Long-Term Anatomic and Visual Outcome Following Vitrectomy for Stage 4B and 5 Retinopathy of Prematurity

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BACKGROUND AND OBJECTIVES: Surgical indications in stages 4B and 5 retinopathy of prematurity (ROP) are not universally accepted. The authors' purpose is to evaluate the long-term anatomic and visual outcomes of vitrectomy for retinal detachment (RD) associated with stages 4B and 5 ROP.

PATIENTS AND METHODS: Data of patients who consecutively underwent vitrectomy for stages 4B and 5 ROP from 1999 to 2013 were retrospectively reviewed and included grade of retinal attachment and visual acuity (VA) at the last follow-up.

RESULTS: Seventy eyes of 38 infants were included: 23 with stage 4B and 47 with stage 5 ROP. Lens-sparing vitrectomy was performed in 11 eyes, combined lensectomy / vitrectomy in 59 eyes. Mean follow-up was 8.5 years. Anatomic success was maintained in 41 eyes (58.5%), and among them, VA greater than 5/200 was achieved in 17 eyes (41.4%).

CONCLUSION: The long-term visual and anatomic success rates were encouraging for the surgical correction of RD associated with late stages ROP.

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INTRODUCTION

Retinopathy of prematurity (ROP) is a retinal vascular disorder that is among the leading causes of blindness for children in developed countries.[1] The overall ROP incidence has remained relatively stable during the last few decades despite the increasing proportion of the most at-risk population of infants.[2] Currently, laser ablation of the avascular retinal periphery remains the gold standard treatment for type 1 ROP.[3] Despite timely and appropriate laser treatment, approximately 12% of eyes progress to retinal detachment (RD).[4]

The benefits in the surgical management of stage 4A have been demonstrated by several authors and are generally accepted.[5] However, the practical utility of surgery for stage 4B and 5 ROP remains a matter of debate.[6] Though several published series seem to demonstrate the efficacy of vitreoretinal surgery for stages 4B and 5,[7-9] surgical indications are not universally accepted, management approaches vary widely, and long-term anatomic and visual outcome data are lacking. This large case series of 70 eyes with stage 4B and 5 ROP operated upon and followed for a mean time of 8.5 years describes the long-term impact of surgery in advanced stages of ROP.

PATIENTS AND METHODS

This is a retrospective study of patients affected by stage 4B and 5 ROP, inborn or referred, at the Pediatric Ophthalmic Unit of the University of Verona, Italy, from 1999 to 2013.

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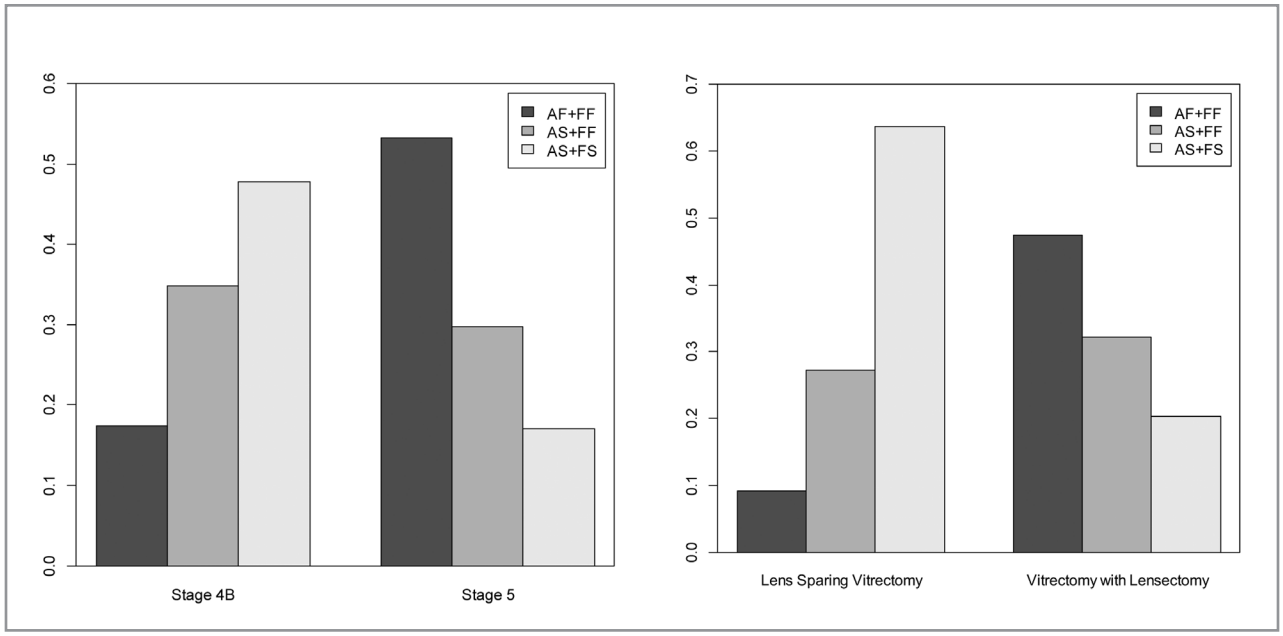

