

# Swept-Source Optical Coherence Tomography in Preschool Children with a History of Treated or Spontaneously Regressed Retinopathy of Prematurity

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## Research Article

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# Abstract

**Purpose:** To evaluate the best-corrected visual acuity (BCVA), the spherical equivalent (SE), the central, parafoveal, and perifoveal macular thickness results of the children with a history of treated or spontaneously regressed retinopathy of prematurity (ROP).

**Methods:** 79 right eyes of 79 children at the age of 5 years old were included in this cross-sectional observational study. 24 infants who received intravitreal bevacizumab (IVB) were in group 1, 27 infants who underwent laser photocoagulation (LPC) were in group 2 and 28 infants who had spontaneous regression were in group 3. Central foveal thickness (CFT) and the thicknesses of four parafoveal and four perifoveal quadrants as superior, temporal, inferior, and nasal were analyzed by using swept-source optical coherence tomography (SS-OCT).

**Results:** BCVA was significantly better ( $p=0.002$ ) and the SE was significantly higher in group 3 than in both groups 1 and 2 ( $p=0.033$ ). CFT was significantly lower in group 3 than in both groups 1 and 2 ( $p<0.001$ ). The parafoveal average, temporal, inferior, and nasal thickness values; the perifoveal average, superior, temporal thickness results were significantly higher in group 2 than in both groups 1 and 3 ( $p=0.003$ ,  $p=0.002$ ,  $p=0.009$ ,  $p=0.009$ , respectively), ( $p=0.003$ ,  $p<0.001$ ,  $p=0.007$ , respectively).

**Conclusion:** CFT was significantly higher in infants who had treatment for ROP. Parafoveal and perifoveal retinal thicknesses in certain quadrants were higher in those receiving LPC treatment than the others. CFT was negatively correlated with both gestational age and birth weight. Myopia was seen more often in children who had treatment.

## Introduction

Retinopathy of prematurity (ROP) is a sight-threatening, vaso-proliferative disorder of preterm infants especially with low birth weights (BW). Ablation of the peripheral avascular retina with laser photocoagulation (LPC) was accepted as the gold standard treatment method to prevent cicatricial complications of ROP [1]. The more recent Bevacizumab Eliminates the Angiogenic Threat of ROP (BEAT-ROP) study showed that intravitreal anti-vascular endothelial growth factor (VEGF) agents are the useful alternatives for the treatment of premature infants with stage 3 + ROP and also more favorable for Zone 1 ROP [2].

There are studies analyzing the macular development of premature infants with spectral-domain optical coherence tomography (SD-OCT) [3–7]. Swept-source OCT (SS-OCT) is a new modality that provides high-density raster scans with a longer wavelength light source that has a deeper resolution [8, 9]. SS-OCT was used to examine both retina and choroid in patients with a history of ROP in more recent studies [10–12].

In this study, we aimed to evaluate the refractive errors and the best-corrected visual acuity (BCVA) and to examine the central, parafoveal, and perifoveal macular thickness results of the children at the age of 5 years old with a history of treatment (with anti-VEGF or LPC) or spontaneously regressed ROP by using an SS-OCT device.

## Methods

This cross-sectional observational study was performed at the ophthalmology clinic of Zeynep Kamil Maternity and Children's Diseases Training and Research Hospital, with approval from the Institutional Review Board (Approval number: 2018/163). The study adhered to the tenets of the Declaration of Helsinki and informed consent was obtained from the parents of all children included in this study.

79 right eyes of 79 children were included in this study. All children were at the age of 5 years old when the ophthalmic examinations were performed. Children with the complications of ROP such as retinal detachment, macular dragging, or macular folds; a history of an ophthalmic surgery were not included. Media opacities or poor cooperation of the patient that cause low signal strength in OCT images were also excluded.

Children were analyzed in 3 groups: the infants who received intravitreal bevacizumab (IVB) injection were included in the first group, the infants who underwent LPC in the second group, and the infants who were followed up without treatment and had spontaneous regression in the third group.

