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Quantitative OCT Angiography Evaluation of Peripapillary Retinal Circulation after Plaque Brachytherapy

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Purpose: To study peripapillary retinal capillary circulation in eyes treated with iodine 125 (I^{125}) plaque brachytherapy for uveal melanoma using optical coherence tomography angiography (OCTA).

Design: Cross-sectional study of 10 participants imaged with OCTA before uveal melanoma treatment and 15 participants imaged after development of radiation retinopathy, optic neuropathy, or both.

Participants: After institutional review board approval, participants were enrolled from an academic ocular oncology clinical practice. All participants had uveal melanoma in 1 eye, and treatment with I^{125} plaque brachytherapy was planned or had taken place previously. Patients with low vision at baseline and uncontrolled hypertension were excluded. In the posttreatment group, 7 participants were men and 8 were women; age range was 38 to 81 years. Visual acuities in the irradiated eyes ranged from 20/20 to counting fingers. Visual acuities in the untreated fellow eyes were 20/25 or better.

Methods: Peripapillary retinal capillary circulation was measured by OCTA (Optovue, Inc). Optic disc scans measuring 4.5 × 4.5 mm were obtained.

Main Outcome Measures: The relationship of the peripapillary retinal capillary density (PPCD) as measured by OCTA to the calculated dose to the optic nerve (the dose to 50% of the disc [D50]) and visual acuity in logarithm of the minimal angle of resolution units were evaluated.

Results: No significant differences were observed in the PPCD as measured by OCTA when comparing the eye with melanoma with the fellow eye before brachytherapy; however, the PPCD was significantly lower in treated eyes (52.9% ± 22.4%) than in fellow eyes that did not receive radiation (73.3% ± 13.7%; $P = 0.004$). There was an inverse linear correlation between D50 and the PPCD (Pearson's $r = -0.528$; $P = 0.043$) and between visual acuity and the PPCD (Pearson's $r = -0.564$; $P = 0.028$).

Conclusions: Among patients with clinically apparent radiation retinopathy, radiation optic neuropathy, or both, PPCD was lower in the treated eye and correlated with the radiation dose to the optic nerve and the visual acuity. Optical coherence tomography angiography provides a measure of capillary changes after radiation and may serve as a quantitative end point to address visual prognosis. *Ophthalmology Retina 2017;■:1–7 © 2017 by the American Academy of Ophthalmology*

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Uveal melanomas are the most common primary intraocular malignancy in adults, with an incidence of approximately 5 to 6 cases per 1 million population.[1–3] Eye-sparing treatment with radiation is an option for many patients diagnosed with uveal melanoma, but often leads to significant loss of vision. The degree of vision loss varies widely, with some patients experiencing only mild decline in measured visual acuity and others becoming entirely blind in the treated eye.[4–7] In the landmark Collaborative Ocular Melanoma Study (COMS), 43% of patients treated with plaque brachytherapy were found to have measured visual acuity in the severely compromised range at 3 years after radiation.[8]

Vision loss after radiation therapy typically occurs because of radiation optic neuropathy and retinopathy caused by vascular compromise leading to ischemia and edema.[9–13] Advanced vascular compromise can be observed with traditional fluorescein angiography, which shows retinal vascular leakage and capillary dropout in eyes with radiation-induced damage.[14,15] Optical coherence tomography angiography (OCTA) is a new, noninvasive method for imaging retinal vasculature and providing quantitative information regarding ischemia in the retina.[16–20] The association of radiation maculopathy with decreased parafoveal capillary density as measured by OCTA has been reported previously.[21] Optical coherence tomography angiography findings may allow for earlier detection of radiation maculopathy.[22] We hypothesized that OCTA can measure radiotherapy-induced changes in retinal vasculature associated with

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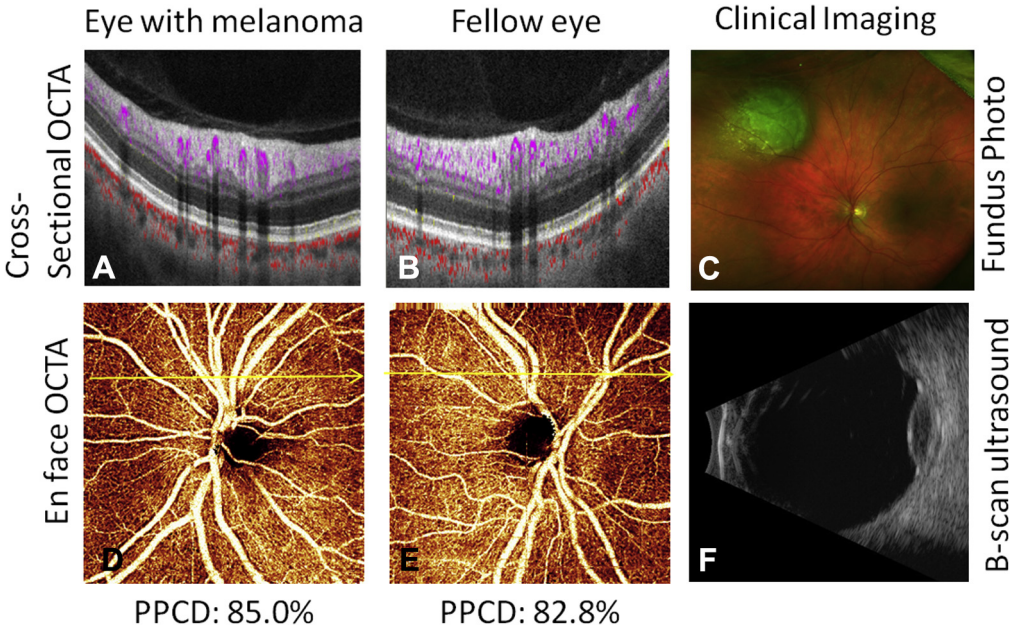

