Original Research Article

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Acute effects of high-intensity interval training on microvascular circulation: a case control study in uveal melanoma

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Abstract

Objectives: The aim of this study was to explore the acute effects of high-intensity interval training (HIIT) on the microvascular circulation and vascular tumor microenvironment (TME) in a patient with uveal melanoma (UM). Additionally, the acceptance of the applied diagnostics and the exercise protocol in a clinical ophthalmic-oncology setting were evaluated.

Methods: This case-control study included a young adult male patient with UM previously treated with radiation and an age-matched healthy control. Participants underwent a baseline assessment of dynamic retinal vessel analysis (DRVA) and cardiopulmonary exercise testing (CPET) to determine endothelial function and intensity for HIIT. Optical coherences tomography angiography (OCTA) was performed before, immediately and 30 min after one session of HIIT. The primary outcome were changes in ocular vessel parameters and whole body oxygen uptake.

Results: The UM patient exhibited lower arterial dilation and constriction in the affected eye compared to his healthy eye and both eyes of the healthy control. OCTA revealed heterogeneous patterns of vascular response to HIIT in both participants. The tumor eye showed an increase followed by a significant decrease in vessel density post-exercise, while the healthy control exhibited minor increases.

Conclusions: The findings of this study highlighted the potential of UM combined with OCTA and DRVA as a model for examine exercise-induced vascular effects within the TME. However, a pre-treated UM as well as detailed image analyses and further research with longitudinal, randomized controlled designs are essential to validate these findings and address methodological limitations. Such investigations could refine integrative cancer treatment.

Keywords: uveal melanoma; endothelial dysfunction; aerobic exercise; oxygen kinetics

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Introduction

Physical activity after cancer diagnosis has been associated with improved outcomes spanning from reduced risk of progression and recurrence to improved survival [1, 2]. However, the underlying mechanisms have not yet been clearly identified limiting the targeted application of exercise intervention in the integrated anticancer treatment. Among the most frequently suggested mechanisms is the exercise-induced modulation of the tumor microenvironment (TME), particularly tumor hypoxia [3]. The insufficient oxygenation of the tumor tissue mainly results from the rapid proliferation of malignant cells that lead to a disorganized, tortuous and immature vascular network forming hypoxic areas with instable perfusion patterns and leaky vessels [4]. The hypoxic TME is now being recognized as a major limiting factor in cancer therapy and associated with increased risk of malignant progression and poor treatment outcomes due to insufficient drug delivery and radiotherapy effectiveness [5, 6]. A hypoxic TME is present in about 90 % of all solid of tumors including pancreatic, prostate, head, neck, breast, cervical cancer and melanoma [7, 8].

Interestingly, aerobic exercise (AE) is increasingly recognized for its potential impacts on the TME. Both animal models [9–11] and studies on humans [11, 12] have suggested that exercise can create a tumor suppressive environment and even lead to tumor regression. It has been proposed that

AE may acutely reduce tumor hypoxia by increasing tumor tissue perfusion [13]. Structural adaptations induced by AE-dependent shear stress on the endothelium can lead to vascular normalization which could potentially result in a less aggressive tumor and further enhance treatment response as shown in an animal model [10]. Overall, the effects of exercise on the TME is a hot topic, with several narrative reviews being published in this area [3, 14, 15]. Still, these reviews only give suggestions and hypotheses regarding the mechanisms of action, and the diagnostic tools being used to capture the effects of exercise training on the TME. There is still a lack of consensus on the selection of the most appropriate imaging technique or diagnostic tool.

Besides blood sampling for angiogenesis associated blood markers, to our knowledge, only three investigations applied immediate vessel analyzing methodology in humans. One randomized controlled trial (2:1 randomization, exercise vs. control) focused on acute responses to AE applying a high-intensity aerobic exercise protocol one day before surgery [16]. The methodology of postsurgical tissue analysis did not yield any significant results regarding micro vessel density (MVD), nor associated tumor hypoxia, in a sample of 30 men with localized prostate cancer. Two other clinical investigations examined chronic vascular adaptations of tumor tissue in response to exercise. Jones and co-authors utilized O-labeled PET scans to report non-significant changes of the tumor vasculature (scans were only available for 25 % of participants) in 20 women diagnosed with stage II-III breast adenocarcinoma randomly (1:1) assigned to either 12 weeks of AE + neoadjuvant chemotherapy vs. neoadjuvant chemotherapy only. Still, the flow-mediated dilation analysis (FMD) yielded significant between-group differences [17]. Another investigation comparing postsurgical tissue analysis of home-based exercising pancreatic cancer patients (n=23) with historical controls (n=13) yielded significant improvements in MVD and a significant increase in endothelial cells [18]. Although the results outlined above are promising, pre-post changes and acute vascular responses to exercise stimuli in the immediate vicinity of the tumor or in the tumor tissue still need to be verified. In this regard, the utilization of ophthalmological vessel diagnostic techniques offers a wide array of advantages, particularly in cost and time efficiency, non-invasiveness, as well as the opportunity of *in vivo* measurements of dynamic and static parameters of vascular status and function. Recently, retinal vessel analysis has been postulated as a surrogate biomarker for assessing overall microvascular circulation and endothelial function [19].

