Revised Indications for the Treatment of Retinopathy of Prematurity

ARCHIVES EXPRESS

Results of the Early Treatment for Retinopathy of Prematurity Randomized Trial

*Early Treatment for Retinopathy of Prematurity Cooperative Group**

Objective: To determine whether earlier treatment using ablation of the avascular retina in high-risk prethreshold retinopathy of prematurity (ROP) results in improved grating visual acuity and retinal structural outcomes compared with conventional treatment.

Methods: Infants with bilateral high-risk prethreshold ROP (n=317) had one eye randomized to early treatment with the fellow eye managed conventionally (control eye). In asymmetric cases (n=84), the eye with high-risk prethreshold ROP was randomized to early treatment or conventional management. High risk was determined using a model based on the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity natural history cohort. At a corrected age of 9 months, visual acuity was assessed by masked testers using the Teller acuity card procedure. At corrected ages of 6 and 9 months, eyes were examined for structural outcome. Outcomes for the 2 treatment groups of eyes were compared using χ^2 analysis, combining data for bilateral and asymmetric cases.

Results: Grating acuity results showed a reduction in unfavorable visual acuity outcomes with earlier treatment, from 19.5% to 14.5% ($P=.01$). Unfavorable structural outcomes were reduced from 15.6% to 9.1% ($P<.001$) at 9 months. Further analysis supported retinal ablative therapy for eyes with type 1 ROP, defined as zone I, any stage ROP with plus disease (a degree of dilation and tortuosity of the posterior retinal blood vessels meeting or exceeding that of a standard photograph); zone I, stage 3 ROP without plus disease; or zone II, stage 2 or 3 ROP with plus disease. The analysis supported a wait-and-watch approach to type 2 ROP, defined as zone I, stage 1 or 2 ROP without plus disease or zone II, stage 3 ROP without plus disease. These eyes should be considered for treatment only if they progress to type 1 or threshold ROP.

Conclusions: Early treatment of high-risk prethreshold ROP significantly reduced unfavorable outcomes to a clinically important degree. Additional analyses led to modified recommendations for the use of peripheral retinal ablation in eyes with ROP. Long-term follow-up is being conducted to learn whether the benefits noted in the first year after birth will persist into childhood.

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DESPITE MAJOR advances in the management of severe retinopathy of prematurity (ROP), retinal detachment and reduced visual acuity from ROP continue to be a major disability occurring in preterm infants[1,2] and one of the most common causes of severe visual impairment in childhood.[3] The Multicenter Trial of Cryotherapy for Retinopathy of Prematurity[4]

See also pages 1697 and 1769

(CRYO-ROP), the largest prospective trial of retinal ablative therapy for ROP, showed that 44.4% of eyes with a history of severe ROP that were treated with cryotherapy had a visual acuity of 20/200 or worse when children were tested at age 10 years. In children whose treated eye had a visual acuity better than 20/200, only 45.4% had a visual acuity of 20/40 or better. As a consequence, those involved in the care of infants with ROP have endeavored to find more effective approaches to treatment. One clinical trial, the Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) study,[5] showed no significant benefit to the use of supplemental oxygen therapy offered at a defined prethreshold point in the disease course. Another clinical trial, the Light Reduction in Retinopathy of Prematurity (LIGHT-ROP) study,[6] showed no benefit to preterm infants from a reduction in light exposure from birth to postmenstrual age 32 weeks.

In the CRYO-ROP study, peripheral retinal ablation was performed when the ocular findings indicated a risk of approximately 50% for retinal detachment.[7] This degree of severity was termed the *threshold* for treatment of ROP and was defined as at least

5 contiguous or 8 cumulative sectors (clock hours) of stage 3 ROP in zone I or II in the presence of plus disease (a degree of dilation and tortuosity of the posterior retinal blood vessels meeting or exceeding that of a standard photograph). During the past several years, the timing indications for treatment of ROP have been questioned, with some physicians advocating earlier treatment and others recommending conventionally timed treatment.[8,9] A concern with earlier treatment is the expected increase in surgical intervention in eyes with ROP that would otherwise regress spontaneously. This concern has led to efforts to identify treatment selection criteria that will result in earlier treatment only in those eyes at highest risk for developing threshold ROP or an unfavorable visual or structural outcome in the absence of treatment.

In 1999, the National Eye Institute (Bethesda, Md) funded a cooperative agreement to study early treatment for ROP (Early Treatment for Retinopathy of Prematurity [ETROP] study).[10] In the study, eyes of infants were randomized to early peripheral retinal ablation or standard (conventional) management if they developed prethreshold ROP and if RM-ROP2, a risk analysis program based on natural history data from the CRYO-ROP study,[11] indicated a high risk of an unfavorable outcome. Prethreshold ROP was defined as zone I, any stage ROP that was less than threshold; zone II, stage 2 ROP with plus disease (dilation and tortuosity of posterior pole retinal vessels in at least 2 quadrants, meeting or exceeding that of a standard photograph); zone II, stage 3 ROP without plus disease; or zone II, stage 3 ROP with plus disease but fewer than 5 contiguous or 8 cumulative clock hours.[7] Our article presents the findings of this study, including implications for the timing of retinal ablative treatment for ROP.

METHODS

Study protocols were approved by the review boards of all participating institutions, and parents provided written informed consent prior to infants' enrollment in the study and again at randomization.

Infants with birth weights less than 1251 g and birth dates between October 1, 2000, and September 30, 2002, were screened at 26 participating centers. Infants who survived at least 28 days underwent serial eye examinations, with the first screening examination occurring by 42 days after birth. If an infant developed ROP, parents were asked to consent to data collection and a possibly increased frequency of examinations. Study-certified ophthalmologists conducted serial examinations to detect rate of progression of ROP, development of prethreshold ROP, and development of threshold ROP. Infants with retinal vessels ending in zone I but no ROP or with zone II, stage 2 ROP received follow-up at least once per week. Infants with zone II, stage 1 ROP were examined at minimum every 2 weeks. If at least 1 eye reached prethreshold ROP, the infant's demographic and ROP information was entered into the RM-ROP2 risk model to determine the likelihood of progression to an unfavorable outcome in the absence of treatment.[11]

