Original Article

Retinal Optical Coherence Tomography Angiography Findings following Retinoblastoma Treatment by Chemotherapy

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Abstract

Purpose: To investigate the macular microvascular changes after different kinds of chemotherapy in patients with extramacular retinoblastoma (RB).

Methods: In this study, 28 eyes of 19 patients with bilateral RB treated with intravenous systemic chemotherapy (IVSC group) and 12 eyes of 12 patients with unilateral RB treated with intra-arterial chemotherapy (IAC group) were compared with 6 normal fellow eyes of 6 patients with unilateral RB treated with IVSC (IVSC fellow eye group), and 7 normal fellow eyes of 7 unilateral RB patients treated with IAC (IAC fellow eye group), as well as 12 age-matched normal eyes. Enhanced depth imaging optical coherence tomography measurements of central macular and subfoveal choroidal thickness (CMT and SFCT) as well as optical coherence tomography angiography measurements such as retinal superficial capillary density (SCD), deep capillary density (DCD), and choriocapillaris density were documented.

Results: Images of 2 eyes in the IVSC group and 8 eyes in the IAC group were excluded from the final image analysis due to severe retinal atrophy. Overall, 26 eyes with bilateral RB treated with IVSC and 4 eyes of 4 patients with unilateral RB treated with IAC were compared with the mentioned control groups. Best-corrected visual acuity was 1.03 logMAR in the IAC patients compared to 0.46 logMAR in the IVSC group at the time of imaging. While the CMT and SFCT were lower in the IAC group in comparison with the IAC fellow eye and normal groups ($P < 0.05$ for all), no remarkable difference was observed between the IVSC group and the control groups based on the mentioned parameters. Although the SCD showed no significant difference between the IVSC and control groups, this parameter was significantly lower in the eyes receiving IAC relative to the corresponding fellow eye group ($P = 0.042$) and normal control eyes ($P = 0.047$). The mean DCD was considerably lower in both the treatment groups compared to the control groups ($P < 0.05$ for all).

Conclusion: Our study showed a substantial decrease in SCD, DCD, CMT, and choroidal thickness in the IAC group, which may explain the lower visual outcome in this group.

Keywords: Enhanced depth imaging optical coherence tomography, Intra-arterial chemotherapy, Intravenous systemic chemotherapy, Optical coherence tomography angiography, Retinoblastoma

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Introduction

Retinoblastoma (RB) is the most common childhood primary malignant intraocular tumor. Advances in treatment methods such as intravenous systemic chemotherapy (IVSC) and intra-arterial chemotherapy (IAC) have been decreased the rate of enucleation while it has improved life expectancy.[1,2]

The reported adverse effects of IVSC are bone marrow suppression, hearing loss, and chemotherapy-induced leukemia in patients with RB.[3,4] While, IAC can cause some local and regional side effects such as periocular edema and hyperemia, ptosis, focal madarosis,[5] neurological complications as third

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and sixth cranial nerve palsy, optic neuropathy, optic atrophy, ophthalmic artery spasm, stroke, transient ischemic attack, seizure, occlusive chorioretinopathy, central retinal artery occlusion, vitreous hemorrhage, and retinal detachment.[6-14]

Thanks to recent advances in optical coherence tomography angiography (OCTA) imaging, the vascular status of the retina can be well investigated.[15] OCTA determines the quantitative metrics of the foveal avascular zone (FAZ) and foveal capillary vessel density (VD) at superficial capillary plexus (SCP), deep capillary plexus (DCP), and choriocapillaris (CC) levels.[16-20]

Attention was drawn to the use of this technology in ocular oncology to identify the impacts of specific tumors on retinal microvasculature.[21,22] Limited studies have been conducted on the status of macular microvascular structure changes after chemotherapy in patients with RB.[21,23] The findings showed that systemic chemotherapy could affect the retinal microstructural and microvascular pattern,[21,23] but the effect of IAC on macular microvasculature should be elucidated.

The aim of this article was to show the structural and microvascular changes in retinal and choroidal tissue using OCTA and enhanced depth imaging optical coherence tomography (EDI-OCT) in RB patients following IVSC and IAC treatment.

