INTRAVITREAL ANTI–VASCULAR ENDOTHELIAL GROWTH FACTOR TREATMENT AT 2-MONTH INTERVALS REDUCES FOVEAL AVASCULAR ZONE ENLARGEMENT AND VISION LOSS IN RADIATION MACULOPATHY

A Pilot Study

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Purpose: To evaluate, in eyes with radiation maculopathy, the effect of 2-month-interval anti–vascular endothelial growth factor therapy on best-corrected visual acuity and foveal avascular zone (FAZ) enlargement using optical coherence tomography angiography.

Methods: Consecutive treatment-naive patients with radiation maculopathy after proton beam irradiation for choroidal melanoma were retrospectively included. Clinical and optical coherence tomography angiography data at baseline and the 6-month visit were recorded. Two independent observers measured FAZ area manually on 3 × 3-mm optical coherence tomography angiography images of the superficial capillary plexus and deep capillary plexus. Patients were encouraged to follow strictly a 2-month-interval intravitreal anti–vascular endothelial growth factor treatment by either bevacizumab or ranibizumab. Findings were analyzed based on the adherence to the treatment scheme.

Results: According to the adherence to the bimonthly anti–vascular endothelial growth factor treatment protocol, patients were categorized into 3 groups: treatment protocol (n = 19, strict adherence), variable intervals (n = 11, intervals other than 2 months), and no treatment (n = 11). The estimated radiation dose to the foveola in each group was 49 ± 16, 46 ± 17, and 46 ± 18 cobalt gray equivalent, respectively ($P = 0.85$). For the entire cohort, best-corrected visual acuity loss ($P < 0.02$) and FAZ enlargement ($P < 0.0001$) were observed over 6 months. Best-corrected visual acuity loss was significantly less pronounced in the treatment-protocol group than in the variable-interval and no-treatment groups ($P = 0.007$ and $P = 0.004$). The FAZ enlargement was lower in the treatment-protocol group compared with the variable-interval group for both superficial capillary plexus ($P = 0.029$) and deep capillary plexus ($P = 0.03$), and to the no-treatment group for the deep capillary plexus only ($P = 0.016$).

Conclusion: Decrease in best-corrected visual acuity and FAZ enlargement on optical coherence tomography angiography occurred over 6 months in eyes with radiation maculopathy and were significantly reduced under 2-month-interval anti-vascular endothelial growth factor therapy.

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Choroidal melanoma is the most frequent primary intraocular malignancy in the adult population.[1] The current treatment strategies for choroidal melanoma consist of local irradiation, mostly by plaque brachytherapy or external beam radiation therapy. Despite the highly localized radiation distribution of these treatment modalities, collateral irradiation of the macula cannot be avoided in tumors involving or

adjacent to the macula, and radiation maculopathy remains a frequent complication.[2] After irradiation, retinal vascular endothelial cell loss and capillary closure induce hypoxic and proliferative changes characterized in the macula by the presence of telangiectasia, microaneurysms, lipid deposits, hemorrhages, edema, nerve fiber layer infarction, and neovascularization.

A variety of treatments have been used for radiation maculopathy. Among the most promising, intravitreal anti–vascular endothelial growth factor (VEGF) agents administered at regular intervals allow the preservation or improvement of visual acuity in selected irradiated patients[3] and have also been proven efficient in reducing the incidence of macular edema when administered preventively at 4-month intervals.[4] Moreover, intravitreal anti-VEGF administered at 2-month intervals after proton beam irradiation is beneficial in preventing anterior segment neovascularization in eyes with choroidal melanoma.[5]

Optical coherence tomography angiography (OCTA) is a noninvasive imaging technology of the macular microvasculature based on the detection of intraluminal blood flow. Its high resolution and the absence of dye diffusion allow to overcome several limitations of conventional fluorescein angiography by visualizing details of the parafoveal capillary network and differentiating retinal vascular plexuses through image segmentation.[6] Foveal avascular zone (FAZ) enlargement and decreased parafoveal capillary network density in both the superficial and the deep plexuses, as compared with fellow nonirradiated eyes, have been recently identified using OCTA in eyes with radiation maculopathy after plaque brachytherapy for choroidal melanoma.[7] However, little is known on the progression rate of FAZ enlargement and its influencing factors.