The fundus examinations and the follow-up of the infants with ROP were performed according to the universal screening guidelines [13]. Early Treatment for Retinopathy of Prematurity (ET-ROP) [1] and BEAT-ROP [2] study recommendations were used for the treatment decision of the eyes with ROP. IVB treatment was applied to the eyes with zone I or posterior zone II disease and LPC was performed to eyes with anterior zone II disease. Parents of the children who were decided to be treated with IVB were informed about the possible side effects and the treatment complications of bevacizumab.

All patients underwent a complete ophthalmic examination, including BCVA, fundoscopy, and OCT imaging. Cycloplegic refraction was examined by a handheld autorefractometer (HandyRef-K Autorefractometer; Nidek, Gamagori, Japan) followed by retinoscopy to confirm the results. BCVA values were converted to the logarithm of minimal angle of resolution (logMAR) for the statistical analysis. Spherical equivalent (SE) results were recorded. An SS-OCT (Deep Range Imaging OCT; Topcon, Tokyo, Japan) device was used for the OCT imaging. This SS-OCT device provides 100 000 A-scans per second, uses a 1050-nm wavelength light source. It has an 8  $\mu\text{m}$  depth resolution and a 20 $\mu\text{m}$  transverse resolution. A 12 $\times$ 9 mm (wide-angle) scan setting was used to examine all the eyes included. The distance between the internal limiting membrane and retinal pigment epithelium was measured to obtain the central foveal thickness (CFT). The retinal map image displays the retinal thickness in nine locations defined by the Early Treatment Diabetic Retinopathy Study as a central foveal area, four parafoveal and four perifoveal locations as superior, temporal, inferior, and nasal quadrants. The thickness of the central 1mm area on the macular map was recorded as CFT. The averages of both parafoveal and perifoveal quadrants were also calculated (Fig. 1).

## Statistical analysis

Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS) 28.0 Version (IBM Corporation, New York, USA). Mean, standard deviation, median, minimum, maximum value, frequency, and percentage were used for descriptive statistics. The distribution of variables was checked with the Kolmogorov-Smirnov test. ANOVA (Tukey test) and Kruskal-Wallis (Mann-Whitney U test) were used for the comparison of the quantitative data. The Chi-Square test was used for the comparison of the qualitative data. P-value < 0.05 was considered statistically significant.

## Results

This cross-sectional observational study includes 79 right eyes of 79 children at the age of 5 years old. Group 1 included 24 infants who received IVB injection, group 2 included 27 infants who underwent LPC treatment and group 3 included 28 infants who were followed up without treatment and had spontaneous regression. Demographic and clinical characteristics of the children are shown in Table 1.

