Original Paper

Ophthalmic Research

Ophthalmic Res
DOI: 10.1159/000490571

Received: April 3, 2018
Accepted after revision: June 3, 2018
Published online: August 17, 2018

# Evaluation of Vascular Changes with Optical Coherence Tomography Angiography after Plaque Radiotherapy of Choroidal Melanoma

Gilda Cennamo[a] Maria Angelica Breve[b] Nunzio Velotti[c] Federica Sparnelli[b] Claudio Iovino[b] Antonio Farella[d] Raffaele Liuzzi[e] Giuseppe de Crecchio[b] Giovanni Cennamo[b]

[a]Public Health Department, University of Naples "Federico II", Naples, Italy; [b]Eye Clinic, Department of Neurosciences, Reproductive and Odontostomatological Sciences, University of Naples "Federico II", Naples, Italy; [c]Department of Surgical Specialties and Nephrology, University of Naples "Federico II", Naples, Italy; [d]Functional and Morphologic Department of Radiotherapy and Legal Medicine, University of Naples "Federico II", Naples, Italy; [e]Institute of Biostructure and Bioimaging, National Research Council (CNR), Naples, Italy

**Keywords**
Choroidal melanoma · Optical coherence tomography angiography · Radiotherapy

**Abstract**
***Aim:*** The purpose of this paper was to evaluate whether optical coherence tomography angiography (OCT-A) can be used to quantify the vascular changes in radiation maculopathy, and changes in the tumor vasculature in eyes treated with plaque radiotherapy for choroidal melanoma. ***Methods:*** In this prospective study, we evaluated 39 Caucasian patients with choroidal melanoma (39 eyes) treated with ruthenium-106 plaque radiotherapy. The patients underwent complete ophthalmic examination, bulbar echography, and OCT-A before and 1 year after treatment. ***Results:*** At baseline, the mean best-corrected visual acuity (BCVA) in the affected eyes was 0.35 ± 0.40 logMAR, and the mean tumor thickness was 2.68 ± 0.25 mm at A-scan echography. After treatment, the mean BCVA increased to 0.41 logMAR, the mean tumor thickness decreased to 1.66 ± 0.23 mm, and the tumor basal diameter was significantly reduced (U = 108, $p = 0.001$). Moreover, the capillary vessel density was significantly lower in all Early Treatment of Diabetic Retinopathy Study sectors, and both the vessel and flow areas were significantly reduced ($p = 0.030$ and $p = 0.001$, respectively). ***Conclusions:*** OCT-A is a noninvasive, reliable method with which to quantify the vessel changes in radiation maculopathy and, given the association between vascularization and malignancy, this procedure may be an aid in treatment decision-making and in monitoring the efficacy of treatment.



## Introduction

Choroidal melanoma is an intraocular malignancy with potential for blindness and life-threatening metastatic disease, and is generally managed with enucleation of the globe or focal radiotherapy directed at the intra-



E-Mail karger@karger.com
www.karger.com/ore

Gilda Cennamo, MD
Public Health Department, University of Naples "Federico II"
Via S. Pansini 5
IT–80133 Naples (Italy)
E-Mail xgilda@hotmail.com