STUDY INTERVENTIONS

Risk determination was made at the Coordinating Center using the RM-ROP2 model[11] to evaluate data provided by each clinical center. If the risk of progression to an unfavorable outcome in the absence of treatment was calculated to be 15% or higher and a second examination by a masked study-certified ophthalmologist confirmed findings consistent with this risk, consent for the randomized trial was obtained and randomization occurred. Eyes that had a risk of 15% or higher were termed *high-risk prethreshold.* Eyes with less than a 15% risk were termed *low-risk prethreshold* and received follow-up every 2 to 4 days for at least 2 weeks until the ROP regressed or the risk progressed to 15% or higher. If both eyes were eligible for randomization, one eye was assigned at random to earlier treatment with ablative therapy within 48 hours of the first diagnosis of high-risk prethreshold ROP. Treatment generally consisted of laser therapy, but cryotherapy was also allowed. The fellow eye served as the control and was managed conventionally, which meant that it was observed until it either reached threshold and was treated or the ROP regressed without progressing to threshold. In cases in which only 1 eye reached high-risk prethreshold ROP, that eye was randomized either to treatment within 48 hours or to serve as a conventionally managed control, receiving treatment only if the ROP progressed to threshold severity. Infants in whom either eye developed threshold ROP prior to randomization were excluded from the study.

Infants born at nonstudy hospitals were eligible for the randomized trial if they were transferred to a participating center and were examined prior to age 42 days. If ROP was observed and reached high-risk prethreshold, consent was obtained and randomization occurred. Complete details concerning the study design and laser technique are described elsewhere (Early Treatment for Retinopathy of Prematurity Cooperative Group, unpublished data, 2003) .

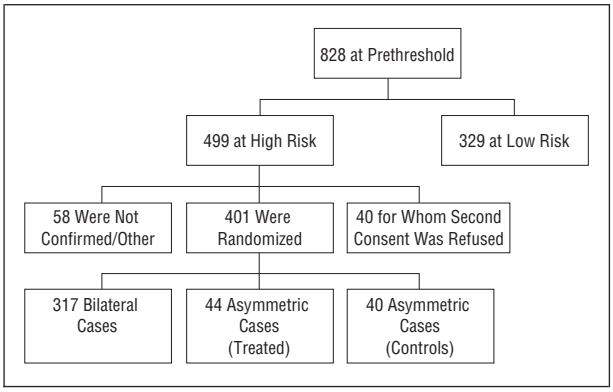
For the analyses, eyes with prethreshold ROP that remained low risk were categorized by the lowest zone and highest stage of ROP that developed. Eyes in the randomized group were classified according to the zone and stage of ROP that were present at the time of randomization, as determined by the confirming examiner's observations.

FUNCTIONAL OUTCOME

The functional outcome of each randomized eye at a corrected age of 9 months was evaluated with assessment of monocular grating acuity, conducted by 1 of 2 testers who were masked to the eye's treatment assignment and traveled to the study centers for testing. When possible, the grating acuity assessments were conducted on the same day as the 9-month follow-up examination. If not, these 2 assessments were done in close temporal proximity. The examining ophthalmologist was masked to grating acuity results at the 9-month examination.

The technique used to evaluate grating acuity was the Teller acuity card procedure,[12,13] as performed previously in the CRYO-ROP study.[14,15] The standard testing distance was 55 cm. Visual acuity was scored as the spatial frequency of the finest grating to which the infant showed a consistent fixation response. Eyes in which visual acuity was too poor to be quantified in this way were categorized as having no light perception (NLP), light perception only (LP), or detection of the grating on the low vision (LV) card only. The LV card has 2.2-cm-wide black-and-white stripes covering half of the card. It was used not to quantify vision but to determine whether the infant had pattern vision. The tester was permitted to move the LV card and present it at any distance or location in the infant's visual field.

Visual acuity data were included in the analyses only if the following criteria were met: (1) an acuity result (measurable acuity, detection of the grating on the LV card, LP, or NLP) was obtained for each eye in cases of bilateral high-risk prethreshold ROP or the randomized eye in asymmetric cases; (2) treatment for amblyopia, if present, had been prescribed for at least 4 weeks prior to the acuity test; and (3) refractive error, if present in either eye in cases of bilateral high-risk prethreshold ROP or the randomized eye in asymmetric cases, had been



Flowchart indicating the status of the 828 infants in the Early Treatment for Retinopathy of Prematurity study who developed prethreshold retinopathy of prematurity in 1 or both eyes.

corrected for at least 2 weeks prior to the acuity test. The criteria for correction of refractive errors were myopia greater than –4.00 diopters (D), hyperopia greater than +5.00 D, and/or astigmatism greater than 2.50 D in one or both eyes. Correction of anisometropia greater than 1.50-D spherical equivalent or 1.50-D cylinder was required only if the examining physician found evidence of amblyopia.

The visual acuity outcome was divided into 4 categories of functional response: normal, defined as greater than or equal to 3.70 cycles per degree[16,17] ; below normal, defined as 1.85 to less than 3.70 cycles per degree (from approximately 4 to ≥2 SDs below the mean grating acuity for a 9-month-old child[17]); poor, if less than 1.85 cycles per degree but measurable with one of the standard acuity cards (not the LV card); and blind/LV (NLP, LP, or LV card). These functional outcome categories of grating acuity results were further grouped into "favorable" and "unfavorable" designations. The favorable grouping included eyes in the normal and below normal categories. The unfavorable grouping included eyes in the poor and blind/LV categories, which would be expected to have a poor long-term prognosis for visual function.[18]

STRUCTURAL OUTCOME

Structural outcome was documented with a dilated fundus examination at corrected ages of 6 and 9 months by study-certified examiners. Although examiners were instructed to refrain from seeking information about randomization assignment, they were not formally masked. Complete ophthalmologic examinations were performed at both of these ages; at the 9-month examination, a developmental questionnaire (Denver Developmental Screening Test[19]; results not reported in this article) was conducted. Refractive errors were determined by cycloplegic retinoscopy after instilling 1% cyclopentolate hydrochloride. When there was a medical contraindication to this eye drop, either 0.5% cyclopentolate or 1% tropicamide was used. At 6 months, an unfavorable outcome was defined as follows: (1) a posterior retinal fold involving the macula, (2) a retinal detachment involving the macula, or (3) retrolental tissue or mass obscuring the view of the posterior pole. If an infant required a vitrectomy or scleral buckling procedure, the 6-month examination was conducted prior to the surgery. At the 9-month examination, eyes that had received a vitrectomy or scleral buckling procedure were classified for study purposes as having an unfavorable structural outcome.

