European Journal of Pediatrics (2026) 185:779
https://doi.org/10.1007/s00431-026-07452-x

RESEARCH

Nine-year ocular developmental outcomes after ranibizumab or laser treatment for zone II retinopathy of prematurity: follow-up of a randomized trial cohort

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Received: 1 August 2026 / Revised: 10 September 2026 / Accepted: 22 September 2026
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Abstract

The purpose of this study is to describe 9-year ocular developmental outcomes in children previously randomized to intravitreal ranibizumab (IVR) or laser photocoagulation (LP) for zone II treatment-requiring retinopathy of prematurity (ROP). In this follow-up of a single-center randomized trial, infants with stage 2 or 3 ROP with plus disease in zone II were randomized in 2014 to bilateral LP ($n=25$) or IVR ($n=25$). At school age, 29 children (10 LP, 19 IVR) underwent assessment of best-corrected visual acuity, cycloplegic refraction, ocular biometry, anterior segment parameters, spectral-domain optical coherence tomography, optical coherence tomography angiography, and full-field electroretinography. Eye-level comparisons used generalized estimating equations. Mean spherical equivalent did not differ significantly between LP and IVR groups (−1.22 vs. −1.90 D; mean difference 0.68 D, 95% CI −2.26 to 3.62; $p=0.65$), nor did best-corrected visual acuity (0.15 vs. 0.21 logMAR; mean difference −0.07, 95% CI −0.27 to 0.13; $p=0.51$). Compared with the LP group, the IVR group showed thinner lens thickness (3.52 vs. 3.75 mm, $p<0.001$), steeper minimum keratometry (43.8 vs. 42.6 D, $p=0.048$), and thinner central internal limiting membrane-retinal pigment epithelium thickness (249.2 vs. 286.9 µm, $p=0.005$). Selected electroretinography abnormalities also differed between groups. *Conclusion*: In this small 9-year follow-up cohort with differential loss to follow-up, visual acuity and refractive outcomes were broadly similar after IVR and LP, while selected ocular structural and electrophysiological differences were observed. These preliminary exploratory findings should be interpreted cautiously and do not provide sufficient evidence to recommend one treatment approach over the other on the basis of long-term ocular outcomes alone.

What is Known:

- *Laser photocoagulation and intravitreal anti-vascular endothelial growth factor therapy are established treatments for severe retinopathy of prematurity.*
- *Long-term ocular developmental and functional outcomes after anti-vascular endothelial growth factor treatment remain incompletely defined, particularly beyond early childhood.*

What is New:

- *This follow-up of a randomized trial cohort provides 9-year multimodal ocular outcome data in children treated with ranibizumab or laser for zone II retinopathy of prematurity.*
- *Visual acuity and refractive outcomes were broadly similar between treatment groups, while selected anterior segment, retinal structural, and electroretinography differences were observed and should be interpreted as exploratory.*

Keywords Retinopathy of prematurity · Premature infants · Ranibizumab · Laser photocoagulation · Anti-vascular endothelial growth factor · Long-term follow-up · Visual development

Abbreviations

AL	Axial length
ACD	Anterior chamber depth
Astig	Astigmatism
ARA	Angle recess area
ATA	Angle-to-angle distance

Communicated by Peter de Winter

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Published online: 28 September 2026

ACW	Anterior chamber width
AOD	Angle opening distance
AS-OCT	Anterior segment OCT
ACA	Anterior chamber angles
BCVA	Best-corrected visual acuity
BW	Birth weight
CCT	Central corneal thickness
CWC	Chang-Waring chord distance
DA	Dark adaptation
Decent	Decentralization
ERG	Electroretinogram
FAZ	Foveal avascular zone
GA	Gestational age
GEE	Generalized estimating equations
IVR	Intravitreal injection of ranibizumab
IVI	Intravitreal injections
ILM	Internal limiting membranes
K	Keratometry
K1	Minimum keratometry
K2	Maximum keratometry
LP	Laser photocoagulation
LT	Lens thickness
logMAR	Logarithm of the minimum angle of resolution
LA	Light adaptation
LV	Lens vault
OCTA	Optical coherence tomography angiography
Ops	Oscillatory potentials
PD	Perfusion density
PMA	Postmenstrual age
ROP	Retinopathy of prematurity
R	Radius of anterior corneal surface
Rf F	Flat radius of anterior corneal surface on a ring in 15° around the corneal apex
Rs F	Steep radius of anterior corneal surface on a ring in 15° around the corneal apex
RPE	Retina pigment epithelium
SE	Spherical equivalent
SphR Min	Spherical radius minimum
SD-OCT	Spectral domain-optical coherence tomography
TCT	Corneal thickness at the thinnest corneal location
TIA	Trabecular-iris angle
TISA	Trabecular-iris space area
VEGF	Vascular endothelial growth factor
VLD	Vessel length density