Optical coherence tomography angiography (OCTA) and dynamic retinal vessel analysis (DRVA) are relatively novel diagnostic tools applied in ophthalmology to analyze eye tissue, vessel structure, blood perfusion and endothelial function [20–22].

In this light, uveal melanoma (UM) seems to be a promising model to investigate exercise and physical activity associated vascular effects on the TME. Employing OCTA and DRVA, UM offers the unique opportunity to analyze vascular changes in the TME *in vivo*. Analogous to subcutaneous melanoma, UM is highly hypoxic and microvascular patterns have been reported to be independent prognostic factors of metastasis development and disease-free survival [8].

Combining DRVA and OCTA in UM might overcome limitations of previous investigations in humans such as lack of acute effect measurement and pre-post assessments. The aim of the present study was to investigate the potentials of these diagnostic tools in analyzing the acute effects of one session of high-intensity interval training (HIIT) on microvascular circulation in a single case-control design. We also aimed to demonstrate acceptance, feasibility, and potential limitations of the aforementioned protocol in UM and healthy control. The summary of this study is presented in Figure 1.

Materials and methods

The study was conducted in accordance with the standards of the Declaration of Helsinki and was approved by the Ethics Committee of the University Hospital of Cologne (approval number 13-050) within the framework of the oncological exercise therapy (OTT) concept. This case-control study included two 29 years old male participants: one UM patient (left eye, ICD-10 code: C69.3) and one age-matched healthy control. Detailed information about the study participants is provided in Table 1. Both participants were informed about the study procedures and provided written informed consent prior to any data collection. These participants underwent extensive laboratory testing and an acute exercise training session protocol at the University Hospital in Cologne.

Study design

This interventional, prospective case-control study was conducted from June 2023 to June 2024. Both participants engaged in racket sports (padel and tennis) up to 2–3 times per week without prior experience of high-intensity interval exercise. Prior to data collection, they were instructed to abstain from moderate-to-vigorous exercise, caffeine,

