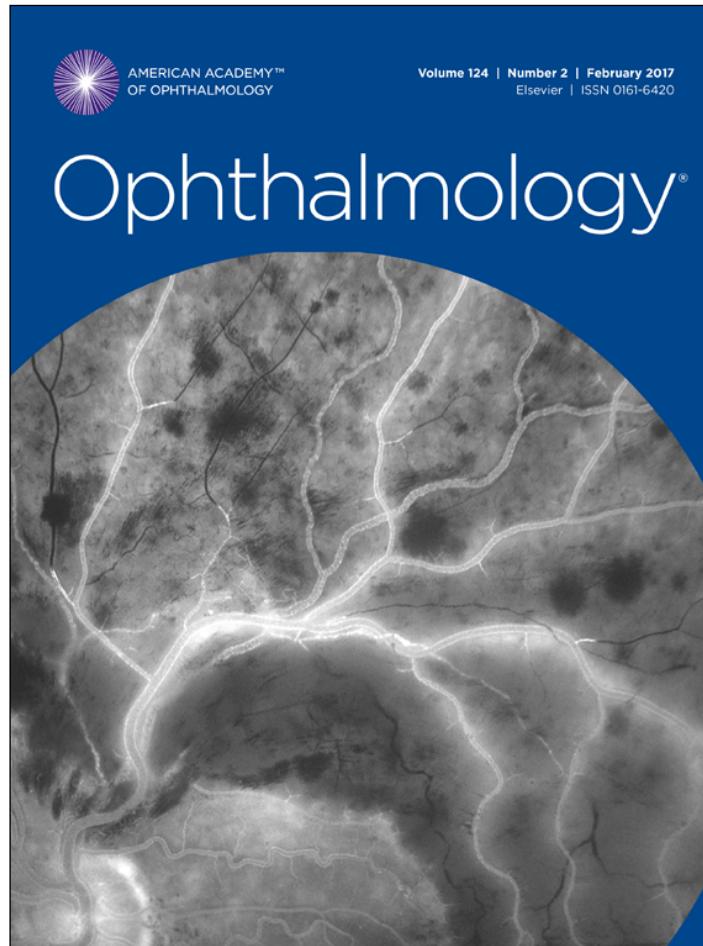


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Optical Coherence Tomography Angiography Characteristics of Iris Melanocytic Tumors

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Purpose: To evaluate tumor vasculature with optical coherence tomography angiography (OCTA) in malignant iris melanomas and benign iris lesions.

Design: Cross-sectional observational clinical study.

Participants: Patients with iris lesions and healthy volunteers.

Methods: Eyes were imaged using OCTA systems operating at 1050- and 840-nm wavelengths. Three-dimensional OCTA scans were acquired. Iris melanoma patients treated with radiation therapy were imaged again after I-125 plaque brachytherapy at 6 and 18 months.

Main Outcome Measures: OCT and OCTA images, qualitative evaluation of iris and tumor vasculature, and quantitative vessel density.

Results: One eye each of 8 normal volunteers and 9 patients with iris melanomas or benign iris lesions, including freckles, nevi, and an iris pigment epithelial (IPE) cyst, were imaged. The normal iris has radially oriented vessels within the stroma on OCTA. Penetration of flow signal in normal iris depended on iris color, with best penetration seen in light to moderately pigmented irides. Iris melanomas demonstrated tortuous and disorganized intratumoral vasculature. In 2 eyes with nevi there was no increased vascularity; in another, fine vascular loops were noted near an area of ectropion uveae. Iris freckles and the IPE cyst did not have intrinsic vascularity. The vessel density was significantly higher within iris melanomas ($34.5\% \pm 9.8\%$, $P < 0.05$) than in benign iris nevi ($8.0\% \pm 1.4\%$) or normal irides ($8.0\% \pm 1.2\%$). Tumor regression after radiation therapy for melanomas was associated with decreased vessel density. OCTA at 1050 nm provided better visualization of tumor vasculature and penetration through thicker tumors than at 840 nm. But in very thick tumors and highly pigmented lesions even 1050-nm OCTA could not visualize their full thickness. Interpretable OCTA images were obtained in 82% of participants in whom imaging was attempted.

Conclusions: This is the first demonstration of OCTA in iris tumors. OCTA may provide a dye-free, no-injection, cost-effective method for monitoring a variety of tumors, including iris melanocytic lesions, for growth and vascularity. This could be helpful in evaluating tumors for malignant transformation and response to treatment. Penetration of the OCT beam remains a limitation for highly pigmented tumors, as does the inability to image the entire iris in a single field. *Ophthalmology* 2017;124:197-204 © 2016 by the American Academy of Ophthalmology

Optical coherence tomography angiography (OCTA) is a new, noninvasive microvascular imaging method that provides angiography by detecting changes in the optical coherence tomography (OCT) signal as blood cells travel through the vessel lumen. This technique does not require injected contrast, which makes it safer and less expensive than traditional ophthalmic angiography techniques. To evaluate posterior segment eye conditions such as retinopathies or choroidal neovascularization, OCTA was initially applied.^{1,2} Evaluation of intratumoral vessels in humans with OCTA is an emerging technique,³ as is OCT of the anterior eye.⁴ Most clinical ophthalmic OCT systems operate at 840-nm wavelength, which penetrates poorly through tumor tissue. We have developed an OCTA system operating at a longer wavelength of 1050 nm to improve penetration into

turbid (highly scattering)⁵ tissues such as the iris and tumors. The approach was chosen because scattering loss decreases with a longer wavelength,⁶ and we use this system to investigate OCTA in iris tumors for the first time.

