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OCT Angiography Analysis of Retinal and Choroidal Flow after Proton Beam Therapy for Choroidal Melanoma

Su-Kyung Jung, MD,[1,2] *Edward H. Lee, MD,*[1] *Kavita K. Mishra, MD,*[3,4] *Inder K. Daftari, PhD,*[3] *Susanna S. Park, MD, PhD*[1]

Purpose: To evaluate the macular and peripapillary retinal and choroidal flow changes in eyes with choroidal melanoma (CM) treated with proton beam radiation therapy (PBRT) using OCT angiography (OCTA).

Design: A prospective, cross-sectional, single-center study.

Participants: All patients seen at the study center between 2019 and 2024 who received PBRT for CM in 1 eye ≥1 year before enrollment with best-corrected visual acuity (BCVA) ≥20/200, unremarkable contralateral eye, and agreed to participate.

Methods: After a comprehensive eye examination, including BCVA, Optovue AngioVue was used to obtain the 4.5-mm optic disc and 6.0-mm macular OCT/OCT angiography (OCTA) images of both eyes. All vascular density (VD) measurements were obtained automatically using the OCTA software, except choriocapillaris VD, which was quantitated using ImageJ. The Wilcoxon signed-rank test was used to analyze differences in OCT/OCTA parameters between the treated and the contralateral eyes. Spearman's ρ was used to identify OCTA parameters associated with BCVA or radiation dose. A P value of <0.05 was considered statistically significant.

Main Outcome Measures: Foveal avascular zone (FAZ) area and perimeter, choriocapillaris and retinal (superficial and deep) capillary VD in the macula and radial peripapillary capillary (RPC) VD on OCTA; macular and retinal nerve fiber layer thickness on OCT, tumor location, laterality and size at baseline, BCVA of both eyes, PBRT dose, and duration of follow-up at enrollment.

Results: Among 24 participants, OCT/OCTA parameters were significantly different in the treated eyes when compared with the contralateral eyes, including increased FAZ area and perimeter, decreased peripapillary retinal nerve fiber layer thickness and RPC VD, and decreased macular choriocapillaris VD and parafoveal and perifoveal superficial retinal plexus VD ($P < 0.05$). Best-corrected visual acuity in the treated eyes correlated significantly with FAZ area and perimeter, parafoveal and perifoveal deep retinal plexus VD, and radiation dose to fovea but not radiation dose to the optic disc.

Conclusions: Although PBRT can affect both retinal and choroidal vascular flow in the macular and peripapillary region in eyes with CM, BCVA after PBRT seems to correlate best with the retinal vascular flow changes in the macula on OCTA and radiation dose to the fovea.

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Radiotherapy with various modalities, including proton beam radiation therapy (PBRT) and brachytherapy, has become the accepted first-line treatment for localized uveal melanoma (UM).[1,2] These globe-preserving treatments have a high success rate of local tumor control and are preferred over enucleation to preserve vision in the affected eye. However, radiotherapy is associated with delayed ocular adverse effects that could limit long-term vision in treated eyes. Radiation-induced retinopathy and papillopathy can develop from vascular changes, such as capillary closure, telangiectasia, microaneurysm formation, hemorrhage, exudates, macular edema, disc edema, and nerve fiber layer infarctions.

OCT angiography (OCTA) is a newer noninvasive imaging technique for visualizing the retinal and choroidal vascular flow rapidly.[3,4] Optovue AngioVue is a commercial OCTA instrument that can obtain 3-dimensional images of retinal and choroidal vascular flow and automatically segment the OCTA images to provide the en face images of flow at various layers of the retina and choroid.[4] The software automatically quantitates the vascular flow density for each layer. The standard segmented layers include the superficial retinal capillary plexus, the deep retinal capillary plexus, and the choriocapillaris. This OCTA instrument also can provide full-depth images of peripapillary retinal vascular flow

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with corresponding quantitation of vascular flow density referred to as peripapillary radial capillary vascular density (VD). Using this OCTA, the quantitative assessment of microvasculature flow changes in the retina and choroid in the macula and peripapillary region is possible.

Commercial OCTA instruments have been used previously to detect retinal vascular abnormalities in eyes with UM treated with radiotherapy. OCT angiography studies in eyes with choroidal melanoma (CM) treated with brachytherapy identified retinal vascular flow abnormalities even in eyes without clinical signs of radiation retinopathy, although the changes were more pronounced in eyes with clinically diagnosed radiation retinopathy.[5,6] In eyes with CM treated with PBRT, the largest study conducted by Matet et al[3] identified increased foveal avascular zone (FAZ) and decreased deep retinal vascular plexus VD as 2 factors associated with vision loss.

