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Longitudinal Changes and Predictive Value of Choroidal Thickness for Myopia Control after Repeated Low-Level Red-Light Therapy

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Purpose: To evaluate longitudinal changes in macular choroidal thickness (mCT) in myopic children treated for 1 year with repeated low-level red-light (RLRL) therapy and their predictive value for treatment efficacy on myopia control.

Design: A secondary analysis of data from a multicenter, randomized controlled trial (RCT; NCT04073238).

Participants: Myopic children aged 8−13 years who participated in the RCT at 2 of 5 sites where mCT measurements were available.

Methods: Repeated low-level red-light therapy was delivered using a home-use desktop light device that emitted red-light at 650 nm. Choroidal thickness was measured by SS-OCT at baseline and 1-, 3-, 6-, and 12-month follow-ups. Visual acuity, axial length (AL), cycloplegic spherical equivalent refraction (SER), and treatment compliance were measured.

Main Outcome Measures: Changes in mCT at 1, 3, 6, and 12 months relative to baseline, and their associations with myopia control.

Results: A total of 120 children were included in the analysis (RLRL group: n = 60; single-vision spectacle [SVS] group: n = 60). Baseline characteristics were well balanced between the 2 groups. In the RLRL group, changes in mCT from baseline remained positive over 1 year, with a maximal increase of 14.755 μm at 1 month and gradually decreasing from 5.286 μm at 3 months to 1.543 μm at 6 months, finally reaching 9.089 μm at 12 months. In the SVS group, mCT thinning was observed, with changes from baseline of −1.111, −8.212, −10.190, and −10.407 μm at 1, 3, 6, and 12 months, respectively. Satisfactory myopia control was defined as annual progression rates of less than 0, 0.05, or 0.10 mm for AL and less than 0, 0.25, or 0.50 diopters for SER. Models that included mCT changes at 3 months alone had acceptable predictive discrimination of satisfactory myopia control over 12 months, with areas under the curve of 0.710−0.786. The predictive performance of the models did not significantly improve after adding age, gender, and baseline AL or SER.

Conclusions: This analysis from a multicenter RCT found RLRL induced sustained choroidal thickening over the full course of treatment. Macular choroidal thickness changes at 3 months alone can predict 12-month myopia control efficacy with reasonable accuracy.

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Myopia has become a prominent ocular disorder worldwide, with increasing prevalence and severity, particularly in East Asia.[1] Continuous myopia progression instigates myopic maculopathy and irreversible vision loss, which is fundamentally characterized by choroidal thinning.[2] According to animal and human research, the choroid plays an important role for regulating eye growth and refractive development.[3-10] Furthermore, macular choroidal thickness (mCT) has been identified as a potential predictor for treatment response to atropine eye drops and orthokeratology in myopic eyes.[11,12]

Repeated low-level red-light (RLRL) therapy has recently emerged as a treatment for myopia control with promising efficacy and safety. Our randomized controlled trial (RCT) found RLRL therapy reduced axial elongation and spherical equivalent refraction (SER) progression by 69.4% and 76.6%, respectively, when compared with single-vision spectacle (SVS) use over 12 months.[13] We also observed significant mCT thickening in the RLRL group, which invites speculation that choroidal thickening or increased blood flow could be the mechanism attributed to the effect on myopia control. If this holds true, the mCT

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thickening should be closely associated with the overall efficacy of the RLRL therapy.

To test this hypothesis, this study explored longitudinal changes in mCT after RLRL therapy over 12 months using data from the previous RCT and investigated their predictive value for myopia control efficacy.

Methods

Study Design

The current study is a secondary analysis of data from a multicenter RCT (ClincalTrial.gov identifier NCT04073238), of which the details have been published.[13] Briefly, a multicenter, parallel, randomized, single-blind clinical trial evaluated the 1-year efficacy and safety of RLRL therapy on myopia control among Chinese children aged 8 to 13 years. Myopic children with cycloplegic SER between −1.00 to −5.00 diopters (D), astigmatism $\leq$ 2.5 D, anisometropia $\leq$ 1.50 D, and best-corrected visual acuity $\geq$ Snellen 20/20 in either eye were enrolled from 5 study sites. Children with ocular or systemic diseases, or previous experiences with myopia control treatment, were excluded.

After screening, children were randomly assigned to an intervention or control group. All children wore SVSs throughout the study period for optical correction and updated their spectacles if needed. Children in the intervention group received RLRL therapy for 3 minutes per session, 2 sessions per day, with a minimum interval of 4 hours between sessions. This was to be done for 5 days per week, in addition to SVS. The control group only wore SVSs. Treatment compliance was recorded by a built-in automated diary function in the device. Follow-up visits were conducted at 1, 3, 6, and 12 months, respectively. Children enrolled at 2 study sites (Ouzhuang, Zhongshan Ophthalmic Center; and Zhujiang New Town, Zhongshan Ophthalmic Center), where the swept-source OCT (SS-OCT) instrument was available, were included in the current analysis.

This trial was conducted in accordance with recognized international standards including the Good Clinical Practice guidelines and ethical guidelines proposed by the Declaration of Helsinki. The protocol was approved by the Ethics Committee of Zhongshan Ophthalmic Centre (2019KYPJ093). All children provided verbal consent, and their parents/guardians provided written informed consent before participation.

Axial Length and Cycloplegic Refraction Assessment

Ophthalmic examinations were performed at baseline and all follow-up time points.[13] Uncorrected visual acuity and best-corrected visual acuity were assessed by an ETDRS visual acuity chart (Precision Vision). Axial length (AL) was measured by IOLMaster (Carl Zeiss 500, Meditec) before cycloplegia. Five readings, differences among them all less than 0.05 mm apart, were obtained and averaged. One drop of 0.5% Alcaine (Alcon) and 1 drop of 1% cyclopentolate (Alcon) at 0 minutes, followed by 2 more drops of 1% cyclopentolate at 5 and 20 minutes induced cycloplegia in both eyes. Cycloplegia was checked by the pupillary light reflex and pupil size 15 minutes after eye drops. Cycloplegic autorefraction was performed with an autorefractor (KR-8800, Topcon), and 3 readings of each eye were taken and averaged until the desired precision (0.25 D for spherical and cylinder power and 5 degrees for axis) was achieved. Spherical equivalent refraction was calculated as the spherical value plus half cylinder value.

OCT Imaging and Choroidal Thickness Measurement

OCT imaging was performed using a commercially available SS-OCT instrument (DRI-OCT Triton, Topcon). This instrument has a scanning speed of 100 000 A-scans per second with a light source of 1050 nm in wavelength. The axial and transverse resolutions are 8 μm and 10 μm, respectively. OCT imaging was carried out in a dark room after full cycloplegia to maximize the image quality and eliminate the effect of accommodation on choroidal thickness (CT).[14] The macula was scanned using the 12-line radial scan pattern with a resolution of 1024 × 12. Each image covered an area of 12 × 9 mm centered on the fovea with an average of 4 consecutive scan overlaps.

