

# Multicenter Trial of Cryotherapy for Retinopathy of Prematurity

## Ophthalmological Outcomes at 10 Years

Cryotherapy for Retinopathy of Prematurity Cooperative Group

**Objective:** To evaluate outcomes at 10 years after randomization for eyes undergoing cryotherapy vs eyes serving as controls, for patients enrolled in the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP).

**Methods:** The randomized cohort originally consisted of 291 preterm children with birth weights less than 1251 g who developed a defined threshold of ROP severity in one or both eyes. Patients with bilateral threshold ROP (n=240) were randomly assigned to receive cryotherapy to one eye and no cryotherapy to the other eye. Those with ROP of less severity than threshold in the fellow eye ("asymmetric"; n=51) were randomly assigned to cryotherapy or no cryotherapy in the eye with threshold ROP. Ten years later, a tester who was masked to treatment status of each eye measured distance and near visual acuity, with "unfavorable" outcome being 20/200 or worse. Patients also were evaluated by study-certified ophthalmologists who assessed ROP residua primarily in the posterior pole of the fundus, with unfavorable outcome being a posterior retinal fold or worse.

**Results:** For the 247 children examined, both func-

tional and structural primary outcomes showed fewer unfavorable outcomes in treated vs control eyes: 44.4% vs 62.1% ( $P<.001$ ) for distance visual acuity and 27.2% vs 47.9% ( $P<.001$ ) for fundus status. Near acuity results were similar to those for distance (42.5% vs 61.6%;  $P<.001$ ). Total retinal detachments had continued to occur in control eyes, increasing from 38.6% at 5½ years to 41.4% at 10 years, while treated eyes remained stable (at 22.0%). A previously disturbing subgroup trend that more control eyes than treated eyes had visual acuity of 20/40 or better (in the 5½-year report) was no longer present at 10 years; eyes that received cryotherapy were found at least as likely as control eyes to have 20/40 or better visual acuity.

**Conclusions:** At 10 years, eyes that had received cryotherapy were much less likely than control eyes to be blind. A previous trend for a higher proportion of sighted control eyes than sighted treated eyes to show acuity in the normal range was not confirmed. The results show long-term value from cryotherapy in preserving visual acuity in eyes with threshold ROP.

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From the Casey Eye Institute, Oregon Health Sciences University, Portland. The authors have no affiliation with or financial interest in the subject matter or materials discussed in the article (eg, employment, consultancies, stock ownership, honoraria), with the exception of Velma Dobson, PhD, who receives a small royalty from the sale of Teller acuity cards. A complete list of the members of the Cryotherapy for Retinopathy of Prematurity Cooperative Group appears in a box on page 1116.

**P**REVIOUS REPORTS from follow-up examinations of the patients in the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) have demonstrated the beneficial effect of cryotherapy on eyes with threshold ROP, defined as 5 contiguous or 8 cumulative clock hours of stage 3+ retinopathy of prematurity (ROP) in zone I or II.<sup>1-6</sup> In the most recent follow-up report, which presented results from the 5½-year examination,<sup>5</sup> detailed analysis indicated that cryotherapy—despite its benefit—did not seem to increase the chance of attaining recognition visual acuity of 20/40 or better. There was even a disturbing trend for fewer treated eyes than control eyes to achieve acuity in this favorable range.<sup>5</sup> The present report

extends the outcome assessment for these patients to 10 years of age, with the addition of visual acuity measured for near fixation.

*See also pages 1120, 1129, and 1200*

### RESULTS

Of the original cohort of 291 children who participated in the randomized trial, 36 (12.4%) died before the 10-year examination, the most recent death occurring between the 4½-year and 5½-year examinations. All but 8 of the remaining 255 children (97%) returned for the 10-year examination. Of the 8 children who did not return, 4 were previously found blind

## PATIENTS AND METHODS

### PATIENTS

The subjects of this report are the 291 children who participated in the randomized trial of cryotherapy. They were born prematurely between January 1, 1986, and November 30, 1987, had birth weights less than 1251 g, and developed threshold ROP as neonates. Those who developed threshold ROP in both eyes at the same time (bilateral threshold group;  $n=240$ ) were assigned at random to receive cryotherapy to one eye and no cryotherapy to the other eye. If threshold ROP had been reached in only one eye at the time of randomization (asymmetric group;  $n=51$ ), that eye was randomly assigned to receive cryotherapy or no cryotherapy. Randomization occurred at an average postmenstrual age of 37.7 weeks<sup>2</sup> (gestational+postnatal age), ie, generally shortly before the typical due date of full-term birth (40 weeks). Based on examinations performed approximately 10 years after randomization, data were compiled for the present report.