Figure 1. Distribution of the three different combined anatomic and functional outcomes according to retinopathy of prematurity stage (left panel) and to the type of surgical intervention (right panel). (a) AF+FF: anatomic failure + functional failure. (b) AS+FF: anatomic success + functional failure. (c) AS+FS: anatomic success + functional success.

By virtue of a collaboration between our department and Associated Retinal Consultants / William Beaumont Hospital, a recognized referral center for advanced pediatric vitreoretinal surgery in the United States, parents of the infants were offered vitreoretinal surgical intervention at this hospital. All infants underwent surgery by a sole experienced pediatric vitreoretinal surgeon (AC) and received preoperative and postoperative care by two pediatric ophthalmologists (EG and SP).

Written informed consent was obtained from parents or legal guardians of all infants before examinations under anesthesia and vitreoretinal surgical interventions were performed in agreement with the tenets of the Declaration of Helsinki. Our institutional review board approved the study.

We reviewed the following data: gestational age and weight at birth, the stage of ROP at the time of surgical intervention, surgery performed, final anatomical and visual outcomes, diagnosis of leukomalacia (by MRI), and ocular complications.

The surgery performed was a lens-sparing vitrectomy (LSV)[10] or vitrectomy with lensectomy (LV), surgical techniques previously described by Trese.[11] If the lens was found to limit adequate intraoperative visualization or to interfere with the management of traction, a lensectomy was performed.

After the early postoperative evaluations, all patients underwent regular examination at a maximum of every 6 months under general anesthesia or deep sedation, depending on age and patient cooperation. Retinal status was analyzed by indirect ophthalmoscopy. Anatomical success at the final visit was defined as the retina successfully reattached at least in zone 1 (a circle with a radius extending from the optic nerve to double the distance to the macula). Eyes that were detached in zone 1 but had a portion of peripheral retina attached at the last follow-up were defined as "partially attached" and not included in the anatomic success group due to the insufficient functional benefit of this type of anatomic result.

Visual function measurements were graded as "no light perception (NLP), "light perception," "form vision," "low vision cards" (Teller cards), and "better than low vision cards" (Snellen acuity chart). If light perception was uncertain due to developmental delay and neurologic abnormalities, patients underwent visual evoked potential. Orthoptic evaluation and low vision rehabilitation were provided with the aim of optimizing visual development. Contact lenses or eyeglasses were prescribed to correct aphakia and refractive errors. Successful visual outcome was considered the achievement of a visual acuity (VA) better than form vision, which corresponds to an ambulatory vision, necessary condition for the patient to ambulate safely in the environment.[5] Lower functional outcomes were considered failure outcomes.

TABLE 1

Long-Term Anatomic Outcome of Vitrectomy for Treatment of Retinal Detachment of Premature Infants According to Selected Variables

		Anatomic Outcome			
		Success	**Failure**	**% Success**	***P* Value**
ROP Stage	4b	19	4	82.6	.005
	5	22	25	46.8	
Type of Surgery	LV	31	28	52.5	.021
	LSV	10	1	90.9	
Previous Surgery	Yes	14	14	50.0	.322
	No	27	15	64.3	
Leukomalachia	Yes	15	14	51.7	.460
	No	26	15	63.4	

Success: retina attached at least in zone 1; Failure: peripheral retina attached or completely detached retina.