Figure 1. Representative example of peripapillary capillary density (PPCD) before treatment in an eye with uveal melanoma located in the superonasal periphery as compared with the normal fellow eye. **A**, **B**, Cross-sectional OCT angiography (OCTA) image for each eye (retinal flow shown in *purple*, and choroidal flow shown in *red*). **D**, **E**, En face OCTA of the peripapillary region. The location of the cross-sectional OCTA image is indicated with a *yellow arrow*. The PPCD for each eye is shown. The clinical imaging included (**C**) Optos fundus photography and (**F**) longitudinal B-scan ultrasonography.

radiation optic neuropathy. Herein, we describe for the first time the use of OCTA to evaluate radiation optic neuropathy by quantitatively measuring the peripapillary capillary density (PPCD) in eyes treated with plaque brachytherapy. We also demonstrated an inverse linear correlation between the calculated PPCD and the radiation dose to the optic nerve as well as the visual acuity (in logarithm of the minimum angle of resolution units) in the treated eye.

Methods

Study Participants

After institutional review board approval (Clinicaltrials.gov identifier, NCT01955941), participants were enrolled from an academic ocular oncology clinical practice. All participants had been diagnosed with ciliary body or choroidal melanoma in 1 eye and previously had undergone plaque brachytherapy or were scheduled to undergo this procedure for the treatment of the tumor. At the time of OCTA imaging after brachytherapy, all participants had clinically apparent radiation optic neuropathy, radiation retinopathy, or both.

Plaque Brachytherapy

Brachytherapy was performed using iodine 125 (I^{125}) seeds (IsoAid Model IAI-125A; IsoAid, LLC, Port Richey, FL) inserted in a silastic carrier and mounted in gold COMS-style plaques. Seed activity was calculated to deliver 85 Gy over 100 hours to a prescription depth dependent on tumor thickness. Starting with a minimum prescription depth of 3 mm, the depth was increased by multiples of 0.5 mm for thicker tumors to assure a margin of 0.5 mm or more but less than 1.0 mm, up to tumor thickness of 5 mm. For tumor thicknesses larger that 5 mm, the prescription depth was set to the tumor depth.

The planned seed activity was calculated using Plaque Simulator version 6.4.1 (Eye Physics LLC, Los Alamitos, CA). The software uses a superposition of a linear source model of all seeds as defined by the approved consensus data of American Association of Physics in Medicine with corrections for the presence of the plaque, carrier attenuation, and air interface.[23] Some of the plaques were modified in house with cut notches to allow implantation around or near the optic nerve. These were modeled specifically to account for the lack of a lip on the notched edge normally found on commercially available notched COMS plaques. The size and variation of the plaque were determined by the surgeon based on the limitations of surgical practicality. The dose to 50% of the optic nerve at the retinal surface (D50) was calculated with positioning based on fundus images loaded into the planning software.

OCT Angiography Data Acquisition and Analysis

A 70-kHz spectral-domain optical coherence tomography instrument (RTVue-XR; Optovue, Inc, Fremont, CA) obtained 4.5 × 4.5-mm optic disc scans for OCTA in tumor and fellow eyes. Two repeated B-scans, each consisting of 304 A-scans, were captured at each of 304 locations in 2.9 seconds. One x-fast and 1 y-fast scan were acquired, registered, and merged, minimizing motion artifacts. The split-spectrum amplitude-decorrelation angiography algorithm was applied to detect flow by calculating the decorrelation of the optical coherence tomography reflectance signal between 2 consecutive B-scans at the same location, as described previously.[24] The projection-resolution algorithm[25] was applied to remove the projection artifacts throughout the entire volume.