All images were checked, and mCT was automatically segmented using the OCT built-in software. Choroidal thickness was defined as the perpendicular distance between the outer choroid-sclera margin and the retinal pigment epithelium−Bruch's complex. The average mCT of the whole ETDRS 9 grid and central mCT (an area centered on the fovea with a diameter of 1 mm) was calculated with the built-in software. Automatic segmentation results were checked manually by the same investigator. Images were excluded from the analysis if the image quality score was less than 90, images were out of focus, or segmentation errors were observed.

Statistical Analyses

Data from the right eyes were analyzed unless they did not meet inclusion criteria; otherwise, data from the left eyes (n = 5) were analyzed. No imputation was performed for missing values. To ensure accuracy of the results, SER data without complete cycloplegia were excluded from this analysis. Changes in mCT, AL, and SER were calculated as a difference between baseline and each follow-up visit. Treatment compliance was defined as a percentage of completed sessions divided by the total number of assigned sessions (2 sessions per day, 5 days per week) during the entire treatment period. The satisfactory control effects at different cutoffs were defined according to previous reports with annual progression rates of less than 0, 0.05, or 0.10 mm for AL and less than 0, 0.25, or 0.50 D for SER.[15-17]

Continuous and categorical data were expressed as means with standard deviations and numbers with percentages, respectively. The baseline characteristics were compared by chi-square tests for gender and unpaired *t* tests for other characteristics. Changes in mCT, AL, and SER at each follow-up time point were compared using longitudinal mixed models, which were developed using a unstructured covariance matrix and restricted maximum likelihood method. Baseline age, gender, group, visit, group by visit interaction, and corresponding baseline parameter (mCT, AL, or SER) were included as fixed factors in the models, and subjects were included as a random factor. Multiple comparisons with sequential Bonferroni adjustment were performed. The estimated mean differences, 95% confidence intervals (CIs), and 2-sided *P* values were calculated.

Linear regression models assessed baseline factors associated with changes in average mCT over 12 months. Potential covariates included group, baseline age, gender, AL, SER, mCT, and treatment compliance. Factors with *P* values < 0.10 in univariate models were entered into the multivariate models. Linear and logistic regression models then determined factors that predicted AL and SER control over 12 months in the RLRL group. Baseline age, gender, AL, SER, and changes in mCT after 1 and 3 months were analyzed. To visualize the results, each 10-μm change in mCT was considered a 1-unit change in the regression models from which odds ratios (ORs) and 95% CIs were calculated. To access the

prediction performance of different models, receiver operating characteristic curve and area under the curve (AUC) quantified the predictive discrimination. A 2-sided P value < 0.05 was considered statistically significant. All statistical analyses were conducted using Stata version 15.1 (StataCorp LP) and R version 4.0.4 (R Foundation for Statistical Computing, www.R-project.org).

Results

Baseline Characteristics

A total of 162 children were enrolled from study sites where the OCT instrument was available. Among the 162 eligible children, 2 lacked baseline OCT data, 11 had no follow-up data, 6 had poor image quality, and 23 had segmentation errors. These children were excluded, leaving 120 children (74.07%) in the present analysis (RLRL group = 60 and SVS group = 60, Fig S1, available at www.aaojournal.org). No significant differences in baseline characteristics between included and excluded participants were noted ($P > 0.05$, Tables S1–S3, available at www.aaojournal.org). The distribution of baseline age, gender, AL, SER, uncorrected visual acuity, and average and central mCT was well balanced between the included SVS and RLRL groups ($P > 0.05$, Table 1).

Longitudinal Changes in mCT

As shown in Figure 1 and Table 2, change in average mCT relative to baseline significantly increased at 1 month with RLRL therapy, with an adjusted change of 14.755 μm (95% CI, 10.450–19.060). A mild decrease in the magnitude of choroidal thickening was noted at 3 and 6 months (5.286 μm, 0.978–9.594, and 1.543 μm, −3.470 to 6.556, respectively). Average mCT in the RLRL group was 9.089 μm (4.705–13.474) thicker at 12 months. A similar trend was observed in central mCT, with changes of 17.957 μm (12.569–23.344), 6.594 μm (1.203–11.985), −1.391 μm (−7.638 to 4.855), and 7.342 μm (1.857–12.827) after 1, 3, 6, and 12 months, respectively.

In the SVS group, average and central mCT significantly decreased. The adjusted changes in average mCT were −1.111 μm (−5.680 to 3.458) at 1 month, −8.212 μm (−13.194 to −3.231) at 3 months, −10.190 μm (−17.740 to −2.640) at 6 months, and −10.407 μm (−15.212 to −5.602) at 12 months. The respective adjusted changes in central mCT were −2.888 μm (−8.597 to 2.822), −11.109 μm (−17.320 to −4.897), −11.868 μm (−21.219 to −2.516), and −12.090 μm (−18.086 to −6.094).

By comparing the RLRL group with the SVS group, the mean differences in average mCT changes were 15.865 μm (5.419–26.312) at 1 month, 13.498 μm (2.539–24.458) at 3 months, 11.733 μm (−3.346 to 26.812) at 6 months, and 19.497 μm (8.676–30.318) at 12 months. Corresponding mean differences in central mCT changes were 20.845 μm (7.781–33.908), 17.703 μm (4.013–31.392), 10.476 μm (−8.235 to 29.187), and 19.432 μm (5.911–32.953).

Figure 2 presents representative cases of a pair of monozygotic twins who were randomly assigned to the RLRL and SVS groups. Over the course of 12 months, 1 twin treated with RLRL therapy showed persistent choroidal thickening, whereas the other showed choroidal thinning.

Table 1. Baseline Characteristics between the Repeated Low-Level Red-Light Group and the Single-Vision Spectacle Group

Characteristics	RLRL Group	SVS Group	P Value*
No. of subjects (eyes)	60 (60)	60 (60)	–
Age, yrs	10.52 (1.53)	10.37 (1.61)	0.590
Male, %	28 (46.67)	27 (45.00)	0.855
UCVA, logMAR	0.24 (0.13)	0.26 (0.16)	0.534
AL, mm	24.52 (0.68)	24.66 (0.89)	0.317
SER, D	−2.30 (0.85)	−2.58 (1.15)	0.153
Average mCT, μm	202.25 (46.43)	204.53 (47.90)	0.792
Central mCT, μm	215.31 (58.52)	215.50 (57.71)	0.985

Data are mean (standard deviation) or number (%).
AL = axial length; D = diopters; logMAR = logarithm of minimum angle of resolution; mCT = macular choroidal thickness; RLRL = repeated low-level red-light; SER = spherical equivalent refraction; SVS = single-vision spectacle; UCVA = uncorrected visual acuity.
*P values were calculated on the basis of unpaired t tests for continuous data and chi-square tests for categorical data.