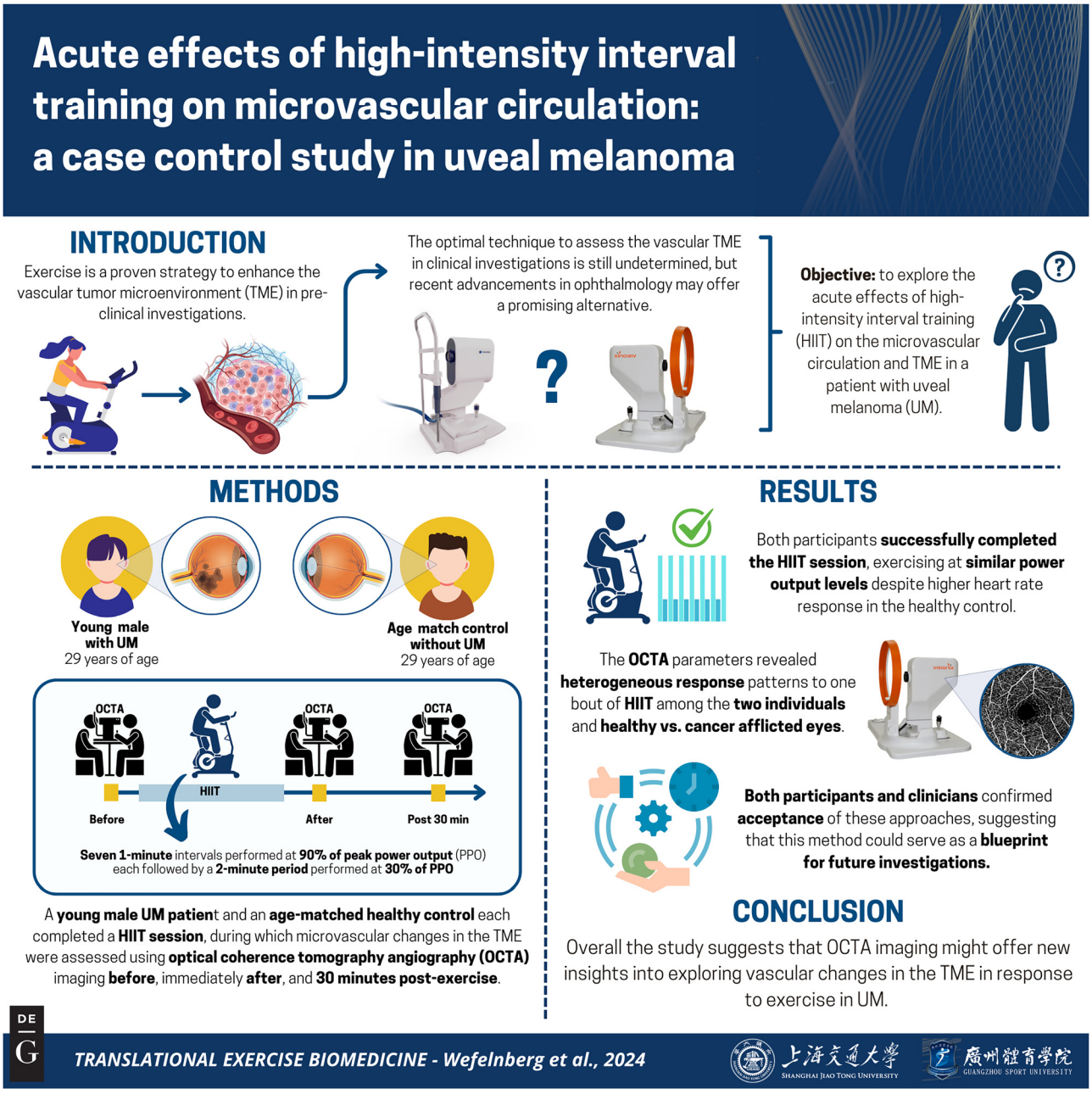

Figure 1: Graphical representation of this study. Key points: (1) This study explores the effects of one of session high-intensity interval training (HIIT) on the microvascular circulation and vascular tumor microenvironment (TME) *in vivo* in uveal melanoma (UM) vs. healthy control. (2) A case-control design of a previously treated young male melanoma patient and an age-matched healthy control performing one session of HIIT was applied. To analyze microvascular alterations in the TME optical coherence tomography angiography (OCTA) imaging before, immediately after and 30 min after exercise was conducted. (3) The OCTA parameters revealed heterogeneous response patterns to one session of HIIT among the two individuals and healthy vs. cancer-afflicted eyes. Overall the study suggests that OCTA imaging might offer new insights into exploring vascular changes in the TME in response to exercise in UM. Figure created with BioRender.

tobacco, and alcohol for at least 24 h. Data were collected on three separate occasions throughout the study. More precisely, after receiving medical clearance, all participants underwent DRVA via flicker light-induced dilation (FiD), followed by a cardiopulmonary exercise testing (CPET) procedure, as described in a previously published work ([23]). During the second visit, the HIIT protocol was conducted on a stationary bycicle ergometer in accordance with previously published research on cancer patients [24]. Exercise intensity was prescribed based on peak power

Table 1: Biometrical and cardiorespiratory profile of study participants.

	Cancer patient	Healthy control
Age	29	29
Sex	Male	Male
Height, cm	189	174
Weight, kg	90.2	73.0
BMI, kg/m^2	25.1	24.1
Tumor location	Left eye (inferior vascular arch extending into macula)	–
Tumor size, mm	7 × 9	–
Inner ocular pressure, mmHg		
Right eye	18	20
Left eye	14	18
Distant refractory visual acuity		
Right eye	1.00	1.00
Left eye	0.32	1.00
Stereopsis screening (lang test)	Negative	Positive
Eye dominance	Right	Left
Frist diagnosed	February 2023	–
Primary treatment completion	April 2023	–
Cardiorespiratory fitness		
$\dot{V}_E$ (L·min^{-1})	133.6	104.9
$\dot{V}O_2$ (L·min^{-1})	3.45	2.77
$\dot{V}CO_2$ (L·min^{-1})	4.23	3.27
RER	1.16	1.13
$\dot{V}O_{2max}$ (mL·kg^{-1}·min^{-1}·)	40.95	38.44
HR_{max}, bpm	172	194
PPO (W·kg^{-1})	3.40	3.45
Borg scale	20	20
Test duration (min:sec)	15:05	13:00
DRVA assessment		
aFID		
Right eye	3.3	3.1
Left eye	2.5	5.6
vFID		
Right eye	6.2	4.3
Left eye	5.6	6.1
aCON		
Right eye	−4.8	−6.0
Left eye	−3.0	−5.0

BMI, body mass index; bpm, beats per minute; DRVA, dynamic retina vessel analyzer; a/vFID, flicker light induced dilation for artery/vein; aCON, artery constriction; $\dot{V}_E$, pulmonary ventilation; $\dot{V}O_2$, oxygen uptake; $\dot{V}CO_2$, carbon dioxide production; RER, respiratory exchange ratio; PO, power output.

output (PPO) attained during a cycling CPET performed at a fixed cadence of 70 rpm. PPO was defined as the highest power output generated during CPET [25]. The HIIT session consisted of seven 1-min intervals performed at 90 % PPO, each followed by a 2-min interval performed at 30 % PPO (1:2 min ratio). Heart rate (HR) was continuously measured using a Polar H10 monitor, and the Borg scale (1–10) was administered at the end of each high intensity interval. The OCTA imaging was performed to assess blood flow and acute vasculature adjustments before the HIIT session, at baseline (prior to HIIT) immediately after HIIT session completion, and 30 min afterwards. Details on all diagnostic procedures are provided below. The primary outcome variables were FiD, CPET, and OCTA-derived parameters, while the secondary outcome variables were feasibility and acceptance. Acceptability was defined as the degree to which participants and healthcare providers found the intervention or study procedures to be appropriate, satisfactory, or agreeable. This information was crucial for us, as this was the first time a cycle-ergometer was mounted in the clinical settings (department of Ophthalmology) to ensure there were no delays in OCTA assessment following HIIT cessation.