Iris melanomas represent approximately 4% of uveal melanomas, and although they tend to be less aggressive than posterior uveal melanomas arising in the ciliary body and choroid, these tumors are associated with risk of metastatic disease as well as vision loss.^{7,8} Decreased vision can occur owing to direct tumor effects, such as development of cataract or progressive glaucoma, or be associated with treatment of iris tumors with excisional surgery or radiation. Metastatic disease associated with iris melanomas occurs in 3% to 11% of patients and remains very difficult to treat, causing death in the majority of those patients in whom

Table 1. Summary of Cases with Iris Lesions

Case	Gender	Age	Eye	Eye Color	Iris Lesion
1	M	61	OS	Green	Freckle
2	F	73	OS	Blue	Nevus
3	F	44	OS	Blue	Freckle, nevus
4	M	86	OS	Blue	Freckle, nevus
5	M	80	OD	Brown	Iris pigment epithelial cyst
6	M	45	OD	Blue	Melanoma
7	M	69	OS	Blue	Melanoma
8	M	48	OD	Blue	Melanoma
9	F	92	OD	Blue	Freckle, melanoma

F = female; M = male; OD = right eye; OS = left eye.

metastatic disease develops.^{8–10} Owing to the significant morbidity of treatment, many iris tumors, even some felt clinically to be melanomas, are observed until they show signs associated with high risk of metastasis. One of the clinical features likely to be indicative of a more aggressive tumor with metastatic potential is increased vascularity.

The purpose of this pilot study was to characterize iris lesions using OCTA, comparing vascular patterns and vessel density between iris melanomas and other melanocytic lesions or lesions that may simulate melanomas. We also present OCTA imaging of iris melanomas treated with radiation to evaluate changes in vascularity associated with tumor regression after treatment.

Methods

Subjects

Participants of this cross-sectional observational pilot study were recruited at Casey Eye Institute, Oregon Health and Science University (Portland, OR) from October 2014 to December 2015. This study followed the tenets of the Declaration of Helsinki and was in accord with the Health Insurance Portability and Accountability Act of 1996. The study protocol was approved by the Oregon Health and Science University institutional review board. Clinical trial registration was not required owing to the observational nature of the study. All subjects were at least 18 years old. Written informed consent was obtained from all subjects. Participants with iris lesions

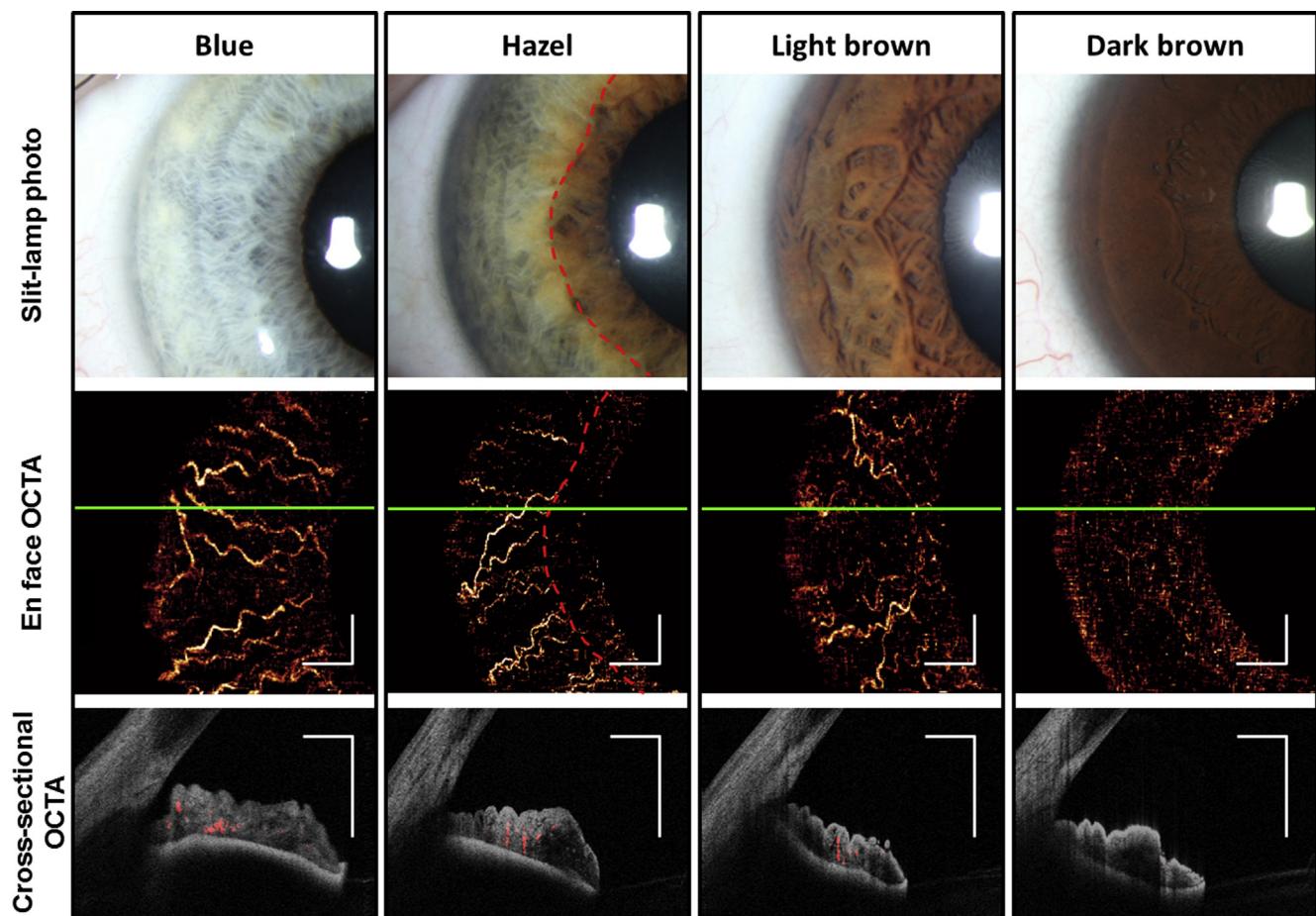


Figure 1. Shown are 1050-nm optical coherence tomography (OCT) and OCT angiography (OCTA) of normal irides with light to dark pigmentation. En face OCTA of iris shows iris vessels in all except the dark brown iris and in the thicker and more pigmented areas of the hazel iris near the pupillary margin (inside red dashed lines). White scale bars are 1 mm in length. Green solid lines indicate the levels at which the cross-sectional OCTAs were obtained. Cross-sectional OCTAs show vessels (flow signal in red) within the iris stroma (reflectance signal in grayscale). The posterior iris epithelium was visible in all irides. However, both reflectance and flow signals in the stroma were faint in the dark brown iris, presumably owing to blocking by the dense pigmentation in the anterior stroma.