Informed consents were obtained from parents prior to initial study entry, prior to randomization, and prior to participation in the 5½- and 10-year follow-up phases of the study. Complete details concerning patients, sample size determination, standardization of ROP classification, eligibility for randomization, and cryotherapy technique are documented in previous publications.<sup>1-4</sup>

### FUNCTIONAL OUTCOME: VISUAL ACUITY

The primary functional outcome, distance recognition visual acuity, was evaluated by linear Snellen (letter) testing with the log of the minimum angle of resolution (logMAR) visual acuity charts that were used in the Early Treatment Diabetic Retinopathy Study (ETDRS) (Lighthouse, Inc, New York, NY).<sup>7</sup> This chart is a modified version of the standard Snellen chart. Because most ophthalmologists are familiar with the term Snellen to describe letter recognition visual acuity testing, we have used this term to refer to the chart, associated testing procedures, and results.<sup>5</sup>

Best-corrected distance and near monocular acuities were measured by 1 of 2 study-trained and certified testers who were masked to (1) the eye's history of being randomized to cryotherapy vs control status, (2) the ophthalmologist's assessment of visual function, and (3) the fundus outcome of the eye. Acuity was estimated as the Snellen value of the line containing the smallest letter size for which the child could identify correctly 3 of the 5 letters on the line. Full details of testing parameters and techniques for distance acuity testing have been reported previously.<sup>5</sup>

Prior to testing, each child was given a pretest requiring the binocular identification of 10 individual letters 6 cm in height (at a distance of approximately 1.5 m) either by name or by matching to a lap board. If the child correctly identified 9 of 10 consecutive letters, monocular distance Snellen testing was undertaken using the distance ETDRS charts. Standard test distance was 4 m, but testing at 1 m or 50 cm was permitted if needed to obtain an acuity measurement. Children who could not pass the pretest were developmentally unable, were uncooperative, or had extremely low form-discrimination visual capability.

Following distance visual acuity testing, near visual acuity was tested using the Near ETDRS modified Snellen charts (Lighthouse, Inc). Standard test distance was 40 cm, with a luminance of 10 or more candelas per square meter. Testing at 20 cm or 10 cm was permitted, if needed to obtain an acuity measurement. Near correction was provided in the event of aphakia, although such eyes typically had poor acuity.

Children were tested while wearing their current glasses prescription and usually prior to the cycloplegic refraction. If an eye's visual acuity was worse than 20/40, and if the difference between the glasses correction worn during acuity testing and the currently measured refractive error was greater than 1.00 diopters (D) of myopia, greater than 3.5 D of hyperopia, or greater than 1.5 D of astigmatism, then the acuity of that eye was retested with appropriate correction in trial frames. If retesting was conducted after cycloplegia, appropriate lenses were added to correct for test distances of 1 m or closer. In an attempt to avoid the need for formal retesting of children whose myopia had progressed since they had

Continued on next page

in both the treated and the control eyes, 1 with bilateral threshold disease had favorable acuity and fundus outcomes in both eyes, 1 child had favorable acuity in the treated eye and was blind in the control eye, and 2 had "asymmetric" (only one eye randomized) control eyes with favorable acuity and fundus outcomes. Of those 247 children who returned, 202 had a history of bilateral threshold ROP and 45 had a history of asymmetric threshold ROP. Hence, results for 227 treated eyes and 222 control eyes were available for the present analysis. The mean  $\pm$  SD gestational age for the returning children was identical to that of the full cohort ( $26.3 \pm 1.8$  weeks), and the mean birth weight was virtually identical ( $799 \pm 166$  g vs  $800 \pm 165$  g).<sup>2</sup> The 10-year examination was scheduled 10 to 10½ years after randomization, with the children at a median chronologic age of 10.5 years.