Based on previous evidence suggesting an interest of intravitreal anti-VEGF therapy in preventing or reducing the severity of radiation maculopathy,[3,4,8] a 2-month-interval anti-VEGF regimen is currently proposed to patients evaluated at our institution as soon as the first signs of radiation maculopathy are detected on multimodal imaging. The objectives of this study were to evaluate, in patients with radiation maculopathy, the influence of intravitreal anti-VEGF therapy at 2-month intervals during 6 months on visual acuity and FAZ area assessed by OCTA.

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Methods

Subjects

This study was designed in accordance with the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the Swiss Federal Health Department (Authorization CER-VD 2016-01861). Consecutive treatment-naive patients diagnosed with radiation maculopathy after proton beam irradiation for choroidal melanoma, between October 1, 2015 and September 30, 2016 were retrospectively reviewed. Comprehensive clinical data and OCTA images at baseline and the 6-month visit were recorded. The diagnosis of radiation maculopathy was made by a senior medical retina and ocular oncology specialist (L.Z.) and relied on the presence of lipid deposits, hemorrhages, or microaneurysms on fundus examination; cystoid macular edema or nerve fiber layer infarction on optical coherence tomography; exudative retinal telangiectasia or capillary nonperfusion on fluorescein angiography; or capillary loss on OCTA.

Acquisition and Analysis of Images

Optical coherence tomography and OCTA images were acquired on the Angiovue RTx 100 device, which is based on the AngioVue Imaging System (Optovue, Inc, Fremont, CA) to obtain amplitude decorrelation angiography images. This instrument has an A-scan rate of 70,000 scans per second, using a light source centered on 840 nm and a bandwidth of 50 nm. Each OCTA volume contains 304 × 304 A-scans with 2 consecutive B-scans captured at each fixed position. Split-spectrum amplitude-decorrelation angiography was used to extract the OCTA information from two orthogonal OCTA volumes, after motion correction. Volumes were automatically segmented by the software provided by the manufacturer to provide images of the superficial plexus (3 μm below the inner limiting membrane to 16 μm below the outer border of the inner plexiform layer) and deep plexus (16–69 μm below the outer border of the inner plexiform layer). We controlled the correct segmentation for each patient before reporting the data.

The central macular thickness was measured on optical coherence tomography volumes in the central subfield of an Early Treatment of Diabetic Retinopathy Study grid centered on the fovea.

Measurements of the FAZ area were performed manually on 3 × 3-mm OCTA images at the level of the superficial capillary plexus and the deep capillary plexus by 2 masked observers (1 retinal photographer and 1 retina specialist), using the publicly available ImageJ software (Version 1.50c4, Wayne Rasband; National Institutes of Health, Bethesda, MD). The mean values of these FAZ area measurements were withheld for further analyses.

Anti–Vascular Endothelial Growth Factor Treatment Protocol

Patients diagnosed with radiation maculopathy were advised to follow a strict treatment protocol by intravitreal anti-VEGF injections. It consisted of intravitreal anti-VEGF injections by either bevacizumab 1.25 mg/0.05 mL (Avastin; Roche, Basel, Switzerland) or ranibizumab 0.5 mg/0.05 mL (Lucentis; Novartis, Basel, Switzerland) administered at 2-month intervals during 6 months (3 injections). Intravitreal injections were performed at our institution or by the referring ophthalmologist, and the final clinical evaluation was carried out at Month 6 at our institution.

Statistical Analyses

Comparative analyses were conducted between the patients who strictly respected the treatment protocol with bimonthly anti-VEGF injections during 6 months, those who did not follow the protocol strictly but received anti-VEGF injections at variable intervals, and those who did not receive any anti-VEGF injection during the 6-month follow-up. The logarithm of the minimal angle of resolution was used to calculate mean values of best-corrected visual acuity (BCVA).