STATISTICAL ANALYSES

The ETROP study was designed to detect a 35% reduction in the percentage of eyes having an unfavorable structural outcome, with a type 1 error rate of 0.05 and a power of 80% (ETROP Cooperative Group, unpublished data, 2003). Using data from the CRYO-ROP study, the percentage of unfavorable eyes managed conventionally was predicted to be 20%. If earlier treatment produced a 35% reduction, 13% of these eyes would have an unfavorable outcome. Assuming that approximately 80% of infants were expected to have both eyes eligible for the study, the number of infants needed for the study was 370. The primary outcome measure for this study was visual function, for which there are limited data with which to conduct sample size calculations. Therefore, we based sample size on structural outcome. This was a conservative approach; in the CRYO-ROP study, unfavorable functional outcome rates were approximately 50% higher than unfavorable structural outcome rates for the ages at which functional outcome was tested.[4,20,21]

The statistical technique used to compare the eyes treated at high-risk prethreshold with the conventionally managed high-risk prethreshold eyes was developed and used in the CRYO-ROP study.[22] It combines the data from infants with bilateral ROP (both eyes eligible) and those with asymmetric disease (1 eye eligible) into an overall χ^2 analysis of outcome differences between the 2 treatment groups. Although not part of the original study design, functional and structural results are also presented for International Classification of Retinopathy of Prematurity[23] (ICROP) and RM-ROP2 categories to allow a more detailed examination of the data.

A Data and Safety Monitoring Committee of researchers, physicians, and an ethicist not directly involved in the ETROP study met in person every 6 months to review adverse event and outcome data and to monitor study progress. The committee approved the protocol and monitored the performance of participating centers. On the basis of their review of our findings, the committee voted in favor of expediting publication of the study results prior to completion of all 9-month follow-up examinations.

RESULTS

At the 26 clinical sites, 828 infants whose parents had given consent for systematic follow-up of ROP were identified as having prethreshold disease in 1 or both eyes. Among the 828 infants with prethreshold ROP, there were 499 (60%) whose eye or eyes were classified as high risk and who were thereby eligible for the randomized trial (**Figure**). Among these 499 infants, consent for randomization was not obtained for 40 infants, and high-risk prethreshold ROP was not confirmed by the required second study-certified examiner or for other reasons in 58 infants. Thus, 401 infants were enrolled in the randomized trial. The remaining 329 infants with prethreshold ROP judged to be low risk received the clinically indicated follow-up and then underwent follow-up study examinations at a corrected age of 6 months to determine retinal outcomes.

Table 1 shows the distribution of prethreshold eyes by RM-ROP2 risk classification[11] and by severity of prethreshold ROP according to the ICROP.[24] One eye per infant, the eye with the higher risk according to the RM-ROP2 model, is represented in Table 1. This Table shows that the ICROP was a good indicator of most of the high-risk prethreshold eyes. For prethreshold zone I eyes with plus disease, 100% were high risk; when stage 3 was present without plus disease, 95.7% were high risk; and with stage 1 or 2 without plus disease, 92.3% were

Table 1. Risk Status by ICROP Category for the Eye With Higher Risk of Poor Structural Outcome for All 828 Infants With Prethreshold Retinopathy of Prematurity in 1 or Both Eyes*

ICROP Category			At Least 1 Eye Prethreshold, No. of Patients	Risk in Prethreshold Eye	
Zone	Stage	Plus Disease		Low Risk, No. of Patients	High Risk, No. (%)
I	3	Yes	29	0	29 (100)
I	3	No	23	1	22 (95.7)
I	1 or 2	Yes	19	0	19 (100)
I	1 or 2	No	117	9	108 (92.3)
II	3	Yes	271	13	258 (95.2)
II	3	No	303	295	8 (2.6)
II	2	Yes	66	11	55 (83.3)
Total			**828**	**329**	**499** (60.3)

Abbreviation: ICROP, International Classification of Retinopathy of Prematurity.[24]
*Risk of poor structural outcome was based on the RM-ROP2 risk model analysis for each eye (a risk analysis program based on natural history data from the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity Study[11]). Low risk was less than 0.15; high risk was 0.15 or greater. Plus disease was defined as a degree of dilation and tortuosity of the posterior retinal blood vessels meeting or exceeding that of a standard photograph.

high risk. In zone II, 95.2% of eyes that were classified as stage 3 with plus disease and 83.3% of eyes with stage 2 and plus disease were high risk, whereas only 8 (2.6%) of the 303 eyes that were zone II, stage 3 without plus disease were high risk. The parallels between the RM-ROP2 model and ICROP are particularly striking even though the former takes into account several demographic and disease-related factors that are not part of the ICROP.

Table 2 provides baseline characteristics for the 401 infants who entered the randomized trial. The mean birth weight was 703 g, and the mean gestational age was 25.3 weeks. At the time of randomization, 79.1% of the infants had bilateral high-risk prethreshold ROP according to the RM-ROP2 model. The remaining 20.9% of infants had asymmetric disease with high-risk prethreshold ROP in only 1 eye; the fellow eye had less severe ROP.

Table 3 shows the distribution of eyes treated at high-risk prethreshold and conventionally managed (control) eyes by ICROP categories at randomization, along with the percentage of conventionally managed eyes that reached threshold ROP. Zone I disease accounted for approximately 40% of randomized eyes. The largest categories of high-risk prethreshold ROP included eyes with zone II, stage 3 and plus disease (42.1% of earlier-treated prethreshold eyes and 43.7% of conventionally managed eyes) and those with zone I, stage 1 or 2 and no plus disease (27.4% of earlier-treated prethreshold eyes and 26.1% of conventionally managed eyes). Table 3 also indicates that 66.4% of eyes in the conventionally managed group progressed to threshold and underwent peripheral retinal ablation at that time.

The mean±SD ages at high-risk prethreshold treatment were postmenstrual age 35.2±2.3 weeks (range, 30.6-42.1 weeks) and chronological age 10.0±2.0 weeks. The mean±SD ages at treatment in the conventionally managed group for eyes that developed threshold ROP were postmenstrual age 37.0±2.5 weeks (range, 31.9-46.6 weeks) and chronological age 11.9±2.2 weeks. Anesthesia with intubation (routine at some hospitals) was used for 36.6% of infants who had high-risk prethreshold treatment compared with 30.9% when treatment was performed at threshold. Although the laser and indirect lens used during treatment were not standardized, the mean±SD number of laser applications for treatment at high-risk prethreshold was 1596±890 (1871 for zone I and 1403 for zone II), and the mean±SD number of applications at threshold was 1582±847 (1825 for zone I and 1439 for zone II). One eye received cryotherapy at threshold as the primary treatment for ROP. Some eyes received supplementary cryotherapy at the time of initial treatment. Retreatment was conducted in 13.9% of earlier treated eyes with high-risk prethreshold ROP and 11.0% of conventionally managed eyes treated at threshold.