Cardiopulmonary exercise test

To assess individual peak oxygen uptake, participants underwent a graded exercise test on a stationary cycle ergometer (Ergoline 900, Hamburg, DE) connected to a metabolic cart (Cortex: Metalyzer® 3B-R2) at each visit. The test followed the modified WHO graded protocol at a fixed cadence of 70 rpm, starting at 30 W and increasing by 15 W every 2 min until task failure. The metabolic cart was calibrated according to the manufacturer's guidelines before each session. Participants wore a silicone mask connected to a turbine and metabolic analyzer, along with a heart rate monitor belt. Task failure was defined as a cadence drop below 70 rpm for more than 10 consecutive seconds despite verbal encouragement. The $\dot{V}O_2$ peak was determined using a 20-s moving average of data recorded during the final minute of the test, while PPO and maximum HR max. were recorded at the end of the test.

DRVA assessment

Retinal endothelial function was assessed using the DRVA (Imedos Health GmbH, Jena, Germany). Trained personnel conducted data collection following the manufacturer's guidelines, utilizing the well-established method of FiD [19]. This technique causes retinal vessel dilation by stimulating an optoelectronic shutter within the retinal camera. Changes in arteriolar and venular diameters were monitored over time in both eyes. Participants were instructed to focus on a green cross-shaped light beam within the camera while the DRVA automatically measured the diameters of an arterial and a venous segment of micro vessels that originate from

the optic nerve head for 350 s. The measurement protocol included a 50-s baseline recording, followed by three phases of a 20-s of flickering light and an 80-s recovery period. The resulting diameter changes were computed using the Retinal Vessel Analyzer (RVA) software (RVA 4.61; IMEDOS Systems GmbH, Jena, Germany) relative to the baseline, quantifying microvascular endothelial function through arteriolar (aFiD) and venular (vFiD) flicker light-induced dilation, and arteriolar constriction post-flicker light exposure (aCON). Detailed information can be found in the studies by Hanssen et al. [19] and Mendes Wefelnberg et al. [23].

OCTA assessment

Before retinal imaging, best-corrected distant visual acuity using an automatic refractometer (ARK-1s, Nidek, Tokyo, Japan), and intraocular pressure (IOP) was assessed with rebound tonometry (ic100, Icare, Vanda, Finland). Fundus examination was performed (OPTOS, P200 DTx, Dunfermline, Scotland, UK) to determine tumor location and size. For OCTA imaging, patients were requested to avoid any physical activity as well as caffeine and nicotine consumption on the days of imaging. OCTA imaging was conducted utilizing a commercial spectral domain OCTA-system (Optovue Solix, Visionix, Jerusalem, Israel). Images were recorded in both eyes by an experienced operator and under standardized mesopic lighting conditions. Per eye, two images each of the central macula (6.4 × 6.4 mm field) and the optic nerve head (4.5 × 4.5 mm field) were taken, including 1 min offset between images. The onboard software (AngioAnalytics, version 2018.0.0.18) offered an automated segmentation of retinal layers and retinal thickness, vessel density and flow parameters as described in detail elsewhere [26]. For quality control, images showing inadequate scan quality (SQ≤7 for healthy eyes and SQ≤5 in the tumor afflicted eye), or an OCTA motion artifact score of three or four and a segmentation accuracy score of two will be excluded from the analysis [26]. We retrieved several OCTA parameters, calculated by onboard software based on en face images of macula (6.4 × 6.4 mm) and optic nerve head (4.5 × 4.5 mm). The parameters retrieved from macula images of the right eye included FAZ (foveal avascular zone) area, FAZ flow density, defined as the flow density of a 300 µm wide zone around the fovea, retinal thickness within the ETDRS (Early Treatment of Diabetic Retinopathy Study) grid as well as superior and deep vessel density within the ETDRS grid. The ETDRS grid is a 6 mm wide area surrounding a 1 mm wide area around the fovea. For the left eye we adjusted the parameters due to the tumor spanning into the ETDRS grid and covering parts of the fovea (see Figure 2D). Here we analyzed those parts of the ETDRS grid not covered by the tumor, the nasal and superior region respectively. FAZ parameters for the left eye had to be excluded. For the optic nerve head, we analyzed RPC (radial peripapillary) vessel density and RNFL (retinal nerve fiber layer) thickness. The RPC is defined as the area between the 2 and 4 mm diameter contour lines and is automatically fitted around the disc margin by the onboard software.