Mann–Whitney and Wilcoxon paired tests were used for quantitative variables and Fisher exact test for categorical variables, where appropriate. Baseline characteristics between the three groups were analyzed by one-way analysis of variance and chi-square test, where appropriate. The Spearman coefficient was used to analyze correlations, using GraphPad Prism (version 5.0f; GraphPad Software, La Jolla, CA). For statistical comparisons, differences with a P-value ≤ 0.05 were considered significant.

Intraclass correlation coefficients (ICCs) were calculated to assess agreement between observers. Based on the lower end of the 95% confidence interval (95% CI) of the ICC, agreement was considered as poor (<0.50), moderate (0.50–0.75), good (0.75–0.90), or excellent (>0.90). The "irr" package was used for ICC calculations on R software (Version 3.3.0, R Foundation for Statistical Computing, R Core Team, 2016, Vienna, Austria; http://www.R-project.org/).

Results

Forty-one patients with radiation maculopathy were included. According to the adherence to the bimonthly anti-VEGF treatment protocol, patients were categorized into 3 groups: treatment-protocol (n = 19 patients who strictly followed the 2-month-interval established treatment scheme), variable-interval (n = 11 patients who received anti-VEGF injections at variable intervals, ranging from 1 to 3 injections) and no-treatment (n = 11 patients who refused the treatment).

Clinical characteristics of the total study population at baseline and the 6-month visit are displayed in Table 1. There was a progressive mean BCVA loss ($P < 0.02$) and an increase in mean FAZ area (measured at the level of the superficial plexus) over the 6-month period, by +64.5% ($P < 0.0001$). The interobserver agreement was excellent for manual FAZ measurements on the superficial plexus at baseline (ICC = 0.997; 95% CI = 0.995–0.999) and the 6-month visit (ICC = 0.998; 95% CI = 0.997–0.999), but it was moderate when FAZ measurements were performed in the deep plexus (ICC = 0.716; 95% CI = 0.509–0.845

Table 1. Clinical and Imaging Characteristics of 41 Patients With Radiation Maculopathy at the Baseline and 6-Month Visits

	Baseline	6-Month Visit	P*
LogMAR BCVA (Snellen equivalent)	0.44 ± 0.38 (~20/50)	0.52 ± 0.44 (~20/63)	0.02
FAZ area on OCTA (superficial plexus), mm^2	0.62 ± 0.67	1.02 ± 1.48	<0.0001
Capillary density, (superficial plexus), %	42.19 ± 5.46	39.78 ± 5.06	<0.0001
FAZ area on OCTA (deep plexus), mm^2	1.05 ± 1.14	1.42 ± 1.55	0.21
CMT, μm			
All patients, n = 41	304 ± 95	285 ± 89	0.03
Subgroup with macular edema at baseline, n = 20	370 ± 85	335 ± 79	0.07

Quantitative continuous variables are reported as mean ± SD.
*Wilcoxon matched-pairs signed rank test.
CMT, central macular thickness; LogMAR, logarithm of the minimum angle of resolution.

at baseline and ICC = 0.843; 95% CI = 0.713–0.917 at the 6-month visit).

There was no statistical difference between the 3 groups regarding the clinical parameters at baseline, except for the number of patients with macular edema, which was lower in the no-treatment group (Table 2). In particular, there was no difference in estimated radiation dose received by the foveola in each group: 49 ± 16, 46 ± 17, and 46 ± 18 cobalt gray equivalent, respectively ($P = 0.85$).

Comparisons between groups regarding the progression of clinical and imaging parameters over the 6-month period are reported in Table 3. The loss in logarithm of the minimal angle of resolution BCVA was significantly less pronounced in the treatment-protocol group (−0.02 ± 0.10) than in the variable-interval (+0.18 ± 0.29) and no-treatment groups (+0.17 ± 0.24) ($P = 0.007$ and $P = 0.004$, respectively). Enlargement of the FAZ area was significantly reduced in the treatment-protocol group (illustrated in Figure 1) compared with the variable-interval group (illustrated in Figure 2), both in the superficial and deep plexus ($P = 0.029$ and $P = 0.035$, respectively). When comparing enlargement of the FAZ area

