

Outcome of Eyes Developing Retinal Detachment During the Early Treatment for Retinopathy of Prematurity Study

Michael X. Repka, MD; Betty Tung, MS; William V. Good, MD; Antonio Capone Jr, MD; Michael J. Shapiro, MD

Objective: To describe the structural and visual outcomes at age 6 years of retinal detachment (RD) from retinopathy of prematurity (ROP) in the Early Treatment for Retinopathy of Prematurity (ETROP) study.

Methods: Prospective multicenter nonrandomized series of infants with high-risk prethreshold ROP who developed an RD by 6 months corrected age treated with observation or vitreoretinal surgery.

Results: Of 401 patients, 63 (89 eyes) experienced RD. Follow-up at age 6 years was available for 70 eyes (79%) of 49 surviving patients. The RDs were stage 4A in 28 eyes (40%), stage 4B in 14 (20%), stage 5 in 13 (19%), and not classi-

fied in 15 (21%). The macula was attached in 17 of 50 eyes (34%) after vitrectomy with or without scleral buckle, in 6 of 9 (67%) after scleral buckle only, and in 2 of 11 eyes (18%) observed. An attached macula at age 6 years after vitreoretinal surgery was present in 5 of 16 eyes (31%) with stage 4A, 6 of 10 (60%) with stage 4B, and 0 of 10 with stage 5. Favorable visual acuity ($>20/200$) was found in 6 of 70 eyes (9%); 5 had stage 4A, and 1 was not classified.

Conclusions: Macular attachment was achieved in approximately one-third of eyes with RD and favorable visual acuity in some eyes with stage 4A.

Arch Ophthalmol. 2011;129(9):1175-1179

RETINAL ABLATION IMPROVES the structural and functional outcomes of children with severe retinopathy of prematurity (ROP).¹⁻³ However, such therapy does not always prevent progression of disease to retinal detachment (RD). Case series^{4,5} have shown that scleral buckling and vitrectomy techniques can successfully reattach the retina of children with stage 4 or stage 5 ROP. However, the visual results after such interventions have been disappointing.⁴⁻⁹ An exception has been the treatment of stage 4A with scleral buckling or lens-sparing vitrectomy, where better structural and visual outcomes have been reported in several case series.^{5,10-13}

The Early Treatment for Retinopathy of Prematurity (ETROP) Cooperative Group compared ablative therapy of high-risk prethreshold eyes with conventional management (ablative retinal surgery for control eyes on reaching threshold or observation of control eyes if the threshold was not reached). The investigators found that early treatment of eyes with high-risk prethreshold ROP significantly improved the structural and functional outcomes.^{1,3} Some eyes progressed to RD. Treatment of RD was not part of the study

protocol, and, therefore, eyes with an RD were observed or treated, with timing and procedure(s) (scleral buckling, vitrectomy, or both) at the investigator's discretion. We previously reported the structural and functional outcomes for those eyes at 9 months corrected age. In this study, we provide follow-up through 6 years of age and the incidence of new RDs in the ETROP cohort.

METHODS

Premature infants with birth weights less than 1251 g who developed ROP were followed prospectively with standardized data collection in the ETROP study at 26 centers between October 1, 2000, and September 30, 2002. The study protocol was approved by investigational review boards at each participating nursery, and written informed consent was obtained from parents and guardians for all the study procedures. Details of the protocol risk model have been previously published.^{1,14,15} Follow-up examinations continued to 6 years of age.

STUDY ELIGIBILITY

Eligible children had at least 1 eye randomized in the ETROP study. Eyes that are included had been randomized to either conventional management or early ablative treatment

Author Affiliations: Wilmer Eye Institute and Department of Pediatrics, The Johns Hopkins University, Baltimore, Maryland (Dr Repka); School of Public Health, University of Texas, Houston (Ms Tung); Smith-Kettlewell Eye Research Institute, San Francisco, California (Dr Good); Associated Retinal Consultants, William Beaumont Hospital—Oakland University School of Medicine, Royal Oak, Michigan (Dr Capone); and Department of Ophthalmology and Visual Sciences, University of Illinois—Chicago, Chicago (Dr Shapiro).