Results

Data collection for both participants took place at the University Hospital Cologne in April 2024. The UM patient was first diagnosed in February 2023 (ICD-10 code: C69.3) and completed primary treatment in late March 2023. Since April 2023, he has completed medical treatment and has been free of cancer therapy ever since. As part of his primary treatment, he was hospitalized for 12 days for the application of plaque brachytherapy in accordance with current medical guidelines [27]. The prescribed dose was 1,117 Gy to the sclera and 130 Gy to the tumor apex. After the completion of medical treatment, he experienced headaches, vertigo, diplopia, fatigue, and overall physical deconditioning.

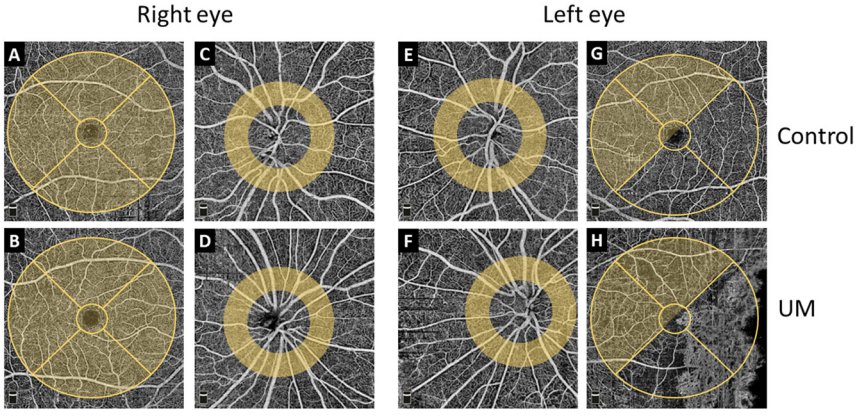

Figure 2: OCTA images of macula and optic nerve head. The regions analyzed are marked in yellow.

Medical treatment and recovery resulted in roughly a month of reduced physical activity. The age-matched control was a healthy participant recruited from the Cologne area with a similar BMI. The cardiorespiratory fitness of the treated UM patient was slightly higher compared to the healthy control, with higher readings of peak oxygen uptake, minute ventilation, and CPET duration. However, the relative PPO achieved was quite similar, as well as the self-perceived exertion. Interestingly, the HR_{max} reached during CPET was 18 bpm lower in the cancer patient compared to the healthy control which could be explained by inter-individual difference in heart rate response to exercise as well as maximum heart rate reachable. Regarding flicker light-induced dilation, similar findings were observed for the right healthy eye in both the cancer patient and the healthy control, while in the left eye the UM patient had two-fold lower readings for artery dilation and constriction compared to the control (Table 1). Table 2 provides an overview of the acute physiological response to one session of HIIT for both participants. They successfully completed the HIIT session, exercising at similar power output levels. The HR response in the healthy control was generally 25–30 beats per minute higher compared to the UM patient, while their self-perceived exertion was similar.

Figure 2 illustrates the regions of interest in all OCTA scans conducted for the UM patient and healthy control respectively. Figure 3 presents the acute changes in the right eye in response to one session of HIIT. For both participants, similar patterns were observed for deep and superficial vessel density, as well as for FAZ area (provided in mm^2), where a transient change over a 30-min time-frame was observed. Interestingly, for FAZ flow density (%), the healthy control had a slight increase in response to one session of HIIT, while the readings for the cancer patient were significantly reduced 30 min after HIIT. Additionally, for retina thickness (ETDRS grid), a significant increase (by ~70 µm) was observed in response to HIIT for the cancer patient, while no change was observed for the healthy control. The image quality, according to the built-in software (AngioAnalytics, version 2018.0.0.18) of the UM patient's right macula and disc scan was consistently ≥7/10, except for the left eye macula scan where quality was 6/10 consistently due to the tumor spanning into the foveal region. For the healthy control the scan quality was consistently ≥8/10 for all macula and disc images respectively. In Figure 4, the RCP vessel density response to one session of HIIT was quite different between the two participants, while the thickness of the RNFL showed almost no response to one session of HIIT in both the healthy and cancer patient. Lastly, Figure 5, due to the position of the tumor and the inherent limitations of the OCTA data analysis, provides data on the response of deep and superficial vessel density of the regions not directly affected by the tumor. However, these regions, as in immediate proximity to the tumor and, therefore, can be regarded has part of the TME. Apparently, one session of HIIT downregulated the vessel density in the treated UM patient, while data on the healthy control appeared to be either A) stable or B) showing a slight increase over time. Acceptance of the exercise and diagnostic protocol was assessed using a simple 'yes/no' question. Both participants and clinicians confirmed acceptance, suggesting that this approach could serve as a blueprint for future investigations.

Discussion

The aim of this study was to investigate the use of two new diagnostic tools to analyze the acute effects of one session of HIIT on microvascular circulation in UM patient and age-matched control. Specifically, we applied a new ophthalmologic diagnostic tool to examine the microvasculature, focusing on endothelial function at baseline and the acute effects on MVD and perfusion patterns after one HIIT session in both the UM patient and healthy control.