Factors Associated with Changes in mCT over 12 Months

Table 3 summarizes baseline factors associated with 12-month changes in average mCT. Children in the RLRL group showed an average mCT change that was 19.59 μm (95% CI, 10.95–28.23, $P < 0.001$) thicker than in the SVS group. With each 1-mm increase in baseline AL, the amount of mCT change increased by 6.41 μm (0.67–12.16, $P = 0.029$; Fig S2, available at www.aaojournal.org). In the RLRL group, treatment compliance was the only factor significantly associated with choroidal thickening. For every percent increase in treatment compliance, 12-month changes in the average mCT increased by 0.31 μm (0.06–0.57, $P = 0.018$; Fig S3, available at www.aaojournal.org). In the SVS group, no significant associations with mCT changes persisted after multivariate adjustment ($P > 0.05$).

Initial mCT Changes with 12-Month Myopia Control Efficacy

In the RLRL group, baseline age and mCT changes at 1 and 3 months were associated with axial elongation over 12 months (Table 4). After adjusting for other confounding factors, 12-month changes in AL decreased by 0.05 mm (95% CI, −0.09 to −0.01, $P = 0.024$) and 0.06 mm (−0.09 to −0.04, $P < 0.001$) for each 10-μm increase in choroidal thickening at 1 and 3 months, respectively. Progression of SER over a 12-month period decreased by 0.12 D (less myopic, 95% CI, 0.05–0.19, $P = 0.001$) with each 10-μm increase in changes of mCT at 3 months.

A total of 19 children (33.33%), 25 children (43.86%), and 31 children (54.39%) had satisfactory myopia control when it was defined as annual AL elongation of less than 0 mm, 0.05 mm, and 0.10 mm, respectively. These proportions were 17 (33.33%), 25 (49.02%), and 34 (66.67%) when the definition was based on annual SER progression of less than 0 D, 0.25 D, and 0.50 D, respectively. Table 5 shows the factors predicting a satisfactory myopia control after 12 months with RLRL therapy. For all 6 criteria, only 3-month choroidal thickening was predictive of AL control (0 mm/yr: OR, 2.14, 1.30–3.54, $P = 0.003$; 0.05 mm/yr: OR, 1.82, 1.22–2.74, $P = 0.004$; 0.10 mm/yr: OR, 1.94, 1.25–3.02, $P = 0.003$) and SER control (0 D/yr OR, 1.92, 1.21–3.03, $P = 0.005$; 0.50 D/yr: OR, 1.84, 1.17–2.90, $P = 0.009$; 0.50 D/yr: OR, 1.69, 1.06–2.69, $P = 0.028$) after RLRL therapy.

Performance of Prediction Models

Figure 3 illustrates the AUCs for logistic regression models on predicting myopia control efficacy. Models that only included

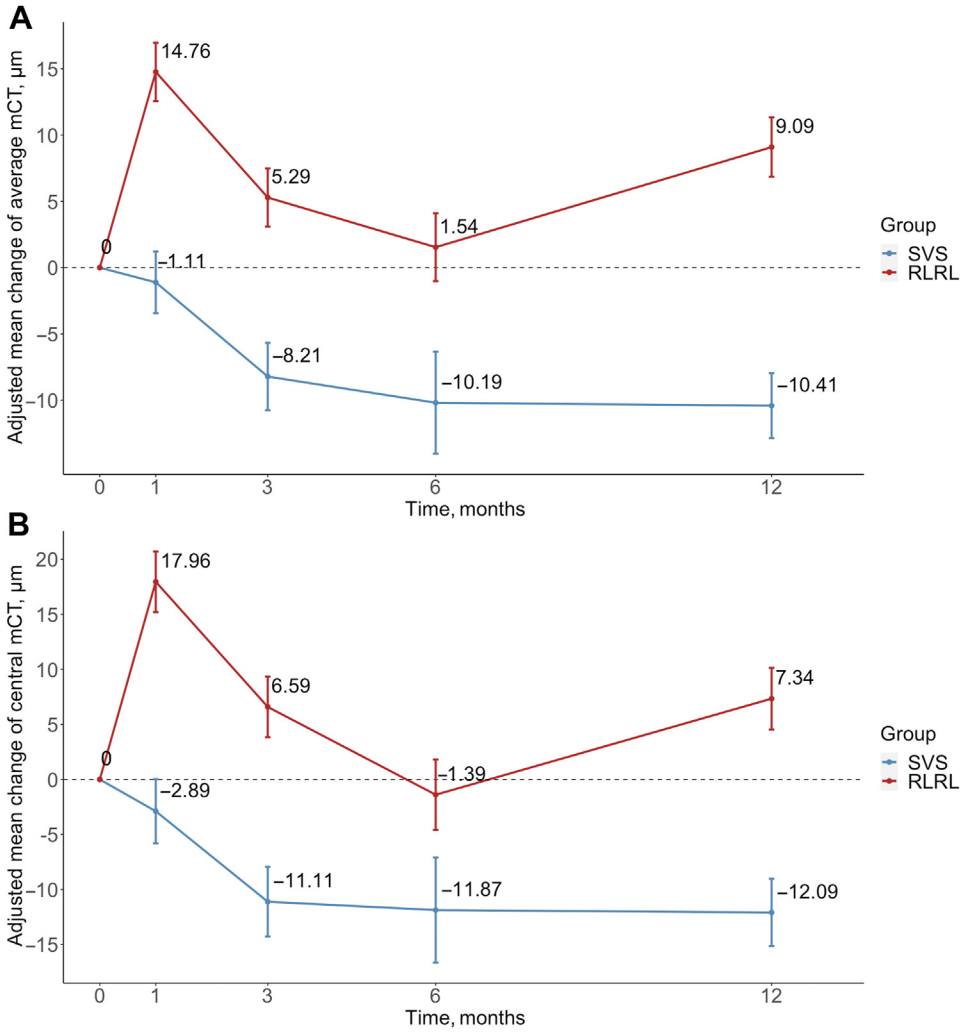

Figure 1. Cumulative adjusted changes in the **(A)** average macular choroidal thickness (mCT) and **(B)** central mCT against different time points in the single-vision spectacle (SVS) and repeated low-level red-light (RLRL) groups.