Table 2. Baseline Characteristics of 401 Randomized Patients*

Patients with bilateral high-risk prethreshold ROP	79.1
Birth weight, mean ± SD, g	703 ± 148
Gestational age, mean ± SD, wk	25.3 ± 1.4
Male	54.4
Singleton births	71.1
Born in the study hospital	80.3
Race	
White	63.8
African American	18.0
Hispanic	14.7
Other	3.5

Abbreviation: ROP, retinopathy of prematurity.
*Data are presented as percentage unless otherwise indicated.

PRIMARY OUTCOME

Grating visual acuity data were obtained from 366 infants (96.6% of patients who survived). Data were not obtained from 22 infants who died prior to the 9-month examination, 8 infants whose parents did not bring them to the examination, or 5 infants who are waiting for visual acuity retesting because of uncorrected refractive error or amblyopia. Mean±SD corrected age (age from expected date of delivery) at the time of grating acuity assessment was 10.3±1.8 months.

Table 4 presents the proportion of randomized eyes with unfavorable grating acuity outcomes at 9 months. Over-

Table 3. Distribution of Severity of ROP at Randomization in Eyes With High-Risk Prethreshold ROP and Percentage of Conventionally Managed Eyes With High-Risk Prethreshold ROP That Reached Threshold*

ICROP Category at Randomization			Eyes Treated at High-Risk Prethreshold (n = 361), No. (%)	Conventionally Managed Eyes (n = 357), No. (%)	Reaching Threshold, %
Zone	Stage	Plus Disease			
I	3	Yes	19 (5.3)	19 (5.3)	94.7
I	3	No	17 (4.7)	16 (4.5)	68.8
I	1 or 2	Yes	14 (3.9)	16 (4.5)	87.5
I	1 or 2	No	99 (27.4)	93 (26.1)	49.5
II	3	Yes	152 (42.1)	156 (43.7)	71.8
II	3	No	5 (1.4)	4 (1.1)	25
II	2	Yes	55 (15.2)	53 (14.8)	66
Total			**361 (100)**	**357 (100)**	66.4

Abbreviations: ICROP, International Classification of Retinopathy of Prematurity[24]; ROP, retinopathy of prematurity.
*High risk was 0.15 or greater. Plus disease was defined as a degree of dilation and tortuosity of the posterior retinal blood vessels meeting or exceeding that of a standard photograph.

Table 4. Nine-Month Grating Acuity Outcome for Randomized Patients*

	Eyes Treated at High-Risk Prethreshold	Conventionally Managed Eyes	χ^2	*P* Value
Bilateral	287 (15.7)	287 (20.9)	7.26†	.007
Asymmetric	43 (7.0)	36 (8.3)	0.05	.82
Total	**330** (14.5)	**323** (19.5)	6.60	.01

*Data are presented as number (percentage unfavorable) unless otherwise indicated.
†Based on discordant pairs (23 infants with favorable outcomes in earlier-treated eyes and unfavorable outcomes in conventionally managed eyes; 8 infants with unfavorable outcomes in earlier-treated eyes and favorable outcomes in conventionally managed eyes).

Table 5. Distribution of 9-Month Grating Acuity Outcomes Among Randomized Eyes by Treatment Assignment*

	Eyes Treated at High-Risk Prethreshold (n = 330)	Conventionally Managed Eyes (n = 323)
Favorable outcome		
Normal (≥3.70 cycles per degree)	213 (64.5)	200 (61.9)
Below normal (1.85 to <3.70 cycles per degree)	69 (20.9)	60 (18.6)
Unfavorable outcome		
Poor (measurable but <1.85 cycles per degree)	15 (4.5)	16 (5.0)
Blind/LV (NLP, LP only, or LV card only)	33 (10.0)	47 (14.6)
Total	**330** (100)	**323** (100)

Abbreviations: LP, light perception; LV, low vision; NLP, no light perception.
*Data are presented as number (percentage).

all, there was a significant benefit for the treatment of eyes with high-risk prethreshold ROP, with a reduction in unfavorable visual acuity outcome from 19.5% to 14.5% (*P*=.01).Within-subject comparison afforded a powerful opportunity to examine treatment effects while controlling for individual characteristics. Results from the 31 infants with bilateral ROP in whom there were discordant outcomes in the 2 eyes provide even stronger evidence of a beneficial effect of treatment at high-risk prethreshold (*P*=.007). Thirty-seven infants with bilateral high-risk prethreshold ROP had an unfavorable outcome in both eyes.

Table 5 provides a more detailed presentation of the grating acuity results. Although differences were not statistically significant in these smaller categories, more eyes treated at high-risk prethreshold than conventionally managed eyes had a grating acuity in the normal range for the patient's age (*P*=.49). In addition, fewer eyes randomized to high-risk prethreshold treatment than conventionally managed eyes were designated as blind or LV (*P*=.08).

SECONDARY OUTCOMES

Structural outcome data were obtained from 366 infants (94.8% of patients who survived) at a corrected age of 6 months and 371 infants (97.9% of patients who survived) at a corrected age of 9 months. Six-month data were not obtained from 15 infants who died prior to the examination or 20 infants whose parents did not bring them to the examination. Mean±SD corrected age at the 6-month examination was 5.5±2.2 months. At 9 months, structural outcome data were not obtained from 22 infants who died prior to the examination or 8 infants whose parents did not bring them to the examination. Mean±SD corrected age at the 9-month examination was 9.8±1.4 months. This is younger than the mean age for visual acuity testing because the final acuity data were sometimes collected during retesting after the 9-month structural outcome examination.

The results for the 9-month structural outcome are presented in **Table 6**. Data indicate a statistically significant benefit for the treatment of eyes with high-risk prethreshold ROP, with unfavorable structural findings reduced from 15.6% in conventionally managed eyes to 9.1% in earlier-treated eyes with high-risk prethreshold ROP (*P*<.001). As with grating acuity outcome, results from infants with bilateral ROP in whom there were discordant outcomes in the 2 eyes provide strong evidence of a beneficial effect for treatment at high-risk prethreshold.