Introduction

Retinopathy of prematurity (ROP) remains an important cause of childhood visual impairment among infants born preterm [1]. Laser photocoagulation has long been used for treatment-requiring ROP, while intravitreal anti-vascular endothelial growth factor (VEGF) therapy has become increasingly used because it can induce rapid disease regression and may preserve peripheral retina [2]. However, systemic VEGF suppression after intravitreal anti-VEGF therapy in infants and the limited availability of long-term developmental follow-up data have raised ongoing concerns about ocular and systemic safety, including effects on refractive development, anterior segment growth, retinal structure, retinal vascular development, and visual function [3–7].

Most comparative studies of laser and anti-VEGF treatment for ROP have focused on short-term disease regression, reactivation, and refractive outcomes in infancy or early childhood [2, 4–7]. Longer-term data are limited, especially from children originally enrolled in randomized treatment trials. School-age follow-up is clinically important because refractive error, visual acuity, ocular biometry, retinal morphology, and electrophysiological function may continue to evolve after infancy and may not be fully captured by early outcome assessments.

Previous school-age studies have reported differences in optical biometry, foveal microvasculature, and refractive outcomes after laser or intravitreal anti-VEGF treatment, but most available evidence is observational and may be affected by selection bias and incomplete imaging in young children [8]. Therefore, long-term follow-up of randomized cohorts, even when sample size is limited, can provide useful pediatric safety data.

We conducted a 9-year follow-up study of children who had participated in a randomized clinical trial comparing intravitreal ranibizumab with laser photocoagulation for stage 2 or 3 ROP with plus disease in zone II [6]. The aim of this study was to describe long-term visual, refractive, anterior segment, retinal structural, microvascular, and electrophysiological outcomes in this trial cohort.

Methods

Study design and participants

This was a 9-year follow-up study of children who had participated in a single-center randomized clinical trial comparing intravitreal ranibizumab (IVR) with laser photocoagulation (LP) for treatment-requiring retinopathy of prematurity (ROP) [6]. In the original trial, 50 Chinese infants with stage 2 or 3 ROP with plus disease in zone II were randomized in 2014 to bilateral LP ($n=25$) or bilateral IVR (0.3 mg in 0.03 mL; Lucentis, Novartis, Basel, Switzerland; $n=25$). The original trial design, treatment procedures, retreatment criteria, and 6-month outcomes have been reported previously [6]. Postmenstrual age at initial ROP screening was calculated as gestational age at birth plus chronological age

at the first ROP screening examination. ROP diagnosis and treatment decisions in the original trial were made independently by experienced pediatric retinal specialists with more than 15 years of experience in ROP screening and treatment, using standardized diagnostic and treatment criteria. The original randomized trial was approved through the institutional ethics process but was not registered in a public clinical trial registry. The present 9-year follow-up study was not separately registered. During post-treatment follow-up, rescue treatment was permitted when clinically indicated.

Nine-year follow-up assessment

Between August 2023 and August 2024, families of trial participants were invited to attend a long-term school-age follow-up visit approximately 9 years after treatment. Age at examination was calculated from the examination date and date of birth and is reported as chronological age. Children examined at school age after the original trial were included in the present analysis. The study was approved by the Institutional Review Board of Shenzhen Eye Hospital (updated ethics approval number: 20191206–01) and adhered to the Declaration of Helsinki. Written informed consent was obtained from the legal guardians of all participating children.