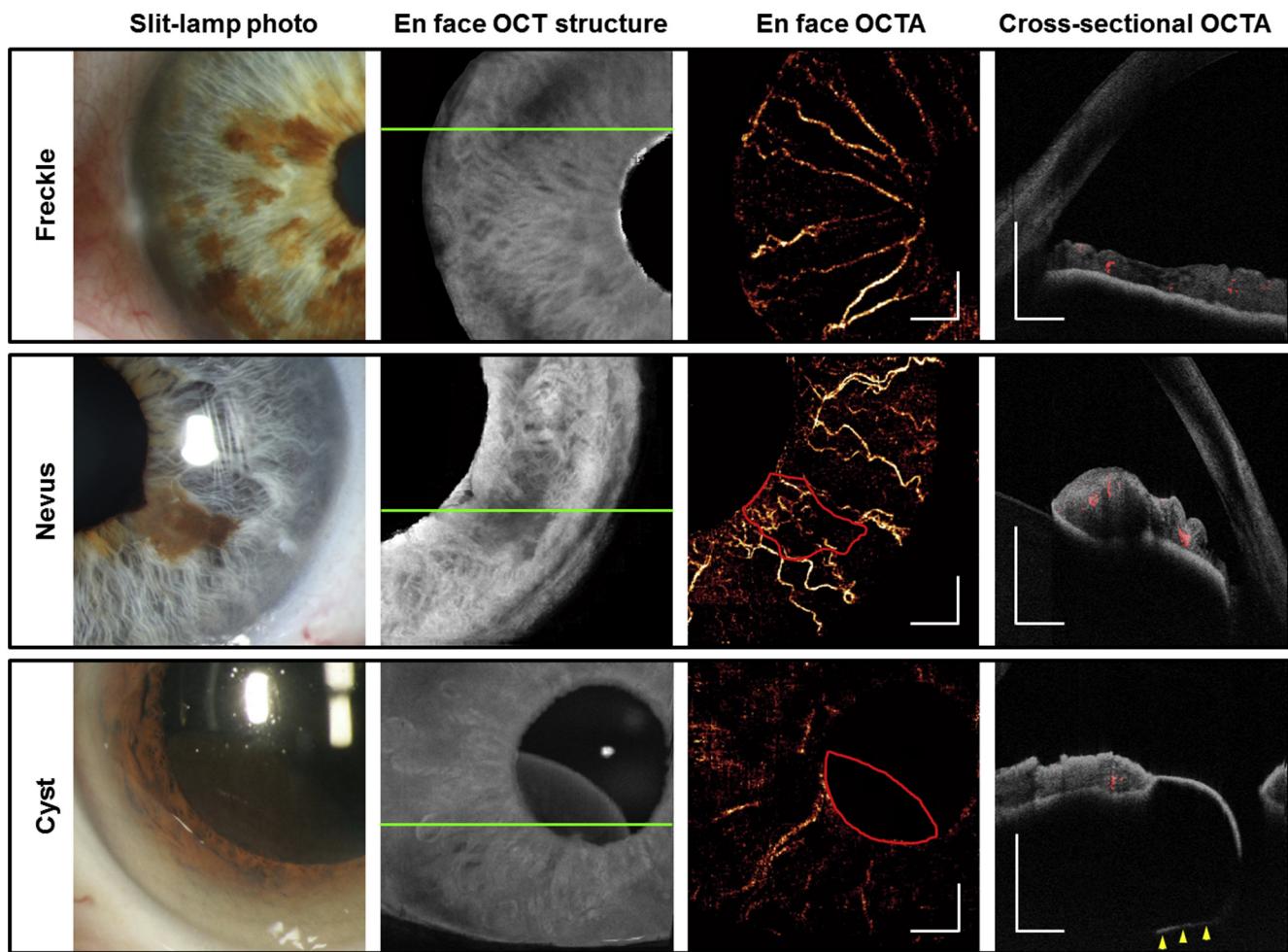


Figure 2. Benign iris lesions imaged by the 1050-nm optical coherence tomography. Green solid lines indicate the locations of the cross-sectional optical coherence tomography angiographies (OCTAs). The areas of the nevus and cyst were outlined in red. White scale bars are 1 mm in length. Cross-sectional OCTAs show blood flow signal in red and reflectance of static pixels in grayscale. The posterior boundary of the iris pigment epithelial cyst (yellow arrowheads) was within the OCTA scan volume. The iris thickness was up to 0.50 mm at the freckles and 0.76 mm at the nevus. The cyst thickness was up to 1.43 mm.

were enrolled from the patients seen at the Ocular Oncology Service. Normal participants were recruited from volunteers.

Clinical Examination

All patients with iris lesions underwent standard clinical evaluation with slit-lamp examination and imaging, including slit-lamp photographs, ultrasound biomicroscopy, and fluorescein angiography (FA), if indicated for clinical care. The clinical examination and review of imaging was performed by an expert in ocular oncology (A.H.S.) with experience in the clinical diagnosis of iris melanocytic tumors. Two subjects with iris melanomas were treated with I-125 radioactive plaque for a total dose of 85 Gy. Fine needle aspirate biopsy was offered to each patient treated for iris melanoma but was performed only on 1 subject, as the others declined biopsy. All normal volunteers had slit-lamp photographs that were reviewed by an ophthalmologist (A.S.).