Table 2. Clinical Parameters at Baseline in 41 Patients With Radiation Maculopathy Divided Into 3 Groups, According to Their Subsequent Adherence to the Bimonthly anti-VEGF Treatment Protocol

	Treatment Protocol (n = 19)	Variable Interval (n = 11)	No Treatment (n = 11)	*P*
Demographic characteristics				
Age, years	58 ± 11	61 ± 14	65 ± 8	0.26*
Male/female, N	7/12	6/11	6/11	0.98†
White, N	19	11	11	—
History of diabetes, N	2	3	2	0.50†
History of hypertension, N	3	3	3	0.68†
Tumor features				
Tumor height at diagnosis, mm	3.57 ± 0.8	4.96 ± 2.0	4.32 ± 2.2	0.15*
Distance of posterior tumor border to the fovea, disc diameter	1.29 ± 1.2	1.52 ± 0.7	1.74 ± 1.2	0.60*
Radiation features‡				
Total irradiation of the foveola, N	8	4	4	0.93†
Total irradiation of the optic nerve head, N	6	4	4	0.95†
Estimated radiation dose to the foveola, CGE	48.9 ± 15.8	45.6 ± 16.8	46.0 ± 18.4	0.85*
Radiation maculopathy features				
Microaneurysms only, N	13	6	6	0.66†
Exudates, N	6	6	4	0.45†
Macular nonperfusion on FA, N	3	1	3	0.52†
Neovascularization, N	0	0	0	—
Macular edema on OCT, N	10	8	2	0.03†
Time from proton beam therapy to the diagnosis of radiation maculopathy, years	2.8 ± 1.5	2.3 ± 0.9	2.4 ± 0.9	0.53*
Clinical and OCTA features				
LogMAR BCVA (Snellen equivalent)	0.35 ± 0.22 (∼20/40)	0.54 ± 0.40 (∼20/70)	0.48 ± 0.55 (∼20/60)	0.37*
FAZ area (superficial plexus), mm^2	0.43 ± 0.30	0.64 ± 0.68	0.92 ± 0.99	0.16*
Capillary density (superficial plexus), %	42.35 ± 5.4	43 ± 6.7	41 ± 4.5	0.72*
FAZ area (deep plexus), mm^2	0.86 ± 0.57	1.02 ± 0.70	1.41 ± 1.98	0.46*
CMT, μm	300 ± 99	285 ± 86	331 ± 99	0.52*
Subgroup with macular edema at baseline, N				
CMT, μm	366 ± 82	366 ± 90	401 ± 141	0.87*

Continuous quantitative values are reported as mean ± SD.
*One-way analysis of variance with Bonferroni posttest.
†Chi-square test.
‡All patients received the same dose of irradiation to the tumor, 60 CGE.
CGE, cobalt gray equivalent; CMT, central macular thickness; FA, fluorescein angiography; LogMAR, logarithm of the minimum angle of resolution; OCT, optical coherence tomography.

Table 3. Comparative Analysis of Clinical Parameters Over 6 Months in 41 Patients With Radiation Maculopathy Who Received Bimonthly, Variable Interval, or No anti-VEGF Treatment

				*P**		
	Treatment Protocol (n = 19)	Variable Interval (n = 11)	No Treatment (n = 11)	Treatment Protocol vs. Variable Interval	Treatment Protocol vs. No Treatment	Variable Interval vs. No Treatment
LogMAR BCVA change	−0.02 ± 0.10	0.18 ± 0.29	0.17 ± 0.24	0.007	0.004	0.82
FAZ area change, superficial plexus, mm^2	0.08 ± 0.12	0.63 ± 1.17	0.69 ± 1.87	0.029	0.07	0.53
FAZ area change, deep plexus, mm^2	0.0009 ± 0.40	0.69 ± 1.17	0.66 ± 1.18	0.035	0.016	1.0
CMT change, μm	−30.42 ± 56.7	−36.71 ± 75.3	18.42 ± 46.3	0.50	0.02	0.02
Subgroup with macular edema, CMT change, μm	40.70 ± 69.8	−44.25 ± 88.2	35.00 ± 45.0	0.80	NA†	NA†