Distance Snellen acuity results were obtained for 144 treated and 106 control eyes, and near Snellen acuity results were obtained for 144 treated and 105 control eyes.

An additional 70 treated eyes and 105 control eyes that were blind were included in the Snellen acuity results as blind and not further quantifiable. Fundus outcome data were obtained from 217 treated and 215 control eyes. The **Figure** shows the percentages of treated and control eyes that had an unfavorable outcome. The data show an overall reduction in unfavorable outcomes of 28.5% ( $P<.001$ ) for distance acuity, 31.0% ( $P<.001$ ) for near acuity, and 43.2% ( $P<.001$ ) for fundus structure in eyes randomized to treatment, compared with control eyes. As indicated in **Table 2**, there were 13 treated eyes and 11 control eyes that were not blind, yet could not be tested with the Snellen acuity procedure. These were eyes of children who could not pass the pretest for Snellen acuity testing because of neurodevelopmental delay, lack of cooperation, or extremely poor form-discrimination visual capability. Examination of functional visual outcomes of these eyes on a case-by-case basis, taking into account grating (Teller card) results obtained at earlier

received their glasses, the following manifest refraction protocol was used for distance acuity testing. If distance acuity was below 20/40, the vision tester placed a -0.75 D trial lens power in front of the eye and remeasured acuity. If acuity did not improve to at least 20/40, the trial lens power was increased to -1.50 D and acuity was remeasured. The best recorded acuity was used in the subsequent analysis.

Children were exempt from acuity testing if (1) the examining physician judged the child to have no light perception in either eye and the parents agreed that the child was behaviorally blind, or (2) the examining physician and parents agreed that the child's binocular vision was only light perception or worse and the child had either bilateral and total retinal detachment, bilateral phthisis bulbi, or bilateral enucleation. History of retinal reattachment surgery, including vitrectomy, was not an exclusion criterion.

## STRUCTURAL OUTCOME

Each child underwent a standardized full comprehensive eye examination performed by a study-certified ophthalmologist. At the conclusion of the examination, the ophthalmologist summarized any residua of ROP that were observed in the posterior retina,<sup>8</sup> using the categories described in **Table 1**.

## DATA ANALYSIS

A Mantel-Haenszel test<sup>9-11</sup> was used for combined statistical analysis of the paired-sample data from children with bilateral threshold disease and the independent-sample data from children with asymmetric disease. When data from the subgroup of children with bilateral threshold disease were analyzed by selected demographic characteristics, the McNemar test for correlated proportions was used, as well as exact *P* values calculated from the binomial distribution.

### Visual Acuity

For analysis of distance and near visual acuity data, favorable visual acuity outcome was defined as Snellen scores

of better than 20/200; scores of 20/200 or worse were classified as unfavorable, as were eyes that were exempted from acuity testing due to blindness. For a more detailed analysis, eyes in the favorable category were divided into 3 visual acuity subgroups: (1) better than or equal to 20/40, (2) worse than 20/40 but better than or equal to 20/60, and (3) worse than 20/60 but better than 20/200. Eyes in the unfavorable category were subdivided into those with and without quantifiable acuity scores. Eyes with quantifiable acuity in the unfavorable category included all those that could be assigned a specific acuity score of 20/200 or worse. Since the closest distance at which children's distance acuity was permitted to be tested was 0.5 m, the poorest quantifiable acuity score was 20/1600 (20/200 equivalent letters presented at 0.5 m). Eyes without quantifiable acuity included those without light perception, those with light perception only, those that were exempt from acuity testing due to complete blindness, and those that were able to detect only the 2.2 cm-wide stripes of the "low vision" Teller acuity card. The low vision card was not used to quantify acuity but was presented at different distances and positions to detect the presence of minimal pattern vision. For analyses of numerical acuity results, scores were converted to logarithmic values.