Methods

This was a retrospective single-center cross-sectional study performed in the ocular oncology ward of Farabi Eye Hospital. Written informed consent was obtained from the patient's parents or legal guardian. Institutional Review Board approval was obtained from Farabi Eye Hospital, Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1397.1093). This study adhered to the tenets of the Declaration of Helsinki.

Subsequent RB patients with extramacular tumors, managed between April 2009 and December 2019, were retrospectively reviewed. It included patients with unilateral or bilateral extramacular RB lesions previously fully treated with IVSC or IAC, and 12 months had passed since the last treatment. During the study, patients had to be ≥4 years of age to cooperate adequately. Patients with a history of preterm birth, any other systemic or ocular disease and previous intraocular surgery, and more than 3 diopter spherical equivalent of refractive error were excluded from the study. Additionally, any patient who received plaque brachytherapy, external beam radiotherapy, and/or subconjunctival chemotherapy was excluded from the study.

Based on the type of treatment performed, the enrolled RB eyes were divided into two groups (IVSC group and IAC group). The healthy fellow eyes of the patients with unilateral RB, who were indirectly exposed to chemotherapy drugs, were enrolled (referred to as IAC fellow eye group and IVSC fellow eye group). Furthermore, both eyes of 6 consecutive normal age-matched children were recruited and considered the healthy eye group. Complete ophthalmic examinations were performed.

The collected data included age at diagnosis, sex, race, laterality (unilateral or bilateral), best-corrected visual acuity (BCVA), intraocular pressure, baseline tumor features including laterality, the number of tumors and size, the distance from the foveola and optic disc (mm), vitreous and subretinal seeding, retinal detachment, and the time between the end of treatment and image acquisition.

The treatment protocol for the IVSC group was at least 6–8 cycles of intravenous chemotherapy with vincristine, etoposide, and carboplatin (VEC). For the IAC group, it was 1–3 cycles by melphalan (5 mg), topotecan (0.6–1 mg), and carboplatin (20 mg). Treatment features included the type of treatment, the number of IVSC or IAC cycles, and the adjunctive treatments. The intravitreal chemotherapy treatment by melphalan and/or topotecan was performed in the cases with vitreous seeds during the treatment course as already described.[24,25]

EDI-OCT (Heidelberg Engineering GmbH, Heidelberg, Germany) and OCTA (Optovue, Inc, Fremont, California, USA) were performed for all patients. The EDI-OCT was used to measure the subfoveal choroidal thickness (SFCT), defined as the vertical distance between the posterior edge of the retinal pigment epithelium-Bruch's membrane (RPE–BM) complex and the choroidoscleral junction. The SFCT was measured using the caliper function on the OCT device software – Heidelberg's eye explorer-2 (HEYEX).

OCTA using the Avanti RTVue XR with AngioVue (version: 2017.1.0.151; Optovue, CA, USA) based on split-spectrum amplitude-decorrelation angiography algorithm was performed after pupillary dilation. This device works based on 840 nm wavelength, the bandwidth of 45 nm, 70,000 A-scans per second, and acquiring two repeated B-scans of 3 mm × 3 mm (304 × 304 pixels) in the transverse dimension. Eyes with low image quality (<5/10) or different artifacts (including shadow defocus, movement, blinking, and decentration artifacts) preventing accurate measurements were excluded. The imaging was repeated to get a proper quality image. After using the projection artifact removal algorithm and the integral module in AngioVue Analytics software, different layers of the retina were segmented automatically and manually corrected if needed.[26]

The retinal slab for SCP en face image was defined from 3 μm under the internal limiting membrane to 15 μm beneath the inner plexiform layer (IPL). The DCP en face image was described between 15 μm beneath the IPL and 70 μm below the IPL. The CC image was derived by 10 μm thick ribbon starting 31 μm below the RPE–BM complex. The program recorded the whole image VD as a grid and in percentage at SCP and DCP. The FAZ area was automatically measured in mm^2 [Figure 1]. Two or three experienced investigators (F.G., H.R., and H.S.E.) rechecked the results. The automatically measured choroidal flow also reported a flow area within a 1 mm radius circle centered at the fovea in the CC slab.

