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Changes in Retinal Thickness on OCT from Intravitreal Melphalan

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Recurrent vitreous seeding in retinoblastoma is a primary cause for failed attempts at globe salvage treatment and resultant enucleation. However, 100% control of vitreous seeding with intravenous chemotherapy followed by intravitreal melphalan (IVM) has been described.¹ Despite the efficacy of treatment, IVM causes chorioretinal toxicity.¹ Limited studies have evaluated structural changes on imaging with IVM use. In our novel study, we quantified changes in central retinal thickness (CRT) on spectral-domain (SD) OCT before and after IVM injection.

This was a retrospective study performed at the Children's Hospital Los Angeles and approved by the institutional review board, adherent to the tenets of the Declaration of Helsinki. Included patients had retinoblastoma without macular tumor involvement treated with IVM injection for vitreous seeding. At Children's Hospital Los Angeles, OCT is used routinely during examination under anesthesia for retinoblastoma for the following indications: any child with positive or unknown serum *RBI* genetic testing as screening for so-called invisible or very small retinoblastoma tumors; monitoring of subclinical scar recurrence; laser application; toxicity after IVM injection, given that severe toxicity has been shown to cause significant retinal thinning by our group²; and classification of seeds. All patients had to have intraoperative SD OCT images of signal strength 7/10 or better before and after IVM injection. Only 5 of 11 patients who had before and after IVM images met the inclusion criteria.

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Author Contributions:

Conception and design: Narala, Kim, Hendargo, Berry

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Data collection: Lang, Le, Hendargo, Branco, Berry

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HUMAN SUBJECTS: Human subjects were included in this study. The human ethics committees at Children's Hospital Los Angeles approved the study. All research adhered to the tenets of the Declaration of Helsinki. Legal guardians provided the written informed consent.

No animal subjects were included in this study.

Automated and manual CRT measurements on SD OCT images before and after IVM injection were segmented by Leica Microsystems, Inc (Wetzlar, Germany). The internal limiting membrane and the outer margin of the retinal pigment epithelium were detected automatically, and CRT was computed as the difference between these 2 boundaries. The foveal center was detected automatically, and the average and standard deviation of thicknesses within each Early Treatment Diabetic Retinopathy Study sector were reported. Manual segmentation was performed for comparison. The B-scan containing the foveal center was selected, and the internal limiting membrane and the retinal pigment epithelium outer margin were traced manually. Then within the central foveal region, every third B-scan away from the foveal center was segmented. For parafoveal and perifoveal regions, every sixth B-scan was segmented to the edge of the macula. In this small cohort, statistical significance could not be determined.

Five eyes of 5 patients were included. Three patients had bilateral retinoblastoma (only 1 eye included) and 2 patients had unilateral retinoblastoma. Based on the International Intraocular Retinoblastoma Classification, 1 eye had group C retinoblastoma, 3 eyes had group D retinoblastoma, and 1 eye had group E retinoblastoma (all American Joint Committee on Cancer, Eighth Edition, tumor—node—metastasis classification of cT2b). All patients received systemic chemotherapy before IVM injection.¹ Mean patient age at first IVM injection was 512 days (range, 133–1005 days). The mean IVM dose given was 25 μg (range, 20–30 μg). The mean number of IVM injections was 2.8 per eye (range, 2–3 injections). Mean follow-up duration from the time of first IVM injection was 266 days (range, 21–532 days).

Based on the chorioretinal toxicity grading system by Munier,³ grades I, IV, and V toxicity developed in 2 eyes, 2 eyes, and 1 eye, respectively. Automated CRT was measured in 3 of 5 eyes, whereas all 5 eyes underwent manual CRT measurements. Mean automated CRT decreased from $316.87 \pm 21.41 \mu\text{m}$ (range, 296.55–339.23 μm) to $248.18 \pm 54.75 \mu\text{m}$ (range, 195.13–244.89 μm), and mean manual CRT decreased from $314.14 \pm 19.37 \mu\text{m}$ (range, 292.37–341.34 μm) to $243 \pm 89.52 \mu\text{m}$ (range, 127.03–332.61 μm) from before to after IVM injection.

Table S1 shows manual and automated CRT for all eyes (available at www.ophtalmologyretina.org). In the 2 eyes with grade 1 toxicity, mean manual CRT before and after IVM was $308.14 \pm 22.30 \mu\text{m}$ and $332.46 \pm 0.22 \mu\text{m}$, respectively. Mean automated and manual CRT decreased from $317.89 \pm 30.18 \mu\text{m}$ to $220.01 \pm 35.18 \mu\text{m}$ and from $320.85 \pm 28.98 \mu\text{m}$ to $211.53 \pm 24.86 \mu\text{m}$, respectively, in eyes with grade IV toxicity from before to after IVM. The 1 eye with grade V toxicity showed a decrease in manual CRT from 312.71 μm to 127.03 μm from before to after IVM injection. This eye received 2 injections, each a 30- μg dose.

To our knowledge, no other study has quantified changes in retinal thickness on SD OCT before and after treatment with IVM. With the more common use of IVM to treat seeding for retinoblastoma, it is important to understand its structural effects on the retina.

In our study, we found no significant difference overall in CRT on SD OCT before and after IVM injection with both automated and manual measurements. Although no significant difference was found, in eyes with grade IV and V chorioretinal toxicity, there is clinically evident thinning on SD OCT before and after IVM injection. Figure 1 demonstrates significant inner and outer retinal atrophy with loss of the foveal contour after IVM injection in a patient with grade V chorioretinal toxicity. In contrast, eyes with grade I chorioretinal toxicity showed no clinically evident retinal thinning on SD OCT. Given that grade IV and V toxicity by definition includes macular involvement, it is understandable that these eyes showed retinal thinning on OCT, whereas eyes with grade I toxicity, defined as involving less than 2 clock hours of the peripheral retina, did not.

Although other studies have not evaluated retinal thickness on SD OCT with use of IVM, Maidana et al⁴ evaluated submacular choroidal thickness OCT changes after intra-arterial melphalan chemotherapy in 9 eyes in patients with unilateral retinoblastoma. The subfoveal choroidal thickness was reduced in treated versus nontreated eyes.⁴ Sioufi et al⁵ compared OCT angiography findings of 10 eyes in 10 patients with bilateral retinoblastoma treated with intravenous chemotherapy 10 years before imaging with 10 fellow eyes of patients with unilateral retinoblastoma treated with chemotherapy and 10 age-matched normal eyes. The deep plexus capillary density was greater in the controls compared with the retinoblastoma fellow and tumor eyes, suggesting that the deep capillary plexus may be affected by systemic chemotherapy.⁵

The positive impact of IVM on children in terms of eye salvage is well documented.¹ Measurement of CRT on SD OCT may be a useful tool for monitoring the degree and progression of chorioretinal toxicity in patients treated with IVM injection. A weakness of our study was the small sample size resulting from the exclusion of any child with macular involvement and the exclusion of children with poor-quality images in which CRT could not be measured accurately.

Future studies are needed to assess further the retinal and choroidal anatomic and vascular changes in a larger cohort of patients treated with IVM. This may provide useful data to predict visual outcomes as well as to discover why certain patients are more predisposed to developing chorioretinal toxicity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and Acronyms:

CRT	central retinal thickness
IVM	intravitreal melphalan
SD	spectral-domain

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Figure 1.

Intraoperative spectral-domain OCT images obtained (**A**) before and (**B**) after intravitreal melphalan (IVM) injection from a patient with grade V chorioretinal toxicity showing significant inner and outer retinal atrophy with retinal thinning after IVM injection. (Patient case, but not images, published previously.²)