Among the 30 eyes treated at high-risk prethreshold that had an unfavorable structural outcome at 9 months, 2 had a partial retinal detachment involving the

macula, 23 had undergone a vitrectomy or scleral buckling procedure, and 5 had a total retinal detachment. Among the 51 conventionally managed eyes with an unfavorable outcome, 4 had a partial retinal detachment involving the macula, 43 had undergone a vitrectomy or scleral buckling procedure, and 4 had a total retinal detachment.

Structural outcome results at the 6-month examination for eyes randomized at high-risk prethreshold were similar to those at 9 months, as indicated in **Table 7**. Six-month structural outcome data were also collected for low-risk prethreshold eyes (determined by the RM-ROP2 program to have <15% risk of an unfavorable outcome). Among this group of 329 infants, 51 (15.5%) had at least 1 eye that progressed to the conventional threshold for treatment and was treated accordingly. An unfavorable outcome occurred in only 4 (1.3%) of the 302 low-risk prethreshold eyes for which 6-month structural outcome data were available.

RELATIONSHIP TO ICROP CLASSIFICATION

Table 8 and **Table 9** present the visual acuity and structural outcomes for randomized eyes stratified by ICROP category and RM-ROP2 risk category. The greatest benefit of treatment at high-risk prethreshold vs conventional management occurred in eyes that had zone I, stage 3 ROP with or without plus disease (30.8% unfavorable vs 53.8% unfavorable). A relative benefit from intervention at high-risk prethreshold for both visual acuity and structural outcomes was also seen among eyes that had zone I, stage 1 or 2 ROP without plus disease or zone II, stage 3 ROP with plus disease.

As shown at the bottom of Tables 8 and 9, examination of outcome by RM-ROP2 risk category showed a greater benefit in both grating acuity and structural outcomes for earlier treatment in high-risk prethreshold eyes with a 30% risk or higher than in those with a risk of 15% to less than 30%.

OTHER OCULAR AND CLINICAL FINDINGS

The distribution of refractive errors at the 9-month examination was similar between the high-risk prethreshold eyes that received early treatment and those that were conventionally managed.

Cataract or aphakia that was not associated with total retinal detachment or vitrectomy was found in 4 eyes (1.2%) in the group treated at high-risk prethreshold and 4 eyes (1.2%) in the conventionally managed group. Nystagmus occurred in 22% of randomized infants with bilateral high-risk ROP.

Table 10 compares other ocular and systemic complications of treatment among infants treated at high-risk prethreshold vs conventionally managed infants in whom high-risk prethreshold ROP progressed and who later underwent treatment at threshold. Ocular complication rates were similar in the 2 groups. Systemic complications were higher following treatment at high-risk prethreshold. Infants with high-risk prethreshold ROP who were randomized to early treatment received peripheral retinal ablation at a mean postmenstrual age of 35.2 weeks compared with 37 weeks in conventionally treated infants who underwent peripheral retinal ablation at threshold.

Table 6. Nine-Month Structural Outcome for Randomized Patients*

	Eyes Treated at High-Risk Prethreshold	Conventionally Managed Eyes	χ^2	*P* Value
Bilateral	289† (10.4)	290† (17.2)	11.7‡	<.001
Asymmetric	42§ (0)	36 (2.8)	1.2	.28
Total	**331** (9.1)	**326** (15.6)	12.6	<.001‖

*Data are presented as number (percentage unfavorable) unless otherwise indicated.
†Less than 292 because of inability to determine the structural outcome.
‡Based on discordant pairs (25 infants with favorable outcomes in earlier-treated eyes and unfavorable outcomes in conventionally managed eyes; 6 infants with unfavorable outcomes in earlier-treated eyes and favorable outcomes in conventionally managed eyes.
§Less than 43 because of inability to determine the structural outcome.
‖Twenty-four eyes with partial retinal detachment not including the macula (stage 4A) had vitrectomy or a scleral buckling procedure prior to the 9-month examination and are included in this Table as having an unfavorable outcome. When the analysis was based on the structural outcome of these eyes observed by the examining ophthalmologist at the 9-month examination, *P* = .002. Stage 4B or 5 eyes were a priori considered unfavorable in this study.

Table 7. Six-Month Structural Outcome for Randomized Patients*

	Eyes Treated at High-Risk Prethreshold	Conventionally Managed Eyes	χ^2	*P* Value
Bilateral	286† (5.6)	283† (11)	8.3‡	.004
Asymmetric	39§ (0)	36 (2.8)	1.1	.29
Total	**325** (4.9)	**319** (10)	9.2	.002

*Data are presented as number (percentage unfavorable) unless otherwise indicated.
†Less than 290 because of inability to determine the structural outcome.
‡Based on discordant pairs (21 infants with favorable outcomes in earlier-treated eyes and unfavorable outcomes in conventionally managed eyes; 6 infants with unfavorable outcomes in earlier-treated eyes and favorable outcomes in conventionally managed eyes).
§Less than 40 because of inability to determine the structural outcome.

COMMENT

This study of treatment for high-risk prethreshold ROP showed a benefit of earlier treatment compared with conventional management for the primary outcome measure of grating visual acuity at a corrected age of 9 months, as well as a much greater benefit for structural outcome at corrected ages of 6 and 9 months. Although the rates of ophthalmologic complications were similar among the 2 treatment arms, infants in the high-risk prethreshold group were more likely to experience systemic complications such as apnea, bradycardia, or reintubation following earlier treatment than with treatment at conventional threshold, perhaps because of the earlier mean postmenstrual age at which treatment was conducted. There was no mortality or known permanent morbidity attributed to treatment in either group.