Ophthalmic and ocular developmental assessments

All children underwent a comprehensive ophthalmic examination, including best-corrected visual acuity (BCVA), cycloplegic refraction, slit-lamp biomicroscopy, indirect ophthalmoscopy, ocular biometry, anterior segment imaging, spectral-domain optical coherence tomography (SD-OCT), optical coherence tomography angiography (OCTA), and full-field electroretinography (ERG). BCVA was measured with a logarithm of the minimum angle of resolution chart. Cycloplegic refraction was performed after repeated instillation of 0.5% compound tropicamide, with adequate cycloplegia confirmed before measurement. Compound tropicamide was used according to the routine pediatric cycloplegic protocol at our institution.

Ocular biometric and anterior segment measurements included axial length, anterior chamber depth, lens thickness, corneal thickness, keratometry, astigmatism, and anterior segment parameters derived from Pentacam and CASIA2 imaging. SD-OCT was used to measure choroidal thickness at the fovea and perifoveal locations. OCTA was used to assess foveal avascular zone area, perfusion density, vessel length density, and central retinal thickness from the internal limiting membrane to the retinal pigment epithelium [9]. Detailed device-specific parameters are provided in Online Resource 1. Widefield fundus imaging was performed using the California ultra-widefield retinal imaging system (Optos plc, Dunfermline, UK). SD-OCT was performed with Spectralis HRA + OCT and OCTA with CIRRUS HD-OCT 5000 using a 6 × 6-mm macular scan. Poor-quality images were excluded. Choroidal thickness was measured manually by one trained grader, and masking was performed when feasible for biometry, OCT/OCTA, and ERG analyses but not for fundus assessment because laser scars could reveal treatment exposure.

Electroretinography

Full-field ERG was performed with RETeval using an International Society for Clinical Electrophysiology of Vision 5-step protocol after cycloplegia and pupil dilation [10, 11]. After dark adaptation, rod-mediated responses were recorded, followed by light-adapted cone responses. ERG responses were classified as abnormal when amplitudes or implicit times fell outside the manufacturer-provided 2.5th to 97.5th percentile reference range for normal eyes [12]. The manufacturer-provided reference intervals were used with the same RETeval skin–electrode recording configuration; however, they were not specifically derived from age-matched former preterm children, and ERG abnormality classification was therefore interpreted cautiously.

Statistical analysis

Baseline characteristics and 9-year outcomes were summarized by original randomized treatment group. Child-level demographic variables were compared using two-sample t tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. Eye-level outcomes were analyzed using generalized estimating equations to account for correlation between fellow eyes from the same child. Continuous outcomes are reported as mean ± standard error unless otherwise specified. Categorical outcomes are reported as number and percentage.

The primary comparisons followed the original randomized treatment allocation. Because supplemental crossover treatment may influence long-term ocular outcomes, treatment exposure was summarized and considered when interpreting between-group differences.

An exploratory monotherapy-only sensitivity analysis was performed for selected key outcomes among children who received the originally allocated treatment without supplemental crossover treatment. This analysis included spherical equivalent, BCVA, axial length, lens thickness, minimum keratometry, central corneal thickness, and central ILM-RPE thickness and was interpreted as a robustness check rather than a confirmatory estimate of a pure treatment effect.

All statistical analyses were performed using SPSS version 23.0. Two-sided p values < 0.05 were considered statistically significant. Because of the modest sample size and multiple ocular outcomes, findings were interpreted as exploratory and hypothesis-generating rather than confirmatory.

Results

Follow-up completion differed by randomized arm: 10 of 25 children (40.0%) in the LP group and 19 of 25 children (76.0%) in the IVR group completed the 9-year visit. Baseline characteristics of completers and non-completers stratified by randomized treatment group are shown in Online Resource 2. Children lost to follow-up had higher birth weight than those who completed follow-up (1.27 vs. 1.05 kg, $p = 0.04$), but gestational age and postmenstrual age at initial ROP screening were similar between groups. Among children who completed follow-up, baseline neonatal characteristics were comparable between the original LP and IVR groups (Table 1). Follow-up attempts and reasons for loss to follow-up are summarized in Online Resource 3. No deaths among non-completers were known from hospital records or follow-up contact.