Table 1  
Demographic and clinical characteristics of the groups

Variables	Group 1 (n = 24)		Group 2 (n = 27)		Group 3 (n = 28)		P value	P value	P value	P value
	Mean ± SD n-%	Median	Mean ± SD n-%	Median	Mean ± SD n-%	Median				
<b>GA at birth, weeks</b>	27.9 ± 2.9	27.0 <sup>23</sup>	29.0 ± 2.0	29.0 <sup>3</sup>	31.4 ± 1.9	31.0	< <b>0.001<sup>K</sup></b>	<b>0.038</b>	< <b>0.001</b>	< <b>0.001</b>
<b>BW, grams</b>	1001.7 ± 293.5	940 <sup>23</sup>	1257.2 ± 333.7	1255 <sup>3</sup>	1607.7 ± 401.6	1640	< <b>0.001<sup>A</sup></b>	<b>0.029</b>	< <b>0.001</b>	<b>0.001</b>
<b>Sex, male/female</b>	12/12 50.0%/50.0%		9/18 33.3%/66.7%		13/15 46.4%/53.6%		0.440 <sup>X<sup>2</sup></sup>	0.227	0.797	0.322
<b>Treatment time, weeks</b>	35.1 ± 2.2	35.0	37.8 ± 2.2	38.0			< <b>0.001<sup>K</sup></b>			
<b>BCVA, logMAR</b>	0.21 ± 0.21	0.15 <sup>3</sup>	0.16 ± 0.13	0.20 <sup>3</sup>	0.06 ± 0.11	0.00	<b>0.002<sup>K</sup></b>	0.599	<b>0.002</b>	<b>0.003</b>
<b>Refractive error, SE</b>	-0.29 ± 2.24	0.00 <sup>3</sup>	-0.62 ± 3.61	-0.30 <sup>3</sup>	1.09 ± 1.46	1.00	<b>0.033<sup>K</sup></b>	0.895	<b>0.035</b>	<b>0.019</b>
<b>Zone I</b>	4 (16.7%)		0 (0.0%)		0 (0.0%)		< <b>0.001<sup>X<sup>2</sup></sup></b>	1	<b>0.013</b>	<b>0.008</b>
<b>Zone II</b>	20(83.3%)		27(100.0%)		20(71.4%)					
<b>Zone III</b>	0 (0.0% <sup>3</sup> )		0 (0.0% <sup>3</sup> )		8 (28.6%)					
<b>Stage I</b>	0 (0.0%)		0 (0.0%)		21(75.0%)		< <b>0.001<sup>X<sup>2</sup></sup></b>	0.097	< <b>0.001</b>	< <b>0.001</b>
<b>Stage II</b>	3 (12.5%)		0 (0.0%)		7 (25.0%)					
<b>Stage III</b>	21(87.5% <sup>3</sup> )		27(100% <sup>3</sup> )		0 (0.0%)					
GA: gestational age; BW: birth weight; BCVA: best corrected visual acuity; log MAR: Logarithm of the Minimum Angle of Resolution;										
SE: Spherical equivalent; SD: standard deviation; <sup>A</sup> ANOVA (Tukeytest) / <sup>K</sup> Kruskal-wallis (Mann-whitney u test) / <sup>X<sup>2</sup></sup> Ki-kare test (Fischer test);										
<sup>2</sup> Difference with LPC Group p < 0.05; <sup>3</sup> Difference with Spontaneous Regression Group p < 0.05										

BCVA was significantly better in group 3 than group 1 (p = 0.002) and group 2 (p = 0.001) while the difference between groups 1 and 2 was not significant (p = 0.599). The SE was significantly higher in infants in group 3 than both the infants in group 1 (p = 0.035) and group 2 (p = 0.019). There was no significant difference between group 1 and group 2 (p = 0.895) (Table 1).

SS-OCT results showed a significant difference in CFT between the groups ( $p < 0.001$ ). CFT was significantly higher in infants in groups 1 and 2 than the infants in group 3 ( $p < 0.001$  and  $p < 0.001$ , respectively). The parafoveal average, temporal, inferior, and nasal thickness values were significantly higher in infants in group 2 than the infants in both group 1 and group 3 ( $p = 0.005$ ,  $p = 0.008$ ,  $p = 0.029$ ,  $p = 0.004$  and  $p = 0.020$ ,  $p = 0.003$ ,  $p = 0.015$ , and  $p = 0.035$ , respectively). The results and the comparison between the groups are shown in Table 2. The perifoveal average, superior, temporal thickness results were significantly higher in group 2 than in both group 1 and group 3 ( $p = 0.002$  and  $p = 0.049$ ,  $p < 0.001$  and  $p = 0.045$ ,  $p =$  and  $p = 0.041$  and  $p = 0.008$ , respectively). The perifoveal nasal thickness was significantly higher in both group 2 and group 3 than in group 1 ( $p = 0.017$  and  $p = 0.039$ , respectively). All perifoveal macular thickness results and comparisons between the groups are given in Table 2. There was no significant difference in SS-OCT results between the girls and the boys included in the study.