age, gender, and baseline AL (or SER) achieved AUCs of 0.623−0.759 (Model 1). Univariate logistic regression models that included 3-month mCT changes (Model 2) had AUCs of 0.786, 0.761, and 0.764 for predicting satisfactory AL control under the thresholds of 0 mm/yr, 0.05 mm/yr, and 0.10 mm/yr, respectively, whereas AUCs for predicting satisfactory SER control under the annual progression rates of 0 D, 0.25 D, and 0.50 D were 0.748, 0.765, and 0.710, respectively. After age, sex, and baseline AL (or SER) were incorporated into the models with 3-month mCT changes (Model 3), however, the predictive discrimination was only marginally and insignificantly improved compared with models with 3-month mCT changes alone (AUCs ranged from 0.740−0.865, all P values > 0.05). The adjusted R^2 for traditional model (age, gender, and baseline AL) were 16.4%, 7.47%, and 5.03% on predicting satisfactory AL control at the levels of less than 0 mm/year, 0.05 mm/year, and 0.10 mm/year, respectively. Corresponding adjusted R^2 increased to 33.4%, 21.1%, and 22.3% when mCT changes at 3 months were added to the model. Regarding satisfactory SER control, adjusted R^2 increased to 13.6% to 24.7% after 3-month mCT change was incorporated into the models with age, gender, and baseline SER (adjusted R^2 ranged from 3.65%−6.80%).

Discussion

This study reported the longitudinal changes in mCT among Chinese myopic children after 12 months of RLRL therapy in a multicenter RCT. Choroidal thickening was observed in the RLRL group and reached maximum thickening at 14.755 µm within 1 month, and positive improvements in mCT were observed thereafter until the RCT ceased at 12 months. Early macular choroidal thickening after commencing RLRL was significantly associated with myopia control efficacy at 12 months. Macular choroidal thickness changes at 3 months alone can predict 12-month myopia control efficacy with reasonable accuracy.

Choroidal Changes after RLRL Treatment

Macular choroidal thickness increased to its maximal magnitude at 1 month, and then the magnitude of the thickening reduced at 3 and 6 months, after which it showed a steady increase at 12 months. Of note, mCT values at all 4

Table 2. Adjusted Changes in Macular Choroidal Thickness, Axial Length, and Spherical Equivalent Refraction over 12 Months

	Cumulative Adjusted Mean (95% CI)*			
	RLRL Group	*SVS Group*	**Mean Difference (95% CI)***	***P* Value***
Average mCT, μm				
1 mo	14.755 (10.450–19.060)	−1.111 (−5.680 to 3.458)	15.865 (5.419–26.312)	**<0.001**
3 mos	5.286 (0.978–9.594)	−8.212 (−13.194 to −3.231)	13.498 (2.539–24.458)	**0.003**
6 mos	1.543 (−3.470 to 6.556)	−10.190 (−17.740 to −2.640)	11.733 (−3.346 to 26.812)	0.503
12 mos	9.089 (4.705–13.474)	−10.407 (−15.212 to −5.602)	19.497 (8.676–30.318)	**<0.001**
Central mCT, μm				
1 mo	17.957 (12.569–23.344)	−2.888 (−8.597 to 2.822)	20.845 (7.781–33.908)	**<0.001**
3 mos	6.594 (1.203–11.985)	−11.109 (−17.320 to −4.897)	17.703 (4.013–31.392)	**0.001**
6 mos	−1.391 (−7.638 to 4.855)	−11.868 (−21.219 to −2.516)	10.476 (−8.235 to 29.187)	1.000
12 mos	7.342 (1.857–12.827)	−12.090 (−18.086 to −6.094)	19.432 (5.911–32.953)	**<0.001**
AL, mm				
1 mo	−0.048 (−0.078 to −0.018)	0.013 (−0.020 to 0.046)	−0.061 (−0.135 to 0.013)	0.341
3 mos	−0.013 (−0.044 to 0.017)	0.099 (0.066–0.132)	−0.112 (−0.188 to −0.037)	**<0.001**
6 mos	0.063 (0.028–0.098)	0.227 (0.184–0.271)	−0.165 (−0.257 to −0.072)	**<0.001**
12 mos	0.122 (0.091–0.152)	0.379 (0.347–0.412)	−0.258 (−0.333 to −0.183)	**<0.001**
SER, D				
1 mo	0.056 (−0.023 to 0.135)	−0.008 (−0.095 to 0.080)	0.063 (−0.133 to 0.260)	1.000
3 mos	−0.013 (−0.093 to 0.066)	−0.199 (−0.290 to −0.109)	0.186 (−0.015 to 0.387)	0.117
6 mos	−0.096 (−0.186 to −0.005)	−0.399 (−0.512 to −0.285)	0.303 (0.061–0.544)	**0.002**
12 mos	−0.224 (−0.304 to −0.144)	−0.799 (−0.883 to −0.716)	0.575 (0.382–0.768)	**<0.001**

AL = axial length; CI = confidence interval; D = diopters; mCT = macular choroidal thickness; RLRL = repeated low-level red-light; SER = spherical equivalent refraction; SVS = single-vision spectacle. Boldface indicates statistical significance.
*Adjusted estimates at each time point were calculated on the basis of longitudinal mixed models, adjusted for baseline age, gender, group, visit, group × visit, and corresponding baseline parameter as fixed factors, and subjects as the random factor. Multiple comparisons with sequential Bonferroni adjustment were performed.

follow-up visits in the RLRL group were significantly greater than those in the SVS control arm. Although the reasons for reduced mCT thickening at 3- and 6-month visits are unknown, it is possible that this can be explained by a compromise on measurement accuracy secondary to poor participation at the 6-month visit (28.3% lost follow-up) due to the Coronavirus Disease 2019 pandemic. A clinical trial of 74 children aged 6 to 16 years observed that subfoveal CT increased by 23.23, 31.58, and 35.30 μm at 1, 3, and 6 months, respectively, after the administration of RLRL therapy (Table S4, available at www.aaojournal.org).[18] A case-series study demonstrated subfoveal CT increased by 45.33 μm after 9 months of RLRL treatment.[19] However, in these previous studies, retrospective design, limited sample size, and manual measurement from 1 single B-scan at a single subfoveal point inhibited the real mCT changes caused by RLRL therapy from being properly assessed. Of note, the magnitude of mCT changes observed in our study was less than those previously reported, which may derive from the different OCT devices, as CT measured on SS-OCT seems to be 5.9 to 49.3 μm thinner than that on spectral domain OCT.[20-25] Atropine 1%, atropine 0.05%, and a combination of atropine 0.01% and orthokeratology induced considerable increases in mCT, with a thickening of 27 μm, 21.20 μm, and 24.14 μm, respectively (Table S4).[11,12,14,18,26-31] Given the inconsistency in the study design, characteristic profiles of studied participants, instruments, and methods to measure mCT, direct comparison of the magnitudes of choroidal thickening between the aforementioned studies should be approached with caution.