The number of eyes available differed across modalities because of cooperation, image quality, and test completion. Modality-specific denominators and reasons for missing data are summarized in Online Resource 4. Widefield fundus imaging at the 9-year follow-up showed no obvious peripheral retinal abnormality, retinal tear, retinal detachment, or late reactivation in either treatment group. No child required additional retinal treatment during the long-term follow-up period after completion of the primary trial follow-up. Fluorescein angiography was not routinely performed; therefore, subtle persistent peripheral avascular retina could not be quantitatively assessed.

During the primary trial follow-up, 13 children developed ROP reactivation. Eleven children in the original IVR arm received rescue LP, 1 child in the original LP arm received crossover IVR, and 1 child with mild IVR reactivation was observed without additional treatment. Thus, reactivation and supplemental crossover treatment were distinguished in the present analysis: 13 children developed reactivation, whereas 12 children received supplemental crossover treatment. Among the 19 IVR children who completed the 9-year follow-up, 12 had not received crossover treatment and 7 had received crossover treatment after initial IVR. In the original LP arm, 1 child completing the 9-year follow-up had received rescue IVR. On re-review of the trial database for the present revision, the mildly reactivated IVR case managed by observation was identified separately; this clarification was not separately described in the primary 6-month report [6].

Table 1 Baseline neonatal and treatment characteristics of children completing 9-year follow-up

	LP	IVR	P value*
No. of patients	10	19	—
No. of eyes	20	38	—
Gender (M/F)	5/5	9/10	0.89
Age at examination (years, mean ± SD)	10.46 ± 0.52	10.31 ± 0.48	0.45
GA (weeks, mean ± SD)	28.02 ± 1.62	27.95 ± 2.31	0.93
PMA (weeks, mean ± SD)	34.47 ± 3.86	34.09 ± 2.64	0.79
BW (kg, mean ± SD)	1.12 ± 0.24	1.03 ± 0.30	0.48

LP laser photocoagulation, *IVR* intravitreal ranibizumab, *GA* gestational age, *PMA* postmenstrual age at initial screening, *BW* birth weight

*Using two-sample *t*-test for independent samples and chi-square tests

At 9 years, visual acuity and refractive outcomes were broadly similar between treatment groups. Refractive outcomes are summarized as mean ± SD in Table 2 and as median with interquartile range in Fig. 1. Mean spherical equivalent was − 1.22 D in the LP group and − 1.90 D in the IVR group ($p = 0.65$), and mean BCVA was 0.15 and 0.21 logMAR, respectively ($p = 0.51$). Two IVR-treated eyes from two children had BCVA worse than 20/400. Both eyes showed marked esotropia. Slit-lamp examination did not reveal obvious anterior segment abnormality or media opacity, and available SLO imaging combined with binocular indirect ophthalmoscopy did not show definite posterior segment structural abnormality. However, because cooperation with detailed testing was limited and sensorimotor findings, nystagmus status, and amblyopia treatment history were not systematically recorded across the cohort, the cause of poor visual acuity could not be determined with certainty, and amblyopia or non-ocular visual factors could not be excluded. The prevalence of myopia was 50.0% in both groups. High myopia was observed in 10.0% of LP-treated eyes and 18.4% of IVR-treated eyes, but this difference was not statistically significant ($p = 0.43$, Table 2 and Fig. 1). In the exploratory monotherapy-only sensitivity analysis, lens thickness, keratometry, and central ILM-RPE thickness were broadly consistent with the primary analysis, whereas spherical equivalent and BCVA estimates changed direction and were imprecise, and the CCT difference was attenuated (Online Resource 5). In an additional descriptive within-IVR comparison among completers, mean spherical equivalent was −0.45 D in eyes with rescue LP after IVR and −0.41 D in eyes without supplemental crossover treatment; corresponding BCVA values were 0.53 and 0.05 logMAR, respectively.