Table 2  
SS-OCT measurements of the eyes

Thickness ( $\mu\text{m}$ )	Group 1	Group 2	Group 3	P value	P value	P value	P value
	(n = 24)	(n = 27)	(n = 28)		Group 1	Group 1	Group 2
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD		Vs	Vs	Vs
					Group 2	Group 3	Group 3
<b>CFT</b>	280.3 $\pm$ 19.7	288.3 $\pm$ 21.1	254.7 $\pm$ 24.0	<b>&lt; 0.001<sup>A</sup></b>	0.394	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>
<b>Parafoveal</b>							
Average	295.5 $\pm$ 11.8	308.9 $\pm$ 18.8	297.9 $\pm$ 12.7	<b>0.003<sup>A</sup></b>	<b>0.005</b>	0.829	<b>0.020</b>
Superior	296.3 $\pm$ 16.3	307.9 $\pm$ 21.8	303.2 $\pm$ 14.3	0.072 <sup>A</sup>	0.058	0.349	0.589
Temporal	292.3 $\pm$ 15.8	305.9 $\pm$ 17.7	291.5 $\pm$ 13.5	<b>0.002<sup>A</sup></b>	<b>0.008</b>	0.978	<b>0.003</b>
Inferior	295.3 $\pm$ 15.0	308.0 $\pm$ 19.9	294.6 $\pm$ 16.8	<b>0.009<sup>A</sup></b>	<b>0.029</b>	0.990	<b>0.015</b>
Nasal	298.0 $\pm$ 14.5	314.0 $\pm$ 22.4	302.3 $\pm$ 12.8	<b>0.004<sup>A</sup></b>	<b>0.004</b>	0.643	<b>0.035</b>
<b>Perifoveal</b>							
Average	266.7 $\pm$ 13.9	281.8 $\pm$ 18.8	271.8 $\pm$ 13.0	<b>0.003<sup>A</sup></b>	<b>0.002</b>	0.466	<b>0.049</b>
Superior	258.1 $\pm$ 16.3	278.4 $\pm$ 19.1	268.3 $\pm$ 15.0	<b>&lt; 0.001<sup>A</sup></b>	<b>&lt; 0.001</b>	0.083	<b>0.045</b>
Temporal	262.5 $\pm$ 21.5	275.8 $\pm$ 21.7	260.0 $\pm$ 13.3	<b>0.007<sup>A</sup></b>	<b>0.041</b>	0.882	<b>0.008</b>
Inferior	272.2 $\pm$ 16.6	282.4 $\pm$ 23.5	273.6 $\pm$ 16.0	0.113 <sup>A</sup>	0.139	0.960	0.204
Nasal	274.1 $\pm$ 20.8	290.4 $\pm$ 21.6	285.4 $\pm$ 16.6	<b>0.033<sup>K</sup></b>	<b>0.017</b>	<b>0.039</b>	0.506
SS-OCT: swept source optical coherence tomography; CFT: central foveal thickness; SD: standard deviation; <sup>A</sup> ANOVA (Tukey test); <sup>K</sup> Kruskal-wallis (Mann-whitney u test)							

The correlation analysis showed that CFT was negatively correlated with both gestational age (GA) and BW ( $r = -0.521$ ,  $p < 0.001$  and  $r = -0.508$ ,  $p < 0.001$ , respectively) (Fig. 2).

## Discussion

The results of this study showed that CFT was significantly higher in infants treated with either IVB or LPC than the infants who had spontaneously regressed ROP while there was no difference between the infants who had IVB or LPC treatment. In addition to that, thicknesses of temporal, inferior, and nasal quadrants of parafovea were significantly higher in infants who had LPC treatment than the others who had IVB treatment or spontaneously regressed ROP. The thickness results of the perifoveal average and the superior and temporal quadrants were significantly higher in infants who had LPC treatment compared with the infants who had IVB treatment and who had spontaneously regressed ROP. And also, the perifoveal nasal thickness was significantly higher in both the infants who underwent LPC treatment and who had spontaneously regressed ROP than the infants who were treated with IVB. Besides these, we found that CFT was negatively correlated with both GA and BW.

It is known that the macular development begins during the 24th -26th weeks of gestation, continues after birth until 3 to 4 years of age, and the foveal development is the last to get completed [5]. Inner retinal cells migrate centrifugally and photoreceptors migrate centripetally during the normal duration of macular development [14–16]. This developmental process is affected by prematurity and particularly ROP. As a result of this interruption, a shallow fovea is seen, and also the presence of the inner retinal layers causes the increased retinal thickness [17]. This interrupted migration process might be accepted as the reason for the negative correlation between the CFT and both GA and BW we found in our study.