The merged volumetric OCTA images were exported for custom processing using the Center for Ophthalmic Optics & Lasers-Angiography Reading Toolkit software.[26] These custom

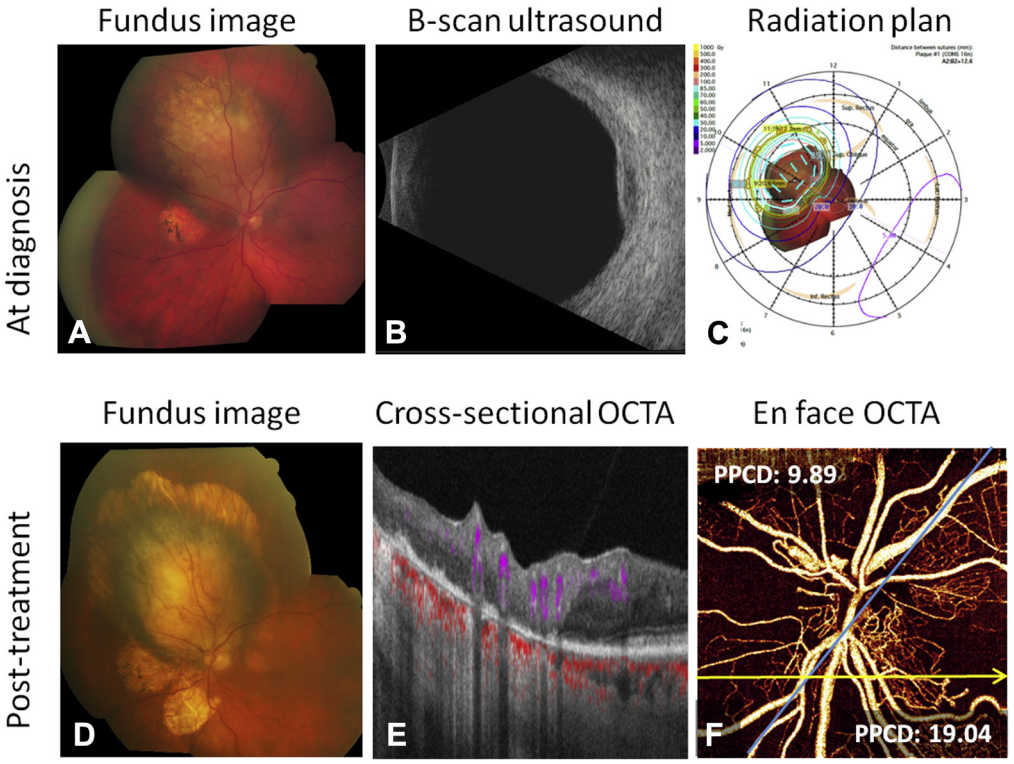

Figure 2. Images showing peripapillary capillary density (PPCD) in an eye treated with iodine 125 plaque brachytherapy for a circumpapillary choroidal melanoma. The calculated dose to 50% of the optic disc for this eye was 62 Gy. **A**, **B**, Clinical imaging at the time of diagnosis and (**C**) radiation plan. **D**, Clinical photograph at the time of OCT angiography (OCTA) imaging after brachytherapy. **E**, Cross-sectional OCTA (retinal flow shown in *purple*, and choroidal flow shown in *red*). **F**, En face OCTA of the peripapillary region. The location of the cross-sectional OCTA image is indicated with a *yellow arrow*. The vessel densities in the peripapillary hemiretina receiving the higher radiation dose (superonasal retina) as compared with the lower regional dose (inferotemporal retina) are shown, with the *blue line* dividing the calculated regions.

programs were developed at the Casey Eye Institute using the MATLAB programming language. The OCTA scans contain both volumetric flow (decorrelation) data as well as structural (reflectance) data. Using the Center for Ophthalmic Optics & Lasers-Angiography Reading Toolkit software, an automated segmentation algorithm isolated the inner retina based on structural optical coherence tomography parameters (inner limiting membrane to the outer boundary of the outer plexiform layer) and produced en face angiograms by projecting the maximum flow signal within the inner retina. The segmentation was corrected manually if needed. Before peripapillary capillary density measurement, the optic disc area (D = 2 mm) and large arterioles and venules were identified automatically and subtracted from the en face angiograms. The measurement was performed consistently on a 4.0 × 4.0-mm region centered on the disc. Peripapillary capillary density is defined as the proportion of flow pixels within all valid pixels on the working region. The method for calculating PPCD has been described in a previous study.[26] Within-visit repeatability of the PPCD was calculated from normal eyes, with 2 sets of scans performed within a single visit. Using the radiation plans, the hemiretina within the peripapillary region receiving the most radiation was divided from the region receiving a relatively lower dose on the en face angiogram. The PPCD then was calculated for each hemiretina within the same eye to determine whether there was regional variation within the same treated eye. The relationship of the PPCD for the entire peripapillary region to the calculated dose to the optic nerve was assessed. Trained observers (L.L., J.W., Y.J.) reviewed scans, and those with poor image quality, as defined by the following criteria, were excluded: (1) signal strength index less than 50, (2) poor scan alignment or failed motion correction, and (3) focal loss of reflectance signal resulting from vitreous floaters.