*Mann–Whitney test.
†Not available: too few patients in the untreated group (n = 2).
CMT, central macular thickness; LogMAR, logarithm of the minimum angle of resolution.

between the treatment-protocol group and the no-treatment group (illustrated in Figure 3), the reduction was statistically significant for FAZ measurements in the deep plexus ($P = 0.016$) but failed to reach significance for FAZ measurements in the superficial plexus ($P = 0.07$). Central macular thickness decreased in both groups receiving anti-VEGF, but there was no statistical difference between the treatment-protocol and the variable-interval groups. Significant improvement in central macular thickness was observed in both treated groups (treatment protocol or variable interval) as compared with the nontreated group ($P = 0.02$).

Finally, there was a moderate but significant correlation between BCVA change and FAZ change from baseline to the 6-month timepoint ($r = 0.35$, $P = 0.028$). Central macular thickness change was not correlated with FAZ change ($r = -0.18$, $P = 0.26$).

Discussion

In this retrospective case series of 41 patients with radiation maculopathy after proton beam irradiation for choroidal melanoma, we observed a progressive enlargement of the FAZ on OCTA and visual acuity loss in patients with radiation maculopathy, over a 6-month period. We also assessed the anatomical and visual benefits of a 2-month-interval anti-VEGF treatment by either bevacizumab or ranibizumab. Both FAZ and BCVA changes were significantly less

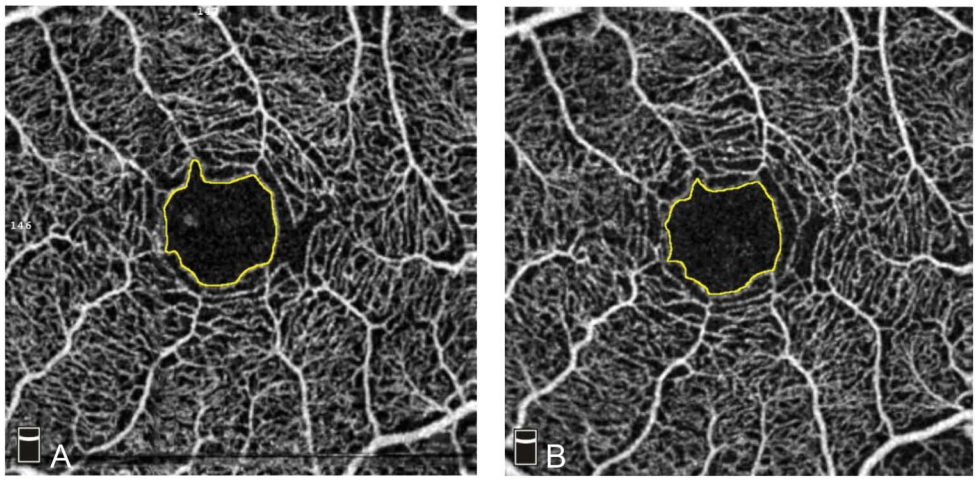

Fig. 1. Absence of significant FAZ enlargement in a case of radiation maculopathy on OCTA after intravitreal anti-VEGF treatment at 2-month interval during a 6-month period ("treatment-protocol" group). Foveal avascular zone area (yellow outline) was 0.393 mm^2 at baseline (**A**) and 0.396 mm^2 at 6 months (**B**).