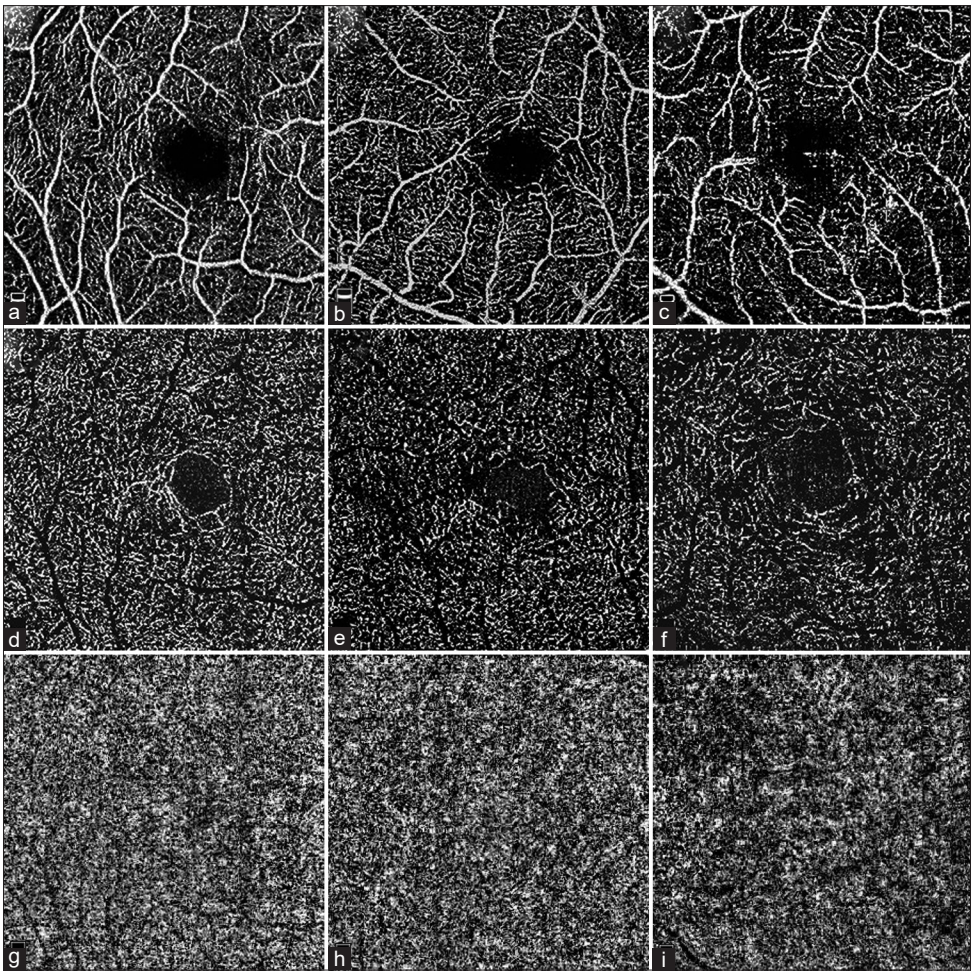

Figure 1: Optical coherence tomography (OCT) angiogram in normal, intravenous systemic chemotherapy (IVSC), and intra-arterial chemotherapy (IAC) groups. The superficial retinal slab of en face OCT angiography reveals the normal status of retinal vasculature in a healthy child (a). Superficial capillary plexus is fairly maintained in the IVSC patient (b); however, significant decrease in vessel density is evident in the IAC group (c) patient. At the level of deep capillary plexus, in comparison to the normal child (d), both patients in the IVSC group (e) and IAC group (f) have severe attenuation of vascular density. Flow void areas are more extensive in the patient with previous IAC treatment. At choriocapillaris level, the flow void areas rise from the normal control case (g) to the IVSC group (h) and then in the IAC group (i) become more significant

Statistical analysis

Predictive Analytics Software (PASW) Statistics for Windows, Version 18.0 (SPSS, Inc., Chicago, IL, USA), was used for statistical analysis. Data are presented as mean with standard deviation and median with range for quantitative variables, or number and percentage for qualitative variables. To compensate for the effect of neighbor eye, generalized estimating equation model was used. For multiple comparisons, the comparison between the groups was performed using the Bonferroni adjustment method. $P < 0.05$ was considered to be statistically significant.