Table 8. Grating Acuity at 9 Months for Infants With Bilateral High-Risk Prethreshold Retinopathy of Prematurity by ICROP Category and RM-ROP2 Risk*

ICROP Classification			Eyes Treated at High-Risk Prethreshold	Conventionally Managed Eyes	Discordant Pairs	
Zone	Stage	Plus Disease			A†	B‡
I	3	Yes or No	26 (30.8)	26 (53.8)	7	1
I	1 or 2	Yes	9 (22.2)	9 (22.2)	0	0
I	1 or 2	No	73 (11.0)	73 (15.1)	3	0
II	3	Yes	109 (15.6)	109 (17.4)	8	6
II	3	No	3 (0)	3 (0)	0	0
II	2	Yes	34 (14.7)	34 (17.6)	2	1
			RM-ROP2 Risk			
0.15 to <0.30			108 (12.0)	108 (13.0)	4	3
0.30 to <0.45			73 (13.7)	73 (17.8)	5	2
≥0.45			80 (22.5)	80 (35.0)	13	3

Abbreviation: ICROP, International Classification of Retinopathy of Prematurity[24]; RM-ROP2, a risk analysis program based on natural history data from the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity Study.[11]

*Data are presented as number (percentage unfavorable) unless otherwise indicated. High risk was 0.15 or greater. Plus disease was defined as a degree of dilation and tortuosity of the posterior retinal blood vessels meeting or exceeding that of a standard photograph.

†For group A, earlier-treated eyes had a favorable outcome, and conventionally managed eyes had an unfavorable outcome.

‡For group B, earlier-treated eyes had an unfavorable outcome, and conventionally managed eyes had a favorable outcome.

Table 9. Structural Outcome at 9 Months for Infants With Bilateral High-Risk Prethreshold Retinopathy of Prematurity by ICROP Category and RM-ROP2 Risk*

ICROP Classification			Eyes Treated at High-Risk Prethreshold	Conventionally Managed Eyes	Discordant Pairs	
Zone	Stage	Plus Disease			A†	B‡
I	3	Yes or No	27 (29.6)	27 (55.6)	8	1
I	1 or 2	Yes	9 (22.2)	9 (22.2)	0	0
I	1 or 2	No	75 (2.7)	75 (9.3)	6	1
II	3	Yes	108 (7.4)	109 (11.0)	6	3
II	3	No	3 (0)	3 (0)	0	0
II	2	Yes	34 (20.6)	34 (20.6)	1	1
			RM-ROP2 Risk			
0.15 to <0.30			109 (5.5)	109 (7.3)	4	2
0.30 to <0.45			73 (9.6)	73 (17.8)	7	1
≥0.45			81 (18.5)	82 (30.5)	12	3

Abbreviation: ICROP, International Classification of Retinopathy of Prematurity[24]; RM-ROP2, a risk analysis program based on natural history data from the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity Study.[11]

*Data are presented as number (percentage unfavorable) unless otherwise indicated. High risk was 0.15 or greater. Plus disease was defined as a degree of dilation and tortuosity of the posterior retinal blood vessels meeting or exceeding that of a standard photograph. Data include only those eyes for which structural outcome was able to be graded.

†For group A, earlier-treated eyes had a favorable outcome, and conventionally managed eyes had an unfavorable outcome.

‡For group B, earlier-treated eyes had an unfavorable outcome, and conventionally managed eyes had a favorable outcome.

The follow-up rate for visual acuity outcome was 96.6%, and for structural outcome it was 97.9%. The results indicate a benefit of earlier intervention for both visual acuity and structural outcome. The results support consideration for treatment of certain groups of eyes (type 1) with prethreshold ROP. Furthermore, the data clearly indicate that monitoring of ROP through serial examinations may be the better approach for other groups of eyes (type 2).

In the ETROP study, a novel risk model that was developed based on natural history data from the CRYO-ROP study was used to identify infants at high risk for adverse outcomes from ROP, and only those infants were randomized.[10,11] The model used demographic characteristics of the infants and clinical features of ROP to classify eyes with prethreshold ROP as high risk or low risk. The validity of the model is demonstrated in the finding that high-risk prethreshold eyes that received conventional management had a much higher percentage of progression to threshold ROP than those at low risk (66.4% vs 15.5%, respectively) and a much higher percentage of unfavorable structural outcome (10% vs 1.3%, respectively, at 6 months). Eyes with low-risk prethreshold ROP were managed conventionally, with treatment administered if conventional threshold was reached. Overall, our study data support the treatment of selected eyes that develop prethreshold ROP.

In the CRYO-ROP study, only about 9.6% of eyes in the natural history cohort with prethreshold ROP had zone I disease; of these eyes, 33.3% had an unfavorable structural outcome.[24] This strongly weighted the risk factor of presence of disease in zone I in the RM-ROP2 model. In the ETROP study, 22.7% of eyes with prethreshold ROP had zone I disease; because of the strong weighting of zone I ROP in the risk model, 94.7% of these eyes were classified as high

risk, representing about 40% of eyes in the ETROP randomized trial.

The differences between the CRYO-ROP study and the ETROP study in frequency of zone I disease and regarding the more benign course of zone I ROP in the ETROP study are noteworthy. It is tempting to attribute the large number of zone I cases to advances in neonatal care and improved survival rates of the smallest premature infants. However, a thorough analysis (not presented in this article) of the data from the 2 studies (CRYO-ROP and ETROP) showed that even when the effects of birth weight and gestational age were controlled, the number of zone I eyes in the ETROP cohort was still significantly higher than in the CRYO-ROP study. Perhaps other changes in the care of premature infants, as yet unrecognized, have caused an increase in zone I disease and a decrease in its severity.

An alternative explanation is that examiners may now be more attentive to diagnosing zone I ROP than they were previously. The CRYO-ROP study showed a clear benefit of retinal ablative therapy, but the results in zone I eyes were not impressive; most of these eyes developed unfavorable visual and structural outcomes even after receiving treatment at threshold. After publication of the CRYO-ROP results, it is possible that eyes were more carefully monitored and observed by ophthalmologists and that some eyes now diagnosed as having zone I ROP might have been categorized as zone II in the era before treatment proved effective. Additionally, some prior investigations considered posterior zone II eyes to be in the same category as zone I.[9] An assignment of posterior zone II eyes to the zone I category might increase the number of zone I eyes in this study. These subtle factors could explain both the increased frequency and improved outcome of zone I eyes in ETROP subjects compared with CRYO-ROP subjects.