Optical Coherence Tomography Angiography

One eye from each participant was evaluated using a swept-source anterior segment OCT system operating at 1050-nm wavelength

and 100-KHz axial scan repetition rate. For some participants, additional scans using the AngioVue OCTA software on the Avanti RTVue-XR spectral-domain OCT system (RTVue-XR; Optvue, Inc; Fremont, CA) operating at 840 nm were also obtained. Participants' pupils were not pharmacologically dilated, with the exception of 1 patient with an iris pigment epithelial (IPE) cyst, whose pupil was dilated to allow visualization of the cyst. The ambient room lights were on during image acquisition. Three-dimensional horizontal and vertical OCTA raster data were acquired over 6×6 mm regions with scan depth of 5 mm in tissue. Each OCTA raster scan took about 2.7 seconds to acquire 3 repeated B-scans at 300 raster positions with each B-scan consisting of 300 axial scans. Subpixel precision pre-registration¹¹ between repeated B-scans was performed before OCTA calculations to reduce line artifacts caused by in-plane motion. The split-spectrum amplitude-decorrelation angiography algorithm was used to calculate decorrelation between repeated B-scans for blood flow detection.¹² Out-of-plane bulk motion artifact was estimated using median decorrelation in tissue of the B-frame as well as the reflectance of the voxel and then subtracted from OCTA. The orthogonal registration was performed to merge 1 horizontal and 1 vertical raster scan into one 3-dimensional volume.¹³ The anterior iris surface and the anterior boundary of the IPE layer were

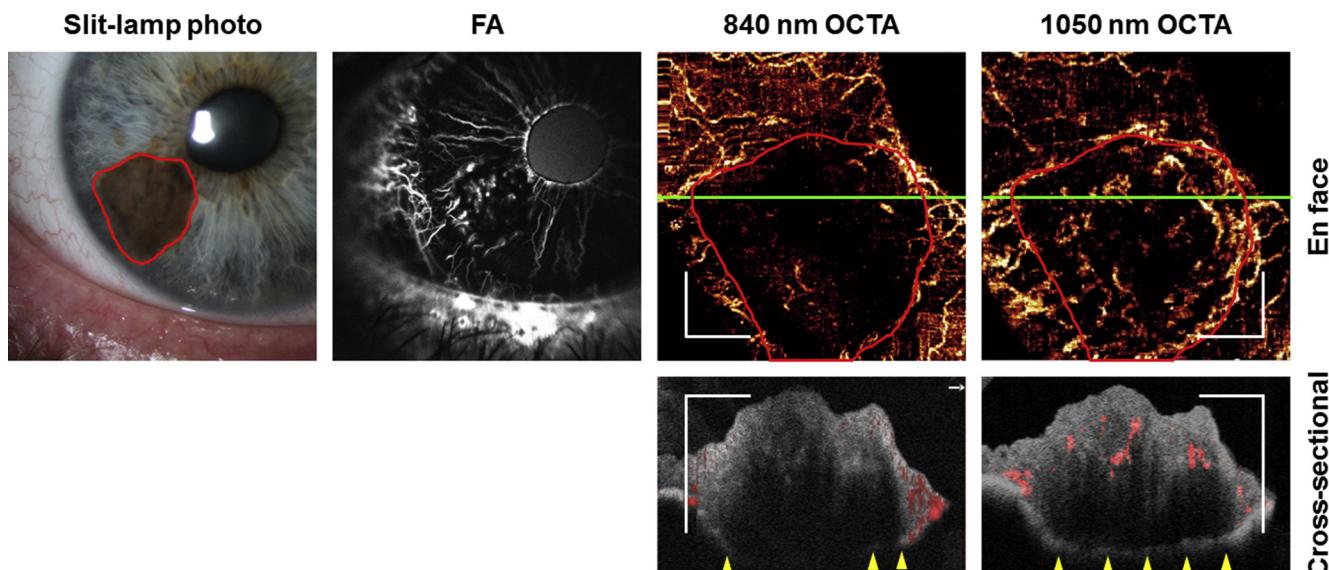


Figure 3. Shown are 840-nm and 1050-nm optical coherence tomography angiography (OCTA) of an iris melanoma (case 6) compared with fluorescein angiography (FA). Early-phase FA at 33 seconds showed normal radial iris vessels and tightly looped vessels within the tumor. Both 840-nm and 1050-nm OCTA showed the normal iris vessels, but only the 1050-nm was able to show the vascular pattern within the tumor (outlined in red). White scale bars are 1 mm in length. Green lines in the en face OCTAs indicate the locations of the cross-sectional OCTAs. The tumor was 1.26 mm between the anterior stromal border and the posterior iris epithelium at the thickest point. The posterior iris epithelium could be visualized by the 1050-nm OCT, but not the 840-nm OCT, at the thicker portions of the tumor. Flow signal (red) could be seen down to the mid-stroma level in the 1050-nm cross-sectional OCTA, but only minimally at the anterior stromal border in the 840-nm OCTA.

segmented in cross-sectional OCT images. The en face iris OCT structure image was calculated by averaging reflectance between the 2 iris boundaries. The en face iris angiogram was constructed by projecting the maximal flow signal between the boundaries. The vessel density was defined as the percentage of area occupied by vessels in en face OCTA.¹⁴ A custom algorithm developed with MATLAB R2010a software (The MathWorks, Inc, Natick, MA) was used to measure vessel density in iris lesions and normal iris tissue areas. Wilcoxon rank sum tests were used to compare vessel density measurements between normal light-colored irides, nevi, and iris melanomas. For iris melanomas treated with radiation therapy, OCTA scans were acquired both before and after the radiation treatment.