### Fundus

Eyes were categorized as having favorable or unfavorable outcomes, as defined in Table 1. Favorable fundus outcomes included eyes with a normal posterior pole appearance, as well as eyes with certain abnormalities, ie, straightening of the temporal retinal vascular arcade, macular ectopia, extramacular retinal fold, stage 4A partial retinal detachment,<sup>12</sup> or abnormalities anterior to the equator, such as scarring or retinoschisis. Essentially, unfavorable fundus outcomes included eyes that had visibly damaged or optically obstructed foveas, in addition to eyes that had total retinal detachment. Eyes that had undergone retinal reattachment procedures such as vitrectomy or lensectomy subsequent to total retinal detachment were categorized as having unfavorable outcomes,<sup>13</sup> regardless of the current appearance of the posterior pole.

ages, suggested that it was unlikely that the results of these 13 treated and 11 control eyes would change the conclusions obtained with Snellen testing.

There were also 8 children who did not undergo examination of function or structure at age 10 years. Examination of the data available from previous evaluations of structural and functional outcomes of the eyes of these children indicated consistency of outcomes with those of the much larger group of study participants who were examined at 10 years.

## SUBGROUPS

Data analysis in the majority subgroup of 202 children with bilateral threshold ROP likewise showed a statistically significant reduction in percentage of unfavorable outcomes among the treated eyes. Distance Snellen acuity test results showed there were 51 such children with a favorable outcome in the treated eye and an unfavor-

able outcome in the control eye, compared with 15 children who had the opposite discordant outcome of unfavorable in the treated eye and favorable in the control eye ( $P<.001$ ). Results of near Snellen acuity testing in these bilateral threshold cases showed there were 52 children with a favorable outcome in the treated eye and unfavorable in the control eye, and 14 children with the opposite discordance ( $P<.001$ ). Paired comparison of distance and near acuity was examined using  $\kappa$  statistics for perfect agreement, for the categories in Table 2. The visual acuity agreement between these 2 test distances was strong (for treated eyes,  $\kappa=0.66$ ; for control eyes,  $\kappa=0.81$ ; perfect agreement would be  $\kappa=1.00$ ). For fundus outcome, 46 children had a favorable result in the treated eye and an unfavorable result in the control eye, compared with 7 children who showed the opposite discordance ( $P<.001$ ). When analyses were restricted to eyes with zone I ROP, an unfavorable visual acuity outcome was found in 94% (15/16) of treated eyes and 94% (15/

**Table 1. Retinal Outcome Categories****Favorable**

Essentially normal posterior pole (near-periphery and zone I), including angle of vessels  
Abnormal angle of major temporal vascular arcade in the posterior pole  
Macular ectopia  
Stage 4A partial retinal detachment, retinoschisis, or fold in the posterior pole (fovea spared)

**Unfavorable**

Stage 4B partial retinal detachment, retinoschisis, or fold—all with foveal involvement  
View of macula (and presumably patient's central vision) blocked owing to partial cataract, partial retrolental membrane, or partial corneal opacity due to retinopathy of prematurity (ROP)  
Stage 5 retinal detachment, or total retinoschisis, or retrolental membrane  
Entire view of posterior pole and near periphery is blocked by total cataract or total corneal opacity from ROP  
Enucleation for any reason  
Unable to grade  
Unable to determine (eg, view impossible because of corneal opacity unrelated to ROP, or because of miotic pupil)  
None of the above (eg, extreme vascular attenuation, optic atrophy)

16) of control eyes, and an unfavorable structural outcome was found in 88% (14/16) of treated eyes and 94% (15/16) control eyes.

Additional subgroup analyses indicated that the beneficial effect of cryotherapy on both function and structure was independent of birth weight category (<750 g, 750-999 g, or 1000-1250 g), sex, race, single or multiple birth, or whether the child was born in a CRYO-ROP study hospital. As previously reported,<sup>5</sup> there was no evidence of a differential treatment effect based on the extent of stage 3+ ROP at threshold (5 to 12 clock-hour sectors).