The severity of ROP, the LPC, and IVB treatments also affect the cellular migration of the retinal cells leading to increased CFT [5, 18–20]. Akula et al. reported that a larger parafoveal area was seen in the infants with more severe ROP and central outer nuclear layer thickness had increased with the severity of the ROP [21]. Ecsedy et al. found that CFT was thicker in the preterm infants with ROP who had LPC treatment than the preterm infants without the need of any treatment for ROP [22]. Lee et al. listed CFT from thickest to thinnest in their study group, as babies who were treated with IVB ± LPC, who were treated only with IVB, who had regressed ROP, and who were born preterm without ROP [19]. Similar to these reports, CFT was thicker in the infants who had treatment than the infants with regressed ROP but there was no significant difference between the LPC and IVB treatment groups in our study. Lee et al. reported that infants who had IVB treatment had thinner retinal thickness in parafoveal and perifoveal areas than the infants who had only LPC or combined LPC and IVB treatment [23]. They commented that the retinal damage and the inflammation caused by LPC could affect the foveal development by interrupting cellular migration. However, migration of the inner retinal cells continued in eyes that had IVB treatment and this process ended up with the thinner parafoveal and the perifoveal retina [23]. Similar to this report, certain quadrants of the perifoveal and parafoveal retina of the eyes that had IVB treatment were found thinner than the eyes that had LPC treatment in our study.

We know that the emmetropization process is interrupted in premature children and the development of myopia is one of the important problem of premature children with ROP [24]. According to the ET-ROP study, myopia and high myopia were seen more often in eyes that had LPC treatment than the eyes with regressed ROP [2, 25]. SE refractive outcomes of the children in the BEAT-ROP clinical trial at a mean age of 2 ½ years were evaluated and the results showed that increased myopia and high myopia were seen in the eyes which were treated with laser compared with the eyes which had IVB treatment [26]. Similar to that, the SE was significantly myopic in children who had treatment compared with the children who had spontaneously regressed ROP in our study. However, there was no significant difference between the LPC and IVB treatment groups.

Villegas et al. suggested that photoreceptor maturation may not depend on inner retinal layer migration and good visual acuity may be more related to cone receptor maturation in children who had a history of ROP [4]. They found a significant correlation between the refractive error and the visual acuity and reported that decreased BCVA was seen more often in myopic children [4]. Similar to their report, more emmetropic children in the spontaneously regressed ROP group had significantly better BCVA than the more myopic children in LPC and IVB treatment groups in our study.

This study had some limitations. First of all, it was a cross-sectional study. Secondly, a power calculation could not have been performed because only the patients who were followed-up in our clinic could have been included. Another limitation was that a group of children who had combined LPC and IVB treatment and also a control group including premature children without ROP could not have been evaluated. So, a prospective study including a larger number of patient groups with a long-term follow-up would give more informative results. Also, axial length and anterior segment parameters of the children that may affect the SS-OCT results were not examined in our study. Lastly, children who had poor cooperation for both ophthalmic and OCT examinations were excluded and this could be biased for the children with higher refractive errors and decreased visual acuity.

In conclusion, CFT was significantly higher in infants who had treatment for ROP. Some parafoveal and perifoveal retinal areas were found to be thicker in those receiving LPC treatment than those receiving IVB treatment. In addition, CFT was negatively correlated with both gestational age and birth weight. Myopia was seen more often in children who had treatment for ROP and this may affect the final visual acuity in these children.