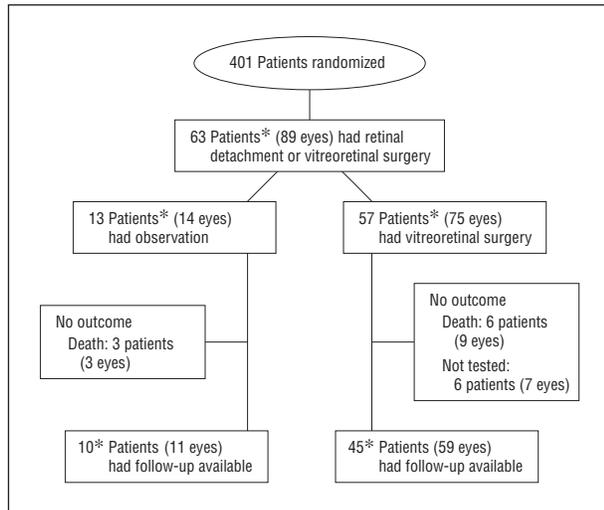


Figure. Flow diagram of patients and eyes with retinal detachment. Two patients developed a retinal detachment after 9 months corrected age and are excluded from this figure. *Six patients had 1 eye in each group.

of high-risk prethreshold ROP and had at least 1 clock hour of RD seen in any zone before the examination at 9 months corrected age. In addition, the performance of vitreoretinal surgery before study examination at 9 months corrected age was considered evidence of RD if a study form was not completed preoperatively (15 eyes). It is possible that vitrectomy was performed in these eyes for other indications. A confirming examination of the RD was not required.

A second and separate group of patients included herein is those with no RD at 9 months with detachment at 6 years. A total of 535 eyes did not have an RD before 9 months and had 6-year follow-up examinations.³ The number and characteristics of eyes with a “late” detachment are described.

PROCEDURES

Eyes that developed RD were not randomized. For eyes undergoing vitreoretinal surgery, the indications, timing, and technique were not specified by the ETROP study protocol but were chosen and performed at the discretion of the surgeon. For this study, vitreoretinal surgery includes vitrectomy, scleral buckling, or both. Procedures were performed by vitreoretinal surgeons located at ETROP clinical centers and by surgeons at non-participating facilities.

Study-certified ophthalmologists conducted retinal examinations at 6 years of age. The status of the retina was categorized as normal, straightened temporal retinal vessels, macular ectopia, partial RD excluding the macula (stage 4A), partial RD including the macula (stage 4B), total RD (stage 5), and uncertain.¹⁶ Echography was used at the discretion of the examining physician.

Recognition letter optotype testing was performed at 6 years of age by traveling study-certified testers masked to the child's treatment. The Early Treatment Diabetic Retinopathy Study (ETDRS) charts were used with a maximum distance of 3 m (Precision Vision, LaSalle, Illinois) following a standardized protocol.³ Visual acuity testing was not undertaken on children who could not perform the test because of developmental limitations or if any of the following were present in both eyes: light perception or worse vision, RDs, phthisis bulbi, or enucleation. Visual acuity results on ETDRS testing were categorized as normal ($\geq 20/40$), below normal ($< 20/40$ to $> 20/200$), poor (measurable acuity of $\leq 20/200$), or blind/low vision/light perception. Favorable acuity was defined by the ETROP study group as better than 20/200.

The study records of 401 randomized patients were reviewed for the presence of an RD or the performance of vitreoretinal surgery (**Figure**). Retinal detachment and vitreoretinal surgery were reported in 89 eyes of 63 patients.

Of the 13 infants (14 eyes) who did not undergo surgery, 3 died before the 6-year outcome examination, leaving 11 observation eyes from 10 patients for analysis. Vitreoretinal surgery was performed in 75 eyes of 57 patients. Of those who underwent surgery, 6 infants died (9 eyes) and 6 infants were not examined (7 eyes), leaving 59 eyes from 45 patients evaluated at age 6 years. Thus, 70 of 89 eyes originally reported (79%) from 55 infants with RD were available for analysis. The 70 RDs were classified as stage 4A in 28 eyes (40%), stage 4B in 14 eyes (20%), stage 5 in 13 eyes (19%), and not classified in 15 eyes (21%). Twenty-six of these 70 eyes (37%) had been randomized to early ablative treatment, and 44 (63%) had conventional management with laser ablation when they reached the study threshold. The 49 surviving patients who underwent surgery had a mean birth weight of 715 g and a mean postmenstrual age at birth of 25.1 weeks. The age at vitreoretinal surgery was not collected, although surgery was performed before 9 months corrected age.