ROP = retinopathy of prematurity; LV = vitrectomy with lensectomy; LSV = lens-sparing vitrectomy

Statistical analysis was performed employing Fisher's exact test that gives exact *P* value for comparing proportions and logistic regression combined with the likelihood ratio test (LRT) to perform adjusted analyses. The odds ratio was used as a measure of "size effect."

RESULTS

Seventy consecutive eyes of 38 patients, 20 males and 18 females, were included. The mean follow-up was 8.5 years (range: 2 years to 16 years). The mean gestational age at birth was 26 weeks (range: 23 weeks to 29 weeks). The mean birth weight was 725 grams (range: 540 grams to 1,215 grams). Retinal ablative treatment had been performed for stage 3 threshold or high-risk pre-threshold ROP on 66 eyes (57 eyes by laser retinopexy and nine eyes by cryopexy) prior to the progression of ROP. Peripheral retinal ablation was not performed on four eyes (5.7%) of outborn infants. None of these patients had previously undergone intravitreal anti-vascular endothelial growth factor injection.

The mean uncorrected age at the time of vitreoretinal surgery was 11 months (range: 5 months to 18 months). LV was carried out on 59 eyes (84.3%): 17 eyes with stage 4B (28.8%) and 42 with stage 5 (71.2%). LSV was performed on the remaining 11 eyes (15.7%): five with stage 5 ROP and six with stage 4B ROP. The percentages of LSV procedures performed in stage 4B (54.5%) and in stage 5 (45.4%) were not significantly different (Fisher's exact test; $P = .159$).

Some eyes underwent more than one procedure to achieve retinal reattachment. Twenty-six of 70 eyes (37.1%) underwent two procedures (Italy and the U.S.), and two eyes (4.3%) underwent three procedures (Italy and the U.S.)

Anatomic Outcomes

Anatomic success was achieved after surgery and maintained at the last follow-up in 41 eyes (58.6%) overall (Table 1). Stage of progression of ROP at the time of surgery was significantly associated with the anatomic success and was achieved in 82.6% of eyes with stage 4B and 46.8% with stage 5 ($P = .005$) with an odds ratio of 5.40.

A significant difference in the percentage of long-term anatomic success was found also comparing the surgical technique LV to LSV ($P = .021$) with an odds ratio of 9.03.

The significantly better outcomes observed with LSV were also confirmed when the ROP stage was taken into account; the stage-adjusted odds of an anatomic success were more than seven-times higher in LSV than in LV operated eyes (LRT test = 4.75; $P = .029$).

Long-term anatomic success was not significantly associated with either multiple procedures ($P = .322$) or with leukomalachia ($P = .460$).

Functional Outcomes

The functional outcomes (Table 2) have been grouped in "better than form vision" (successful outcome) or lower (failure) according to selected variables (Table 3).

Functional success was recorded in 19 eyes, and a significant difference ($P = .010$) was found

TABLE 2

Number (N) and Percentage (%) of Subjects According to Functional Outcome and ROP Stage

	Stage 4B		Stage 5	
Functional Outcome	**N**	**%**	**N**	**%**
No light perception	4	17.4	2	4.3
Light perception	6	26.1	5	10.6
Forms perception	1	4.3	1	2.1
Low vision cards	9	39.1	25	53.2
> Low vision cards	3	13.0	14	29.8
Total	23	100	47	100

ROP = retinopathy of prematurity

between stage 4B (47.8%) and stage 5 (17%), with an odds ratio of 4.47.

A significant difference in the percentage of long-term functional success was found also between the eyes operated with LV and those operated with LSV ($P = .007$), with an odds ratio of 6.85. The significantly better outcomes observed with LSV were also confirmed when the ROP stage was taken into account; the stage-adjusted odds of a VA better than form vision were about six-times higher in LSV than in LV operated eyes (LRT test = 5.78; $P = .016$). Long-term functional success was negatively correlated with both multiple surgeries ($P = .424$) and leukomalacia ($P = .415$).