Results

Eight eyes (2 blue, 2 green, 2 hazel, 1 light brown, and 1 dark brown) of 8 healthy participants (2 male, 6 female; average age 40.1 ± 10.9 [mean \pm standard deviation], range, 26–62 years) and 9 eyes of 9 patients (6 male, 3 female; average age 66.4 ± 18.0 , range, 44–92 years) with iris lesions were prospectively included in this observational case series. Information regarding the iris color and clinical diagnoses for patients with iris lesions is listed in Table 1. En face OCTA in normal eyes showed blood vessels in the iris stroma with predominantly radial orientation consistent with the previously described FA appearance of the iris vasculature (Fig 1). These vessels are slightly accordioned with pupil in mid-dilated state. There was good penetration of flow signal in the iris stroma in OCTA of light to moderately pigmented irides. However, visualization of iris vessels in the dark brown iris and in the most pigmented portion of the hazel iris was impeded by low OCT signal below the anterior iris stroma (Fig 1).

Optical coherence tomography-angiography of a variety of benign iris lesions was performed (Fig 2); OCTA of iris freckles

showed no increased vascularity associated with these lesions. Three eyes with iris nevi were evaluated with OCTA. In 2 eyes with nevi there was no increased vascularity; in another (Fig 2), fine vascular loops were noted near an area of ectropion uveae close to the pupil margin. IPE cysts are thin-walled, avascular cysts located immediately posterior to the iris that can mimic ciliary body melanomas. We imaged a midzonal IPE cyst with OCTA and, as expected, demonstrated absence of flow (Fig 2).

Traditional iris FA from an eye with cytologically confirmed spindle-cell iris melanoma demonstrated increased vascularity consisting of tight loops within the tumor (Fig 3). The 1050-nm en face OCTA images demonstrated a similar vascular pattern (Fig 3). Vessels in the superficial and midstroma were visualized with 1050-nm OCTA. In contrast, the tumor vasculature was masked by the pigmentation in the anterior stroma in the 840-nm OCTA. The 1050-nm OCT was able to visualize the full thickness (1.26 mm) of the pigmented tumor, whereas the 840-nm OCT could not. Because of the better penetration provided by the 1050-nm OCTA, it was used preferentially for imaging iris tumors in this study.

Two additional cases of iris melanoma treated with I-125 plaque brachytherapy were imaged. These tumors were not histologically confirmed to be melanoma, because the patients declined fine needle biopsy. However, the tumors were large, elevated, and highly vascular and had documented growth, consistent with a clinical diagnosis of iris melanoma. Before treatment, OCTAs (Figs 4 and 5) showed very dense and disorganized intratumoral vessels. In the case of a moderately pigmented melanoma, cross-sectional OCTA showed that most vessels were located in the mid-stroma (Fig 4). In the case of variably pigmented but mainly amelanotic melanoma (Fig 5), there was extremely dense anterior stromal vascularization with obvious shadowing below the vessels. Six months after plaque brachytherapy, the iris tumors were reimaged with OCTA. Repeat scans after treatment demonstrated reduced vascularity of the lesions, although each