STRUCTURAL OUTCOME

At 6 years of age, attachment of the macula was noted in 25 of 70 eyes (36%). Two of 11 eyes (18%) had macular attachment after observation, 6 of 9 (67%) after scleral buckle only, and 17 of 50 (34%) after vitrectomy with or without scleral buckle (**Table 1**).

The eyes that underwent vitrectomy surgery were subdivided by International Classification of Retinopathy of Prematurity classification of the RD at the time of the first vitreoretinal procedure (Table 1). After surgery, an attached macula was present in 5 of 16 eyes (31%) with stage 4A before surgery, 6 of 10 with stage 4B before surgery (60%), and 0 of 10 with stage 5 before surgery.

The 50 eyes that underwent vitrectomy were subdivided by initial randomization with the structural outcomes listed in **Table 2**. Early treatment and conventional management had similar rates for partial and total reattachment.

FUNCTIONAL OUTCOME

Favorable visual acuity was found in 6 eyes (1 normal and 5 below normal) (**Table 3**). Of children with favorable visual acuity at age 6 years, 5 had been stage 4A, and the sixth eye was not classified. Of eyes with favorable visual acuity, 5 of 6 followed vitreoretinal surgery. Unfavorable acuity outcomes were classified into 4 categories: poor but measurable in 9 eyes, low vision card in 9 eyes, light perception in 7 eyes, and no light perception in 30 eyes. Vitreoretinal surgery for stage 5 ROP produced no eyes with better than light perception vision.

Table 1. Structural Outcome 6 Years After Observation or Treatment for RD

Treatment by Preoperative ROP Stage at 6 mo	Structural Outcome at 6 y, No. of Eyes							
	Normal Posterior Pole	Totally Attached	Macula Attached (Stage 4A)	Some Retina Attached (Stage 4B)	Stage 4C ^a	Total RD (Stage 5)	Unable to Grade ^b	Total
Observation								
4A	2	0	0	1	0	2	1	6
4B	0	0	0	0	0	2	0	2
5	0	0	0	0	0	2	1	3
Scleral buckling								
4A	1	4	0	0	0	0	1	6
4B	0	0	0	0	0	2	0	2
Not classified or missing	1	0	0	0	0	0	0	1
Vitreectomy with or without scleral buckling								
4A	0	5	0	5	0	6	0	16
4B	1	4	1	1	0	2	1	10
5	0	0	0	1	2	7	0	10
Not classified or missing	1	5	0	1	0	7	0	14

Abbreviations: RD, retinal detachment; ROP, retinopathy of prematurity.

^aStage 4C was defined by the study group to be a partial RD in which the macula cannot be seen because of cataract, corneal opacity, retrolental membrane, or other obstruction.

^bIndicates unable to grade because of inability to examine the retina.

Table 2. Structural Outcome at 6 Years for the Vitrectomy Subgroup by ETROP Randomization: Early Treatment Compared With Conventional Management

Treatment	Structural Outcome at 6 y, No. of Eyes							
	Normal Posterior Pole	Totally Attached	Macula Attached (Stage 4A)	Some Retina Attached (Stage 4B)	Stage 4C ^a	Total RD (Stage 5)	Unable to Grade ^b	Total
Conventional management	2	8	0	6	1	16	1	34
Early treatment	0	6	1	2	1	6	0	16

Abbreviations: ETROP, Early Treatment of Retinopathy of Prematurity; RD, retinal detachment.

^aStage 4C was defined by the study group to be a partial RD in which the macula cannot be seen because of cataract, corneal opacity, retrolental membrane, or other obstruction.

^bUnable to grade because of inability to examine retina.