Statistical Analysis

Within-visit repeatability was assessed by the coefficient of variation. The Mann−Whitney *U* test was used to compare groups between tumor and fellow eyes before and after radiation and between the hemiretina with higher dose and opposite hemiretina on tumor eyes. Pearson correlation was used to determine the relationship between PPCD and radiation doses. All statistical analyses were performed with SPSS software version 20.0 (SPSS, Inc, Chicago, IL) and MedCalc software version 10.1.3.0 (MedCalc Software, Ostend, Belgium).

Results

Both eyes of 10 participants recently diagnosed with ciliary body or choroidal melanoma, or both, underwent imaging with OCTA before planned I^{125} plaque brachytherapy. Three participants were men and 7 participants were women, with ages ranging from 43 to 70 years. Visual acuities in the eye with melanoma ranged from 20/20 to 20/40 and in the fellow eye ranged from 20/20 to 20/30. No significant difference was seen between PPCD in eyes with tumor (71.6±9.9%) and the fellow eye (70.9±9.7%) before radiation among participants who were evaluated before brachytherapy ($P = 0.838$, Wilcoxon signed-rank test). A representative example

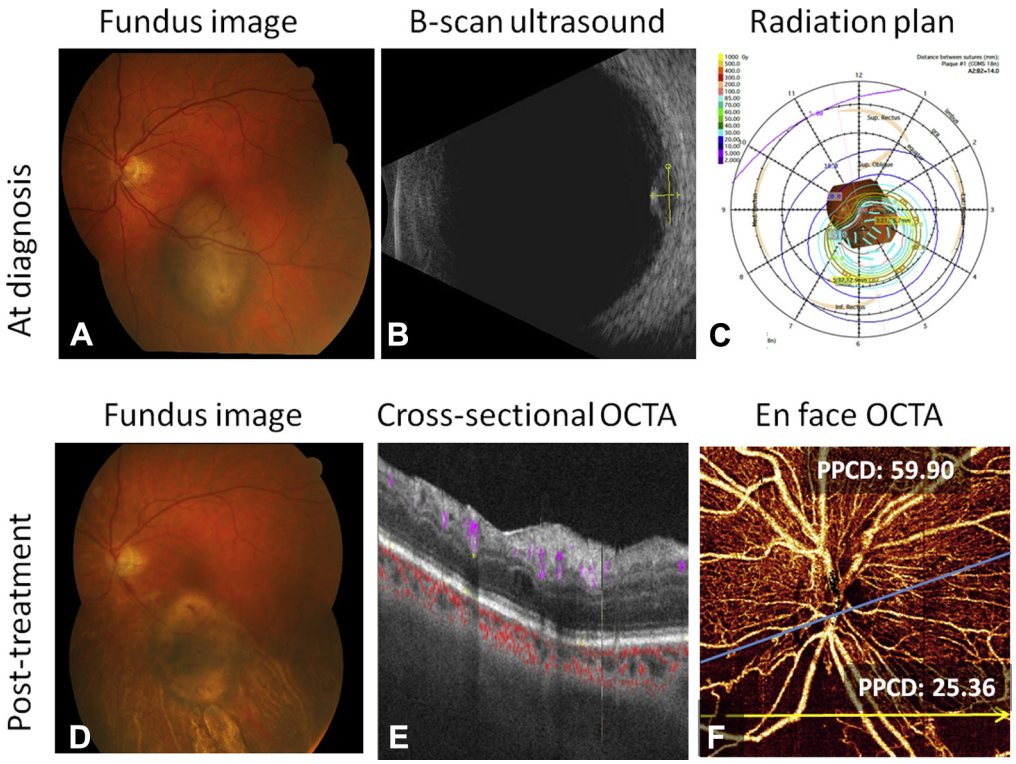

Figure 3. Peripapillary capillary density (PPCD) in an eye treated with iodine 125 plaque brachytherapy for choroidal melanoma in the posterior pole. The calculated dose to 50% of the optic disc for this eye was 53 Gy. **A**, **B**, clinical imaging at the time of diagnosis and (**C**) radiation plan. **D**, Clinical photograph at the time of OCT angiography (OCTA) imaging after brachytherapy. **E**, Cross-sectional OCTA (retinal flow shown in *purple*, and choroidal flow shown in *red*). **F**, En face OCTA of the peripapillary region. The location of the cross-sectional OCTA image is indicated with a *yellow arrow*. The vessel densities in the peripapillary hemiretina receiving the higher radiation dose (inferotemporal retina) as compared with the lower regional dose (superonasal retina) are shown, with the *blue line* dividing the calculated regions.

of OCTA imaging in a patient before brachytherapy is shown in Figure 1.