Concerning endothelial function parameters retrieved by DRVA, the tumor-afflicted eye showed the lowest values

Table 2: Acute physiological response to high intensity interval training session.

	Warm-up	HIIT1	REC	HIIT2	REC	HIIT3	REC	HIIT4	REC	HIIT5	REC	HIIT6	REC	HIIT7	REC
Cancer patient															
Heart rate, bpm	109	127	110	135	109	137	123	139	123	140	120	145	123	156	124
RPE, 1–10	–	5	–	5	–	6	–	6	–	7	–	7	–	8	–
PO, W	50	250	60	250	60	250	60	250	60	250	60	250	60	250	60
Control															
Heart rate, bpm	109	157	128	167	132	169	126	163	125	167	123	170	124	171	121
RPE, 1–10	–	7	–	7	–	7	–	8	–	8	–	8	–	9	–
PO, W	50	225	60	225	60	225	60	225	60	225	60	225	60	225	60

HIIT, high-intensitiy interval training; REC, active recovery.

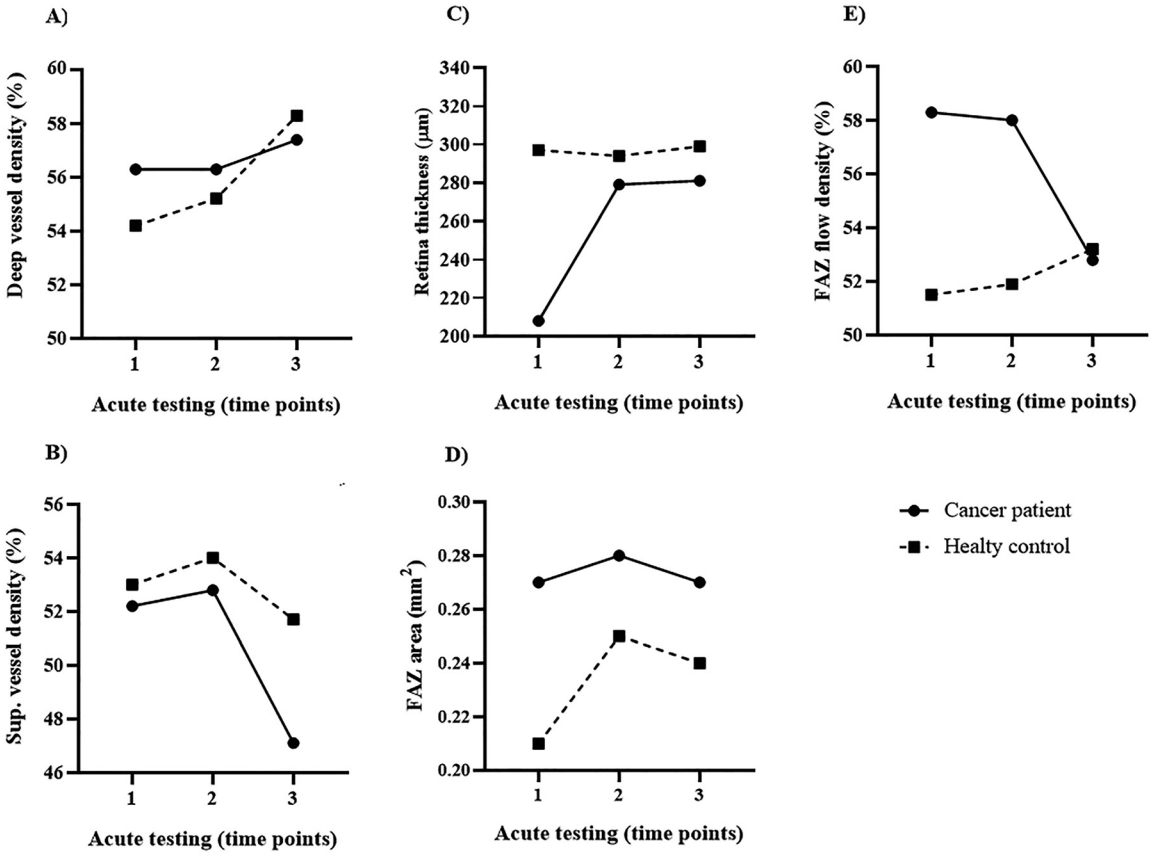

Figure 3: OCTA images of macula and papillary region. Abbreviation: FAZ, foveal avascular zone.