Table 2 Visual, refractive, and anterior segment outcomes at 9 years

	LP	IVR	Difference (95%CI)	*p* value*
Refractive error: No. of eyes	20	38		
≤ −0.50 D (*n*, %)	10 (50.0)	19 (50.0)	0.00 (−0.35, 0.35)	1.00
≤ −5.0 D (*n*, %)	2 (10.0)	7 (18.4)	0.08 (−0.12, 0.29)	0.43
Spherical equivalent (D, mean ± SD)	−1.22 ± 3.93	−1.90 ± 5.04	0.68 (−2.26, 3.62)	0.65
BCVA: No. of eyes	20	36		
BCVA (mean ± SE)	0.15 ± 0.06	0.21 ± 0.08	−0.07 (−0.27, 0.13)	0.51
BCVA 20/40 or better (*n*, %)	19 (95.0)	28 (77.8)	0.17 (−0.03, 0.37)	0.09
Vision impairment: worse than 20/40 (*n*, %)	1 (5.0)	6 (16.7)	0.12 (−0.05, 0.28)	0.16
Blindness: worse than 20/400 (*n*, %)	0	2 (5.6)	NA	0.53
Biometry: No. of eyes	20	36		
AL (mm, mean ± SE)	23.00 ± 0.41	22.96 ± 0.42	0.04 (−1.11, 1.19)	0.95
ACD (mm, mean ± SE)	3.15 ± 0.09	3.30 ± 0.06	−0.15 (−0.37, 0.07)	0.17
LT (mm, mean ± SE)	3.75 ± 0.05	3.52 ± 0.05	0.23 (0.09, 0.36)	< 0.001
CCT (mm, mean ± SE)	0.53 ± 0.01	0.56 ± 0.01	−0.02 (−0.04, −0.01)	0.012
CWC (mean ± SE)	0.28 ± 0.03	0.43 ± 0.09	−0.15 (−0.34, 0.05)	0.13
K1 (mean ± SE)	42.57 ± 0.43	43.78 ± 0.42	−1.20 (−2.39, −0.01)	0.048
K2 (mean ± SE)	44.47 ± 0.52	45.81 ± 0.46	−1.34 (−2.69, 0.02)	0.053
Astig (D, mean ± SE)	1.89 ± 0.21	1.88 ± 0.36	0.02 (−0.81, 0.84)	0.96
TCT (μm, mean ± SE)	539.33 ± 7.86	554.38 ± 6.15	−15.04 (−34.60, 4.52)	0.13
SphRMin (mm, mean ± SE)	7.74 ± 0.08	7.47 ± 0.07	0.27 (0.05, 0.49)	0.015
Rf F (mm, mean ± SE)	7.93 ± 0.08	7.75 ± 0.06	0.18 (−0.03, 0.38)	0.086
Rs F (mm, mean ± SE)	7.59 ± 0.08	7.37 ± 0.08	0.22 (0.01, 0.45)	0.058

LP laser photocoagulation, *IVR* intravitreal ranibizumab, *CI* confidence interval, *SD* standard deviation, *SE* standard error, *BCVA* best-corrected visual acuity, *AL* axial length, *ACD* anterior chamber depth, *LT* lens thickness, *CCT* central corneal thickness, *CWC* chang-waring chord distance, *K1* minimum keratometry, *K2* maximum keratometry, *Astig*, astigmatism, *TCT* corneal thickness at the thinnest corneal location, *SphRMin* spherical radius minimum, *Rf F* flat radius of anterior corneal surface on a ring in 15° around the corneal apex, *Rs F* steep radius of anterior corneal surface on a ring in 15° around the corneal apex

*Using generalized estimating equations. For spherical equivalent, group values are presented as descriptive mean ± SD; between-group differences, 95% CIs, and *p* values were estimated using GEE

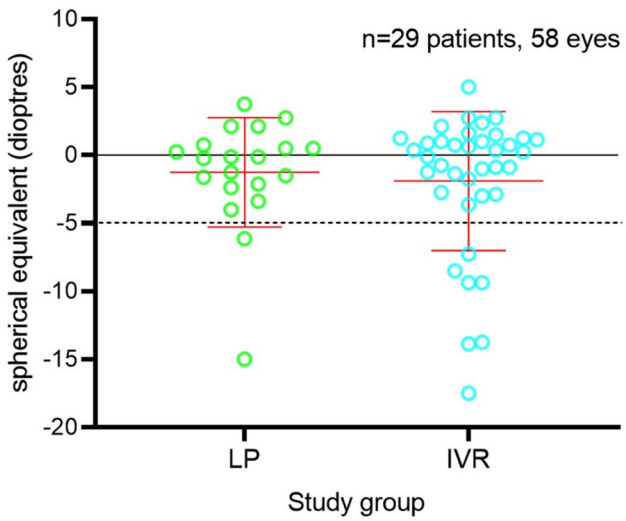


Fig. 1 Cycloplegic spherical equivalent refraction at the school-age follow-up. The dashed line represents high myopia defined as −5D. Error bars show median and 25th and 75th quartiles. LP, laser photocoagulation; IVR, intravitreal ranibizumab