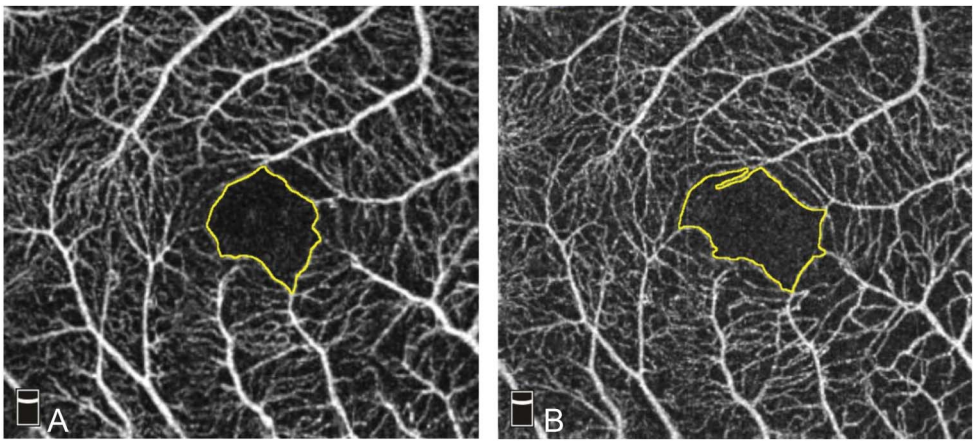

Fig. 2. Foveal avascular zone enlargement in a case of radiation maculopathy on OCTA who received only one intravitreal anti-VEGF injection during the 6-month period ("variable-interval" group). Foveal avascular zone area (yellow outline) was 0.325 mm^2 at baseline (**A**) and 0.415 mm^2 at 6 months (**B**).

pronounced in patients who strictly followed this treatment protocol, as compared with those who did not.

These results are consistent with previous studies[3,8] reporting the benefit of intravitreal anti-VEGF in reducing macular edema and preserving visual acuity in eyes irradiated for intraocular malignancies. In patients with documented radiation maculopathy after proton beam irradiation for uveal melanoma who received anti-VEGF treatment, Seibel et al[8] have reported BCVA stabilization or improvement in 92.1% of cases and a significant improvement in retinal thickness on optical coherence tomography. In cases with radiation maculopathy after plaque brachytherapy, Finger et al[3] observed BCVA preservation within 2 lines of initial levels in 80% of cases after anti-VEGF treatment, over a mean 6.8-year follow-up.

Foveal avascular zone enlargement on OCTA has been recently described in eyes with radiation maculopathy,[7] but to the best of our knowledge, its progressive enlargement over a follow-up period and the influence of anti-VEGF treatment have not been previously investigated.

The beneficial effects of anti-VEGF therapy on FAZ area enlargement, observed in the present study using OCTA, were recently studied in macular edema of other causes.[9] A prospective case series of 18 eyes with macular edema secondary to diabetes or central vein occlusion identified a preservation of the FAZ area after a single injection of anti-VEGF.[9] These investigations became possible since the advent of the OCTA technology, which images high-resolution details of the macular microvasculature and provides reproducible measurements of the FAZ dimensions.[10–12] However, in the present study, the observed reduction in FAZ enlargement after bimonthly anti-VEGF treatment compared with no treatment was statistically significant in the deep plexus only and near-significant in the superficial plexus. Whether the FAZ dimensions should be evaluated in the superficial or deep plexus remains to be determined, even if

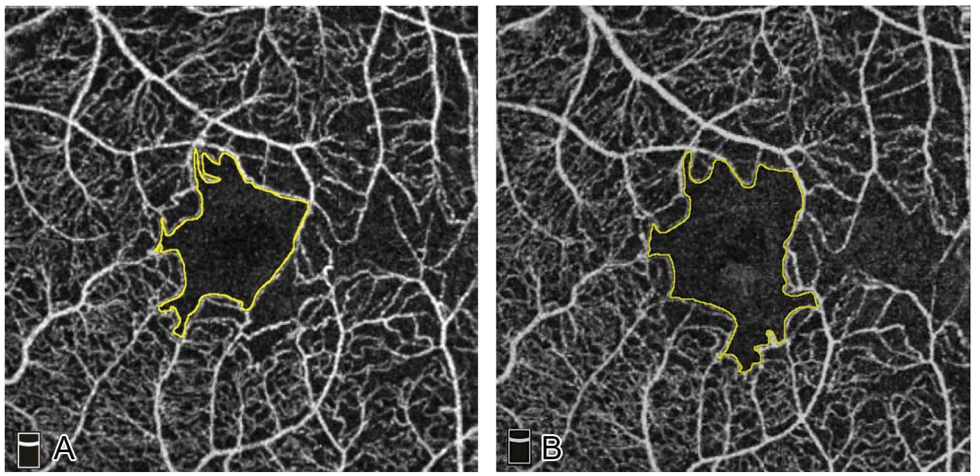

Fig. 3. Foveal avascular zone enlargement in a case of radiation maculopathy on OCTA who did not receive intravitreal anti-VEGF treatment during a 6-month period ("no-treatment" group). Foveal avascular zone area (yellow outline) was 0.531 mm^2 at baseline (**A**) and 0.736 mm^2 at 6 months (**B**).

we found a higher repeatability of FAZ measurements in the superficial plexus.