STRUCTURE AND FUNCTION AFTER VITREORETINAL SURGERY

The impact of the structural outcome on function is given in **Table 4** for the 59 eyes that had vitreoretinal surgery. Total retinal attachment was a reliable indicator of measurable visual acuity at 6 years. Of the 22 eyes with retinas totally attached, 11 (50%) had measurable ETDRS visual acuity. Only 2 of 8 eyes with a portion of retina attached had measurable acuity, poor in both cases. Light perception was reported rarely by patients with total detachments. There were 11 eyes after vitreoretinal surgery with retinal attachment and measurable ETDRS visual acuity (Table 4). In these patients, 4 fellow eyes were stage 1, 3 were stage 2, 2 were stage 3, and 1 each were stages 4B and 5A.

“LATE” DETACHMENT AFTER 9 MONTHS

Of the 535 eyes that had no RD through the examination at 9 months corrected age, only 2 developed a detachment before age 6 years. The first patient had macular ectopia at 9 months, with a stage 4B detachment at 6

years and poor visual acuity by ETDRS testing. The second child had normal examination findings at 9 months, with a stage 5B detachment (closed funnel) at 6 years and vision that could not be graded.

COMMENT

Early retinal ablative treatment of high-risk prethreshold ROP reduced the rate of unfavorable structural and functional outcomes through 6 years of age.^{1,3} However, RD occurred in 89 of 718 randomized eyes (12%) before 9 months corrected age.¹ In the ETROP study, infants with an RD were observed or underwent vitreoretinal surgery at the discretion of the individual investigator. There was no protocol for management of patients with an RD. Vitreoretinal surgery for RD in the ETROP study was associated with macular attachment in 17 of 56 eyes (30%) at 9 months corrected age. Visual acuity outcomes using forced-choice preferential looking at 9 months corrected age were poor.⁵

This study describes the structural and functional outcomes of eyes with RD associated with ROP at age 6 years.

Table 3. ETDRS Visual Acuity Outcome at 6 Years for Children With Retinal Detachment After Observation or Treatment

Treatment by Preoperative ROP State at 6 mo	ETDRS Outcome at 6 y, No. of Eyes ^a							Total
	Favorable		Unfavorable					
	Normal	Below Normal	Poor	Low Vision Card Only	Light Perception Only	No Light Perception	Unable to Perform	
Observation								
4A	1	0	1	2	1	0	1	6
4B	0	0	0	0	0	2	0	2
5	0	0	0	0	1	1	1	3
Scleral buckling								
4A	0	3	1	0	0	1	1	6
4B	0	0	0	0	0	1	1	2
Not classified or missing	0	0	0	1	0	0	0	1
Vitreotomy with or without scleral buckling								
4A	0	1	2	4	1	7	1	16
4B	0	0	2	1	1	3	3	10
5	0	0	0	0	1	8	1	10
Not classified or missing	0	1	3	1	2	7	0	14

Abbreviations: ETDRS, Early Treatment Diabetic Retinopathy Study; ROP, retinopathy of prematurity.

^aETDRS visual acuity categories: normal (20/40 or better), below normal (worse than 20/40 to 20/200), and poor (measurable but worse than 20/200).

Table 4. Correlation of Structure and Function for 59 Eyes Undergoing Vitreoretinal Surgery

ETDRS Outcome at 6 y ^a	Structural Outcome at 6 y, No. of Eyes						Total (%)
	Totally Attached	Macula Attached (Stage 4A)	Some Retina Attached (Stage 4B)	Stage 4C ^b	Total RD (Stage 5)	Unable to Grade	
Favorable ETDRS acuity	5	0	0	0	0	0	5 (8)
Poor but measurable ETDRS acuity	6	0	2	0	0	0	8 (14)
Low vision card only	3	0	3	0	1	0	7 (12)
Light perception only	0	0	1	0	4	0	5 (8)
No light perception	6	0	1	2	17	1	27 (46)
Unable to perform	2	1	1	0	2	1	7 (12)

Abbreviations: ETDRS, Early Treatment Diabetic Retinopathy Study; RD, retinal detachment.

^aETDRS visual acuity categories: normal (20/40 or better), below normal (worse than 20/40 to 20/200), and poor (measurable but worse than 20/200).

^bStage 4C was defined by the study to be a partial RD in which the macula cannot be seen because of cataract, corneal opacity, retrolental membrane, or other obstruction.