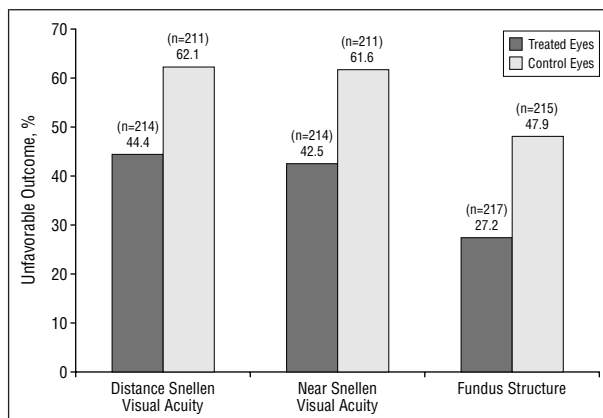
**DETAILED ANALYSIS OF VISUAL ACUITY**

Table 2 shows a more detailed presentation of the distance and near Snellen acuity results. For distance acuity, the percentage of eyes with visual acuity of 20/40 or better that were treated with cryotherapy was similar to that of control eyes, 25.2% vs 23.7% for controls ( $P = .63$ ). Data for eyes in the unfavorable category were divided into measurable acuity worse than 20/200 vs designated blind, ie, acuity was too poor to be quantified. At this low end of the spectrum of function, there were fewer treated eyes than control eyes categorized as blind (32.7% vs 49.8%;  $P < .001$ ).

For near acuity, the percentage of eyes with 20/40 or better was essentially the same in the 2 treatment groups (22.4% for treated eyes and 22.7% for control eyes;  $P = .96$ ); and the percentage of blind eyes was again lower in the treated group (32.7%) than in the control group (50.2%) ( $P < .001$ ).

**FUNDUS DETAILS**

In **Table 3**, data for eyes with favorable structural outcome are divided into either essentially normal posterior pole or mild abnormalities that included abnor-



Percentages of control and treated eyes showing an unfavorable outcome at the 10-year follow-up examination.

mally straightened temporal retinal vessels and macular ectopia. Eyes with unfavorable structural outcome are subgrouped into those with and without total retinal detachment. There are more treated than control eyes with normal-appearing posterior poles (53.5% vs 36.7%, respectively;  $P < .001$ ), while fewer treated than control eyes had total retinal detachment (21.7% vs 41.4%, respectively;  $P < .001$ ).

In addition to assigning the category score for ROP residua in the posterior pole, the examining physician recorded detailed information about structure and function for each eye. **Table 4** presents these data for the children who had bilateral threshold ROP, in whom one eye was treated and the other served as control. Outcome variables are arranged approximately in the order in which they would be encountered during a clinical examination. Results favored treatment for all variables in which there was a significant difference between treated and control eyes.

**COMMENT**

The CRYO-ROP study primarily is devoted to the evaluation of the efficacy and safety of cryotherapy for ROP. In recent years, retinal ablative therapy for ROP in the United States has been performed far more often with laser photocoagulation than with cryotherapy. It is likely that the results of the CRYO-ROP study are relevant to laser treatment for severe ROP, because other studies have suggested that results obtained with laser therapy are similar to those with cryotherapy.<sup>14-19</sup>

Consistent with our previous reports,<sup>3-5</sup> the results at age 10 years indicate a significantly beneficial effect of cryotherapy on visual acuity ( $P < .001$ ) and on the anatomic status of the posterior pole of the fundus ( $P < .001$ ) in eyes that develop severe (defined threshold) ROP during the neonatal period. A detailed list of findings from ophthalmologic examination (Table 4) supports the beneficial effects of cryotherapy for eyes with threshold ROP. Despite the benefit from cryotherapy, treated threshold eyes still have a substantial percentage of unfavorable functional outcomes (44.4%); this reflects the severity of ROP at the time of randomization, as well as the effect of neurological factors of prematurity that can affect visual func-

**Table 2. Visual Acuity Outcome at 10 Years\***

Outcome	Distance Snellen Visual Acuity, No. (%)		Near Snellen Visual Acuity, No. (%)	
	Treated Eye	Control Eye	Treated Eye	Control Eye
Favorable	119 (55.6)	80 (37.9)	123 (57.5)	81 (38.4)
20/40 or better	54 (25.2)	50 (23.7)	48 (22.4)	48 (22.7)
Worse than 20/40, but 20/60 or better	15 (7.0)	7 (3.3)	42 (19.6)	14 (6.6)
Worse than 20/60, but better than 20/200	50 (23.4)	23 (10.9)	33 (15.4)	19 (9.0)
Unfavorable	95 (44.4)	131 (62.1)	91 (42.5)	130 (61.6)
Equal to or worse than 20/200	25 (11.7)	26 (12.3)	21 (9.8)	24 (11.4)
Blind (not quantifiable)	70 (32.7)	105 (49.8)	70 (32.7)	106 (50.2)
Missing evaluation	13	11	13	11
<b>Total</b>	<b>227</b>	<b>222</b>	<b>227</b>	<b>222</b>

\*Percentages were computed for eyes that could be evaluated. Eyes missing evaluations were of children who could not be tested because of neurodevelopmental delay, lack of cooperation, or extremely poor form-discrimination visual capability.