Results

Forty eyes with RB (28 eyes in the IVSC group and 12 eyes in the IAC group) who met the inclusion criteria were enrolled in this cross-sectional study. OCTA images of 2 eyes in the IVSC group and 8 eyes in the IAC group were excluded from the final image analysis due to severe retinal atrophy where no distinction was possible between retinal layers. Finally, 26 eyes of 19 patients with bilateral RB treated with the IVSC group and 4 eyes of 4 patients with unilateral RB treated with the IAC group, were compared with 6 normal fellow eyes of 6 patients with unilateral RB treated with IVSC (IVSC fellow eye group), and 7 normal fellow eyes of 7 unilateral RB patients treated with IAC (IAC fellow eye group). Twelve eyes from 6 age-matched healthy control subjects were also enrolled.

The patient demographics are listed in Table 1. There was no significant difference in patients' age, sex, weight, height, and the time between the last treatment and imaging, among the subgroups. The clinical features of the tumor and treatment are listed in Table 2. No significant difference was observed between local adjunctive treatments (intravitreal chemotherapy, transpupillary thermotherapy, and cryotherapy) in both the treated eye groups ($P > 0.05$).

BCVA was 1.03 logMAR in the IAC patients compared to 0.46 logMAR in the IVSC group at the time of imaging.

Table 1: Demographic characteristics of the enrolled patients

Group, mean (median, range)	Intravenous systemic chemotherapy (*n*=26)	Intra-arterial chemotherapy (*n*=4)	Fellow eye of systemic chemotherapy (*n*=6)	Fellow eye of intra-arterial chemotherapy (*n*=7)	*P**
Age (years)	8 (7, 4-14)	8 (8, 6-10)	7 (7, 4-9)	8 (8, 6-10)	0.830
Sex, *n* (%)					
Male	16 (61.5)	2 (50)	2 (33.3)	3 (42.9)	0.766
Female	10 (38.5)	2 (50)	4 (66.6)	4 (57.1)	
Weight (kg)	32 (27, 15-63)	29 (27, 17-45)	29 (29, 19-40)	27 (24, 17-45)	0.349
Height (mm)	130 (121, 104-162)	123 (120, 111-142)	129 (132, 110-149)	122 (122, 106-142)	0.639
Duration of last treatment to imaging (years)	6.9 (6, 2-12)	6.4 (6, 5-8)	6 (7, 3-12)	7.1 (7, 5-8)	0.821

**P*: Based generalized estimating equation model

Table 2: Clinical features of retinoblastoma and treatment modality in eyes recruited in the study

	Systemic chemotherapy (*n*=26), *n* (%)	Intra-arterial chemotherapy (*n*=4), *n* (%)
Location		
Posterior pole	14 (20)	1 (25)
Equator	1 (4)	0
Peripheral	2 (4)	0
Posterior pole and equator	9 (36)	3 (75)
Number of tumors		
1	8 (32)	3 (75)
>1	18 (68)	1 (25)
Number of treatments		
≤6	10 (38)	4 (100)
>6	16 (62)	0
Distance to fovea (mm), mean (median, range)	3.6 (3, 2.5-18)*	3 (2.5, 2.5-9)*
Distance to optic nerve (mm), mean (median, range)	4.2 (2, 0-20)	6.2 (5, 0-15)
ICRB classification at the time of first diagnosis		
Group A	5 (19.2)	0
Group B	9 (34.6)	2 (50)
Group C	11 (42.3)	2 (50)
Group D	1 (3.8)	0
Group E	0	0
Size of the largest tumor	7.5 (6, 1.5-13)	7 (7, 4-10)
Thickness of the largest tumor	3.4 (4, 1-6)	3.25 (3, 2-5)
Vitreous seeds	12 (46.1)	2 (50)
Subretinal seeds	2 (7)	0
Number of treatment session	9 (8, 6-18)	3 (1, 1-9)
Intravitreal chemotherapy	6 (23)	1 (25)
Transpupillary thermotherapy	20 (77)	4 (100)
Cryotherapy	9 (34)	1 (25)