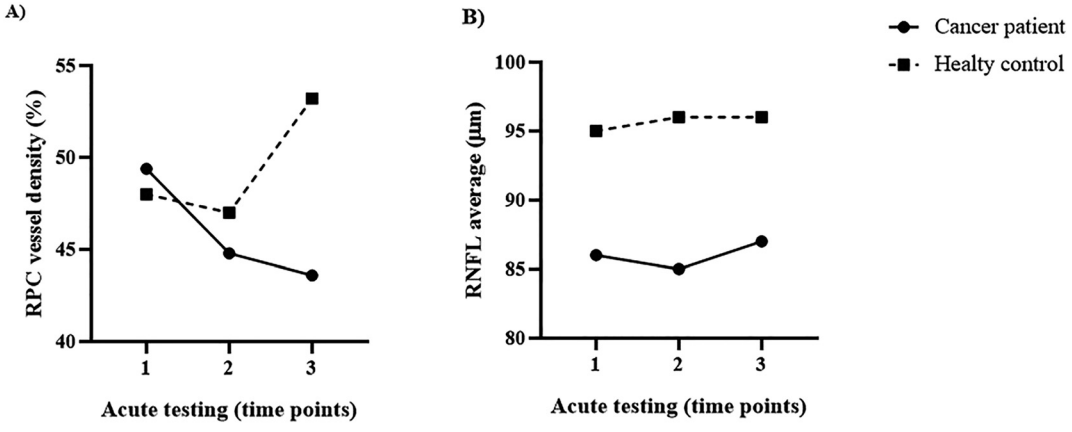

Figure 4: OCTA results of the papillary region in the right eye. Abbreviations: RNFL, retinal nerve fiber layer; RPC, radial peripapillary capillary.

for arterial dilation and constriction compared to the left and right eyes of healthy control and the healthy right eye of the cancer patient (Table 1). Whether this difference originated from the neoplasia or the vessel compromising nature of radiation treatment cannot be answered within the scope of the present case-control study. Our previous study demonstrated the external validity of the DRVA measurement in cancer patients by showing improvements in arterial dilation and constriction after 8 weeks of aerobic exercise, which were aligned with improvements in cardiorespiratory fitness [23]. The work of Stresse et al. (2020) [22] and Twerenbold et al. [28] in cardiovascular patients also demonstrated that DRVA provides a robust estimate of cardiovascular health and offers a more

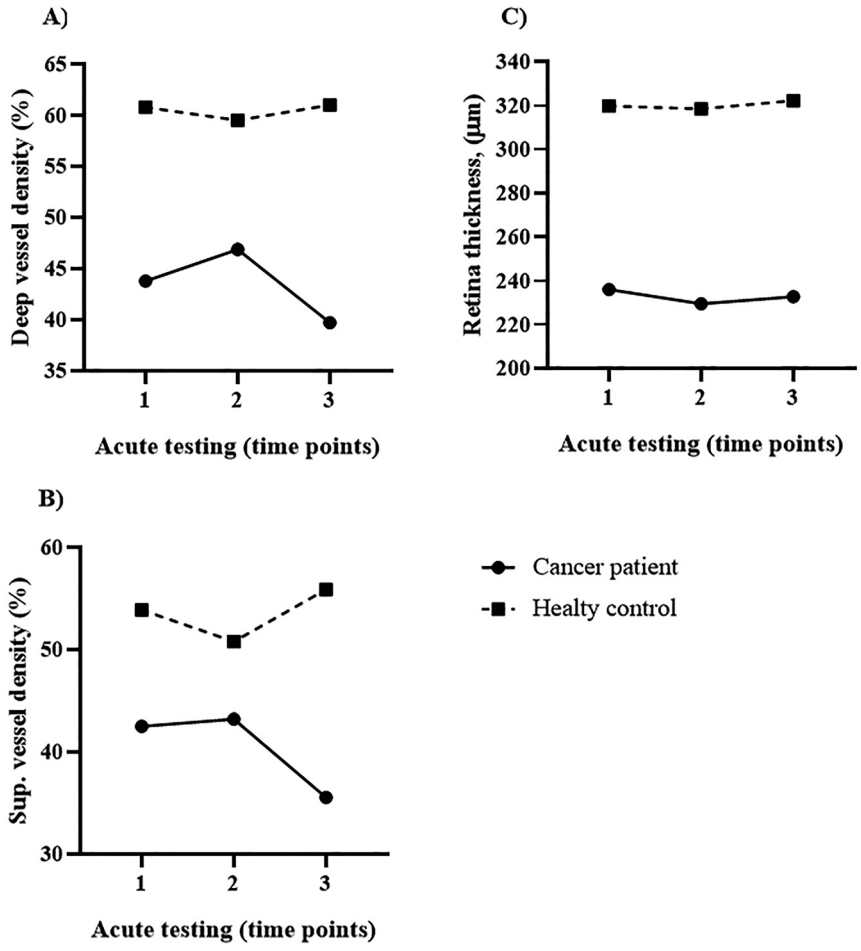

Figure 5: OCTA results of macula region in the left (tumor vs. control) eyes. Abbreviation: Sup., superficial.

comprehensive insight into blood vessel compliance compared to the traditional gold-standard FMD.