**Table 3. Retinal Structural Outcome Categories at 10 Years Based on Most Severe ROP Residua\***

Diagnosis	No. (%)†	
	Treated Eye	Control Eye
Favorable	158 (72.8)	112 (52.1)
Normal	116 (53.5)	79 (36.7)
Mild abnormality	42 (19.4)	33 (15.3)
Unfavorable	59 (27.2)	103 (47.9)
Unfavorable, but not total retinal detachment	10 (4.6)	8 (3.7)
Total retinal detachment‡	47 (21.7)	89 (41.4)
Other unfavorable	2 (0.9)	6 (2.8)
Unable to be categorized	10	7
<b>Total</b>	<b>227</b>	<b>222</b>

\*ROP indicates retinopathy of prematurity; normal, no retinal abnormalities posterior to the equator except for abnormal angle of temporal vessels; mild abnormality, macular ectopia or partial retinal detachment or fold that spared the fovea; unfavorable, but not total retinal detachment, view of macula blocked by cataract, retrolental membrane, or corneal opacity owing to ROP; total retinal detachment, eyes with view of fundus blocked by total retrolental membrane or corneal opacity owing to ROP; and other unfavorable, enucleation.

†Percentages were computed for eyes that could be categorized.

‡Eyes that had undergone a vitrectomy are included in this category.

tion, eg, hydrocephalus, intracerebral hemorrhage, and periventricular leukomalacia<sup>20,21</sup> with subsequent optic atrophy or hypoplasia due to transsynaptic degeneration. Optic atrophy occurred in similar proportion in both treated and control eyes that could be assessed for this variable. Premature infants with enlarged cerebral ventricles as a sequela of neonatal intracranial hemorrhage,<sup>22</sup> as well as those with cystic periventricular leukomalacia, seem more likely to have visual impairment on a neurological basis.<sup>23</sup> Several authors have reviewed and discussed the association between ROP and central nervous system sequelae,<sup>24,25</sup> and severity of ROP is significantly correlated with functional neurodevelopmental outcomes among our studied children.<sup>26</sup>

### VISUAL ACUITY

Data collected at the 10-year examination provide a more complete assessment of visual acuity than was obtained at earlier examinations, owing to a high follow-up rate

of 97% (247/255) and the increased maturity and cooperation of the children. The visual acuity benefit of cryotherapy at 10 years is represented by a decrease in the proportion of eyes with poor acuity ("legally blind" at 20/200 or worse) and an increase in the proportion of eyes with acuity better than 20/200.

In the highest vision category, the finding of similar percentages of eyes with 20/40 or better visual acuity in both treated and control groups at 10 years (Table 2) differs from data for eyes examined at age 5½ years.<sup>5</sup> At 5½ years, there were more control eyes than treated eyes with acuity in the 20/40 or better range (13.4% vs 20.0%;  $P = .06$ ), raising the possibility of a detrimental effect of neonatal cryotherapy on visual acuity outcome in the best-sighted group of eyes with a history of threshold ROP. In the present report, the number of children who could complete visual acuity testing with the ETDRS charts was increased over that at 5½ years, due to an increase in the proportion of children who could pass the pretest from 86.5% at 5½ years to 94.7% at 10 years, and to an increase in the follow-up rate from 91.8% at 5½ years to 96.9% at 10 years. With this increased sample size, the potential adverse effect of cryotherapy on the development of normal visual acuity seen at the 5½-year examination was not confirmed, suggesting that cryotherapy did not damage foveal acuity. Testers were not instructed to attempt acuity better than 20/40, yet there were several treated and control eyes noted to have 20/20 acuity, revealing that such good acuity is potentially achievable after threshold ROP, with or without cryotherapy.