Factors Associated with Choroidal Thickening

Treatment compliance was strongly associated with choroidal thickening after RLRL therapy, and this aligns with the observations of the Low-Concentration Atropine for Myopia Progression study, in which atropine induced choroidal thickening in a concentration-dependent manner.[14] For children whose treatment compliance increased from < 50% to > 75% in this study, the proportion of children with choroidal thickening (defined as an increase in mCT of at least 8 μm) after 12-month RLRL therapy increased from 33.3% (3/9) to 62.5% (15/24), and each percentage increase in compliance yielded a 0.31-μm improvement in mCT after 12 months. The observed dose–response curve provides evidence to support the causal effect of RLRL therapy on mCT. Its mechanism and pathway are under investigation and will be reported separately. Despite treatment compliance of at least 75%, choroidal thinning still occurred in 9 children, with no significant differences in baseline age, gender, AL, SER, or mCT among these children ($P > 0.05$). Reasons for this poor response are thus unknown and require further investigation.

Associations of Choroidal Thickness Changes and Treatment Efficacy

Choroidal thinning has been shown to be associated with the development of myopia, faster axial elongation, and the onset of myopic macular degeneration in previous

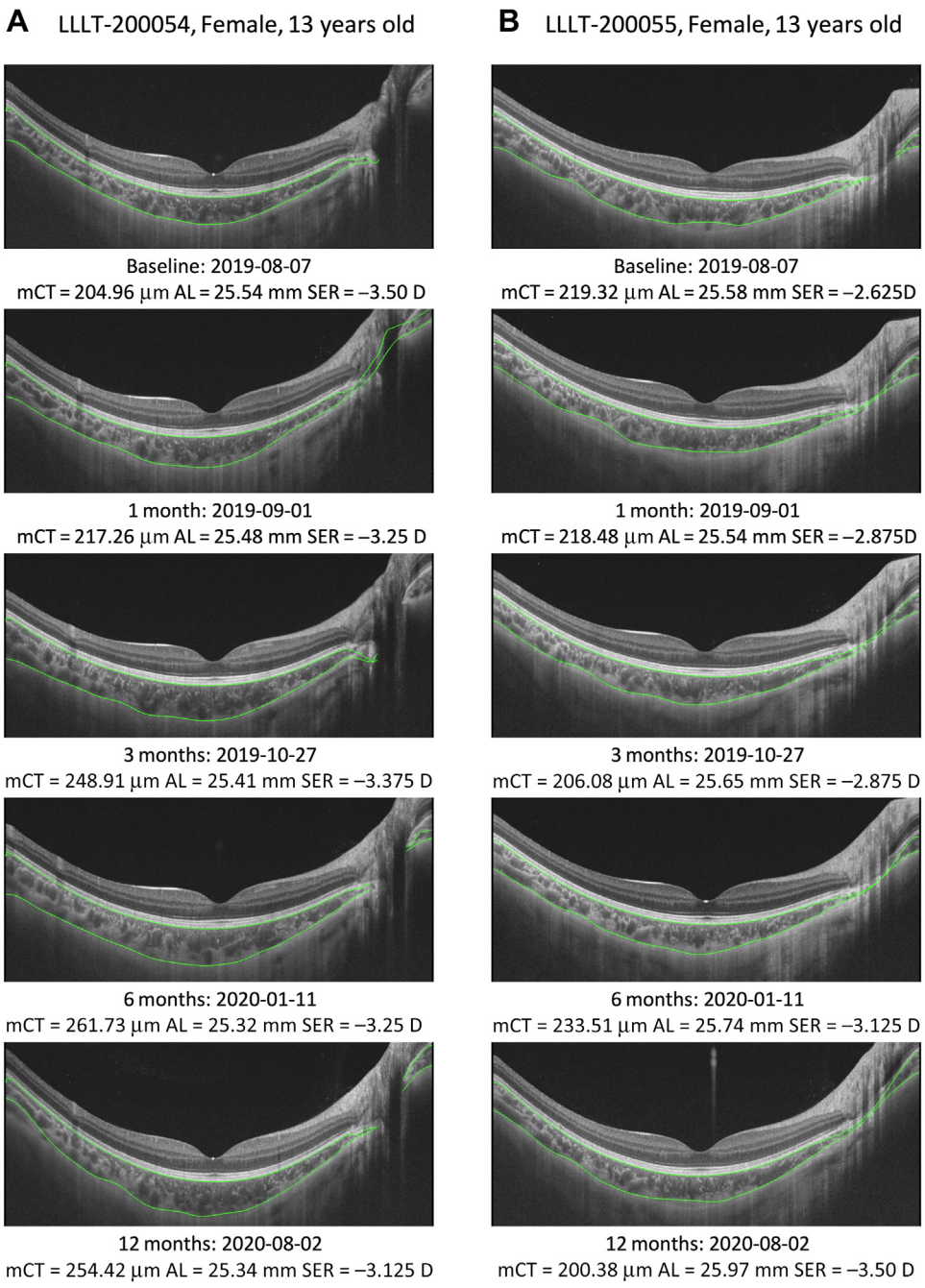

Figure 2. Representative cases of a pair of monozygotic twins. LLLT-200054 and LLLT-200055 were randomly allocated to the repeated low-level red-light (RLRL) and single-vision spectacle (SVS) groups, respectively. **A,** OCT images show macular choroidal thickening after 12 months of RLRL therapy. **B,** OCT images show macular choroidal thinning after 12 months of SVS treatment. AL = axial length; D = diopter; mCT = macular choroidal thickness; SER = spherical equivalent refraction.

observational studies,[3,7,9,10,32,33] indicating that mCT could be a potential biomarker of myopia. However, associations between mCT changes and myopia control efficacy have yet to be fully demonstrated in RCTs. After 2 years of low-dose atropine treatment, the associations between mCT changes and treatment efficacy were noted, with every 10-μm of CT increase associated with axial elongation reduction of 0.045 mm and SER progression control of 0.074 D.[14] Each 10-μm choroidal thickening after 1 week of atropine 1% reduced 6-month axial elongation by 0.016 mm, but the association between initial mCT changes and long-term SER progression was not mentioned.[11] Of note, in this study, we reported the associations between mCT changes as early as 1-month and 12-month axial elongation and SER progression after RLRL therapy. The effect of RLRL therapy on myopia control was thought to be

Table 3. Baseline Factors Associated with Changes in Average Macular Choroidal Thickness over 12 Months