The effect of radiation on the choroidal flow of treated UM eyes has not been studied in detail using OCTA. A prior study detected flow voids in the macular choriocapillaris in a majority of eyes that received 100% dose of PBRT in the macula for small CM.[7] However, detailed quantitation of the flow changes in the choriocapillaris and possible effect on vision was not studied. A case report detected progressive radiation retinopathy in the macula using OCTA in an eye with peripheral CM treated with brachytherapy, but choriocapillaris in the macula did not seem affected, suggesting that choroid flow may be less affected by radiation than retinal vascular flow.[8] This eye maintained good visual acuity despite the development of macular edema and macular ischemia on OCT and OCTA. Whether the preservation of choriocapillaris played a role in preserving visual acuity in this eye is unknown.

In this study, we investigated both the retinal and choroidal circulation in the macula and peripapillary region using OCTA in eyes with CM treated with PBRT to identify the vascular flow changes affected by PBRT and associated with vision loss and radiation dose.

Methods

This is a prospective, cross-sectional, single-center study of all patients seen at the University of California Davis Eye Center between May 2019 and May 2024 who received PBRT for CM in 1 eye $\geq$1 year before enrollment and agreed to participate in the study. The study followed the principles of the Declaration of Helsinki. The study followed a protocol that was reviewed and approved by the Institutional Review Board of the University of California Davis Office of Human Research (No 1406362). All participants signed an informed consent form before study enrollment.

All study participants were diagnosed with unilateral CM and received PBRT according to an individualized protocol established on the EyePlan Software (I.D., K.M.) after implantation of tantalum clips.[9,10] Each eye received 56 GyE of PBRT divided into 4 fractions. The study included patients with no visually significant abnormality in the retina and optic nerve in the contralateral eye who agreed to participate in the study. Enrollment criteria also included best-corrected visual acuity (BCVA) in both eyes of at least 20/200, no media opacity in either eye, the ability to position and maintain fixation for OCTA imaging, and being able to complete the informed consent process.

On the day of study enrollment, all the study participants received a full ophthalmic examination, including BCVA, intraocular pressure, and dilated fundus examination of both eyes. Information obtained from electronic medical records included sex, age, and the presence of any concurrent systemic diseases that may affect the vasculature, such as hypertension, hyperlipidemia, prediabetes or diabetes, and any other concurrent ocular disease. In addition, tumor-related data (baseline tumor dimension, laterality, and location in the eye) and treatment-related data (radiation dose and time of PBRT) were obtained.

OCT/OCT angiography images were obtained of both eyes on the day of study enrollment. Optovue AngioVue (Avanti system 2016.2.0) was used to capture standard macular OCT and 4.5-mm optic disc and 6.0 mm macular OCTA images of both the treated eye and the fellow untreated eye. All OCTA images were reviewed for proper centration, and an image quality of $\geq$6 was considered good and included in this study. The OCTA software was used to obtain automated measurements of the radial peripapillary capillary (RPC) density, FAZ area and perimeter, and retinal VD of the superficial and deep retinal plexus in the macula. The software calculated the capillary density as the proportion of A-scans representing vessels <3 pixels in width, subtracting out the larger blood vessels using a binary mask. The RPC VD (%) is the percentage of the en face OCTA scan image obtained between the internal limiting membrane and the posterior boundary of the nerve fiber layer where vascular flow is detected. Foveal avascular zone area was evaluated using the nonflow area tool from the software, which automatically delineates the FAZ. The en face OCTA image was then automatically segmented with an inner boundary at 3 μm beneath the internal limiting membrane and an outer boundary at 15 μm beneath the inner plexiform layer to obtain images of the superficial capillary plexus (SCP). The segmentation for the deep capillary plexus (DCP) layer was delineated by an inner boundary at 15 μm beneath the inner plexiform layer and an outer boundary at 70 μm beneath the inner plexiform layer. The retinal vascular flow density for SCP and DCP was automatically quantitated by the OCTA software. Choriocapillaris flow density was measured using ImageJ to threshold signal void areas using the Phansalkar algorithm with a radius of 15 pixels in a 9 mm^2 box around the fovea (Fig 1).[11] For each OCTA scan, B-scan OCT/OCTA images were reviewed to ensure correct segmentation of the various layers. Any errors in segmentation were manually corrected before reviewing the en face images.