Fifteen participants who had been treated with plaque brachytherapy for ciliary body or choroidal melanoma and had demonstrated clinically apparent radiation optic neuropathy, radiation retinopathy, or both were enrolled in the study. Seven participants were men and 8 were women, with ages ranging from 31 to 80 years at the time of melanoma treatment. There were no significant differences between the group imaged before brachytherapy and the group imaged after radiation side effects developed in terms of age ($P = 0.54$, t test) or gender ($P = 0.68$, Fisher exact test). Patients in the group with radiation retinopathy or optic neuropathy were treated between 1 and 9 years before being enrolled in the study. Each patient was treated with I^{125} plaque brachytherapy per standard of care. The treated eye was the left eye in 10 participants and the right eye in 5 participants. According to records, the baseline visual acuities ranged from 20/20 to 20/60 in the eye with melanoma and from 20/20 to 20/40 in the fellow eye. One participant also underwent imaging before brachytherapy and is included in the pretreatment analyses above.

After brachytherapy, the visual acuities in the irradiated eyes ranged from 20/20 to counting fingers, whereas visual acuities in the untreated fellow eye were 20/25 or better (Table 1, available at www.ophthalmologyretina.org). After radiation treatment, the PPCD as measured by OCTA was lower significantly in treated eyes (52.9±22.4%) than in fellow eyes that did not receive radiation (73.3±13.7%; $P = 0.004$). The PPCD was lower in the portion of the peripapillary retina that received the higher radiation dose than in the opposite hemiretina. Representative examples of OCTA imaging in eyes treated for choroidal melanoma in various anatomic locations are shown in Figures 2 to 4. The most severe ischemia was seen in eyes treated for juxtapapillary or circumpapillary tumors, which was not unexpected because these eyes typically received higher radiation doses to the optic disc.

There was an inverse linear correlation between radiation dose (D50) and the PPCD (Pearson $r = -0.528$; $P = 0.043$; Fig 5A). There was also a significant inverse correlation between the visual acuity and the PPCD (Pearson $r = -0.564$; $P = 0.028$), as shown in Figure 5B. When the PPCD was "normalized" by comparing it with the fellow eye (PPCD fellow eye − PPCD treated eye = ΔPPCD), an even stronger correlation was seen between ΔPPCD and D50 (Pearson $r = 0.664$; $P = 0.013$; Fig 5C). The change in logarithm of the minimum angle of resolution visual acuity from baseline before treatment to visual acuity measured at the time of OCTA imaging correlated with the PPCD as well (Pearson $r = 0.665$; $P = 0.007$; Fig 5D).

Discussion

Radiation optic neuropathy is a significant cause of morbidity in patients undergoing radiation therapy for uveal melanoma. Optical coherence tomography angiography provides a unique, quantitative method for evaluating regional retinal blood flow and vessel density in regions