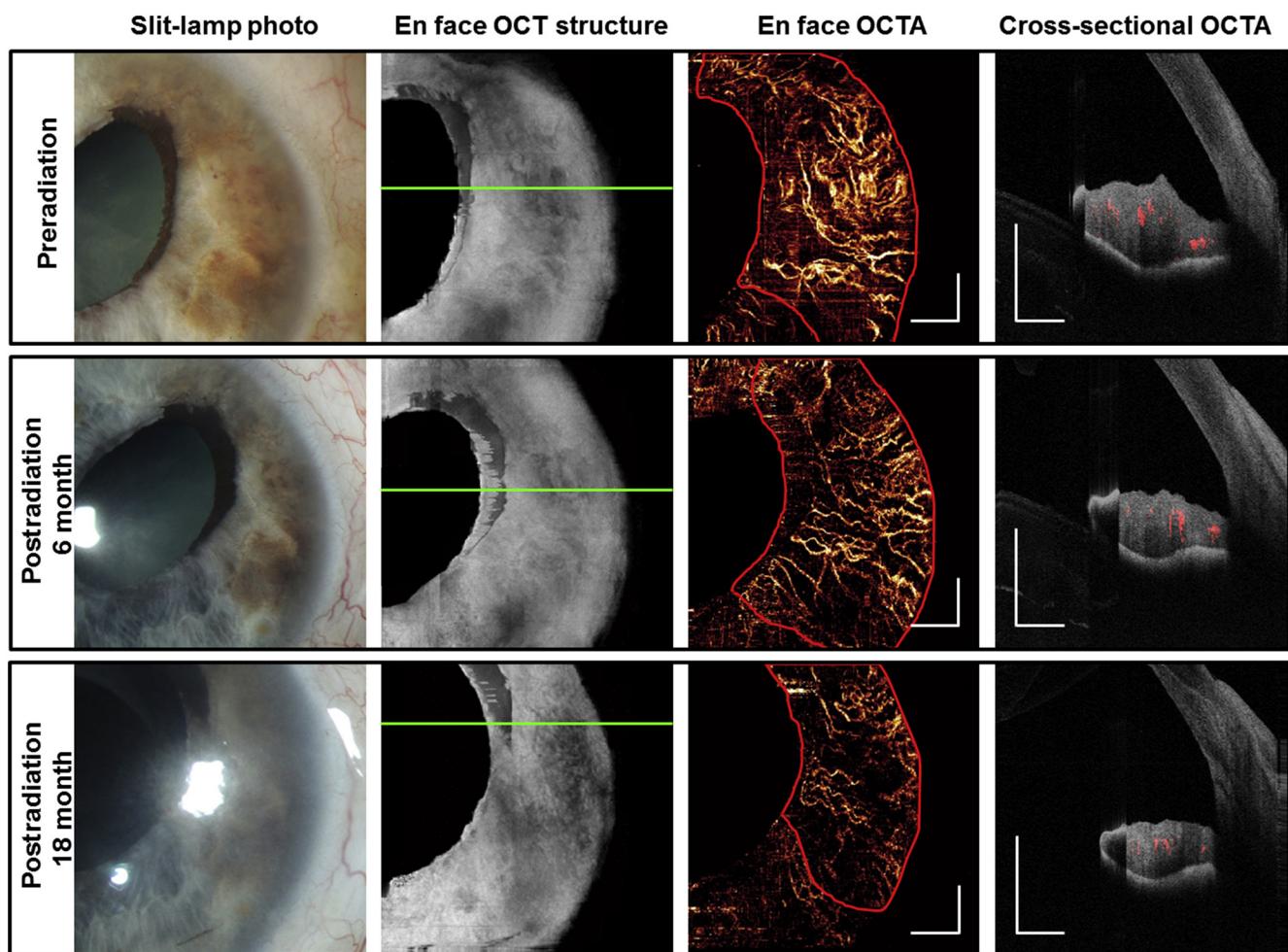


Figure 4. Changes in 1050-nm optical coherence tomography angiography (OCTA) feature of an iris melanoma (case 7) after radiation therapy. The tumor region is outlined in red in the en face OCTAs. White scale bars are 1 mm in length. In the cross-sectional OCTAs, flow signal is shown in red and the reflectance of static pixels is in grayscale. The tumor thickness decreased from 1.01 mm before radiation to 0.77 mm 18 months after treatment, as measured by OCT at the thickest location.

tumor continued to demonstrate abnormal disorganized vascular patterns as compared with normal regions of the iris. There was further regression 18 months postradiotherapy, as evidenced by reduced vascularity and thickness on OCTA (Figs 4 and 5).

The vessel density within iris lesions and in normal iris tissue was measured from en face OCTA images. The vessel density was significantly higher within 3 malignant iris melanomas ($34.5\% \pm 9.8\%$, range, 23.3%–41.1%) than in 3 benign iris nevi ($8.0\% \pm 1.4\%$, range, 6.7%–9.4%; $P = 0.034$), whose vessel density more closely matched 4 normal irides (green or blue in color, $8.0\% \pm 1.2\%$, range, 6.3%–9.0%). A progressive reduction in tumor vessel density over time was observed in iris melanomas treated with radioactive plaques (Fig 6).

Although 1050-nm OCTA provided sufficient penetration to show high vessel density on en face angiograms of most tumors, this was not so in 1 case of highly pigmented iris melanoma (Fig 7). It was evident that dense pigmentation at the anterior stromal border blocked the visualization of tumor vessels, as the tumor vessels could be seen in the less pigmented portion of the tumor. In this study, 1050-nm OCT visualized the full thickness of moderately pigmented iris lesions with thickness between a range of 0.50 and 1.43 mm, but could not fully penetrate a thick iris melanoma and a highly pigmented

melanoma (2.37 mm and 1.49 mm thick, respectively, as measured by ultrasound biomicroscopy).

Discussion

Optical coherence tomography-angiography provides a unique, noninvasive method for evaluating blood flow and vessel density, and is now beginning to be applied to anatomy beyond the retinal vasculature. The imaging of intraocular tumors with OCTA is a developing area, with data from animal models showing promise and 1 published description of OCTA for choroidal tumors in humans.^{3,15} Here we demonstrate that OCTA operating at 1050 nm can be used to image melanocytic iris tumors.

Solid tumors undergo initial avascular and subsequent vascular phases of growth. Increased vascularity is a hallmark of malignant transformation.^{16,17} This occurs through a process of angiogenesis, in which neovascularization creates a network of disorganized, highly permeable intratumoral vessels.^{17,18} Increased intratumoral microvessel