The Wilcoxon signed-rank test was used to compare continuous data such as BCVA, peripapillary retinal nerve fiber layer thickness, FAZ area and perimeter, RPC, and retinal and choroidal VD. Correlation analysis with Spearman's ρ was done to investigate the association between OCTA parameters and posttreatment BCVA or radiation exposure. A P value of <0.05 was considered statistically significant. Statistical evaluations were performed using the Statistical Package for the Social Sciences, version 24.0 (SPSS Inc).

Results

In total, 24 patients were included in this study. All were diagnosed with unilateral CM and received PBRT between 2009 and 2022 (Table 1). The mean age was 68 $\pm$ 17 years (range, 20−87 years). A total of 12 patients (50%) were female. Concurrent medical conditions of note present at the time of PBRT included 4 patients (17%) with type 2 diabetes mellitus, 3 patients (12.5%) with prediabetes, 10 patients (42%) with hypertension, and 16 patients (67%) with hyperlipidemia.

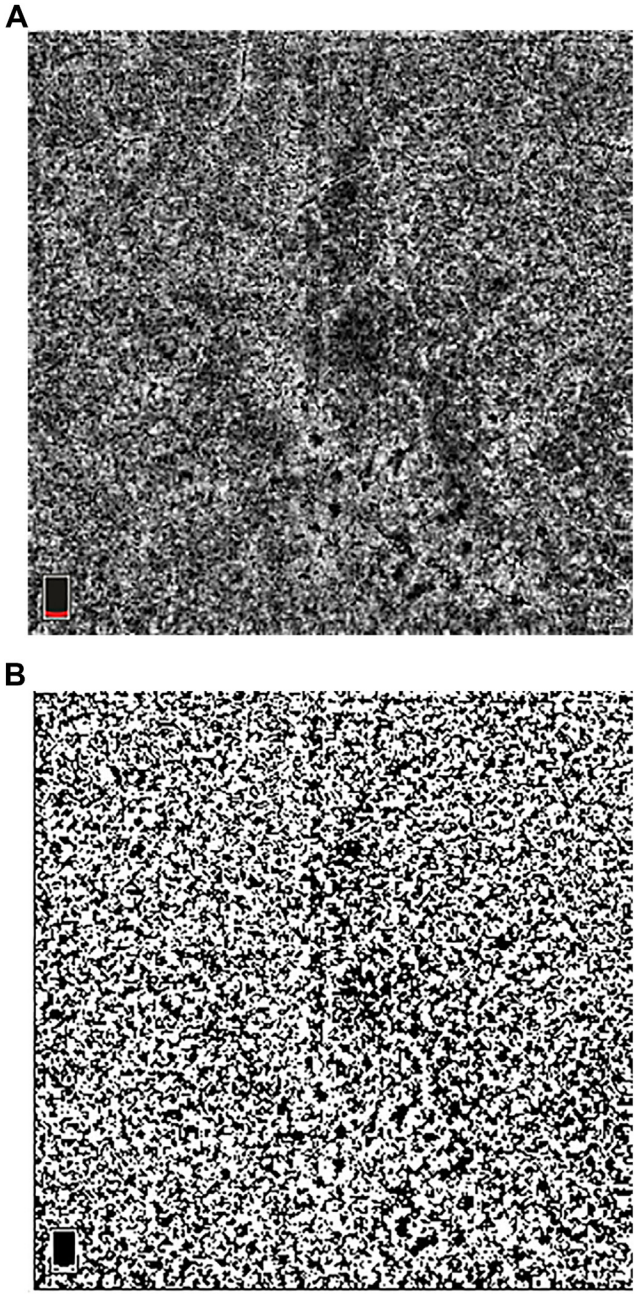

Figure 1. Representative en face macular OCT angiography (OCTA) image of the choriocapillaris showing conversion of the grayscale image into a black/white image for quantitation with ImageJ program using the Phansalkar algorithm. A 6 × 6 mm OCTA image of the choriocapillaris layer of the eye treated with PBRT for choroidal melanoma before **(A)** and after **(B)** Phansalkar auto local thresholding. Flow voids are represented by the darker spaces. Note the relatively higher density of flow voids around the fovea in this eye.