For all groups of eyes in the ETROP study, the effect of treatment at high-risk prethreshold was more pronounced for structural outcomes than for visual acuity outcomes. A similar discrepancy between the magnitude of difference between treatment groups for visual acuity vs structural outcomes was observed in the CRYO-ROP study.[4,20,21] Because vision is the most important measure of treatment designed to prevent visual loss from severe ROP, the ETROP study chose visual acuity as its primary outcome measure. Also, there was a safety concern that treatment at high-risk prethreshold with laser could have a previously unrecognized deleterious effect on visual acuity. The Teller acuity card procedure was selected as the assessment tool for measurement of visual acuity at the 9-month examination because it allows quantification of visual acuity in infants and it had been used successfully to test infants at a similar age in the CRYO-ROP study.[14,20]

As in the CRYO-ROP study,[4,20,21] the finding of a discrepancy between the magnitude of the treatment group differences in visual acuity vs structural outcomes in the ETROP study is likely due in part to non–ROP-related ophthalmologic and neurologic problems that can occur in premature infants. Children with severe ROP may develop visual impairment secondary to neural insult or other cerebral factors.[25,26] In addition, nystagmus, which reduces visual acuity, was found in more than 20% of randomized infants with bilateral disease. These non–ROP-related factors may have resulted in reduced acuity in conventionally managed eyes as well as in eyes treated at high-risk prethreshold, thereby decreasing the difference in visual acuity outcome between the 2 groups.

Table 10. Complications Accompanying Treatment*

Complication	Eyes Treated at High-Risk Prethreshold† (n = 361)	Eyes Treated Conventionally at Threshold† (n = 236)
Intraoperative ocular complications		
Conjunctival or subconjunctival hematoma	30 (8.3)	16 (6.8)
Conjunctival laceration, unintended	16 (4.4)	5 (2.1)
Hemorrhage (retinal, preretinal, or vitreous)	14 (3.9)	12 (5.1)
Closure of the central retinal artery	0 (0)	2 (0.8)
Inadvertent burn or freeze to area outside target zone	2 (0.6)	1 (0.4)
Other	2 (0.6)	0 (0)
Systemic complications		
Apnea, bradycardia, or arrhythmia	31 (8.6)	10 (4.2)
Acquired or increased cyanosis	13 (3.6)	4 (1.7)
Need for reintubation within 10 days of treatment after stopping artificial ventilation	40 (11.1)	12 (5.1)
Other	1 (0.3)	1 (0.4)

*Data are presented as number (percentage).
†Mean ± SD postmenstrual age at treatment in the early-treatment group was 35.2 ± 2.3 weeks and in the threshold treatment group was 37.0 ± 2.5 weeks.

Another likely contributor to the difference between functional and structural outcomes in this study is the immaturity of the visual system at 9 months postterm. Because the visual acuity of a 9-month-old infant is lower than that of a healthy adult, certain visual deficits that result from structural abnormalities may not be apparent until an older age, when acuity in healthy eyes has improved to near-adult levels. Follow-up testing using recognition (letter) visual acuity charts at older ages would be expected to reveal these deficits in visual acuity, as it did in the CRYO-ROP study.[4,21]

In evaluating the benefit of treatment at high-risk prethreshold, it is important to take into account possible adverse effects and trade-offs related to earlier treatment. These include an increased rate of systemic complications, potential long-term risks of earlier treatment, an increased frequency of treatment in eyes that would otherwise have undergone spontaneous regression of ROP, and an increase in the number of eye examinations needed to detect prethreshold ROP. We discuss these issues as follows.

In the ETROP study, systemic complications including apnea, bradycardia, and reintubation occurred more frequently when peripheral retinal ablative therapy was performed at high-risk prethreshold than at conventional threshold, probably because of the younger mean postmenstrual age at which the infants with high-risk prethreshold ROP were treated. Ophthalmic complications following retinal ablative therapy were comparable in eyes treated at high-risk prethreshold and conventionally managed eyes, as were ophthalmic complications (other than

retinal detachment) when the entire group of conventionally managed eyes was compared with the group of eyes treated at high-risk prethreshold. One potentially deleterious effect of earlier treatment that was not evaluated in this study is that of peripheral retinal ablation on peripheral vision. It is possible that ablation in zone I will result in a greater loss in visual field extent than peripheral ablation in zone II.

Another issue related to earlier treatment of ROP concerns the treatment of eyes that would have undergone spontaneous regression without treatment. The following question arises: "How many eyes must receive treatment unnecessarily to achieve the benefit of earlier treatment for those eyes that need it?" According to the structural outcome data at 6 months for a cohort of eyes with prethreshold ROP of all degrees of severity that were conventionally managed, it is possible to determine the number of eyes with high-risk prethreshold ROP that had a favorable outcome without peripheral retinal ablation. The results are illustrated in **Tables 11**, **12**, and **13**.

The results are based on a natural history cohort of eyes from 664 infants who had 1 eye identified at prethreshold ROP that was not treated unless the ROP progressed to threshold. These results were used to consider the implications of alternative treatment strategies for managing prethreshold eyes. Included in this natural history cohort were all control eyes in the asymmetric randomized group, the conventionally managed eyes of infants with bilateral high-risk prethreshold disease, and 1 eye selected at random from the infants with low-risk prethreshold disease. Table 11 summarizes the results of an analysis of data from the natural history cohort of prethreshold eyes in the ETROP study. The Table shows that 136 (36.6%) of the 372 high-risk prethreshold eyes in the conventionally managed group that were examined at 6 months had favorable structural outcomes and never developed threshold ROP. In other words, these eyes met the criteria for early treatment, yet without treatment they had a favorable outcome at 6 months.

To reduce the number of eyes treated that would have had a favorable outcome without intervention, additional strategies for selecting eyes for earlier treatment were explored using this same cohort of prethreshold eyes. Table 12 gives the results for eyes classified by ICROP categorization, and it indicates that nearly 100% of zone I eyes were classified as high risk. However, eyes with zone I, stage 1 or 2 ROP without plus disease and eyes with zone II, stage 3 ROP without plus disease had lower rates of progressing to threshold or unfavorable outcome than eyes in the other ICROP categories. In addition, when treated at conventional threshold, those 2 groups of eyes had less than 5% unfavorable structural outcomes.

The results of this analysis along with the results in Tables 8 and 9 led to a clinical algorithm in which treatment should be considered for eyes with zone I, any stage ROP with plus disease; eyes with zone I, stage 3 ROP without plus disease; and eyes with zone II, stage 2 or 3 ROP with plus disease (type 1), with the remaining prethreshold eyes designated as type 2. The outcome results achieved by the proposed grouping of eyes, dividing the cohort into type 1 and type 2 ROP based on the ICROP classification, appear in Table 12. Use of this ICROP-based, limited-selection algorithm would have resulted in the treatment of 91 eyes that showed favorable outcomes and never reached threshold disease. This is a reduction of 33% from the 136 similar eyes that would have been treated using the RM-ROP2 risk model as applied in the ETROP study (Table 11).