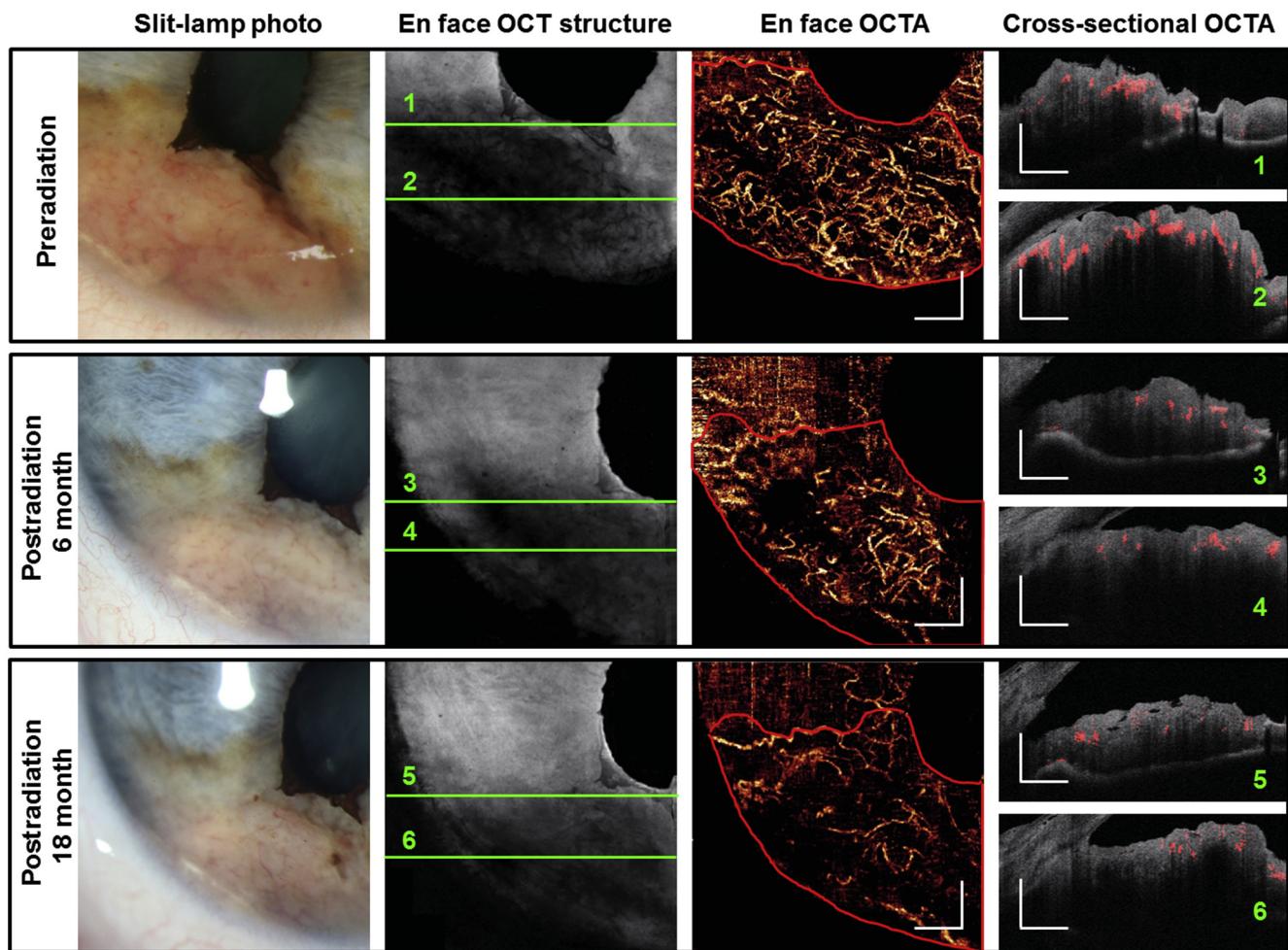


Figure 5. Changes in 1050-nm optical coherence tomography (OCTA) feature of an iris melanoma (case 8) after radiation therapy. The tumor region is outlined in red in the en face OCTAs. White scale bars are 1 mm in length. In the cross-sectional OCTAs, flow signal is shown in red and the reflectance of static pixels is in grayscale. The 1050-nm OCTA did not penetrate the full thickness of the tumor at some locations. Ultrasound biomicroscopy measured the tumor thickness to be 2.37 mm.

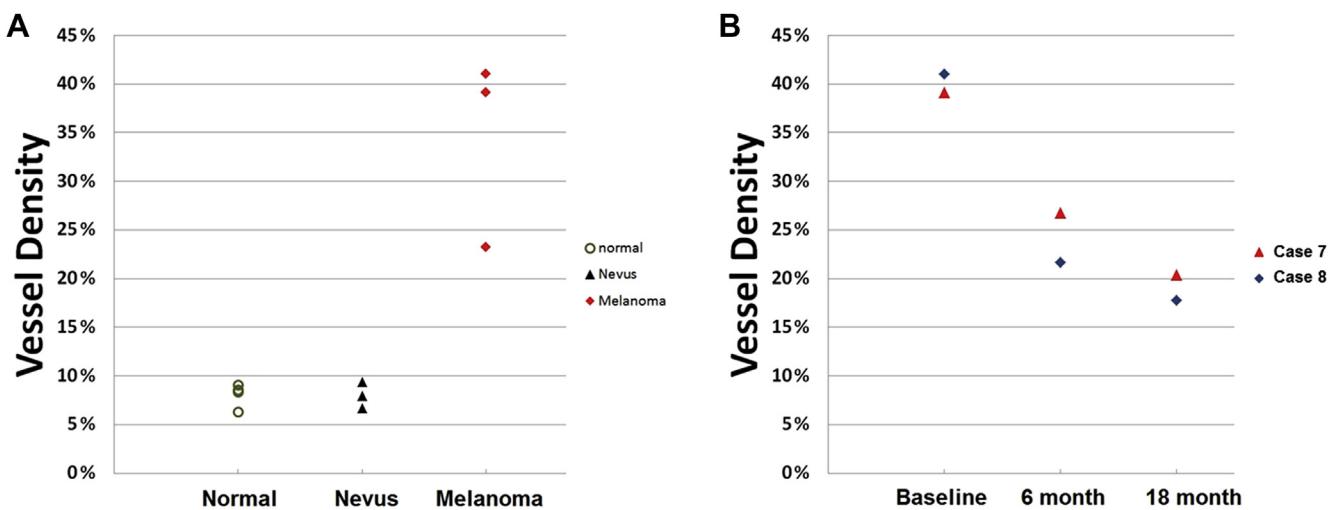


Figure 6. Iris and lesion vessel density plots. A, Vessel density measured in normal iris tissue and within iris lesions (nevi and melanomas). B, Vessel density of 2 iris melanoma cases (cases 7 and 8) decreased after I-125 plaque brachytherapy.