## Declarations

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### Author Contributions:

All authors contributed to the study conception and design. Material preparation and data collection were performed by Osman Kizilay. Data analysis was performed by Ozge Pinar Akarsu Acar. The first draft of the manuscript was written by Ozge Pinar Akarsu Acar and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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**Ethics Approval:** *This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Zeynep Kamil Maternity and Children's Diseases Training and Research Hospital (19.12.2018/163).*

**Consent to Participate:** *Written informed consent was obtained from the parents of the children.*

**Consent to Publish:** *The authors affirm that parents of the child provided informed consent for publication of the image in Figure 1*

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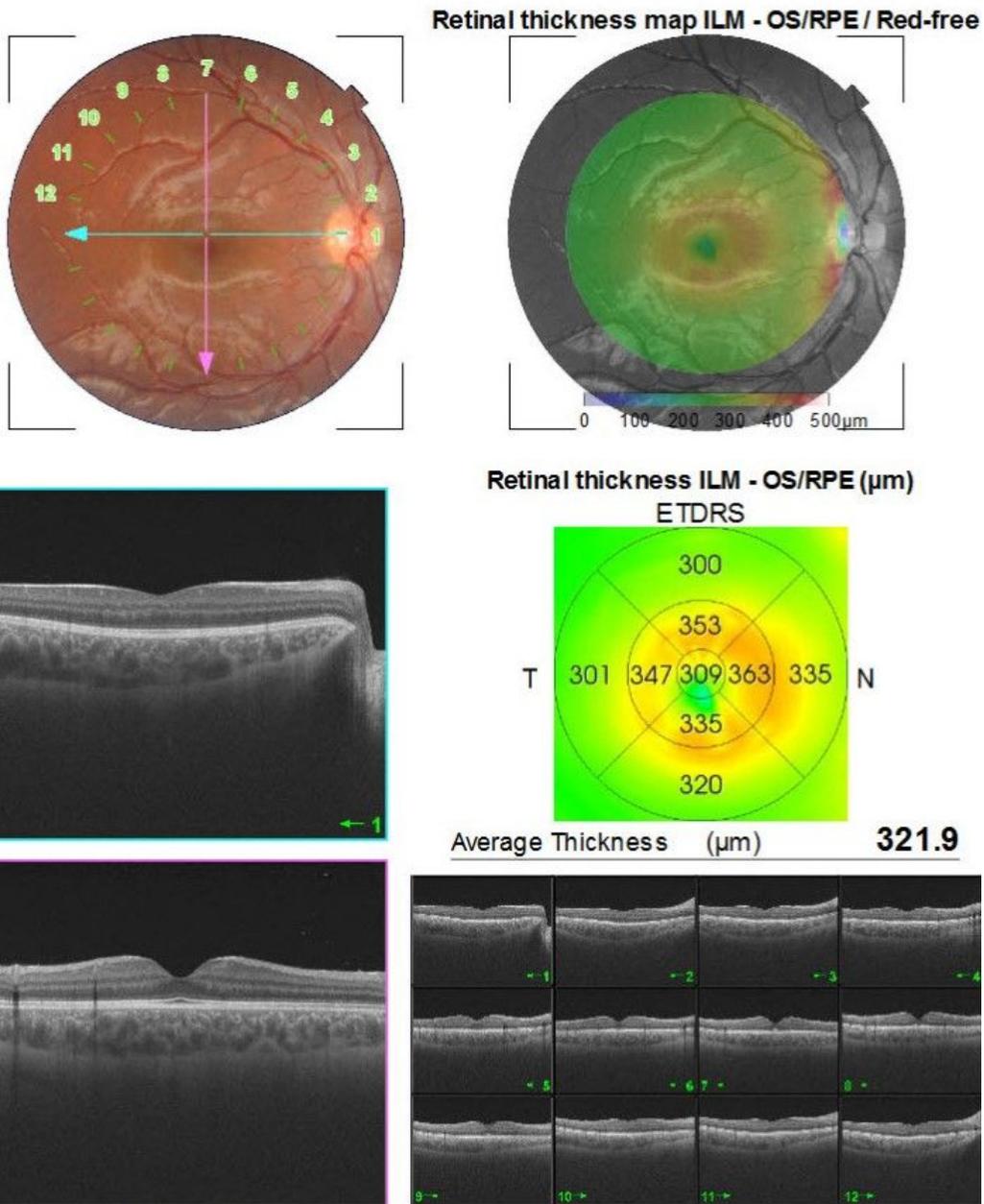
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## Figures