Table 1. Characteristics of Study Participants Treated with Proton Beam Radiation Therapy for Choroidal Melanoma

Variable	Number
Age, yrs	
Mean age (SD)	68 (17)
Median age (range)	74 (20–87)
Sex	
Male	12 (50%)
Female	12 (50%)
Involved eye	
Right	16 (67%)
Left	8 (34%)
Tumor location	
Macula	3 (13%)
Macula to equator	18 (74%)
Equator to ora	3 (13%)
Tumor height (mm), mean ± SD (range)	3.0 ± 2.0 (1.1–9.4)
Largest tumor diameter (mm), mean ± SD (range)	9.7 ± 2.6 (6.1–14.6)
Tumor distance to fovea (mm), mean ± SD (range)	5.9 ± 4.7 (0–13.5)
Tumor distance to optic disc (mm), mean ± SD (range)	5.1 ± 4.1 (0–15.0)
Radiation dose (cGy), mean ± SD (range)	
Macula	1680 ± 2410 (0–5600)
Optic disc	1344 ± 2195 (0–5600)
Follow-up (mos), mean ± SD (range)	66 ± 31 (20–139)

SD = standard deviation.

The mean logarithm of the minimum angle of resolution BCVA after PBRT in the treated eye was 0.36 ± 0.36 (Snellen equivalent 20/50; range 0–1.0) at study enrollment; the mean logarithm of the minimum angle of resolution BCVA in contralateral eye was 0.11 ± 0.16 logarithm of the minimum angle of resolution (Snellen equivalent 20/25; range, 0–0.4) at the time of study enrollment and OCTA imaging (Table 2). There were 4 study participants who had concurrent ocular disease, which was not visually significant in 1 or both eyes, including early age-related macular degeneration and inactive uveitis. At the time of PBRT, 20 study eyes were phakic and 4 were pseudophakic. At the time of study enrollment, 16 eyes were phakic and 8 were pseudophakic.

As summarized in Table 1, most CMs (18 eyes, 74%) were located between the equator and macula; 13% (3 eyes) had tumor involving the macula. The mean tumor height was 3.0 ± 2.0 mm (range 1.1–9.4 mm), and the largest mean tumor diameter was 9.7 ± 2.6 mm (range 6.1–14.6 mm). The mean follow-up period after PBRT at study enrollment was 66 ± 31 months (median 71 months; range, 20–139 months). Seven eyes (7 patients) were diagnosed with radiation retinopathy or papillopathy with macular edema requiring ongoing intravitreal injections of drugs that inhibit anti-VEGF at the time of study enrollment with residual macular edema (Fig 2).

Figure 2 shows the representative ultrawide fundus images and macular OCT and OCTA images of study eyes with CM treated with PBRT. Panel A (Fig 2A) shows a study eye of a 71-year-old woman with BCVA of 20/20 with minimal vascular flow changes in SCP, DCP, and choriocapillaris detected on OCTA at 22 months after PBRT despite the peripapillary location of the tumor. In contrast, panel B (Fig 2B) shows the ultrawide fundus image and OCT and OCTA images obtained from a 70-year-old

Table 2. Clinical and OCT/OCTA Features of Study Eyes with Choroidal Melanoma after PBRT Compared with the Contralateral Eye

	Treated Eye, n = 24	Fellow Eye, n = 24	P*
BCVA before PBRT, logMAR, mean±SD (range)	0.17 ± 0.18 (0–0.6)	0.06 ± 0.08 (0–0.3)	<0.001
BCVA after PBRT, logMAR, mean ± SD (range)	0.36 ± 0.36 (0–1.0)	0.11 ± 0.16 (0–0.4)	<0.001
Peripapillary RNFL thickness, μm, mean ± SD (range)	88.54 ± 20.18 (53–118)	106.50 ± 11.37 (88–126)	<0.001
Radial peripapillary capillary density, %, mean ± SD (range)	41.36 ± 8.10 25–52)	48.10 ± 3.87 (42–54)	<0.001
Central macular thickness, μm, mean ± SD (range)	294.42 ± 75.40 (169–435)	271.46 ± 35.24 (222–379)	0.353
FAZ area, $mm^{2,}$ mean ± SD (range)	0.37 ± 0.15 (0.21–0.67)	0.23 ± 0.08 (0.09–0.39)	<0.001
FAZ perimeter, mm, mean ± SD (range)	2.58 ± 0.82 (1.5–4.8)	1.85 ± 0.34 (1.1–2.4)	<0.001
Parafoveal capillary density, %, mean ± SD (range)			
Superficial plexus	39.90 ± 6.40 (30–56)	45.58 ± 6.33 (35–56)	<0.001
Deep plexus	46.88 ± 6.75 (35–64)	50.12 ± 6.13 (36–63)	0.095
Perifoveal capillary density, %, mean ± SD (range)			
Superficial plexus	40.12 ± 5.39 (32–51)	45.03 ± 4.63 (37–53)	0.01
Deep plexus	37.14 ± 7.08 (34–50)	40.1 ± 8.99 (29–59)	0.136
Choriocapillaris flow ratio, mean ± SD (range)	0.60 ± 0.07 (0.50–0.72)	0.64 ± 0.07 (0.53–0.74)	0.03