Combining Anatomic and Functional Outcomes

Anatomic and functional outcomes have been combined in a new categorical variable with three levels, according to the previous definition of anatomic and functional success / failure. The combined data have been distributed according to ROP stage (Figure 1, left panel) and surgery performed (Figure 1, right panel). The percentage of both anatomic and functional success achieved was higher in stage 4B (47.8%) than in stage 5 (17.0%), whereas the percentage of both anatomic and functional failure achieved was lower in stage 4B (17.4%) than in stage 5 (53.2%). These differences were highly significant (Fisher's exact test; $P = .005$). The percentage of both anatomic and functional success achieved was higher in LSV (63.6%) than in LV operated (20.3%), whereas the percentage of both anatomic and functional failure achieved was lower in LSV (9.1%) than in LV operated (47.5%). These differences were highly significant (Fisher's exact test; $P = .006$).

The significantly better outcomes observed with LSV with respect to LV were confirmed also when the ROP stage was taken into account (LRT test = 7.31; $P = .026$). The distribution of the combined anatomic and functional outcomes was not significantly different between eyes previously operated in Italy and eyes operated only in the U.S. (Fisher's exact test; $P = .527$), nor between patients with and without leukomalacia (Fisher's exact test, $P = .536$).

Complications

During follow-up, intraocular hemorrhage occurred in six eyes (8.6%), corneal opacity in three eyes (4.3%), and phthisis in five eyes (7.1%).

Glaucoma occurred in 10 eyes (14.3%), nine of which had undergone LV. Glaucoma occurred bilaterally in three children, none of whom had function better than light perception, even if the retina was successfully attached. Only two eyes had functional results greater than or equal to that of the low vision cards. All the cases of glaucoma occurred more than 3 years after surgery. Only one case required surgery (Baerveldt tube implant; Johnson & Johnson, New Brunswick, NJ).

Long-term complications were more common in eyes without retinal attachment (76%).

DISCUSSION

The management of RD in advanced stages of ROP remains controversial. Comparison of anatomic success data from published series (Table 4) is challenging, in large part because the International Classification of Retinopathy of Prematurity inadequately addresses the complex and variable anatomy of advanced ROP.[12] Consequently, literature is plagued by a lack of uniformity, making comparison between series difficult; whether an eye with advanced ROP (stage 4A / 4B or 5) had or not been treated with either cryopexy or laser, the timing of

TABLE 3

Long-Term Visual Outcome of Vitrectomy for Treatment of Retinal Detachment of Premature Infants According to Selected Variables

		Visual Outcome			
		Success	**Failure**	**% Success**	***P* Value**
ROP Stage	4B	11	12	47.8	.010
	5	8	39	17.0	
Type of Surgery	LV	12	47	20.3	.007
	LSV	7	4	63.6	
Previous Surgery	Yes	6	22	21.4	.424
	No	13	29	31.0	
Leukomalachia	Yes	6	23	20.7	.415
	No	13	28	31.7	

Success = visual acuity better than form vision; Failure = lower than form vision; P = exact P value

ROP = retinopathy of prematurity; LV = vitrectomy with lensectomy; LSV = lens-sparing vitrectomy

surgery with regard to vascular activity or the age of the infant at surgery, the precise anatomy of detachments, whether subretinal blood is present and to what extent, and the presence and severity ocular and systemic comorbidities are key features that vary between series.

The consistency of the pediatric ophthalmology caregivers and single-surgeon management approach are distinguishing elements of the current study. For organizational and travel requirements, the age of patients at the time of surgery was never under the postnatal age of 5 months (with an average of 11 months). Nevertheless, our anatomical results are encouraging as compared to the ETROP study,[5] wherein among 10 eyes that underwent vitrectomy, only six of 10 with stage 4B ROP and zero of 10 eyes with stage 5 ROP maintained anatomic success at the long-term evaluation. Admittedly, the ETROP was not designed to evaluate the utility of surgery in the management of advanced ROP.

Functional outcomes are also extremely difficult to compare between published series[5,7-9,13-17] (Table 4) due to variability in the extent to which visual rehabilitation was pursued and diverse approaches to assessing vision. In our series, 46.3% of eyes with anatomic success after vitrectomy could maintain an "ambulatory vision,"[5] and this supported a positive correlation between anatomic outcome and visual function. An NLP outcome was uncommon among eyes with anatomic success: 0% for stage 4B and 9.1% for stage 5 ROP eyes, respectively. In the literature (Table 4),[4,8,9,16,18-21] poor visual outcomes have been reported in most cases of advanced ROP stages, even if retinal reattachment is achieved after surgery, especially for stage 5.