Compared with the LP group, the IVR group had thinner lens thickness (3.52 vs. 3.75 mm, $p < 0.001$) and steeper minimum keratometry (43.8 vs. 42.6 D, $p = 0.048$). Maximum keratometry was also higher in the IVR group, although the difference did not reach conventional statistical significance (45.8 vs. 44.5 D, $p = 0.053$). Axial length, anterior chamber depth, astigmatism, and corneal thickness measures were similar between groups (Table 2). No cataract, glaucoma, or clinically significant anterior segment abnormality was detected at the 9-year examination. CASIA2-derived anterior chamber, lens, and angle parameters did not differ significantly between groups (Online Resource 6).

Choroidal thickness at the fovea and perifoveal locations was similar between treatment groups (all $p \geq 0.17$, Online Resource 7). OCTA measures of foveal avascular zone area and retinal perfusion density did not differ significantly. Because FAZ area showed a skewed distribution, it is presented descriptively as median with interquartile range in Table 3. The LP group showed greater central ILM-RPE thickness than the IVR group (286.9 vs. 249.2 μm,

$p = 0.005$), while FAZ area tended to be smaller in the LP group, although the difference was not statistically significant ($p = 0.097$, Table 3).

The distribution of ERG implicit times and amplitudes is shown in Online Resource 8 and Online Resource 9. Compared with the LP group, the IVR group had a lower proportion of eyes with abnormal dark-adapted 0.01 amplitude (13.3% vs. 50.0%, $p = 0.02$), but a higher proportion with abnormal dark-adapted 3.0 b-wave implicit time (33.3% vs. 0%, $p = 0.008$). Other ERG abnormality rates did not differ significantly between groups (all $p \geq 0.07$, Table 4).

Table 4 Abnormal full-field electroretinography responses at 9 years

	LP ($n = 18$, %)	IVR ($n = 30$, %)	p value*
DA 0.01 implicit time	1 (5.6)	2 (6.7)	0.89
DA 0.01 amplitude	9 (50)	4 (13.3)	0.02
DA 3.0 a-wave implicit time	0	4 (13.3)	0.28
DA 3.0 a-wave amplitude	8 (44.4)	7 (23.3)	0.17
DA 3.0 b-wave implicit time	0	10 (33.3)	0.008
DA 3.0 b-wave amplitude	7 (38.9)	4 (13.3)	0.11
Ops implicit time	3 (16.7)	2 (6.7)	0.27
Ops amplitude	2 (11.1)	3 (10)	0.91
LA 3.0 a-wave implicit time	1 (5.6)	6 (20)	0.21
LA 3.0 a-wave amplitude	1 (5.6)	3 (10)	0.55
LA 3.0 b-wave implicit time	6 (33.3)	10 (33.3)	1.00
LA 3.0 b-wave amplitude	0	4 (13.3)	0.28
LA 3.0 flicker implicit time	1 (5.6)	8 (26.7)	0.07
LA 3.0 flicker amplitude	5 (27.8)	7 (23.3)	0.77

LP laser photocoagulation, *IVR* intravitreal ranibizumab, *DA* dark adaptation, *LA* light adaptation, *Ops* oscillatory potentials

*Values are abnormal eyes, *n* (%). All ERG parameters were available for 18 eyes in the LP group and 30 eyes in the IVR group. ERG comparisons were exploratory because of small cell counts and inter-eye correlation. GEE was used for between-group comparisons of continuous ERG parameters, whereas Fisher's exact test was used for comparisons of abnormality proportions shown in this table

Discussion

In this 9-year follow-up of a randomized trial cohort, children treated for zone II treatment-requiring ROP with IVR or LP had broadly similar visual acuity and refractive outcomes at school age. No obvious anterior segment abnormality, cataract, glaucoma, retinal tear, retinal detachment, or late reactivation was detected at follow-up. However, selected differences in ocular biometry, foveal structure, and ERG findings were observed. Given the modest sample size, rescue treatment in some participants, and differential attrition, these findings should be interpreted as exploratory pediatric safety data rather than definitive evidence of treatment superiority, equivalence, or harm.