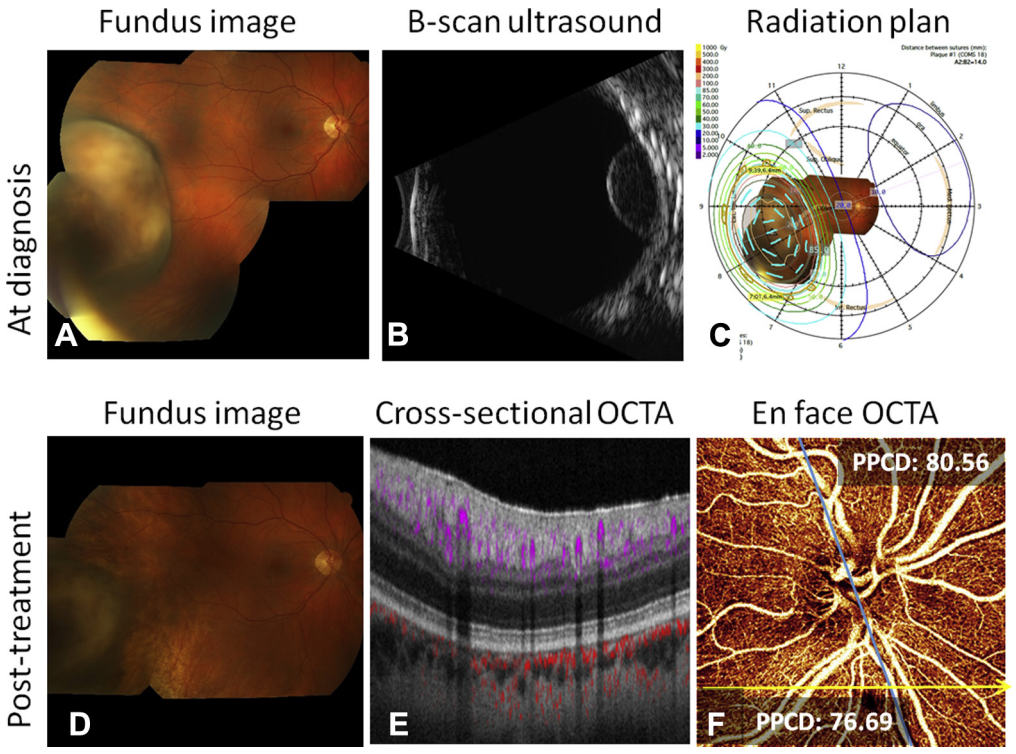

Figure 4. Peripapillary capillary density (PPCD) in an eye treated with iodine 125 plaque brachytherapy for choroidal melanoma in the temporal periphery. The calculated dose to 50% of the optic disc for this eye was 14 Gy. **A**, **B**, clinical imaging at the time of diagnosis and (**C**) radiation plan. **D**, Clinical photograph at the time of OCT angiography (OCTA) imaging after brachytherapy. **E**, Cross-sectional OCTA (retinal flow shown in *purple*, and choroidal flow shown in *red*). **F**, En face OCTA of the peripapillary region. The location of the cross-sectional OCTA image is indicated with a *yellow arrow*. The vessel densities in the peripapillary hemiretina receiving the higher radiation dose (temporal retina) as compared with the lower regional dose (nasal retina) are shown, with the *blue line* dividing the calculated regions.

critical for vision. Herein we demonstrated that OCTA can be used to evaluate vascular compromise after radiation therapy in eyes with uveal melanoma and that this compromise can be observed as lower capillary vessel densities in the peripapillary regions. Furthermore, the degree of regional ischemia, as measured by the PPCD, correlates inversely with the calculated radiation dose to the optic nerve as measured by D50 and with the visual acuity in the eye. No significant differences were found when comparing PPCD in eyes with melanoma and fellow eyes before treatment. This suggests that the differences demonstrated here in PPCD between treated eyes with radiation optic neuropathy and fellow eyes are not the result of the presence of the tumor.

Optical coherence tomography angiography measurements provide a highly reproducible, quantitative method for measuring retinal circulation and vessel density that may allow development of a model for clinicians to predict vision loss better for patients treated with radiation for uveal melanomas and other ocular tumors. This technology also may assist in evaluating emerging therapies for radiation retinopathy, such as anti−vascular endothelial growth factor, and in determining which patients may respond best to therapeutic interventions directed at reducing vision loss after radiation therapy. Future studies will evaluate further the relationships among visual acuity, radiation dose to the optic nerve and fovea, and degree of vascular compromise in these areas as detected by OCTA. In particular, a longitudinal study of the local microvascular response to radiation therapy as measured by OCTA will improve understanding of the timing and significance of decreased PPCD and macular capillary density.

The quantitative nature of OCTA is an important advantage over traditional fluorescein angiography, which has been the major method for observing radiation-induced changes in the eye in the past. In addition to being used for vessel density measurements, OCTA also can be used to evaluate perfusion by calculating the flow index as defined by the average decorrelation values in the segmented area. We found the flow index and vessel density provided similar results in prior studies,[27,28] and therefore have focused on reporting vessel densities for subsequent work, including the current study. Optical coherence tomography angiography provides a 3-dimensional volumetric scan that can allow segmentation of blood circulation into individual plexi, something not possible with traditional fluorescein angiography. These analyses require segmentation of various tissue layers in the retina and choroid. In the current study, we limited calculations to the inner retina circulation (inner limiting membrane to outer plexiform layer) because accurate segmentation of each layer in eyes with retinal edema or atrophy remains challenging, as evidenced in the