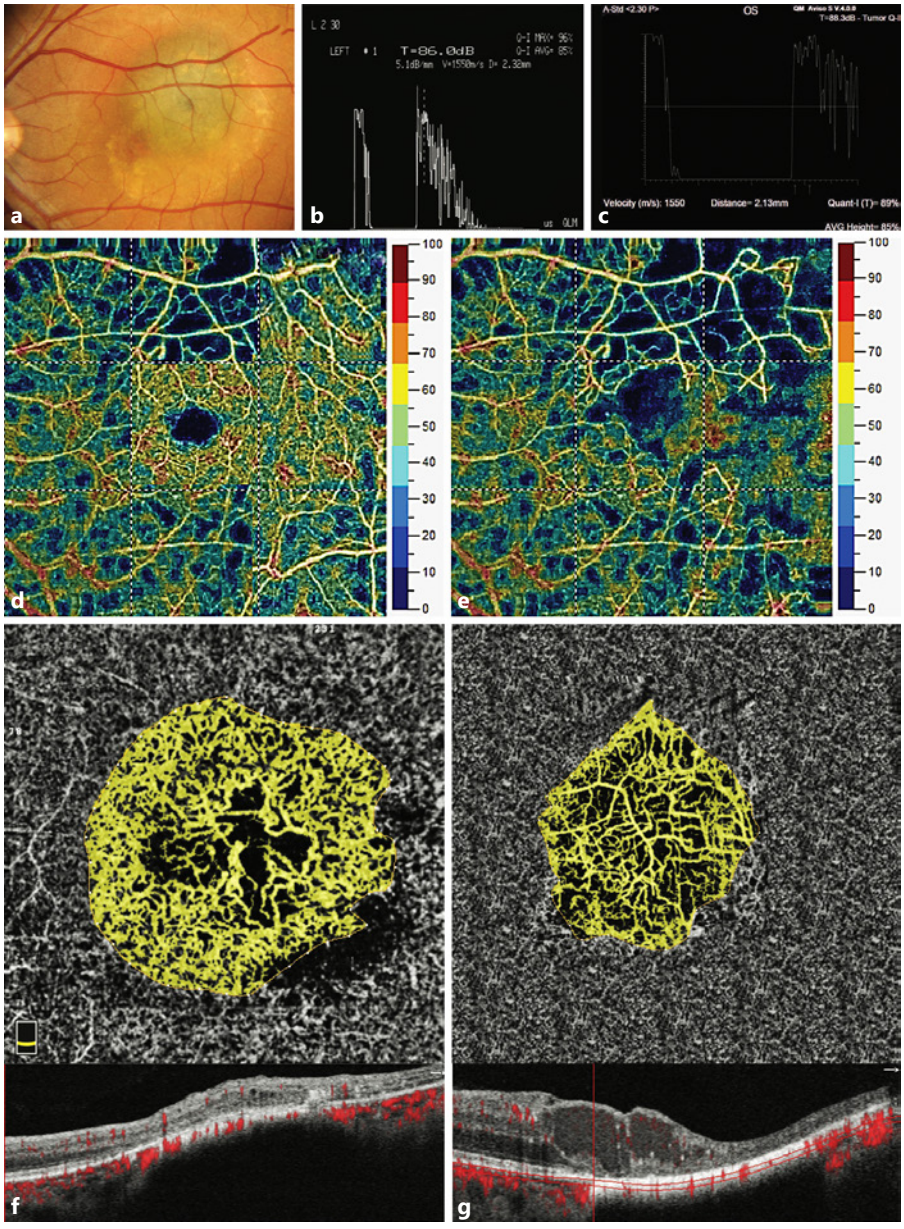


**Fig. 1.** Choroidal melanoma before and 1 year after treatment with ruthenium plaque radiotherapy. **a** Color fundus examination of a choroidal melanoma located at the posterior pole. **b** A-scan standardized echography showing a tumor thickness of 2.39 mm before treatment. **c** A-scan standardized echography showing a tumor thickness of 2.13 mm after treatment. **d** Angio-OCT image of CVD before treatment. **e** Angio-OCT image showing reduced CVD after treatment. **f** Pretreatment angio-OCT showing a dense microvascular network in the tumor. **g** Posttreatment angio-OCT showing a reduction in the density of the microvascular network and the presence of large vessels in the tumor.

ocular mass to achieve tumor control [1, 2]. Focal radiotherapy is delivered via plaque brachytherapy that can result in both short-term and long-term damage to the neurosensory retina and choroid [3]. This, in turn, can lead to vascular damage with consequent leakage, edema, hemorrhage, nonperfusion, and neovascularization [4–7], and permanent vision loss [3].

Generally, malignant choroidal melanoma is diagnosed based on the presence of vascularization within the neoplasia using standardized A-scan echography [8]. The introduction of optical coherence tomography angiography (OCT-A) into the clinical practice allows the detection and visualization of blood flow and morphology of retinal vessels [9]. Very recently, we have demonstrated that OCT-A is a reliable, noninvasive procedure with which to evaluate the vascularization of small choroidal tumors [10]. The aim of the present study was to evaluate whether OCT-A can be used to quantify the extent of vascular changes in radiation maculopathy, and changes in the tumor vasculature in eyes treated with plaque radiotherapy for choroidal melanoma.