	Univariate		Multivariate Model 1*		Multivariate Model 2*	
	β (95% CI)	P Value	β (95% CI)	P Value	β (95% CI)	P Value
Overall						
Age, yrs	2.83 (−0.44 to 6.10)	0.089	1.59 (−1.52 to 4.69)	0.313	2.05 (−0.98 to 5.07)	0.181
Male vs. female	−2.41 (−12.37 to 7.54)	0.631	-	-	-	-
Baseline AL, mm	**7.04 (1.08–13.00)**	**0.021**	**6.41 (0.67–12.16)**	**0.029**	-	-
Baseline SER, D	−2.40 (−7.17 to 2.38)	0.321	-	-	-	-
Baseline mCT, per 10 μm	**−1.10 (−2.16 to −0.03)**	**0.044**	-	-	−0.98 (−1.97 to 0.02)	0.054
Group (RLRL vs. SVS)	**19.24 (10.27–28.21)**	**<0.001**	**19.59 (10.95– 28.23)**	**<0.001**	**19.47 (10.78–28.16)**	**<0.001**
RLRL Group						
Age, yrs	1.72 (−3.00 to 6.44)	0.467	-	-	-	-
Male vs. female	−5.02 (−18.48 to 8.44)	0.456	-	-	-	-
Baseline AL, mm	8.28 (−1.22 to 17.77)	0.086	5.64 (−3.63 to 14.92)	0.226	-	-
Baseline SER, D	−4.47 (−12.41 to 3.47)	0.262	-	-	-	-
Baseline mCT, per 10 μm	−1.17 (−2.54 to 0.20)	0.092	-	-	−0.96 (−2.26 to 0.34)	0.142
Compliance, %	**0.35 (0.10–0.60)**	**0.008**	**0.31 (0.06–0.57)**	**0.018**	**0.33 (0.08–0.58)**	**0.012**
SVS Group						
Age, yrs	**3.98 (0.39–7.56)**	**0.031**	2.79 (−1.04 to 6.62)	0.148	3.02 (−0.98 to 7.03)	0.134
Male vs. female	−3.58 (−15.80 to 8.65)	0.557	-	-	-	-
Baseline AL, mm	**6.90 (0.89–12.90)**	**0.026**	5.02 (−1.43 to 11.48)	0.123	-	-
Baseline SER, D	**−4.88 (−9.68 to −0.08)**	**0.047**	-	-	−3.27 (−8.44 to 1.90)	0.208
Baseline mCT, per 10 μm	−1.12 (−2.50 to 0.25)	0.107	-	-	-	-

AL = axial length; CI = confidence interval; D = diopters; mCT = macular choroidal thickness; RLRL = repeated low-level red-light; SER = spherical equivalent refraction; SVS = single-vision spectacle. Boldface indicates statistical significance.
*The covariates in the multivariate linear models were variates with *P* values of 0.10 or less in the univariate models. SER, AL, and CT were separately included in model 1 and model 2 due to the collinearity.

mediated in part via choroidal thickening (adjusted R^2 in linear regression models ranged from 13% to 40% for mCT changes at 1 to 12 months), similar to that of atropine.[14] Choroidal signaling pathways may induce changes that mitigate scleral hypoxia and remodeling. Other ocular structures may be involved in the process of RLRL-induced myopia control; however, no significant changes in anterior segmental structures such as the cornea and the anterior chamber were observed.[13] Further animal experiments are necessary to uncover this process.

Table 4. The Relationship between Initial Changes of Macular Choroidal Thickness and the Efficacy of Controlling Axial Length and Spherical Equivalent Refraction over 12 Months in the RLRL Group

	Univariate Model		Multivariate Model 1*		Multivariate Model 2†	
	β (95% CI)	P Value	β (95% CI)	P Value	β (95% CI)	P Value
Change in AL						
Age, per 1 yr	**−0.07 (−0.11 to −0.03)**	**0.001**	**−0.06 (−0.10 to −0.01)**	**0.022**	**−0.05 (−0.09 to −0.01)**	**0.010**
Male vs. female	0.04 (−0.09 to 0.17)	0.538	0.09 (−0.06 to 0.24)	0.249	0.06 (−0.06 to 0.18)	0.312
Baseline AL, per 1 mm	−0.09 (−0.18 to 0.01)	0.070	−0.07 (−0.18 to 0.04)	0.196	−0.03 (−0.11 to 0.06)	0.545
1-m mCT change, per 10 μm	**−0.06 (−0.11 to −0.02)**	**0.009**	**−0.05 (−0.09 to −0.01)**	**0.024**	-	-
3-m mCT change, per 10 μm	**−0.06 (−0.09 to −0.03)**	**<0.001**	-	-	**−0.06 (−0.09 to −0.04)**	**<0.001**
Change in SER						
Age, per 1 yr	0.09 (−0.004 to 0.18)	0.059	0.10 (−0.02 to 0.21)	0.088	0.08 (−0.02 to 0.17)	0.102
Male vs. female	−0.08 (−0.37 to 0.20)	0.562	−0.08 (−0.41 to 0.24)	0.606	−0.09 (−0.35 to 0.18)	0.518
Baseline SER, per 1 D	−0.08 (−0.24 to 0.09)	0.341	−0.07 (−0.28 to 0.13)	0.478	0.03 (−0.12 to 0.19)	0.670
1-m mCT change, per 10 μm	0.05 (−0.06 to 0.15)	0.366	0.03 (−0.07 to 0.14)	0.530	-	-
3-m mCT change, per 10 μm	**0.11 (0.04–0.17)**	**0.003**	-	-	**0.12 (0.05–0.19)**	**0.001**

AL = axial length; CI = confidence interval; D = diopter; mCT = macular choroidal thickness; RLRL = repeated low-level red-light; SER = spherical equivalent refraction. Boldface indicates statistical significance.
*Multivariate model 1: Covariates were baseline age, gender, baseline AL/SER, and 1-month change in mCT. The adjusted R^2 of models using AL and SER change as independent factors was 0.31 and 0.05, respectively.
†Multivariate model 2: Covariates were baseline age, gender, baseline AL/SER, and 3-month change in mCT. The adjusted R^2 of models using AL and SER change as independent factors was 0.40 and 0.20, respectively.