Attachment of the macula was present in 25 of 70 eyes (36%) irrespective of treatment and in 23 of the 59 eyes (39%) that underwent vitreoretinal surgery and were available for analysis. Regarding visual acuity, 6 children had favorable ETDRS visual acuity at age 6 years. Of these eyes, 5 of 6 had been stage 4A and the other was not classified. No eye with stage 5 developed vision better than light perception. For stage 4B, vision was restored in 2 eyes to poor. These results are worse than those reported at 9 months corrected age, likely due to the more demanding optotype test of visual acuity used at age 6 years.

The 6-year visual function was compared with the final retinal structure. Total retinal reattachment was reported in 22 eyes. These eyes had a 23% chance of a favorable visual outcome as defined by the study group. Partial reattachment was rarely associated with measurable visual acuity and never with a favorable level. However, the cause of poor vision after successful reattachment is uncertain. Most of the fellow eyes of patients successfully undergoing vitreoretinal surgery with mea-

surable visual acuity were less severely affected. These results are consistent with the findings of the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study, which found poor visual outcomes with observation of a partial detachment in the late 1980s¹⁷ and no useful vision with either observation or vitreoretinal surgery for stage 5 disease.⁹

In the ETROP study, vitrectomy for stage 4A was not as successful as reported in other case series.^{5,10-13} Outcomes in the ETROP study may vary from such single-center series because of differing indications, timing of surgery, or experience of the vitreoretinal surgeons. For example, some researchers have suggested that vitreoretinal surgery should be considered earlier in the disease course to achieve better attachment rates than were seen in the CRYO-ROP and ETROP studies.^{10,11,13,18} Conversely, the ETROP study results may represent more generalizable outcomes.

The strengths of this study include its multicenter prospective design, standardized acuity testing, masked vi-

sual acuity testers, and 6 years of follow-up. There are important limitations to this study. First, the few eyes in each treatment category prevents comparison. Second, the classification of the RD in 15 eyes was not recorded before surgery. Third, there was no randomization of treatment of the RD. Fourth, there was no standardized approach for the indications, timing, and techniques of vitreoretinal surgery. Surgeons recommended vitreoretinal surgery for differing levels of severity of ROP and had varying experience. Fifth, the timing of surgical intervention was not standardized. In some cases, timely vitreoretinal surgery may not have been performed because of other medical issues for the infants.

We observed late RDs in children with a history of successful ablative therapy for high-risk ROP and attached retinas at 6 months corrected age.¹⁹⁻²¹ The rate of late RDs was low, with only 2 of 535 eyes affected by age 6 years. Our rate is much lower than that reported by Smith and Tasman,²¹ perhaps because they had longer follow-up (mean, 35 years), their case series did not have complete cohort follow-up, and their patients had not been treated with retinal ablation. Despite the low rate of late RD, we advocate periodic retinal examination in children with treated ROP because late detachments may be asymptomatic, as they may commence in the retinal periphery, and occur in children with an attached retina in their fellow eye.

In conclusion, assessment of eyes with RD from ROP in the ETROP study at age 6 years found few children with favorable vision and then only after repair of stage 4A disease. Vitrectomy for stage 4A eyes was associated with macular attachment in 31% (5 of 16), with favorable vision noted in 6% (1 of 16). Vitrectomy for stage 5 produced 1 of 10 eyes with peripheral retinal reattachment and 1 of 10 eyes with light perception. These data confirm the difficulty of successfully reattaching the retina and obtaining useful vision once the RD has progressed to include the macula.

Submitted for Publication: December 22, 2010; final revision received March 16, 2011; accepted March 18, 2011.

Correspondence: Michael X. Repka, MD, Wilmer Eye Institute, Wilmer 233, 600 N Wolfe St, Baltimore, MD 21287-9028 (mrepka@jhmi.edu).

Financial Disclosure: None reported.

Funding/Support: This study was supported by cooperative agreements 5U10 EY12471 and 5U10 EY12472 with the National Eye Institute, National Institutes of Health.

1. Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the Early Treatment for Retinopathy of Prematurity randomized trial. *Arch Ophthalmol.* 2003;121(12):1684-1694.
2. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter Trial of Cryotherapy for Retinopathy of Prematurity: ophthalmological outcomes at 10 years. *Arch Ophthalmol.* 2001;119(8):1110-1118.
3. Good WV, Hardy RJ, Dobson V, et al; Early Treatment for Retinopathy of Prematurity Cooperative Group. Final visual acuity results in the Early Treatment for Retinopathy of Prematurity Study. *Arch Ophthalmol.* 2010;128(6):663-671.
4. Trese MT, Droste PJ. Long-term postoperative results of a consecutive series of stages 4 and 5 retinopathy of prematurity. *Ophthalmology.* 1998;105(6):992-997.
5. Repka MX, Tung BG, Good WV, et al. Outcome of eyes developing retinal detachment during the Early Treatment for Retinopathy of Prematurity Study (ETROP). *Arch Ophthalmol.* 2006;124(1):24-30.
6. Greven C, Tasman W. Scleral buckling in stages 4B and 5 retinopathy of prematurity. *Ophthalmology.* 1990;97(6):817-820.
7. Noorily SW, Small K, de Juan E Jr, Machermer R. Scleral buckling surgery for stage 4B retinopathy of prematurity. *Ophthalmology.* 1992;99(2):263-268.
8. Quinn GE, Dobson V, Barr CC, et al. Visual acuity in infants after vitrectomy for severe retinopathy of prematurity. *Ophthalmology.* 1991;98(1):5-13.
9. Quinn GE, Dobson V, Barr CC, et al; Cryotherapy for Retinopathy of Prematurity Cooperative Group. Visual acuity of eyes after vitrectomy for retinopathy of prematurity: follow-up at 5 1/2 years. *Ophthalmology.* 1996;103(4):595-600.
10. Hinz BJ, de Juan E Jr, Repka MX. Scleral buckling surgery for active stage 4A retinopathy of prematurity. *Ophthalmology.* 1998;105(10):1827-1830.
11. Capone A Jr, Trese MT. Lens-sparing vitreous surgery for tractional stage 4A retinopathy of prematurity retinal detachments. *Ophthalmology.* 2001;108(11):2068-2070.
12. Prenner JL, Capone A Jr, Trese MT. Visual outcomes after lens-sparing vitrectomy for stage 4A retinopathy of prematurity. *Ophthalmology.* 2004;111(12):2271-2273.
13. Hubbard GBI III, Cherwick DH, Burian G. Lens-sparing vitrectomy for stage 4 retinopathy of prematurity. *Ophthalmology.* 2004;111(12):2274-2277.
14. Hardy RJ, Palmer EA, Schaffer DB, Phelps DL, Davis BR, Cooper CJ; Multicenter Trial of Cryotherapy for Retinopathy of Prematurity Cooperative Group. Outcome-based management of retinopathy of prematurity [published correction appears in *J AAPOS.* 1997;1(3):137]. *J AAPOS.* 1997;1(1):46-54.
15. Hardy RJ, Palmer EA, Dobson V, et al; Cryotherapy for Retinopathy of Prematurity Cooperative Group. Risk analysis of prethreshold retinopathy of prematurity. *Arch Ophthalmol.* 2003;121(12):1697-1701.
16. Committee for the Classification of Retinopathy of Prematurity. An international classification of retinopathy of prematurity. *Arch Ophthalmol.* 1984;102(8):1130-1134.
17. Gilbert WS, Quinn GE, Dobson V, Reynolds J, Hardy RJ, Palmer EA; Multicenter Trial of Cryotherapy for Retinopathy of Prematurity Cooperative Group. Partial retinal detachment at 3 months after threshold retinopathy of prematurity: long-term structural and functional outcome. *Arch Ophthalmol.* 1996;114(9):1085-1091.
18. Lakhnpal RR, Sun RL, Albini TA, Holz ER. Anatomic success rate after 3-port lens-sparing vitrectomy in stage 4A or 4B retinopathy of prematurity. *Ophthalmology.* 2005;112(9):1569-1573.
19. Terasaki H, Hirose T. Late-onset retinal detachment associated with regressed retinopathy of prematurity. *Jpn J Ophthalmol.* 2003;47(5):492-497.
20. Park KH, Hwang JM, Choi MY, Yu YS, Chung H. Retinal detachment of regressed retinopathy of prematurity in children aged 2 to 15 years. *Retina.* 2004;24(3):368-375.
21. Smith BT, Tasman WS. Retinopathy of prematurity: late complications in the baby boomer generation (1946-1964). *Trans Am Ophthalmol Soc.* 2005;103:225-236.