*All patients had tumor margin 2.5 mm from the foveola outside the range of the 3 mm × 3 mm-parafoveal optical coherence tomography angiography scan. ICRB: International Classification of Retinoblastoma

Furthermore, both the treated groups had significantly lower BCVA than the control groups. The imaging results and BCVA are listed in Table 3.

While the central macular thickness (CMT) and SFCT were lower in the IAC group in comparison with the IAC fellow eye and normal groups ($P < 0.05$), this study could not specify any remarkable difference in CMT and SFCT between the IVSC group and the control groups ($P > 0.9$).

In terms of the mean FAZ area, there was no statistically significant difference between the IVSC group and the control groups ($P > 0.90$). Although the FAZ area was larger in the IAC group compared to the IAC fellow eye group, it was not statistically significant (0.38 vs. 0.31, $P = 0.50$).

The superficial capillary density (SCD) showed no significant difference between the IVSC group and the corresponding fellow eye group (46% vs. 48%; $P > 0.90$) and normal control eyes (46% vs. 49% $P = 0.115$). The SCD was significantly lower in the eyes receiving IAC relative to the corresponding fellow eye group (43% vs. 49%; $P = 0.042$) and normal control eyes (43% vs. 49% $P = 0.047$).

Table 3: Summary of the optical coherence tomography (OCT) and OCT angiography outcomes following systemic chemotherapy and intra-arterial chemotherapy and comparison with the fellow eye

Outcome mean (median, range)	Mean (median, range)					*P**			
	IVSC	IAC	Fellow IVSC	Fellow IAC	Normal	IVSC versus IVSC fellow eye	IAC versus IAC fellow eye	IVSC versus normal	IAC versus normal
BCVA (LogMAR)	0.46 (0.3, 0-2)	1.03 (1.35, 0.7-2)	0.02 (0, 0-0.1)	0 (0, 0-0)	0 (0, 0-0)	<0.001	<0.001	<0.001	<0.001
CMT (µm)	261 (257, 215-428)	146 (133, 104-201)	255 (252, 238-281)	243 (245, 213-270)	230 (237, 208-243)	>0.9	<0.001	>0.9	<0.001
SFCT (µm)	320 (294, 124-491)	247 (238, 157-356)	353 (366, 305-386)	382 (385, 311-460)	334 (328, 230-438)	0.784	<0.001	0.534	0.047
FAZ (mm^2) 3 mm	0.29 (0.27, 0.13-0.89)	0.38 (0.37, 0.06-0.70)	0.29 (0.27, 0.18-0.45)	0.31 (0.32, 0.18-0.39)	0.25 (0.31, 0.07-0.38)	>0.9	0.50	>0.9	>0.9
Density (%)									
SCP	46 (47, 34-51)	43 (41, 37-51)	48 (48, 45-54)	49 (50, 43-52)	49 (49, 43-54)	0.990	0.042	0.115	0.047
DCP	48 (50, 36-58)	44 (44, 34-55)	53 (50, 49-60)	54 (53, 51-60)	52 (53, 47-59)	0.028	0.038	0.025	0.042
Density (%) CC	64 (68, 23-75)	64 (65, 56-70)	68 (69, 64-71)	69 (69, 65-73)	68 (68, 50-76)	>0.9	>0.9	0.127	0.197
Flow area at CC	2.16 (2.17, 1.41-2.64)	1.92 (1.93, 1.61-2.21)	2.17 (2.14, 2.08-2.13)	2.17 (2.20, 1.91-2.31)	2.24 (2.25, 1.74-2.55)	>0.9	0.496	0.025	0.015

**P*: Based generalized estimating equation model. BCVA: Best-corrected visual acuity, CC: Choriocapillaris, CMT: Central macular thickness, FAZ: Foveal avascular zone, DCP: Deep capillary plexus, SCP: Superficial capillary plexus, SFCT: Subfoveal choroidal thickness, IVSC: Intravenous systemic chemotherapy, IAC: Intra-arterial chemotherapy

According to deep capillary density (DCD), there was a significant difference between the IVSC group and the IAC group, and the corresponding control groups ($P < 0.05$ for all) [Table 3].