Table 5. Predictors for the Satisfactory Control Effect on Axial Length and Spherical Equivalent Refraction at Different Cutoff in the RLRL Group

	Univariate Model		Multivariate Model*	
	OR (95% CI)	*P Value*	*OR (95% CI)*	*P Value*
Axial elongation < 0 mm per yr				
Age, per 1 yr	**1.86 (1.19–2.92)**	**0.006**	**1.99 (1.11–3.55)**	**0.020**
Male vs. female	1.70 (0.56–5.17)	0.351	1.55 (0.29–8.22)	0.609
Baseline AL, per 1 mm	**2.60 (1.03–6.54)**	**0.043**	1.76 (0.45–6.99)	0.419
1-m mCT change, per 10 μm	1.31 (0.86–1.99)	0.213	-	-
3-m mCT change, per 10 μm	**1.83 (1.23–2.74)**	**0.003**	**2.14 (1.30–3.54)**	**0.003**
Axial elongation < 0.05 mm per yr				
Age, per 1 yr	**1.56 (1.06–2.31)**	**0.025**	1.41 (0.86–2.31)	0.178
Male vs. female	0.92 (0.32–2.63)	0.881	0.63 (0.14–2.77)	0.541
Baseline AL, per 1 mm	1.60 (0.71–3.61)	0.261	1.22 (0.38–3.90)	0.740
1-m mCT change, per 10 μm	1.41 (0.92–2.16)	0.110	-	-
3-m mCT change, per 10 μm	**1.73 (1.18–2.52)**	**0.005**	**1.82 (1.22–2.74)**	**0.004**
Axial elongation < 0.10 mm per yr				
Age, per 1 yr	1.42 (0.98–2.07)	0.064	1.30 (0.78–2.18)	0.317
Male vs. female	0.71 (0.25–2.01)	0.514	0.42 (0.09–2.01)	0.280
Baseline AL, per 1 mm	1.38 (0.61–3.10)	0.439	1.24 (0.37–4.12)	0.724
1-m mCT change, per 10 μm	1.39 (0.91–2.11)	0.130	-	-
3-m mCT change, per 10 μm	**1.79 (1.20–2.66)**	**0.004**	**1.94 (1.25–3.02)**	**0.003**
SER progression < 0 D per yr				
Age, per 1 yr	1.40 (0.92–2.13)	0.115	1.46 (0.87–2.44)	0.153
Male vs. female	0.55 (0.16–1.81)	0.322	0.36 (0.08–1.65)	0.188
Baseline SER, per 1 D	0.65 (0.32–1.29)	0.217	0.89 (0.39–2.04)	0.779
1-m mCT change, per 10 μm	1.11 (0.73–1.69)	0.622	-	-
3-m mCT change, per 10 μm	**1.74 (1.16–2.61)**	**0.008**	**1.92 (1.21–3.03)**	**0.005**
SER progression < 0.25 D per yr				
Age, per 1 yr	1.07 (0.74–1.55)	0.714	1.04 (0.63–1.70)	0.878
Male vs. female	1.26 (0.42–3.80)	0.683	0.86 (0.21–3.57)	0.832
Baseline SER, per 1 D	0.60 (0.31–1.19)	0.144	0.71 (0.31–1.62)	0.416
1-m mCT change, per 10 μm	1.17 (0.78–1.76)	0.434	-	-
3-m mCT change, per 10 μm	**1.81 (1.19–2.77)**	**0.006**	**1.84 (1.17–2.90)**	**0.009**
SER progression < 0.50 D per yr				
Age, per 1 yr	1.38 (0.91–2.09)	0.127	1.45 (0.83–2.56)	0.193
Male vs. female	0.89 (0.28–2.86)	0.842	0.93 (0.21–4.18)	0.928
Baseline SER, per 1 D	0.60 (0.29–1.26)	0.179	0.97 (0.41–2.31)	0.953
1-m mCT change, per 10 μm	1.37 (0.86–2.20)	0.189	-	-
3-m mCT change, per 10 μm	**1.54 (1.03–2.32)**	**0.037**	**1.69 (1.06–2.69)**	**0.028**

AL = axial length; CI = confidence interval; D = diopters; mCT = macular choroidal thickness; OR = odds ratio; RLRL = repeated low-level red-light; SER = spherical equivalent refraction. Boldface indicates statistical significance.
*Multivariate model: Covariates were baseline age, gender, baseline AL/SER, and 3-month change in mCT.

Predictive Value of Choroidal Thickness for Treatment Efficacy

More notably, we demonstrated the predictive value of initial mCT changes for identifying the satisfactory myopia control efficacy over a long term. Previous myopia control studies had only assessed the associations between initial mCT changes and long-term axial elongation, but the discriminative ability of mCT changes for treatment efficacy had yet to be illustrated. For children treated with atropine 0.01%, 25.9% of 6-month AL changes could be explained by 1-week mCT change, age, gender, and the presence of peripapillary atrophy.[11] Likewise, 58.0% of 13-month changes in axial elongation after orthokeratology could be explained by 1-month mCT changes, baseline age, and 1-month changes in biometric measurements.[12] Three-month mCT changes alone could predict satisfactory RLRL treatment efficacy on both the AL and SER controls in this study, with AUCs of 0.710 to 0.786 and adjusted R^2 of 9.8% to 18.5%. Baseline demographic and refractive information did not contribute significantly to the improvement in predictive performance. Of note, 3-month mCT changes performed better in predicting satisfactory RLRL treatment efficacy on axial elongation than on SER progression. This discrepancy may be in part explained by the complexity of SER, which should be due to the combined effect of the cornea, crystalline lens, and AL. In addition, because 1-month mCT changes were associated with but not predictive of myopia control efficacy, this absence of predictability is likely from our limited sample size. Choroidal thickening as early as 1 month may also serve as a predictor of RLRL treatment efficacy on myopia control to optimize treatment strategies, but other studies on RLRL should seek to confirm this.