BCVA = best-corrected visual acuity; FAZ = foveal avascular zone; logMAR = logarithm of the minimum angle of resolution; OCTA = OCT angiography; PBRT = proton beam radiation therapy; RNFL = retinal nerve fiber layer; SD = standard deviation.
*The Wilcoxon signed-rank test was used to compare the 2 groups. A *P* value <0.05 was considered to indicate statistical significance.

man, 20 months after PBRT for a peripapillary CM involving the macula. As shown, OCT shows diffuse cystoid macular edema from radiation retinopathy despite monthly intravitreal anti-VEGF therapy. Best-corrected visual acuity was decreased to 20/200 in the treated eye. OCT angiography images show markedly reduced retinal and choroidal vascular flow in the macula.

Table 2 shows the OCT and OCTA parameters after PBRT in the eye with treated CM when compared with the fellow eye. Best-corrected visual acuity was reduced in the eye with CM when compared with the fellow eye both at baseline and after PBRT ($P < 0.001$). The optic disc parameters, namely peripapillary retinal nerve fiber layer thickness and RPC VD, both showed a significant decrease in the eye treated with PBRT when compared with the contralateral eye ($P < 0.001$). Regarding the macula, central macular thickness did not show significant differences between treated and fellow eyes ($P = 0.353$). On OCTA, a statistically significant increase in FAZ area and perimeter was noted ($P < 0.001$) in melanoma eyes treated with PBRT when compared with the fellow eye. In addition, a significant decrease in perifoveal and parafoveal SCP ($P < 0.05$) and choriocapillaris ($P = 0.03$) VD was observed in the melanoma treated eye when compared with the contralateral eye. No significant difference in DCP VD was detected between the eyes ($P > 0.05$), but parafoveal DCP VD showed a nonsignificant decrease in the eye treated with PBRT when compared with the contralateral eye ($P = 0.095$).

Given the various OCTA parameters that were altered in eyes after PBRT, we analyzed which of these OCTA parameters correlated with BCVA after PBRT (Table 3). Both FAZ area and perimeter showed a statistically significant correlation with post-PBRT BCVA. In addition, deep parafoveal and perifoveal capillary density correlated with posttreatment BCVA, although these OCTA parameters were not significantly different in the eye that had PBRT when compared with the contralateral eye (Table 3). Vascular density of the parafoveal and perifoveal SCP, choriocapillaris, and RPC did not correlate significantly with BCVA after PBRT. Radiation dose to the fovea had a significant correlation with post-PBRT BCVA but radiation dose to the optic disc did not.

To determine which OCTA parameters are more sensitive to the PBRT effect, we analyzed the correlation between the radiation dose and OCTA parameters (Table 4). Radiation dose to the optic disc showed a significant correlation only with perifoveal DCP. There was no significant correlation with any of the other OCTA parameters including RPC VD. On the other hand, the radiation dose to the fovea showed a significant correlation with FAZ area, FAZ perimeter, and parafoveal and perifoveal DCP VD (Table 4). Vascular density of the macular choriocapillaris and SCP parafoveal and