### CHANGES IN ANATOMIC OUTCOMES

These 10-year outcome data provide evidence that both mild and severe ocular structural defects in the randomized children do not necessarily remain stable over time. Compared with previous data, we find that the net prevalence of mild abnormalities (macular ectopia and partial retinal detachment sparing the fovea) decreased slightly in both control and treated eyes. For control eyes, the prevalence was 21.7% at 5½ years and 15.3% at 10 years. In eyes treated with cryotherapy, the proportion of eyes that have macular ectopia as the worst ROP sequela decreased from 23.6% to 19.4% during this same period. These changes are concordant with the increase

**Table 4. Outcome Variables of Children With Bilateral Threshold ROP\***

Variable	% Present		% Unable to Assess/Uncertain		Discordant Pairs	P
	Treated Eyes	Control Eyes	Treated Eyes	Control Eyes		
Fixation behavior						
Unmaintained	38.1	57.5	6.4	10.4	49/15	<.001
Questionable or no light perception	18.6	35.2	1.5	4.5	41/8	<.001
Corneal clouding owing to ROP	9.0	17.0	1.5	4.0	24/10	.02
Depth of anterior chamber, shallow or flat	12.2	15.6	6.4	10.9	18/12	.36
Afferent defect of pupillary light reaction	3.2	11.7	7.4	15.3	19/5	.006
Peripheral retrolental tissue present	5.8	15.3	14.9	28.7	12/1	.003
Posterior synechiae present	8.0	16.5	1.5	4.0	22/8	.02
Clinically apparent cataract, or aphakia	20.5	30.8	5.9	14.9	30/10	.002
Cataract obscuring view of fovea	4.8	13.2	6.9	17.3	18/6	.02
Optic atrophy	17.2	15.5	22.3	45.5	7/2	.18
Glaucoma or history of glaucoma	4.7	11.0	5.0	10.4	12/1	.003
Opaque cornea present	7.0	19.6	1.5	4.0	34/9	<.001
Pupil closed	5.2	10.1	5.4	16.3	14/5	.06
Total retrolental membrane/retinal detachment	11.6	23.8	10.4	25.2	19/3	<.001
Abnormal angle of insertion of vessels	40.3	43.2	23.8	45.0	15/7	.13
Retinal fold in zone I	5.7	9.8	22.3	44.6	9/1	.02
Foveal ectopia	20.4	26.1	24.8	45.0	17/9	.17
Macular pigmentary disturbance	18.7	15.6	23.3	46.0	6/10	.45

\*Sample size is 202 for all variables. ROP indicates retinopathy of prematurity.

in the rates of normal-appearing posterior structural findings in control and treated eyes (from 32.9% at 5½ years to 36.7% at 10 years for control eyes, and from 49.5% at 5½ years to 53.5% at 10 years for treated eyes). In the absence of photographic documentation, it cannot be determined whether this represents true improvement in some cases, or simply the random vacillations of judgment that are inherently associated with equivocal findings.

Rates of total retinal detachment reported among the control eyes over time were relatively stable at 3 months, 1 year, and 3½ years (32.4%, 33.0%, and 34.1%, respectively), but an apparent increase at 5½ years (38.6%) continued at 10 years (41.4%). In contrast, among the treated eyes, no appreciable trend toward increasing detachments was observed (3 months [18.0%], 1 year [18.3%], 3½ years [20.3%], 5½ years [22.1%], and 10 years [21.6%]).<sup>1-5</sup> This comparison of treated vs control eyes suggests enduring benefit from cryotherapy.

Late rhegmatogenous retinal detachments due to ROP tend to occur between the ages of 5 and 15 years.<sup>27</sup> Tasman<sup>28</sup> stated that these most commonly occur at age 14 years, compared with a mean age of 5.7 years for tractional or exudative detachments from ROP. Such reports have provided no denominators with which to determine the frequency of these acquired catastrophes. Continued follow-up beyond 10 years in our prospective cohort should permit estimates of late retinal detachment rates in both treated and control eyes. Such data would bear on the need for vigilant monitoring in clinical practice, and facilitate the prospective counseling of patients.