Concerning the acute effects of one session of HIIT on vascular modulations of the TME, MVD and perfusion parameters, the presented radiated UM case poses one major limitation. Noteworthy, investigating acute exercise-induced vascular responses in the tumor microenvironment (TME) is only practical in the vicinity of intact tumor tissue, as radiated tissue becomes fibrotic and exhibits different metabolic characteristics. Even precise radiation impacts the surrounding tissue of the tumor [29]. In our case-control investigation, deep vessel density parameters demonstrated highly heterogeneous patterns between the two individuals and eyes assessed (Figures 2–4). More precisely, the radiated left eye showed an immediate increase followed by a major decrease in superficial and deep vessel density while the healthy control's left eye demonstrated minor increases. More precisely, the vessel density parameters reacted analogously in the comparison of the right eye (Figure 3). Whether the overall heterogeneity observed was originated from the cancer and radiation-associated effects, or from limitations of the application of OCTA with achievable SQ of 6 in the UM eye cannot be clarified by the present case-control design. Still, OCTA technology is based on the amplitude and the delay of reflected light [30] which limits achievable SQ by the light absorbing nature of the fibrotic mass of the radiated tumor tissue [31].

Additionally, another inherent limitation of the technique is the built-in AngioAnalytics software, which does not provide data on choroid layer perfusion. The choroid layer, with about 90 % the most common sight for UM manifestation [32], holds the majority of eye micro vasculature. To overcome this limitation and to provide more detailed insights into potential exercise-induced TME remodeling patterns, post-hoc analysis of OCTA, including the en face images, needs to be performed. In this regard, standardized software like OCTAVA (OCTA vessel analysis) depicts promising potentials [33, 34], and should be applied in future work.

Importantly, this was the first time that a cycle-ergometer was integrated into Clinical Ophthalmology here at Center for Integrative Oncology in order to achieve immediate measurement of exercise effects on eye vasculature.

Standardization of such measurements encompassing optimal timing of immediate OCTA application in UM are still to be evaluated. Unfortunately, we did not measure blood pressure or IOP responses to exercise. Therefore, our data cannot determine whether the eye's intrinsic autoregulatory mechanisms for maintaining stable blood flow were overwhelmed by the protocol [35]. Future studies should consider this, as elevated intraocular blood pressure could theoretically increase diffusion distances to key tissues, making it essential to understand exercise potentials to mitigate tumor hypoxia in UM.

However, OCTA was applied in investigations on acute [36–39] and chronic [20, 40, 41] responses to exercise that generally demonstrated the tool's capacity to monitor exercise-induced vascular, tissue and blood flow changes in healthy and cardiovascular patients so far, but not eye cancer patients.

For future investigations, the capacity of OCTA to provide detailed insights into dysfunctional or leaky vessels in the TME as well as the performance in distinguishing functional from dysfunctional vessel adaptions has to be addressed by examining UM eyes before radiation treatment. Generally, dysfunctional vasculature characterized by dilated and tortuous structure for UM has already been visualized in a previous investigation employing OCTA [31]. Consequently, OCTA is likely capable of providing detailed insights into MVD and functioning as well as vascular conductance in close tumor proximity. As pointed out by Ghassemi and colleagues [31] these examinations are limited to tumors in the visualizable range of the OCTA. However, as the eye operates as a relatively closed metabolic unit, UM induced hypoxia has several downstream effects on the ocular metabolism and vasculature beyond the tumor site. Consequently, the entire eye can be considered as part of an expanded TME [42].

Regardless of disease rarity and some of the limitations delineated above, UM is characterized by low symptom and side-effect burden. We believe that pre-treatment conditioning with HIIT is a promising path to follow and UM is a feasible model to investigate associated effects on the TME.

In theory, exercise-induced improvements in the microvasculature would reduce intratumoral hypoxia and increase the accessibility of circulating immune cells to the tumor milieu, inhibiting tumor development and improving cancer treatment [3].

Conclusions

Overall, our case-control study demonstrates the practicability of using UM to investigate exercise associated effects on TME using OCTA and DVRA. However, further research involving pre-treated UM as well as detailed image analyses and IOP responses to exercise is required to refine our understanding of the applications and limitations of these methodologies. To validate our findings, future investigations employing longitudinal, randomized controlled designs are imperative.

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Research ethics: All research has been conducted in concordance with the Declaration of Helsinki (as revised in 2013) and the standards for Good Clinical Practice (GCP), and was approved by the Ethics Committee of the University Hospital of Cologne (approval number 13-050).
Informed consent: Informed consent was obtained from all individuals included in this study, or their legal guardians or wards.
Author contributions: DZ: data collection, writing, conceptualization, revision, creation of graphs and tables; MMW: data collection, writing, conceptualization, revision, creation of figures, patient recruitment, coordination and organization of measurements; JH: DRVA measurement, support in writing and data analysis; FTB: conceptualization, provision of resources. The authors have accepted responsibility for the entire content of this manuscript and approved its submission.
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Conflict of interests: The authors declare no conflict of interest.
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Data availability: The raw data can be obtained on request from the corresponding author.

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