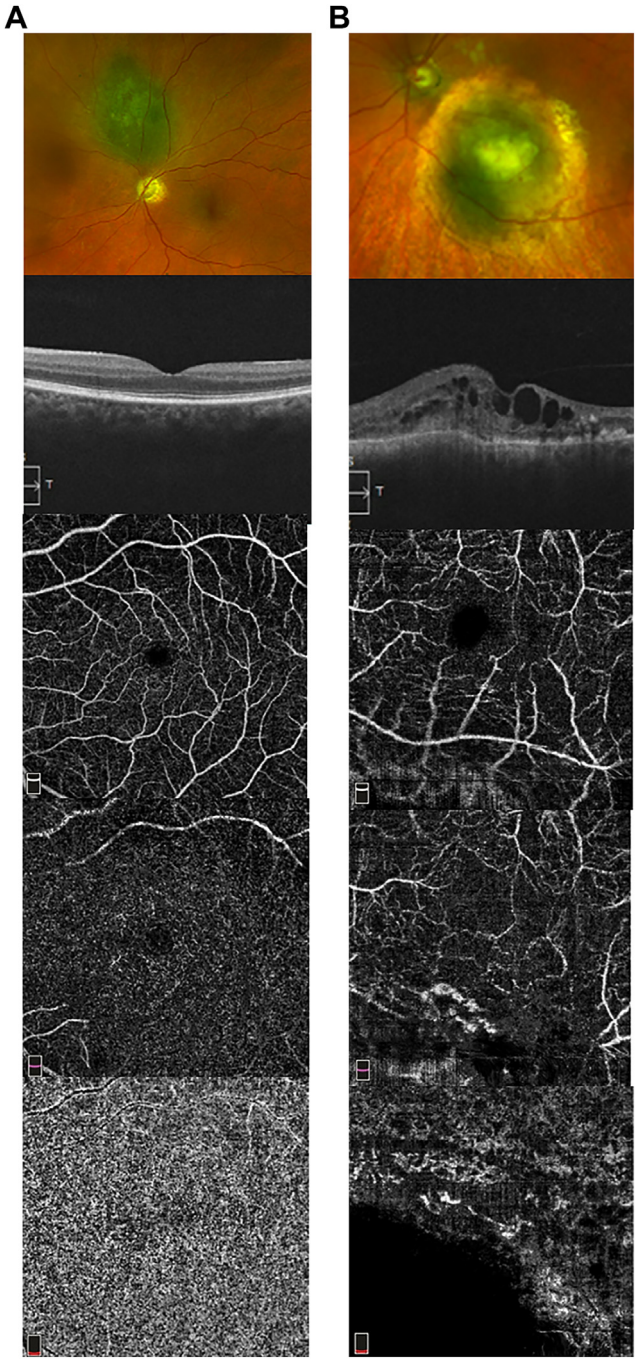

Figure 2. Representative fundus images and macular OCT and OCT angiography (OCTA) images of 2 study eyes with choroidal melanoma after treatment with proton beam radiation therapy (PBRT). **A,** Top shows ultrawide field scanning laser ophthalmoscopy (SLO) fundus image showing a choroidal melanoma just superior to the disc in the left eye of a 71-year-old woman with BCVA 20/20 at 22 months after PBRT. The macular OCT (second row) of this eye is unremarkable. The macular OCTA image (third and fourth rows) of the superficial and deep capillary plexus shows only minimal flow abnormalities. **B,** Ultrawide SLO fundus image (top) the left eye of a 70-year-old man with a peripapillary choroidal melanoma involving the inferior macula with BCVA 20/200 at 20 months after PBRT. The macular OCT image of this eye (second row) shows diffuse cystoid macular edema persisting despite monthly anti-VEGF therapy. Corresponding macular OCTA images of the superficial plexus (third row), deep plexus (fourth row), and choriocapillaris (fifth row) show flow voids, especially in the inferior macula where the tumor is located.

Table 3. Correlation Analysis between OCTA Parameters and the Posttreatment BCVA (logMAR)

Characteristics	ρ	P*
Peripapillary RNFL thickness	−0.05	0.818
Radial peripapillary capillary density	−0.25	0.249
Central macular thickness	0.11	0.616
FAZ area	0.57	0.003
FAZ perimeter	0.65	<0.001
Parafoveal capillary density		
Superficial plexus	−0.23	0.283
Deep plexus	−0.52	0.009
Perifoveal capillary density		
Superficial plexus	−0.36	0.088
Deep plexus	−0.46	0.027
Choriocapillaris flow ratio	−0.23	0.286
Radiation dose to fovea	0.56	0.011
Radiation dose to optic disc	0.05	0.822

BCVA = best-corrected visual acuity; FAZ = foveal avascular zone; logMAR = logarithm of the minimum angle of resolution; OCTA = OCT angiography; RNFL = retinal nerve fiber layer.
*Spearman's correlation analysis was used. A *P* value <0.05 was considered to indicate statistical significance.

perifoveal SCP VD did not demonstrate a significant correlation with radiation dose to the fovea.