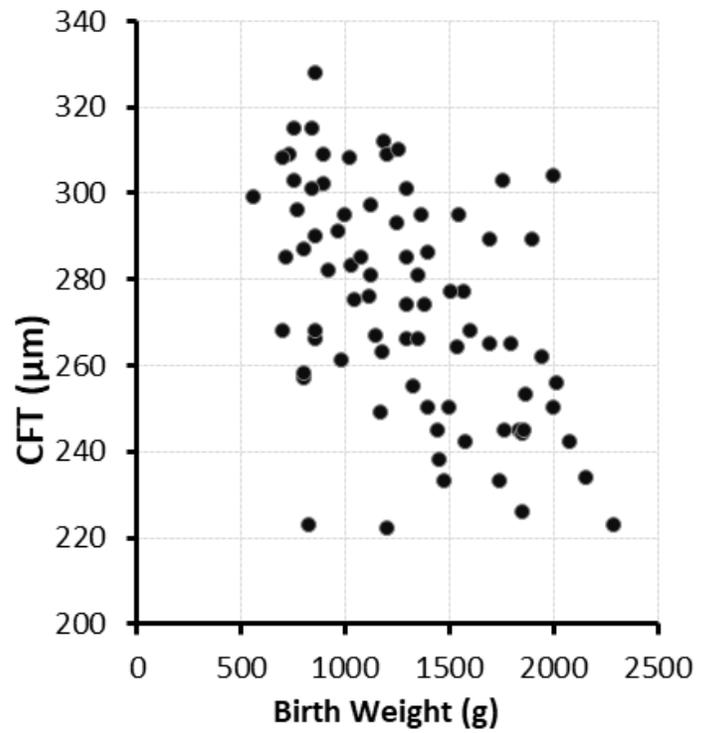
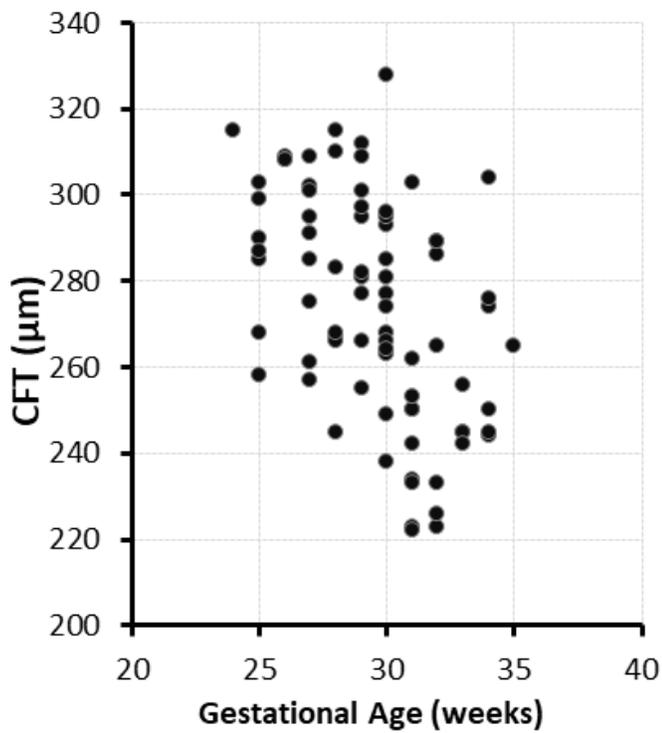
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TopQ Image Quality: **99** mode: Fine(2.0.7)  
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**Figure 1**

The swept-source optical coherence tomography image of a child at the age of 5 years old who had laser photocoagulation treatment for the retinopathy of prematurity



**Figure 2**

The plot on the left shows the negative correlation between the gestational age (GA) and the central foveal thickness (CFT) ( $r=-0.521$ ,  $p<0.001$ ) and the plot on the right shows the negative correlation between the birth weight (BW) and the CFT ( $r=-0.508$ ,  $p<0.001$ ) in children with retinopathy of prematurity