Interpretation of the between-group comparisons is limited by rescue treatment and differential attrition. Although the primary analysis followed original randomized allocation, some children subsequently received supplemental crossover treatment, and this was clinically linked to disease reactivation and severity. In the IVR arm, supplemental crossover treatment was more frequent among non-completers than completers, suggesting that the IVR completer group may have been skewed toward children with milder or more treatment-responsive disease. This attrition pattern may have favored apparently better long-term outcomes in the IVR group. These issues mean that the present findings should be viewed as long-term exploratory safety observations rather than estimates of a pure treatment effect.

Long-term ocular outcomes after anti-VEGF treatment for ROP remain an important clinical question. The 5-year RAINBOW extension study reported similar visual acuity across ranibizumab and laser groups, a lower frequency of high myopia after ranibizumab, and no detected treatment effect on non-ocular developmental or health outcomes, with 156 of 180 children evaluated at 5 years [13]. In contrast, our cohort provides longer follow-up to approximately 9 years

Table 3 Foveal microstructural and microvascular outcomes at 9 years

	LP ($N = 18$ eyes)	IVR ($N = 34$ eyes)	Difference (95% CI)	p value*
FAZ area (mm^2, median [IQR])	0.02 (0.00, 0.10)	0.08 (0.00, 0.18)	−0.21 (−0.45, 0.04)	0.097
PD 6 mm (%, mean ± SE)	19.23 ± 7.17	17.45 ± 5.07	1.78 (−15.43, 19.00)	0.84
PD 1 mm (%, mean ± SE)	12.89 ± 4.98	12.69 ± 3.77	0.20 (−12.04, 12.44)	0.97
VLD (%, mean ± SE)	15.59 ± 2.05	17.71 ± 0.85	−2.13 (−6.48, 2.23)	0.34
ILM-RPE central thickness (μm, mean ± SE)	286.94 ± 7.59	249.21 ± 11.28	37.74 (11.10, 64.38)	0.005

LP laser photocoagulation, *IVR* intravitreal ranibizumab, *CI* confidence interval, *FAZ* foveal avascular zone, *PD* perfusion density, *VLD* vessel length density, *ILM-RPE* internal limiting membranes to retina pigment epithelium

*Using generalized estimating equations. FAZ area is presented as median (IQR) because of its skewed distribution; the between-group difference, 95% CI, and *p* value were estimated using GEE

but had lower retention, which increases uncertainty and requires more cautious interpretation. Other studies have also reported less myopic refractive error after intravitreal anti-VEGF treatment than after laser treatment for ROP [4, 8, 14, 15], although findings have not been fully consistent across treatment agents, doses, disease zones, reactivation patterns, and follow-up durations [7, 8, 16–18]. Thus, the absence of a statistically significant refractive difference in this cohort should not be interpreted as evidence of equivalence.

Myopic refractive error after prematurity and ROP treatment may be influenced by anterior segment development rather than axial elongation alone [19, 20]. In the present study, axial length and anterior chamber depth were similar between treatment groups, whereas the IVR group showed thinner lens thickness and steeper keratometry. The greater lens thickness observed in the LP group may reflect altered anterior segment development after prematurity and ROP treatment, and laser-related effects on ocular growth cannot be excluded. However, because anterior segment measurements were not available before treatment or during infancy, this finding should be interpreted cautiously. Taken together, these data suggest that long-term follow-up after ROP treatment should include ocular biometry and anterior segment assessment, not only refraction and visual acuity.

The foveal structural findings should be interpreted in the context of foveal maturation after prematurity and ROP. Although central ILM-RPE thickness was lower in the IVR group than in the LP group, the IVR value was closer to reported pediatric central macular thickness, whereas the greater central thickness and smaller FAZ area in the LP group may reflect greater persistence of inner retinal layers and foveal immaturity. Previous studies have reported altered macular structure, reduced or absent FAZ, and changes in foveal development in children with a history of prematurity or ROP [21–27]. Laser treatment has also been associated with altered foveal structure and retinal thickness, possibly related to effects of peripheral ablation on retinal development [19, 26, 27]. Therefore, our findings should not be interpreted simply as anti-VEGF-related retinal thinning. Because formal foveal hypoplasia grading and layer-specific inner retinal segmentation were not performed, this interpretation remains exploratory.