Discussion

Proton beam radiation therapy (PBRT) has been associated with a high rate of local tumor control when used to treat UM.[12] Radiation retinopathy and papillopathy can occur after PBRT for CMs near the disc and macula, but prior studies have shown that most of these eyes maintain functional vision due to localized targeting of radiation possible via PBRT.[13,14]

Recently, noninvasive OCTA imaging has been used to study microvascular changes in the macula in the eyes after radiotherapy for UM. Prior studies have shown retinal vascular flow changes in the retina after brachytherapy or PBRT, including capillary nonperfusion, telangiectasia, and FAZ alterations. These flow changes within the retina have been observed even in eyes without clinical signs of radiation retinopathy.[5,6]

Changes in choroidal flow also have been observed after radiation therapy. Prior histologic studies showed choroidal circulation alterations including sclerosis and hyalinization of choroidal vessels, atrophy of different layers of the choroid and Bruch membrane, proliferation of the retinal pigment epithelium, and vascular closure after brachytherapy.[15,16] These changes were observed at and around the tumor.[16] Prior imaging analysis showed changes in choroidal flow at the base of the tumor in eyes with CM treated with brachytherapy.[17] For eyes treated with PBRT, Sellam et al[7] performed OCTA in 17 patients who had received 100% of the dose of 60 Gy PBRT to the macula for small CM. This study showed that the choriocapillaris density of the macula in eyes treated with PBRT was lower than in healthy subjects. Changes in the choroidal

Table 4. Correlation Analysis between OCTA Parameters and the Radiation Dose to Fovea/Optic Disc

Characteristics	P (Fovea Radiation)	P	P (Optic Disc Radiation)	P
Peripapillary RNFL thickness	0.341	0.141	−0.023	0.923
Radial peripapillary capillary density	0.187	0.430	0.016	0.945
Central macular thickness	0.179	0.449	−0.041	0.864
FAZ area	0.510	0.022	0.363	0.116
FAZ perimeter	0.676	0.001	0.410	0.073
Parafoveal capillary density				
Superficial plexus	−0.321	0.168	−0.118	0.620
Deep plexus	−0.711	<0.001	−0.211	0.373
Perifoveal capillary density				
Superficial plexus	−0.436	0.062	−0.503	0.028
Deep plexus	−0.641	0.003	−0.403	0.087
Choriocapillaris flow ratio	−0.156	0.511	0.090	0.707

FAZ = foveal avascular zone; OCTA = OCT angiography; RNFL = retinal nerve fiber layer.
*Spearman's correlation analysis was used. A P value <0.05 was considered to indicate statistical significance.

circulation using OCTA included "signal void" or "rarefaction or dilatation of choroidal vessels." However, because all eyes received a full dose of PBRT to the macula, this study could not correlate these OCTA changes to visual acuity or radiation dose.

In our study, we conducted a comprehensive analysis of OCTA changes in the retina and choroid and peripapillary region in eyes with CM treated with PBRT to determine the vascular flow changes on OCTA that are most affected by PBRT and correlate with posttreatment BCVA. We included all eyes with CM, regardless of location and tumor size. However, our study was limited to eyes with BCVA of 20/200 or better and with good OCTA images. Because radiation retinopathy usually is seen ≥1 to 2 years after radiotherapy, we only included eyes with ≥1-year follow-up after PBRT. In fact, our study population had a follow-up of ≥20 months after PBRT.

As shown in Table 2, our study found significant increases in FAZ area and perimeter, decreases in SCP parafoveal and perifoveal capillary VD, and a decrease in macular choriocapillaris flow density in eyes treated with PBRT when compared with the contralateral untreated eye. In addition, we found a significant decrease in peripapillary retinal nerve fiber layer thickness and RPC VD in eyes treated with PBRT when compared with the contralateral untreated eye. However, the OCTA parameters significantly associated with posttreatment BCVA only included FAZ area and perimeter and deep parafoveal and perifoveal capillary flow density. Changes in these OCTA parameters correlated with the radiation dose to the fovea but not radiation dose to the disc. In addition, our study found that changes in macular choriocapillaris flow, superficial parafoveal and perifoveal capillary flow, and RPC flow on OCTA did not correlate significantly with posttreatment BCVA. Thus, in our study population, the main cause of vision loss appears to be due to macular ischemia from radiation retinopathy affecting the DCP and FAZ. Choroidal ischemia in the macula and peripapillary retina ischemia were detected on OCTA but appear less significant in affecting posttreatment BCVA.