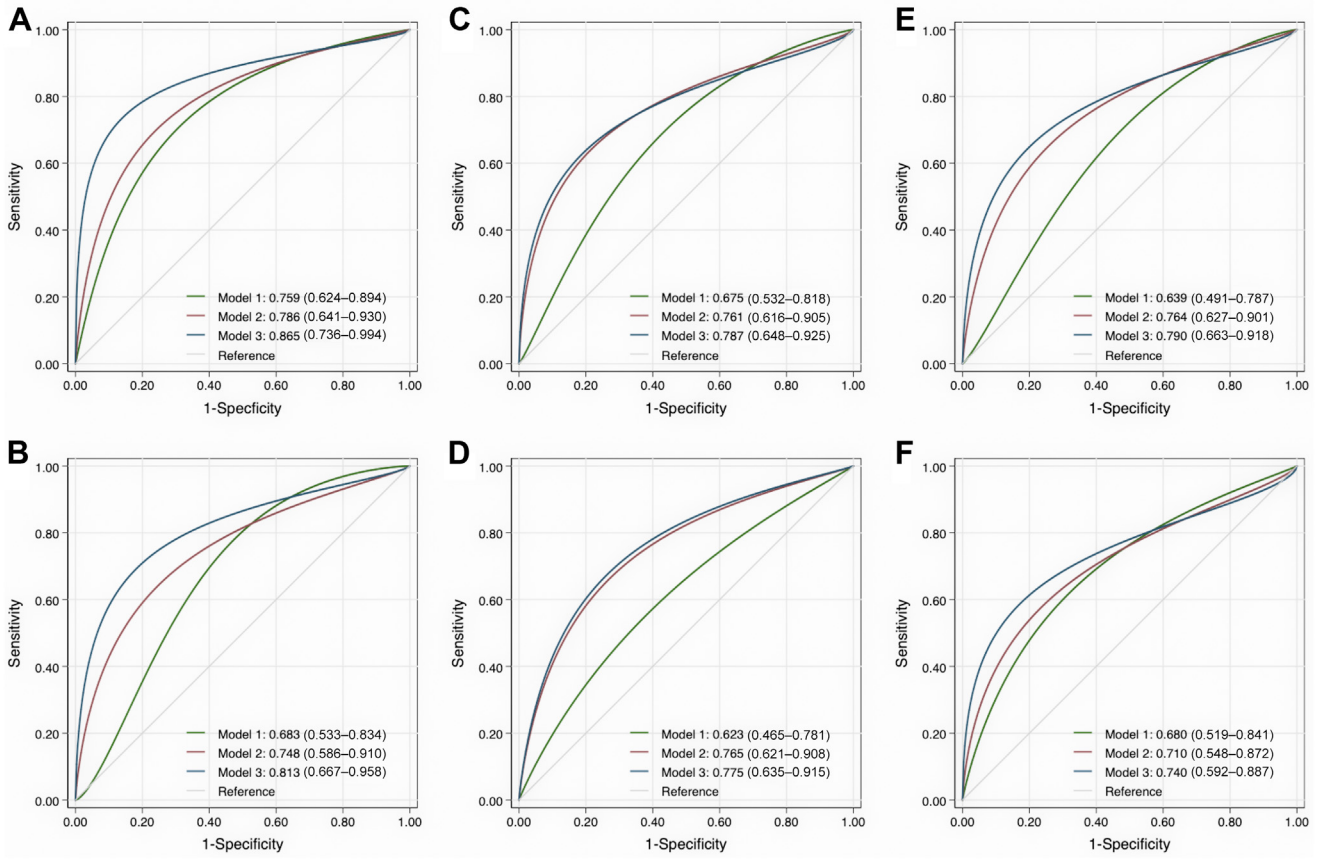

Figure 3. Receiver operating characteristic curves of the prediction models for discriminating a satisfactory control effect on axial length (AL) and spherical equivalent refraction (SER) over 12 months in the repeated low-level red-light (RLRL) group. Axial elongation < 0 mm/year **(A)**, SER progression < 0 diopter (D)/year **(B)**, axial elongation < 0.05 mm/year **(C)**, SER progression < 0.25 D/year **(D)**, axial elongation < 0.10 mm/year **(E)**, and SER progression < 0.50 D/year **(F)**. Model 1 included 1-month change in macular choroidal thickness (mCT). Model 2 included 3-month change in mCT. Model 3 included 3-month change in mCT and baseline age, gender, and baseline AL/SER.

Study Strengths and Limitations

This study was advantaged by the reliable data from a multicentered RCT that was followed up regularly throughout the study period with a control group. Another important strength was that we used fully automatic image segmentation with built-in software and only imaging after full cycloplegia to achieve high-quality mCT assessment. Several limitations should be acknowledged. First, the duration of this trial was 1 year; therefore, longer-term changes in mCT after RLRL therapy require further examination. Second, SS-OCT data were available at only 2 of 5 study sites, and the number of participants with available OCT data was relatively small (60 in the RLRL group and 60 in the SVS group). This might compromise the power to detect potential differences and associations. However, one should note that despite this small sample size, substantial differences on mCT measurement between these 2 groups were demonstrated. Baseline characteristics were also well balanced among children and between intervention groups. Third, a high proportion of children (28.3% in the RLRL group and 55.0% in the SVS group) were lost to follow-up at 6 months because of the Coronavirus Disease 2019 pandemic, which may affect the evaluation of longitudinal changes in mCT. However, the predictive performance of 3-month mCT changes on myopia control efficacy was reliable, with retention rates in the RLRL group of 96.7% and 95.0% at 3- and 12-month follow-ups, respectively. Fourth, information on environmental factors (i.e., time outdoors) was not collected, which limited our ability to detect potential risk factors that led to poor responses to the RLRL therapy. Fifth, we intentionally selected the same criteria, age 8 to 13 years and SER range from −1 to −5 D, the same as those in many other previous studies on myopia, to have a meaningful comparison on efficacy. However, this would lead to enrolling some children with an early onset higher degree of myopia, for example, those 8 to 10 years old with −4 to −5 D, who might require active myopia control. We think this is a limitation of the study, but we found that only 3 of 90 participants assigned to the SVS group were in this category. Last but not least, research into the

generalizability of choroidal thickening after RLRL therapy for children of other ethnicities, age groups, and myopia degrees is needed.

Conclusions

As early as 1 month after RLRL therapy, macular choroidal thickening reached its peak magnitude and was associated with 12-month myopia control efficacy. Acceptable predictive discrimination of satisfactory treatment efficacy of RLRL therapy was obtained on the basis of initial 3-month mCT changes. Macular CT may be a proxy for future treatment response and serve as a reference for guiding treatment regimens. Further studies should elucidate mechanisms underlying choroidal thickening after RLRL therapy.

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Footnotes and Disclosures

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HUMAN SUBJECTS: Human Subjects were used n this study. This trial was conducted in accordance with recognized international standards including the Good Clinical Practice guidelines and ethical guidelines proposed by the Declaration of Helsinki. The protocol was approved by the Ethics Committee of Zhongshan Ophthalmic Centre (2019KYPJ093). All children provided verbal consent and their parents/guardians provided written informed consent before participation.

No animal subjects were used in this study.

Author Contributions:

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Analysis and interpretation: Xiong, Zhu, Jiang, Wang, Zhang, He

Obtained funding: N/A

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Abbreviations and Acronyms:
AL = axial length; **AUC** = area under the curve; **CI** = confidence interval; **CT** = choroidal thickness; **D** = diopters; **mCT** = macular choroidal thickness; **OR** = odds ratio; **RCT** = randomized controlled trial; **RLRL** = repeated low-level red-light; **SER** = spherical equivalent refraction; **SS-OCT** = swept-source OCT; **SVS** = single vision spectacle; **UCVA** = uncorrected visual acuity.

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