ERG findings in this cohort should also be regarded as hypothesis-generating. The higher frequency of reduced dark-adapted 0.01 amplitude in the LP group may plausibly reflect the effect of peripheral retinal ablation on rod-mediated responses. By contrast, the higher frequency of delayed dark-adapted 3.0 b-wave implicit time in the IVR group has no clear mechanistic explanation in this small cohort. Previous electrophysiological studies in ROP have been inconsistent [28, 29]. Differences in age at testing, treatment agent, disease severity, retinal maturation, and ERG protocol may partly explain the variability across studies. Because our study lacked a term-born control group and included multiple ERG comparisons, these ERG findings should be interpreted with caution.

From a clinical perspective, the broadly similar visual and refractive outcomes in this small cohort do not support a treatment preference based on these long-term findings alone. Treatment choice should continue to consider acute disease features, feasibility and duration of laser treatment, need for anesthesia or sedation, risk of reactivation after anti-VEGF therapy, ability to ensure prolonged follow-up, and the need to monitor peripheral retinal vascularization.

This study has several strengths, including long-term follow-up of children from a randomized treatment cohort and comprehensive school-age phenotyping across visual, refractive, biometric, anterior segment, retinal, vascular, and electrophysiological domains. The principal limitation of this study is the small follow-up sample with substantial and differential loss to follow-up, which may have introduced selection bias and reduced the comparability originally achieved by randomization. Use of 0.5% compound tropicamide rather than cyclopentolate may have allowed residual accommodation and could bias refractive estimates toward myopia. Although no cataract or glaucoma was detected at the 9-year examination, the small sample size limits assessment of uncommon long-term complications. Given the small number of child-level clusters, GEE-based variance estimates may be unstable; therefore, all eye-level comparisons were interpreted as exploratory. These limitations support a cautious interpretation focused on long-term safety surveillance and hypothesis generation for future larger studies.

Conclusions

In this small 9-year follow-up cohort, visual acuity and refractive outcomes were broadly similar between children originally randomized to IVR or LP for zone II treatment-requiring ROP. Selected anterior segment, foveal structural, and ERG differences were observed, but these findings are preliminary and limited by substantial differential attrition, rescue treatment, modality-specific missing data, and small sample size. These data do not establish treatment superiority, equivalence, or long-term safety differences, and do not provide sufficient evidence to recommend one treatment approach over the other on the basis of long-term ocular outcomes alone. Larger long-term studies with detailed peripheral retinal assessment are needed before treatment-specific long-term safety conclusions can be drawn.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00431-026-07452-x.

Authors' contributions Y.L., J.T., X.Z., G.Y., and G.Z. conceived and designed the study. Y.L., J.T., L.C., X.L., X.Ze., and M.Z. collected the data. Y.L., J.T., and X.Z. performed the follow-up examinations and organized the dataset. Y.L., J.T., and G.Y. analyzed and interpreted the data. Y.L. and J.T. wrote the main manuscript text. X.Z. prepared Fig. 1. Y.L., J.T., X.Z., G.Y., and G.Z. revised the manuscript critically for important intellectual content. All authors reviewed and approved the final manuscript.

Funding This study was supported by China Postdoctoral Science Foundation (2026M792291); National Natural Science Foundation of China (82271103 and 82671377); Shenzhen Medical Research Fund (C2301005, C2501034, and D250403004); Shenzhen Science and Technology Program (ZDYJ20251211141301002); and Sanming Project of Medicine in Shenzhen (SZSM202311018).

Data availability The data that support the findings of this study are available from the first author, Liu YL, upon reasonable request.

Declarations

Ethics approval This follow-up study was approved by the Ethics Committee of Shenzhen Eye Hospital. All institutions abided by the tenets of the Declaration of Helsinki.

Consent to participate Written informed consent was obtained from the parents of all enrolled infants.

Consent for publication This article has been approved for publication by the authors.

Competing interests The authors declare no competing interests.

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