In the treated groups, the VD of CC was lower than in the fellow eye groups and the normal control group, although this difference was not significant in the pairwise comparison between the groups [Table 3].

Discussion

The current research showed pronounced retinal and choroidal structural and vascular damage after chemotherapy in patients undergoing IAC. We observed a marked decline in DCD in both the treatment groups (IVSC and IAC groups) and a significant SCD reduction in comparison with the control groups in IAC-treated eyes. While the CMT and SFCT were lower in the IAC group in comparison with the IAC fellow eye and normal groups, this study could not specify any remarkable difference in CMT and SFCT between the IVSC group and the control groups.

Using EDI-OCT, some studies have shown that RB therapy can cause retinal andchoroidal injuries.[18] Using OCTA, the toxic effects of IVSC on retinal capillary plexuses and CC have been documented.[21] They documented no difference in treated versus fellow eye and normal control eyes in CMT, choroidal thickness, superficial and deep FAZ, or SCD.[21] To the best of the author's knowledge, our study is the first to evaluate the microvascular changes of the retina and choroid in RB patients after IVSC and IAC with or without local adjunctive therapies.

Comparable to the research of Sioufi *et al*., in terms of CMT and SFCT, the IVSC group had no significant differences from the control groups.[21] We observed less CMT and SFCT in the IAC group relative to the control groups. Decreased macular thickness after IAC has been reported in some other studies.[27,28] This may be attributed to reduced macular perfusion as well as choroidal atrophy or direct macular toxicity.[21,27-30]

Interestingly, the eyes in the IVSC group had the highest mean CMT compared to the other groups even more than the normal control group, without reaching statistical significance. Intraocular tumors of any type may cause macular edema due to the blood–ocular barrier breakdown.[31] We believed that this breakdown could be enhanced and would remain permanent after systemic chemotherapy as in our series 6–7 years after treatment. This claim remains to be determined in future studies. In accordance with other studies, we did not document any difference in the FAZ of the treated eyes compared to the control eyes.[13]

We had nonhomogeneous treated groups, regarding this point that quality OCTA acquisition was not possible in 8 IAC and 2 VEC eyes. This may be due to highly retinal destructive changes that have occurred in these treated patients precluding proper fixation and measurements.

Sioufi *et al*. showed that DCD is less in the IVSC group compared with the normal fellow eye and normal control groups.[21] In our series, although the IAC resulted in less measures, the DCD was apparently less than control fellow eyes, in both the treatment groups.

The standard protocol for RB systemic chemotherapy includes VEC protocol. These drugs have not yet been reported to cause direct ocular toxicity in RB patients. In contrast, it has been shown that melphalan, topotecan, and carboplatin used for IAC have more toxic vasculopathy.[21,29,32]

There may be several mechanisms to explain post-IAC choroidal thinning and also the reduction of SCD and DCD in this study in accordance with others.[32,33] Possible reasons include chemotherapy agent-related, dose, concentration, and PH-related vascular toxicity. Chemotherapy-related thrombosis and mechanical vasospasm are already reported.[27] Although pharmacokinetics and potential toxicity of melphalan to the eye are unclear, its instability and poor solubility may be potentially the cause of retinal and CC vessel toxicity at high concentrations.[33]

The potential toxicity of melphalan to primate choroidal vascular tissue has been reported to be due to leukostasis, retinal and choroidal artery occlusion, and birefringent intravascular drug precipitation.[28] Transient arterial precipitates in the retinal vessels also have been shown in an animal model study by Wilson *et al*.[29] Later on, these precipitates were reported in a patient receiving a lower dose of the chemotherapy drugs during the IAC.[30]