Matet et al[3] reported similar OCTA results in 35 patients with CM after PBRT. They found an enlargement of the FAZ and a decrease of parafoveal capillary density in both superficial and DCPs in tumor eyes when compared with the contralateral eye. They did not evaluate choroidal flow. In our study, FAZ enlargement and decrease in superficial parafoveal and perifoveal plexus capillary VD were also observed, but we did not find a significant difference in deep parafoveal and perifoveal plexus VD. This subtle difference in the study results likely resulted from differences in BCVA of the study population. In the study by Matet et al[3] only 20% of treated eyes had ≥20/40 BCVA (Snellen). In contrast, in our study, 54% of treated eyes had BCVA ≥20/40. Poorer vision likely reflects more severe maculopathy with more possible structural change in the retina. Deep capillary plexus nonperfusion has recently been identified as a more critical determinant of BCVA than SCP nonperfusion in several different types of retinal vasculopathy, including diabetic retinopathy and retinal vein occlusion.[18] Although DCP VD was not significantly decreased in our study population, there was a trend for a decrease in deep parafoveal plexus VD in the treated eye when compared with the contralateral eye ($P = 0.095$). Furthermore, deep parafoveal and perifoveal plexus VD was significantly associated with posttreatment BCVA on correlation analysis.

Several prior studies hypothesized that the DCP of the retina of irradiated eyes may be more severely altered than the SCP from radiation because of the anatomical structure of the capillary plexus or cell cycle differences. It is puzzling that our study showed relatively less damage of deep plexus capillary circulation in the macula after PBRT when

compared with SCP. Relative preservation of the deep parafoveal and perifoveal retinal capillary flow may explain the relatively good BCVA of our study eyes after PBRT, even though 87% of eyes had tumors located posterior to the equator. It is possible that our study findings reflect the precise targeting of PBRT, which would minimize radiation damage to adjacent tissue, including the macula. Because 29.2% of study eyes had macular edema from radiation retinopathy or papillopathy and were being treated regularly with intravitreal anti-VEGF drugs at the time of OCTA imaging, the potential effect of chronic anti-VEGF therapy in minimizing retinal vascular damage from radiation retinopathy cannot be ruled out.[19]

There are several limitations to our study. First, we had a relatively small sample size with variable duration of follow-up after PBRT. Nonetheless, we noted significant changes in many OCTA parameters in the treated eye relative to the contralateral eyes and all study participants had a follow-up of $\geq$20 months after PBRT. Second, we used the contralateral eye as a control, but a few contralateral eyes were affected by conditions, such as early dry age-related macular degeneration or inactive uveitis, not thought to be visually significant but with the potential for subtle effects on retinal or choroidal flow. In addition, OCTA segmentation of the choriocapillaris layer for tumors involving the macula may be subject to distortion from the choroidal replacement of the tumor. Although any segmentation error was corrected manually, the correction may not fully negate the anatomic distortion associated with the tumor and may have limited our accuracy in measuring choriocapillaris flow in such eyes. Fortunately, in our 24 study eyes, only 3 eyes had tumors involving the macula. Finally, most of our study participants had relatively good BCVA after PBRT because we included in our study only eyes that had good OCTA image quality and enrollment BCVA of 20/200 or better. Thus, our study findings may not be applicable to eyes with more severe vision loss after PBRT.

In conclusion, our study showed that eyes that have PBRT for CM have signs of retinal and choroidal ischemia in the macula and peripapillary region detected on OCTA when compared with the contralateral eye. However, the OCTA parameters that correlated significantly with BCVA after PBRT were FAZ area and perimeter and parafoveal deep retinal capillary plexus VD. Changes in these OCTA parameters correlated significantly with the dose of radiation to the fovea. Thus, minimizing the radiation dose to the fovea may be a good strategy to minimize vision loss after PBRT for CM.

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[1] Department of Ophthalmology and Vision Science, University of California Davis Eye Center, Sacramento, California.

[2] Department of Ophthalmology, Hospital, National Cancer Center, Gyeonggi-do, Korea.

[3] Department of Radiation Oncology, University of California San Francisco, San Francisco, California.

[4] Osher Center for Integrative Health, University of California San Francisco, San Francisco, California.

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Author Contributions:

Conception and design: Park

Analysis and interpretation: Jung, Lee, Dafteri, Mishra, Park

Data collection: Jung, Lee, Park

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Abbreviations and Acronyms:
BCVA = best-corrected visual acuity; **CM** = choroidal melanoma; **DCP** = deep capillary plexus; **FAZ** = foveal avascular zone; **OCTA** = OCT angiography; **PBRT** = proton beam radiation therapy; **RPC** = radial peripapillary capillary; **SCP** = superficial capillary plexus; **UM** = uveal melanoma; **VD** = vascular density.

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Correspondence:
Susanna S. Park, MD, PhD, 4860 Y Street, Sacramento, CA 95817. E-mail: sscpark@ucdavis.edu.

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