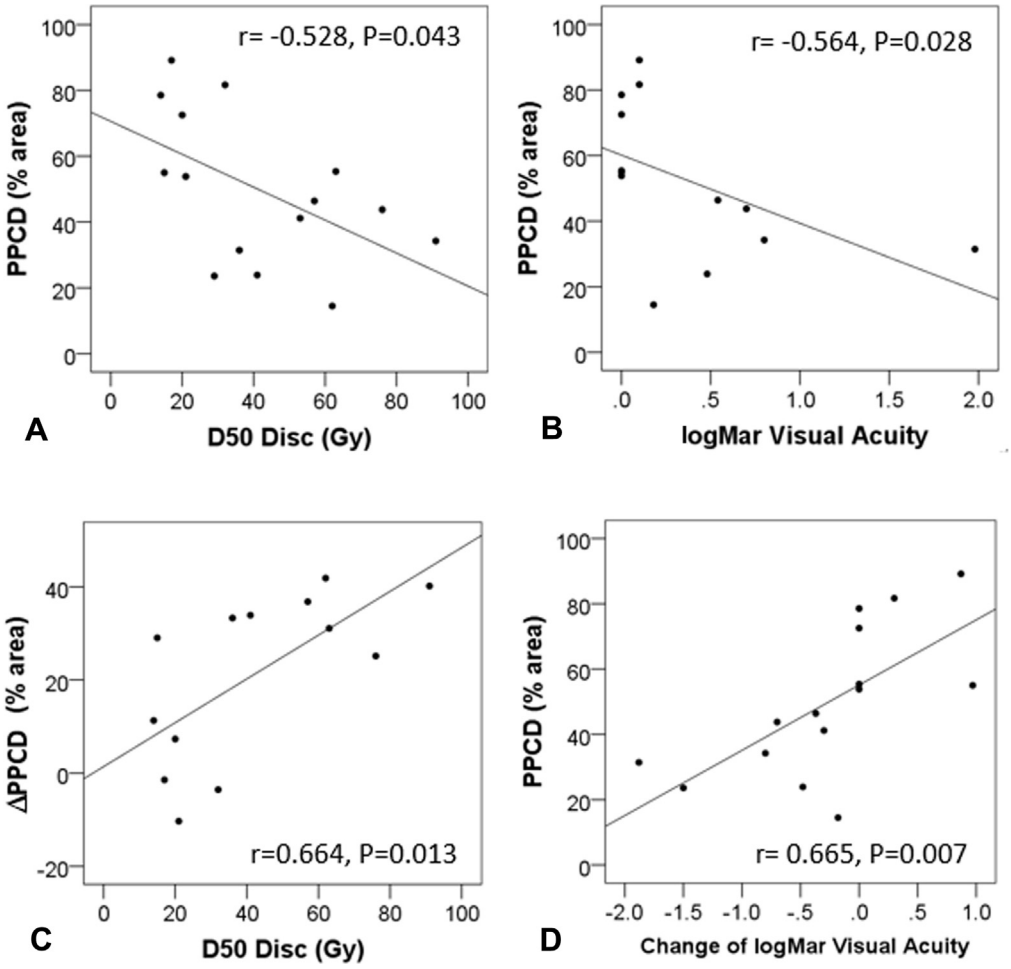

Figure 5. Graph showing that the peripapillary capillary density (PPCD) correlates with the radiation dose to the optic nerve as measured by the radiation dose to 50% of the optic disc (D50) and with the logarithm of the minimum angle of resolution (logMAR) visual acuity. The relationship between PPCD and D50 was examined using the Pearson's correlation coefficient. Each participant is indicated with a point on the plot. **A**, Best-fit line. **B**, Visual acuity (logMAR) was correlated inversely with the PPCD. **C**, Relationship between D50 and the difference in PPCD between the treated eye and the fellow eye (ΔPPCD). **D**, Change in visual acuity (logMAR) from time of tumor diagnosis and time of optical coherence tomography angiography imaging was correlated with PPCD.

case shown in Figure 2. Similarly, retinal edema and atrophy also affected our ability to calculate choroidal blood perfusion. Efforts to optimize our algorithm for the quantification of choroidal layers are underway.

The data presented here, together with previously published work demonstrating macular changes after brachytherapy as measured by OCTA,[21,22] set a framework for future studies in which retinal microcirculation can be assessed quantitatively before and after radiation treatment and correlated with vision outcome. Future studies using longitudinal data and emerging OCTA technologies that may allow wide-field imaging will improve our understanding of the microvascular changes associated with radiation therapy.

References

1. Wilkes SR, Robertson DM, Kurland LT, Campbell RJ. Incidence of uveal malignant melanoma in the resident population of Rochester and Olmsted County, Minnesota. *Am J Ophthalmol*. 1979;87:639–641.
2. Singh AD, Turell ME, Topham AK. Uveal melanoma: trends in incidence, treatment, and survival. *Ophthalmology*. 2011;118:1881–1885.
3. Mahendraraj K, Lau C, Lee I, Chamberlain R. Trends in incidence, survival, and management of uveal melanoma: a population-based study of 7,516 patients from the Surveillance, Epidemiology, and End Results database (1973–2012). *Clin Ophthalmol*. 2016;10:2113–2119.
4. Gragoudas ES, Li W, Lane AM, et al. Risk factors for radiation maculopathy and papillopathy after intraocular irradiation. *Ophthalmology*. 1999;106:1571–1578.
5. Gragoudas ES. Proton beam irradiation of uveal melanomas: the first 30 years. The Weisenfeld Lecture. *Invest Opthalmol Vis Sci*. 2006;47:4666–4673.
6. Puusaari I, Heikkonen J, Kivelä T. Ocular complications after iodine brachytherapy for large uveal melanomas. *Ophthalmology*. 2004;111:1768–1777.
7. Puusaari I, Heikkonen J, Kivelä T. Effect of radiation dose on ocular complications after iodine brachytherapy for large uveal