If it is assumed that conventional threshold ROP continues to occur in 6% of infants weighing less than 1251 g at birth, as in the CRYO-ROP study,[27] the early-treatment algorithm based on the RM-ROP2 program

Table 11. Structural Outcomes of Low-Risk Prethreshold Eyes and Conventionally Managed High-Risk Prethreshold Eyes at 6 Months Postterm*

	Low-Risk Prethreshold (n = 292)		High-Risk Prethreshold (n = 372)	
6-Month Outcome	Never Developed Threshold	Developed Threshold	Never Developed Threshold	Developed Threshold
Favorable	245	44	136	205
Unfavorable	1	2	4	27

*Data are presented as number of eyes. Low risk was less than 0.15; high risk was 0.15 or greater.

Table 12. Prethreshold Eyes That Reached High-Risk Prethreshold ROP and Prethreshold Eyes That Reached Threshold or Unfavorable Structural Outcome at 6 Months Postterm*

ICROP Category					
Zone	Stage	Plus Disease	Sample Size	High-Risk Prethreshold	Threshold or Unfavorable
I	3	Yes	19	19 (100)	19 (100)
I	3	No	14	14 (100)	9 (64.3)
I	1 or 2	Yes	18	18 (100)	15 (83.3)
I	1 or 2	No	101	93 (92.1)	41 (40.6)
II	3	Yes	172	167 (97.1)	118 (68.6)
II	3	No	274	5 (1.8)	44 (16.1)
II	2	Yes	66	56 (84.8)	37 (56.1)
Total			**664**	**372** (56)	**283** (42.6)
Type 1 ROP			289	274 (94.8)	198 (68.5)
Type 2 ROP			375	98 (26.1)	85 (22.7)

Abbreviations: ICROP, International Classification of Retinopathy of Prematurity[24]; ROP, retinopathy of prematurity.
*Data are presented as number (percentage) unless otherwise indicated. High risk was 0.15 or greater. Plus disease was defined as a degree of dilation and tortuosity of the posterior retinal blood vessels meeting or exceeding that of a standard photograph. Shaded rows represent type 2 ROP.

Table 13. Effect of Using ICROP-Based Criteria to Select Infants for Peripheral Ablative Treatment*

6-Month Outcome	Type 2 Prethreshold (n = 375)		Type 1 Prethreshold (n = 289)	
	Never Developed Threshold	Developed Threshold	Never Developed Threshold	Developed Threshold
Favorable	290	77	91	172
Unfavorable	1	7	4	22

Abbreviation: ICROP, International Classification of Retinopathy of Prematurity.[24]

*Data are presented as number of patients. The ICROP-based criteria refer to type 1 and type 2 retinopathy of prematurity.

would result in the treatment of 9% of infants. The ICROP-based, limited-selection criteria described previously would result in the treatment of 8% of infants while retaining the advantage of early treatment for eyes at highest risk for adverse outcomes.

An alternative approach to using the ICROP-based, limited-selection algorithm is to base treatment on the RM-ROP2 risk model using a risk of 30% or higher instead of 15% or higher as the criterion for early treatment. Because the absolute risk of an unfavorable outcome is low, with a risk range of 0.15 to 0.30 (Tables 8 and 9), and therefore the relative benefit is not as great as in the higher-risk categories, use of the higher-risk criterion would reduce the treatment of eyes that did not progress to threshold while maintaining the benefit of earlier treatment in higher-risk eyes. However, using such a model may be more difficult in a clinical setting than using a revised treatment algorithm based on the eye findings of the ICROP alone.

Timely identification of prethreshold ROP is important to the successful application of an early-treatment program. In the ETROP protocol, infants received follow-up on a weekly basis after developing zone II, stage 2 ROP or if they had retinal vessel immaturity with vessels ending in zone I but no ROP in that zone. Infants with low-risk prethreshold disease received follow-up twice weekly and were treated conventionally unless a change in status caused by the development of more severe ROP resulted in advancement into the high-risk category. Thus, a screening program aimed at identifying eyes for treatment prior to the conventional threshold may require an increase in the number of screening examinations conducted in the neonatal nursery.

The long-term effects of earlier treatment for ROP are as yet unknown. Because visual acuity develops considerably between infancy and childhood and it is possible to measure aspects of visual function in childhood that are not easily assessed in infancy, the National Eye Institute has funded continued follow-up of randomized children in the ETROP study until age 6 years. At that age, recognition visual acuity will be measured with charts from the Early Treatment Diabetic Retinopathy Study.[28] Visual field extent, contrast sensitivity, and ocular status will also be evaluated, and each child's developmental condition will be assessed. This longer follow-up period will give a more detailed evaluation of the effect of earlier treatment on the visual, ophthalmologic, and general developmental status of study participants.

CONCLUSIONS

The results of this study show that it is possible to identify characteristics of ROP that predict which eyes are most likely to benefit from early peripheral retinal ablation. Based on study data, a clinical algorithm was developed to identify eyes with prethreshold ROP that were at highest risk for retinal detachment and blindness while minimizing treatment of prethreshold eyes likely to show spontaneous regression of ROP.

The use of this algorithm circumvents the need for computer-based calculation of low risk or high risk, as was used in this study. The clinical algorithm shows that in most circumstances, peripheral retinal ablation should be considered for any eye with type 1 ROP:

- Zone I, any stage ROP with plus disease
- Zone I, stage 3 ROP with or without plus disease
- Zone II, stage 2 or 3 ROP with plus disease

Plus disease, in this instance, requires at least 2 quadrants (usually 6 or more clock hours) of dilation and tortuosity of the posterior retinal blood vessels and hence the presence of significant disease. The algorithm does not take into account all of the other known risk factors (eg, extent of stage 3 or birth weight), and therefore clinical judgment is required in applying this initial step to the management of ROP. The clinical algorithm also indicates that continued serial examinations as opposed to peripheral retinal ablation should be considered for any eye with type 2 ROP:

- Zone I, stage 1 or 2 ROP without plus disease
- Zone II, stage 3 ROP without plus disease

Treatment should be considered for an eye with type 2 ROP when progression to type 1 status or threshold ROP occurs.

Even with the addition of early treatment for selected eyes with prethreshold ROP, some eyes will still progress to an unfavorable visual and/or structural outcome. Thus, additional research is needed to identify better methods for the prevention and treatment of severe ROP.

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