Regarding the severity of macular edema, there was a decrease in central macular thickness that was significant in patients following anti-VEGF treatment than in those who did not, without reaching statistical significance between treatment-protocol or variable-interval groups.

Mechanisms leading to a preservation of the FAZ area after VEGF treatment in irradiation-induced microangiopathy have not been fully understood. In a study of 666 patients with diabetic macular edema, monthly intravitreal anti-VEGF treatment slowed down the perifoveal retinal capillary closure.[13] The authors hypothesized that hyperglycemia induces capillary closure and subsequent VEGF production. In turn, VEGF accelerates capillary closure by inducing leukostasis. Treatment by anti-VEGF agents would interrupt this VEGF-related positive feedback loop, slowing disease progression. Similarly, irradiation induces vascular endothelial cell loss, which leads to progressive capillary closure and a delayed-onset microangiopathy.[14] However, the underlying mechanisms differ from diabetic retinopathy. Radiation-induced vascular endothelial cell loss results mainly from impaired cell division because radiation produces DNA damage, either direct or indirect via free radical generation.[15] Although endothelial cell turnover is slow, a small proportion of endothelial cells undergo mitosis over the months after irradiation, driven in part by VEGF. Vascular endothelial growth factor, a strong inducer of vascular endothelial cell proliferation, is the most selective vascular endothelial cell mitogen,[16,17] consequently its inhibition by anti-VEGF treatment could slow down the vascular endothelial cell division process, and therefore reduce subsequent capillary occlusion and ischemia. This hypothesis is supported by experimental observations that bevacizumab limits the proliferation of VEGF-enriched retinal[18] and choroidal endothelial cells[19,20] by stabilizing the cell cycle in the G_0/G_1 phase and inhibiting the G_2/M phase in a dose-dependent fashion.[20]

Clinically, the 2-month intervals between anti-VEGF injections proposed in this study may provide a favorable balance between inhibition of endothelial cell mitosis and excessive macular edema drainage. However, the optimal timing to initiate anti-VEGF treatment is still debated. Whether treatment should be started preventively at the time of irradiation, or when the first signs of maculopathy are detected on OCTA, should be further investigated.

Limitations of this study include its retrospective nature, the moderate number of patients in both groups and the short follow-up. There was no matching between the 3 subgroups, yet baseline characteristics did not differ, except the proportion of eyes with macular edema that was lower in the nontreated group (as reported in Table 2). Importantly, the estimated radiation dose to the foveola was similar in all groups, warranting intergroup comparability regarding postradiation complications. Moreover, patients received either ranibizumab or bevacizumab, two anti-VEGF recombinant monoclonal antibodies that share pharmacological similarities, and injections were performed in different referring centers. However, the indication for treatment was always decided by a single senior ocular oncology expert (L.Z.). In addition, criteria for the diagnosis of radiation maculopathy change over time, especially in the era of multimodal retinal imaging, and the variable presentations of radiation maculopathy, of microaneurysms, exudates, macular edema, and their visual consequences, may have introduced selection bias between groups. The patients with less severe disease may have adhered less to the treatment protocol. Prospective studies with larger patient numbers, longer follow-up periods, and alternative anti-VEGF injection intervals would be needed to confirm these results.

In conclusion, FAZ enlargement on OCTA is a progressive phenomenon in the natural, short-term course of radiation maculopathy. Over a 6-month period, treatment with intravitreal anti-VEGF injections at 2-month intervals significantly reduced both FAZ enlargement and BCVA loss.

Key words: anti–vascular endothelial growth factor, foveal avascular zone, radiation maculopathy, optical coherence tomography angiography, choroidal melanoma, proton beam irradiation.

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