## Materials and Methods

*Patients*

Thirty-nine eyes of 39 consecutive patients with a choroidal melanoma located at the posterior pole seen at the Eye Clinic of the University of Naples "Federico" from October 2015 to January 2017 were enrolled in this prospective study. Exclusion criteria were clinically relevant opacities of the optic media and low-quality images obtained with angio-OCT, presence of congenital eye disorders, pre-existing macular diseases (e.g., age-related macular degeneration, severe macular scar, or severe subfoveal exudates), pathologic myopia, history of ocular surgery, previous diagnosis of glaucoma, optic disk anomaly, and other ocular pathologic features (e.g., combined retinal vein, artery occlusive disease). All patients underwent complete ophthalmic examination, including best-corrected visual acuity (BCVA) according to the Early Treatment of Diabetic Retinopathy Study (ETDRS) visual logarithm of the minimum angle of resolution scale, bulbar echography, and angio-OCT at study entry and 1 year after ruthenium-106 plaque treatment. Radiation parameters included radiation dose (cGy) to the tumor apex, tumor base, and optic disc.

The study was approved by our institutional review board, and informed consent to the study was obtained from all subjects. All investigations adhered to the tenets of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013).

*Optical Coherence Tomography Angiography*

OCT-A images were acquired with the Angiovue System (Optovue Inc. Fremont, CA, USA), which is based on split-spectrum amplitude decorrelation angiography. The instrument has an A-scan rate of 70,000 scans per seconds with a tissue axial resolution of 5 μm and a 15-μm beam width. Each B-scan contained 304 A-scans. Two consecutive B-scans were captured at a fixed position before proceeding to the next sampling location. Size volumes were recorded, and the B-scan images were compared with each other to calculate decorrelation in the images [11]. Blood flowing through vessels causes a change in reflectance over time and results in localized areas of flow decorrelation between frames. The spectrum of the light source was split into multiple component parts to decrease the noise present in the image; each part was used to perform the decorrelation step, and the results of all split spectra were averaged. In any given region of tissue, the projection image can be viewed to obtain an image of the contained blood flow [12]. Cross-sectional registered reflectance intensity images and flow images were summarized and viewed as an en face maximum flow projection from the inner limiting layer to the retinal epithelial pigment. The macular capillary network was visualized in scans centered on the fovea by performing a 6 × 6 mm scan over the macular region; capillary vessel density (CVD) was defined as the percentage area occupied by the large vessels and the microvasculature in the analyzed region. The flow area was measured by the summation of the pixel area with the active vascular flow in the cleaned region selected by the operator in the retinal angiogram. The OCT-A software, according to the ETDRS classification of diabetic retinopathy, includes a grid that divides the macular region into foveal and parafoveal areas and further divides the parafoveal area into superior and inferior hemisphere, temporal section, nasal section, inferior section, and superior section. For each eye analyzed, the software automatically calculates vessel density in the whole scanned area and in all sections of the grid. In the case of eyes with a choroidal melanoma located at the posterior pole, an 8 × 8 mm scan was also performed over the lesion, vessel, and flow areas of the tumor using a specific measurement tool of the OCT software. Two expert examiners (N.V. and Gilda Cennamo) independently measured the tumor vessel and flow area tracing contours of each lesion manually by the embedded software. A third investigator (Giovanni Cennamo) reassessed the measurements in case of discordance between each independent measurement with more than 10% of variation in the tumor area. Poor-quality images with a signal strength index <50 or image sets with residual motion artefacts (discontinuous vessel pattern or discontinuous disc boundary) were excluded from the analysis.

**Table 1.** Patients' demographics, OCT features, and radiation parameters ($n$ = 39)

| | |
|---|---|
| Mean age, years | 58.62 |
| Female | 30 |
| Right eye | 15 |
| Mean radiation dose, cGy | |
| Tumor apex | 100 |
| Tumor base | 205.8 |
| Optic disk | 205 |
| OCT features | |
| Macular subretinal fluid | 17 |
| Subfoveal fluid | 10 |
| Cystoid macular edema | 5 |

Values are presented as numbers, unless otherwise stated.