IAC-induced vasospasm, probably due to pulsatile injection, might be the other reason for choroidal and retinal ischemia.[27] The pulsatile injection can increase the turbulent flow of the vascular wall and the shearing stress[27,34] and subsequent intimate hyperplasia and internal elastic laminate fracture.[28] Vascular damage of any type and cause and extravasation of a chemotherapy agent and more concentrated condition of the drug in the retinal and choroidal stroma will cause some gliotic, fibrotic, and cicatricial changes that would impair the cell-to-cell talk or connection causing a vicious circle of functional deterioration.

In addition, in the IVSC group, only DCD was significantly lower compared to the fellow eye groups as well as the normal control group, but SCD remained unchanged. Likewise, Sioufi *et al*. revealed less DCP level in IVSC patients.[21] Furthermore, our analysis indicates more influence of IAC on both SCD and DCD in comparison with both IAC fellow eyes and normal eyes. The DCP was shown to be connected to the SCP by vertically ascending anastomoses and vortex-like channels.[35] This capillary plexus is likely to be terminal vessels and seems to be more susceptible to any ischemic stress than superficial counterparts, equivalent to terminal capillaries in other end organs, such as the kidney.[35,36]

Compared to IAC, IVSC delivers a small dose of chemotherapy agents to the retina and probably causes lower turbulence of the bloodstream in the retina and choroidal circulation. It seems that, relative to DCP, SCP is crucial to maintain blood circulation.[21,35] Higher blood flow disorders, repeated ischemic attacks of the retina and choroid due to intentional occlusion of the ophthalmic artery during IAC, and higher doses of chemotherapy drugs may explain the damage to all SCP, DCP, and choroidal circulation.

It is impossible to rule out the direct effect of the tumors on macular microvasculature. Some tumor-related growth factors in some intraocular malignancies can lead to macular ischemia and other toxic effects.[37,38] Actually, it seems that chemotherapy plays a more important role in the development of ischemia than the tumor itself.

Certainly, there are some limitations to this study. First, the number of cases between the groups is heterogeneous, although we have partially compensated for this heterogeneity by statistical methods. Larger studies should be necessary to validate these results. Second, poor image quality due to children's poor cooperation and different moving and blinking artifacts may be another potential limitation that precludes obtaining quality images. In the IAC category, eight eyes were excluded from the final analysis while most of them had severe retinal atrophy. While this has contributed to a small sample size in the IAC population in our study, this finding can also suggest the extremely destructive effect of the IAC. Third, tumor consolidation therapies such as TTT and cryotherapy may have some effects on macular microvasculature, though we chose patients who had extramacular tumors. Furthermore, intravitreal chemotherapy was done for about one-fourth of cases in each treatment group that may have some effects on choroidal and retinal microvasculature. We suggest evaluating the effect of different intravitreal chemotherapy agents on retinal and choroidal vasculature in feature studies. Fourth, some other factors such as axial length and refractive error,[39] the duration of the tumor before primary diagnosis which may also affect the capillary density, and FAZ measurements were not controlled in this study. Finally, we did not evaluate retinal vasculature status at baseline and its alteration over time. These data would be valuable to determine the initiation time of vascular damage and plan further treatments. This concept should be evaluated in future prospective studies. Noteworthy, the retrospective nature of the current study limits its result-derived conclusions, and perhaps with the introduction of handheld OCTA, prospective investigations in children with RB might be more feasible. Therefore, OCTA may 1 day be useful in assessing treatment response and residual tumor.[40,41]

In summary, OCTA has demonstrated retinal microvascular changes at the level of the SCP and DCP, as well as in choroidal circulation. These damages are significant with IAC for the eyes with extramacular RB, which may be related to applied chemotherapy agents, especially melphalan during the IAC procedure. These findings should be taken into account when making decisions about the treatment of extramacular RB tumors, particularly for patients with good macular structure

with a single eye. Further clinical trials with a wider patient population will be needed to assess the clinical relevance of these results.

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Conflicts of interest

There are no conflicts of interest.

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