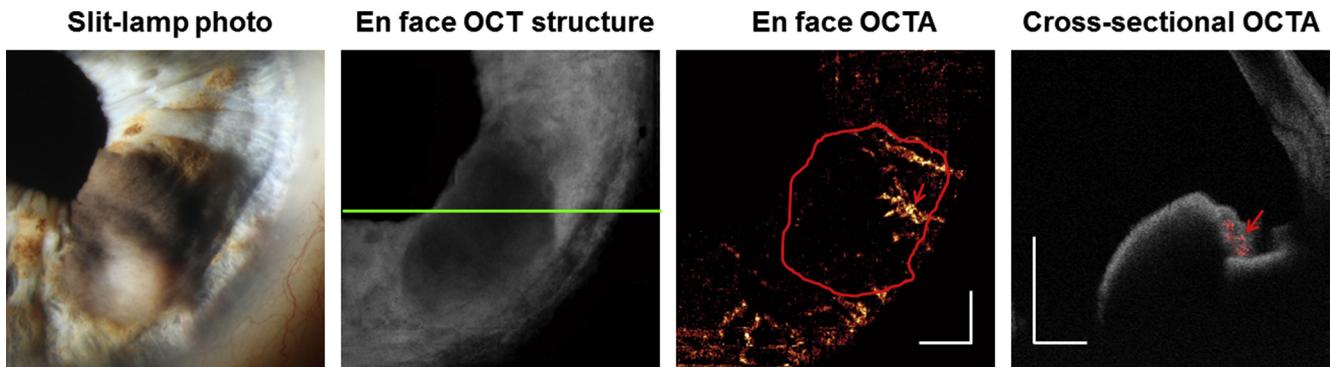


Figure 7. Poor penetration of highly pigmented iris melanoma with 1050-nm optical coherence tomography angiography (OCTA). On the en face structural OCT, the location of the cross-sectional OCTA is marked by a green line. On the en face OCTA, the tumor is outlined in red. White scale bars are 1 mm in length. In the cross-sectional OCTA, flow is shown in red while the reflectance is shown in grayscale. Most of the tumor vasculature was not visible owing to shadowing under the intensely pigmented anterior stromal border, except for a small portion of the tumor that was amelanotic (red arrows). Ultrasound biomicroscopy measured the tumor thickness to be 1.49 mm.

density is associated with various measures of increased tumor aggressiveness, and is a morphologic measure of angiogenesis.¹⁹ Optical coherence tomography-angiography has the potential to provide a noninvasive method for examining intratumoral microvessel density and has potential applications in imaging a variety of ocular tumors as well as cutaneous, gastrointestinal, and gynecologic tumors.¹⁵

Benign iris lesions including freckles, cysts, and nevi do not demonstrate increased intrinsic intratumoral vascularity by OCTA as compared with normal iris tissue. In contrast, iris melanomas are characterized by hypervascularity, with disorganized and tortuous intratumoral vascular patterns and increased vessel density. This is consistent with previous reports of disorganized intratumoral vasculature in iris melanomas imaged with traditional FA.^{20–23} Moreover, we demonstrated that regression of the lesions after radiation treatment is associated with a demonstrable and quantifiable change in the density of the abnormal intratumoral vessels. Other groups have evaluated changes in retinal vasculature associated with radiation treatment of intraocular tumors,^{24,25} but changes within the tumor vasculature associated with radiation have not previously been described. Quantitative changes in vessel density as measured by OCTA may provide useful information regarding tumor regression after radiotherapy.

Eyes with iris melanocytic tumors are often asymptomatic with good vision. As there can be considerable morbidity associated with excisional biopsy or radiation therapy for the treatment of iris melanoma, and observation of lesions is associated with a risk for metastatic disease, developing a noninvasive method to assist in predicting tumor behavior is desirable. Previously, FA has been proposed as a method for differentiation of malignant lesions from benign tumors; however, this testing is costly, is time-intensive, and carries risk associated with dye injections. Owing to these considerations many clinicians do not perform iris FA routinely for clinical care. OCTA may provide a simple, cost-effective, and safe alternative that could be used to monitor iris tumors and help identify those lesions at highest risk for malignancy and metastatic spread.

Adding OCTA to a “watchful waiting” protocol used for tumors that are not yet demonstrating other high-risk features for metastasis may allow clinicians to more easily detect concerning changes in intratumoral vascularity, so that treatment discussions could be initiated. This technique could also allow clinicians to avoid unnecessary excisional biopsy or radiation treatment. Further study is necessary to determine the clinical utility of this approach.

There are several limitations of current OCTA technology for imaging the iris. First of all, good patient cooperation is required, as the scan acquisition takes approximately 3 seconds. Secondly, OCTA image size was limited and not large enough to capture the entire iris in 1 scan. We investigated both 6×6-mm and 9×9-mm scan sizes containing the same axial scan numbers. The 6×6-mm scan size was preferable because it provides better vasculature detail. One important limitation of OCTA in imaging iris tumors is inadequate penetration through highly pigmented lesions and thicker tumors. Although it could not fully image all iris lesions, the 1050-nm OCT system was superior to an 840-nm system in the penetration of iris tumors. The en face vascular pattern and the posterior iris pigment epithelium could both be visualized in most iris tumors evaluated with the 1050-nm system, enabling vessel density and volume measurements. Full OCT and OCTA penetration of the tumors appears to depend upon tumor thickness as well as the degree of pigmentation and vessel density within the tumor, owing to shadowing. It is possible that longer-wavelength systems working at 1310-nm wavelength may be able to overcome these deficiencies, allowing for successful OCTA imaging of intratumoral vasculature in tumors not well imaged with the 1050-nm system.

In conclusion, this is the first demonstration of OCTA in iris tumors. OCTA working at 1050-nm wavelength can successfully image vasculature within moderately pigmented and nonpigmented iris melanocytic tumors. This technique may serve as a less invasive alternative to conventional FA for assessing tumor vascularity and monitoring response to treatment and has the advantage of providing quantitative measurement of vessel density within tumors.

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Footnotes and Financial Disclosures

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Data collection: Skalet, Li, Lu, Lee

Analysis and interpretation: Skalet, Li, Jia, Husvogt, Huang

Obtained funding: Skalet, Huang

Overall responsibility: Skalet, Li, Huang

Abbreviations and Acronyms:

FA = fluorescein angiography; **IPE** = iris pigment epithelial; **OCT** = optical coherence tomography; **OCTA** = optical coherence tomography angiography.

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