*Bulbar Echography*

The mean tumor thickness and basal dimension were measured with standardized bulbar echography before and after treatment. A-scan and B-scan ultrasound were performed with an AVISO-S Echograph (Quantel Medical, Clermont-Ferrand, France) and 10 and 20 MHz probes.

*Statistical Analysis*

Statistical analysis was performed with the Statistical Package for Social Sciences (Version 20.0 for Windows; SPSS Inc, Chicago, IL, USA). The Mann-Whitney U test was used to evaluate differences in macular vessel density parameters between pre- and post-treatment eyes; it was also used to evaluate differences in the tumor basal diameter, flow area, and vessel density of the lesion before and after ruthenium-106 plaque treatment. A $p$ value <0.05 was considered statistically significant.

## Results

Thirty-nine consecutive eyes of 39 patients affected by choroidal melanoma were studied. The median age of patients was 58.62 ± 17.48 years; 9 patients were male. At baseline, the mean BCVA in affected eyes was 0.35 ± 0.40

**Table 2.** Vessel density measured by OCT-A and echograhic features in melanoma eyes at baseline and after 1 year of follow-up

| | Patients at baseline | Patients at the 1-year follow-up | Baseline vs. follow-up (*p* value) |
|---|---|---|---|
| Macular CVD | | | |
| Whole image[a] | 50.96±0.44 | 43.63±3.74 | 0.001 |
| Fovea[a] | 36.10±6.05 | 26.64±8.22 | 0.001 |
| Parafovea[a] | 54.04±1.87 | 46.01±4.56 | 0.001 |
| Superior hemisphere[a] | 54.12±2.16 | 45.70±5.30 | 0.001 |
| Inferior hemisphere[a] | 53.95±2.29 | 46.32±4.54 | 0.001 |
| Temporal sector[a] | 53.42±2.56 | 46.89±5.86 | 0.001 |
| Superior sector[a] | 54.18±2.73 | 45.53±7.07 | 0.001 |
| Nasal sector[a] | 53.80±2.13 | 46.28±5.00 | 0.001 |
| Inferior sector[a] | 54.86±2.16 | 45.26±5.68 | 0.001 |
| Tumor vessel area, $mm^2$ | 11.61±4.71 | 9.16±2.96 | 0.030 |
| Tumor flow area, $mm^2$ | 6.05±2.38 | 4.09±1.51 | 0.001 |
| Tumor basal diameter, mm | 7.88±1.45 | 5.19±1.03 | 0.001 |

Values are presented as mean ± SD. CVD, capillary vessel density. [a] Data are expressed as vessel density percentages.

logMAR. At standardized A-scan echography, the mean tumor thickness was 2.68 ± 0.25 mm. All tumors were located at the posterior pole (Fig. 1a), and most melanomas were in the left eye (24 vs. 15 cases).

The patients' baseline characteristics, tumor features, and radiation parameters are summarized in Table 1.

After ruthenium-106 plaque treatment, the mean BCVA increased to 0.41 logMAR, and the mean tumor thickness to 1.66 ± 0.23 mm; a statistically significant reduction was also seen in the tumor basal diameter (U = 108, $p = 0.001$) (Fig. 1b, c). Moreover, CVD was significantly lower in all ETDRS sectors after ruthenium 106–106 plaque treatment (Fig. 1d, e). As shown in Table 2 and Figure 1f, g, OCT-A measurements within tumors revealed a statistically significant reduction of the vessel area and flow area between baseline and the 1-year follow-up (U = 543, $p = 0.03$; U = 423, $p = 0.001$).

## Discussion

The aim of this study was to evaluate whether OCT-A can be used to quantify the vascular changes in radiation maculopathy and changes in the tumor vasculature in eyes treated with plaque radiotherapy for choroidal melanoma. Currently, OCT-A is the most sensitive method with which to detect radiation maculopathy [3, 13]. In fact, in a recent study of 65 patients, Shields et al. [14] identified parafoveal changes on OCT-A. Here, we report the extent of changes in the superficial capillary plexus, which included the reduction in CVD in all ETDRS sectors. Based on these findings, we believe that OCT-A is a remarkably sensitive technology with which to detect radiation maculopathy.