melanoma: empirical data and simulation of collimating plaques. *Invest Ophthalmol Vis Sci*. 2004;45:3425−3434.
8. Melia BM, Abramson DH, Albert DM, et al. Collaborative ocular melanoma study (COMS) randomized trial of I-125 brachytherapy for medium choroidal melanoma. I. Visual acuity after 3 years COMS report no. 16. *Ophthalmology*. 2001;108:348−366.
9. Brown GC, Shields JA, Sanborn G, et al. Radiation retinopathy. *Ophthalmology*. 1982;89:1494−1501.
10. Seibel I, Cordini D, Hager A, et al. Predictive risk factors for radiation retinopathy and optic neuropathy after proton beam therapy for uveal melanoma. *Graefes Arch Clin Exp Ophthalmol*. 2016;254:1787−1792.
11. Yousef YA, Finger PT. Optical coherence tomography of radiation optic neuropathy. *Ophthalmic Surg Lasers Imaging*. 2012;43:6−12.
12. Wen JC, Oliver SC, McCannel TA. Ocular complications following I-125 brachytherapy for choroidal melanoma. *Eye (Lond)*. 2009;23:1254−1268.
13. Stack R, Elder M, Abdelaal A, et al. New Zealand experience of I125 brachytherapy for choroidal melanoma. *Clin Exp Ophthalmol*. 2005;33:490−494.
14. Hayreh SS. Post-radiation retinopathy. A fluorescence fundus angiographic study. *Br J Ophthalmol*. 1970;54:705−714.
15. Guyer DR, Mukai S, Egan KM, et al. Radiation maculopathy after proton beam irradiation for choroidal melanoma. *Ophthalmology*. 1992;99:1278−1285.
16. Hwang TS, Gao SS, Liu L, et al. Automated quantification of capillary nonperfusion using optical coherence tomography angiography in diabetic retinopathy. *JAMA Ophthalmol*. 2016;134:367−373.
17. Hwang TS, Zhang M, Bhavsar K, et al. Visualization of 3 distinct retinal plexuses by projection-resolved optical coherence tomography angiography in diabetic retinopathy. *JAMA Ophthalmol*. 2016;134:1411−1419.
18. Jia Y, Bailey ST, Hwang TS, et al. Quantitative optical coherence tomography angiography of vascular abnormalities in the living human eye. *Proc Natl Acad Sci U S A*. 2015;112:201500185.
19. Jia Y, Bailey ST, Wilson DJ, et al. Quantitative optical coherence tomography angiography of choroidal neovascularization in age-related macular degeneration. *Ophthalmology*. 2014;121:1435−1444.
20. Jia Y, Wei E, Wang X, et al. Optical coherence tomography angiography of optic disc perfusion in glaucoma. *Ophthalmology*. 2014;121:1322−1332.
21. Shields CL, Say EAT, Samara WA, et al. Optical coherence tomography angiography of the macula after plaque radiotherapy of choroidal melanoma. *Retina*. 2016;36:1493−1505.
22. Veverka KK, AbouChehade JE, Iezzi R, Pulido JS. Noninvasive rading of radiation retinopathy: the use of optical coherence tomography angiography. *Retina*. 2015;35:2400−2410.
23. Rivard MJ, Butler WM, DeWerd LA, et al. Supplement to the 2004 update of the AAPM Task Group No. 43 Report. *Med Phys*. 2007;34:2167−2205.
24. Jia Y, Tan O, Tokayer J, et al. Split-spectrum amplitude-decorrelation angiography with optical coherence tomography. *Opt Express*. 2012;20:4710−4725.
25. Zhang M, Hwang TS, Campbell JP, et al. Projection-resolved optical coherence tomographic angiography. *Biomed Opt Express*. 2016;7:816−828.
26. Zhang M, Wang J, Pechauer AD, et al. Advanced image processing for optical coherence tomographic angiography of macular diseases. *Biomed Opt Express*. 2015;6:4661−4675.
27. Liu L, Jia Y, Takusagawa HL, et al. Optical coherence tomography angiography of the peripapillary retina in glaucoma. *JAMA Ophthalmol*. 2015;133:1045−1052.
28. Jia Y, Morrison JC, Tokayer J, et al. Quantitative OCT angiography of optic nerve head blood flow. *Biomed Opt Express*. 2012;3:3127−3137.

Footnotes and Financial Disclosures

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Analysis and interpretation: Skalet, Liu, Binder, Miller, Wang, Wilson, Crilly, Thomas, Huang, Jia

Data collection: Skalet, Liu, Binder, Miller, Wang, Huang, Jia

Obtained funding: Skalet, Huang, Jia

Overall responsibility: Skalet, Liu, Binder, Jia

Abbreviations and Acronyms:
COMS = Collaborative Ocular Melanoma Study; **D50** = radiation dose to 50% of the optic disc; **I^{125}** = iodine 125; **logMAR** = logarithm of the minimal angle of resolution; **OCTA** = optical coherence tomography angiography; **PPCD** = peripapillary retinal capillary density.

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