Although the results we have presented and discussed are encouraging, surgical treatment for threshold ROP does involve ablation of peripheral retina. One

would expect such eyes to demonstrate a reduction in visual field extent even if retinal detachment is prevented. Indeed, several previous reports of small studies have suggested that visual fields are constricted in eyes of children who have undergone peripheral retinal cryotherapy or laser photocoagulation for severe ROP.<sup>29-31</sup> We previously reported results of white-sphere kinetic perimetry<sup>32</sup> in a subset of the CRYO-ROP study population at the 5½-year examination.<sup>33</sup> The data showed an average visual field reduction of approximately 6° in treated eyes compared with untreated control eyes of patients who had sight in both their treated eye and control eye. Goldmann perimetry was conducted as part of the 10-year CRYO-ROP study examination, and a detailed analysis will be the subject of another report.

## IMPLICATIONS

Even allowing for a modest constriction of visual field due to peripheral retinal ablation, the risk-benefit ratio clearly favors treatment of the more severe (threshold) cases of ROP. Our previously expressed concern about an unanticipated adverse side effect of cryotherapy on visual acuity outcome<sup>5</sup> is allayed by the finding at 10 years that cryotherapy does not reduce the proportion of eyes that achieve acuity of 20/40 or better. It appears that constriction of the peripheral visual field may represent the only undesirable side effect likely to be seen during the first decade of life following cryotherapy for threshold ROP.

Results from the CRYO-ROP study indicate that, even with treatment, acuity outcomes for eyes with confirmed threshold ROP are favorable in only slightly more than half of the eyes. Does this finding, in combination with the acceptable level of adverse effects attributable

The CRYO-ROP investigators who participated during the 10-year examination period are as follows:

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to cryotherapy, and the improved convenience of laser therapy,<sup>17</sup> mean that ophthalmologists should begin to intervene with treatment at a milder disease category than the research-designed "threshold" that was used in the CRYO-ROP study? Data from the CRYO-ROP study cannot answer this question, but our natural outcome data<sup>34</sup> do suggest that treatment of milder ROP will result in the unnecessary treatment of a substantial number of eyes. Because zone I ROP carries the possibility of rapid progression to retinal detachment<sup>35</sup> and showed a high proportion of unfavorable functional and structural outcomes in the present study, a certain clinical bias toward earlier treatment for zone I ROP is understandable. Nevertheless, a randomized study of earlier intervention for zone I ROP did not show it to be advantageous.<sup>36</sup> The overwhelming majority of eyes with ROP less severe than the threshold severity defined and used for the CRYO-ROP study have good structural outcome and will likely have good visual function.<sup>5,34,37</sup> Thus, ophthalmologists who treat at any severity level less than that threshold should recognize that their good success could be entirely due to the good prognosis for these eyes, even without treatment.

Continuing well-designed research is needed to identify more effective ways of preventing or treating ROP. One potential approach to therapy is to use the known additional risk factors for individual infants beyond the classification of the infant's ROP to predict the likelihood of reaching threshold severity. These additional risk factors include "infant" variables such as birth weight and gestational age, as well as the rate of progression of ROP in the eye.<sup>37</sup> Based on such data, a multifactorial risk analysis program (Risk Management of ROP; RM-ROP) has been developed that can predict the likelihood for an eye to progress to threshold ROP and from there to an unfavorable functional outcome.<sup>38</sup> This program can be downloaded from the Internet at <http://www.sph.uth.tmc.edu/rmrop/>. Even though the program is based on the actual historical and outcome data of the CRYO-ROP study, it has not been adequately tested in a clinical setting, and consequently must still be considered theoretical. Thus, while the program may serve as a guideline for predicting progression of ROP, there remain many "soft" factors, such as interexaminer variation in ROP classification standards, the concordance of ROP severity between the 2 eyes, the current state of vigor of the infant, and the attitude of the infant's family, that must enter into the clinician's decision concerning the indications for treating relatively advanced ROP.

The National Eye Institute has funded a study that uses a modified version (RM-ROP2) of the risk analysis program, which predicts the likelihood of an unfavorable structural outcome at several points during the clinical course of ROP, from the onset of ROP throughout its progression. This new Early Treatment for ROP study is designed to determine whether using this method to select eyes for treatment prior to attainment of the classic threshold of severity will improve outcomes in those eyes.

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