In terms of tumor vascularization changes after radiotherapy, using echography with contrast agent, Forte et al. [8] documented a significant reduction in the size of choroidal melanomas and the absence of a dense microvascular network inside the tumor after transpupillary thermotherapy and proton beam brachytherapy. We obtained similar results using noninvasive OCT-A and were also able to quantify the differences in the vessel and flow between baseline and 1 year after brachytherapy. However, we should mention that OCT-A is limited by the fact that image artefacts (blink lines, out-of-focus scans, or segmentation errors) can reduce the capillary density. In conclusion, given that vascularization reflects the malignancy of the lesion [15], OCT-A could be used for the differential diagnosis, prognosis, and follow-up treatment of malignant melanomas.

## Acknowledgments

We thank Jean Ann Gilder (Scientific Communication Srl., Naples, Italy) for editing this article.

## Disclosure Statement

This research paper received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The authors have no financial or proprietary interest in products, methods, or materials used for this research.

## References

1 Shields CL, Shields JA: Recent developments in the management of choroidal melanoma. Curr Opin Ophthalmol 2004;15:244–251.
2 Shields JA, Shields CL: Management of posterior uveal melanoma: past, present, and future: the 2014 Charles L. Schepens lecture. Ophthalmology 2015;122:414–428.
3 Shields CL, Shields JA, Cater J, Gündüz K, Miyamoto C, Micaily B, Brady LW: Plaque radiotherapy for uveal melanoma: long-term visual outcome in 1,106 consecutive patients. Arch Ophthalmol 2000;118:1219–1228.
4 Gündüz K, Shields CL, Shields JA, Cater J, Freire JE, Brady LW: Radiation retinopathy following plaque radiotherapy for posterior uveal melanoma. Arch Ophthalmol 1999;117:609–614.
5 Horgan N, Shields CL, Mashayekhi A, Teixeira LF, Materin MA, Shields JA: Early macular morphological changes following plaque radiotherapy for uveal melanoma. Retina 2008;28:263–273.
6 Bianciotto C, Shields CL, Pirondini C, Mashayekhi A, Furuta M, Shields JA: Proliferative radiation retinopathy after plaque radiotherapy for uveal melanoma. Ophthalmology 2010;117:1005–1012.
7 Horgan N, Shields CL, Mashayekhi A, Shields JA: Classification and treatment of radiation maculopathy. Curr Opin Ophthalmol 2010;21:233–238.
8 Forte R, Cennamo G, Staibano S, De Rosa G: Echographic examination with new generation contrast agent of choroidal malignant melanomas. Acta Ophthalmol 2005;83:347–354.
9 Savastano MC, Lumbroso B, Rispoli M: In vivo characterization of retinal vascularization morphology using optical coherence tomography angiography. Retina 2015;35:2196–2203.
10 Cennamo G, Romano MR, Breve MA, Velotti N, Reibaldi M, De Crecchio G, Cennamo G: Evaluation of choroidal tumors with optical coherence tomography: enhanced depth imaging and OCT-angiography features. Eye 2017;31:906–915.
11 Chhablani J, Rao HB, Begum VU, Jonnadulla GB, Goud A, Barteselli G: Retinal ganglion cells thinning in eyes with nonproliferative idiopathic macular telangiectasia type 2A. Invest Ophthalmol Vis Sci 2015;56:1416–1422.
12 Jia Y, Tan O, Tokayer J, et al: Split-spectrum amplitude-decorrelation angiography with optical coherence tomography. Opt Express 2012;20:4710–4725.
13 Say EA, Samara WA, Khoo CT, Magrath GN, Sharma P, Ferenczy S, Shields CL: Parafoveal capillary density after plaque radiotherapy for choroidal melanoma: analysis of eyes without radiation maculopathy. Retina 2016;36:1670–1678.
14 Shields CL, Say EA, Samara WA, Khoo CT, Mashayekhi A, Shields JA: Optical coherence tomography angiography of the macula after plaque radiotherapy of choroidal melanoma: comparison of irradiated versus nonirradiated eyes in 65 patients. Retina 2016;36:1493–1505.
15 Valverde-Megias A, Say EAT, Ferenczy SR, Shields CL: Differential macular features on optical coherence tomography angiography in eyes with choroidal nevus and melanoma. Retina 2017;37:731–740.