Lack of visual function in the presence of anatomic success could be explained by non-ocular visual pathway damage related to complications of extreme prematurity.[22] The impact of RD and subsequent reattachment on the developing photoreceptor-retinal pigment epithelial complex may also explain the poor visual function despite retinal reattachment. These results reinforce the tenet that maximal efficacy derives from efforts directed toward preventing RD.[21]

There is robust support in the literature on late-stage ROP surgery for superior anatomic and, consequently, functional outcome of LSV compared to LV.[8,9,13,23] Clearly a phakic eye will fare better, all other things being equal. However, the lens is not spared at the expense of a less effective posterior segment intervention, as when fibrovascular tissue extends toward the vitreous base and reaches the ciliary body and / or the posterior lens surface.[24] Surgical removal of the vitreous framework, by reducing tractional force on the fibrovascular tissue, may suppress new vessel growth activated by the traction.[25] The decision to perform lensectomy in infants with complex ROP-related RDs has long-term implications, particularly regarding the management of aphakia and the increased lifetime risk of aphakic glaucoma,[26,27] the pathogenesis of which remains to be clearly elucidated. It has been hypothesized that early lensectomy may interfere

TABLE 4

Long-Term Efficacy of Surgery for Advanced Stages of Retinopathy of Prematurity (Stages 4B / 5)

Authors	Follow-Up (Years)	No. of Eyes ROP 4B / 5	Eyes With Any Attachment (%) ROP 4B / 5	Mean VA > LP (% of Eyes) ROP 4B / 5	NLP (% of eyes) ROP 4B / 5	Percentage of Complications (Vitreous Hemorrhage, Corneal Opacity, Glaucoma)
Karacorlu[13] 2016	6.9	38 / 31	63 / 42	58/35	26 (18 / 69)	NS, 13 / 19, 8 / 29
Gadkari[14] 2015	0.5	20 / 11	90 / 45	71 overall	29 (9 / 31)	NS, NS, NS
Choi[9] 2011	5.6	13 / 8	62 / 13	78 of attached	47 (10 / 21)	43, 29, 33
Shah[15] 2009	1.6	9 / 14	44 / 14	NS	NS	NS, NS, NS
Wu[7] 2008	4	— / 80	— / 69	81	14	NS, 7.5, 7.5
El Rayes[8] 2008	3	56 / —	73.2 / —	97.4	0	NS, NS, 31
Fuchino[16] 1995	NS	— / 49	— / 59	95 of attached	5	NS, NS, NS
Seaber[1] 1995	5.1	— / 51	25	78 of attached	15	NS, 14, 6
Trese[17] 1998	3.7	16 / 16	83/50	78/63	18 / 37	NS, NS, NS

ROP = retinopathy of prematurity; VA = visual acuity; LP = light perception; NLP = no light perception

with maturation of the trabecular meshwork,[26,28] confirmed by alterations found on gonioscopy, such as flat iris insertion and poorly developed angle recess.[29] Examination under anesthesia at 6 months interval is often necessary given that the infants are not uniformly cooperative with intraocular pressure measurement, and the often insidious and painless presentation of this problem. In our series, the detection of the elevated IOP occurred always on routine examination under anesthesia.

Rehabilitation of aphakia requires a coordinated team of low-vision expert ophthalmologists, optometrists, pediatricians, and most importantly the collaboration of the family.[27] Aphakic spectacles or contact lenses were prescribed to our patients in order to address amblyopia, together with occlusion therapy when needed.[27] Management of unilateral aphakia is more challenging as the use of contact lenses is mandatory to optimize development of useful vision.

This study has a number of limitations. It is a retrospective study, and this influences the inhomogeneous characteristics of the groups (stage 4B vs. 5, LSV vs. LV). Secondly, the relatively late timing of the surgery due to logistic issues despite prompt referral renders comparison with series wherein surgery was performed promptly difficult. The fact that some cases were operated upon earlier in Italy represented another limitation and, interestingly, this affected the visual and not the combined anatomical and visual outcome.

In conclusion, after a mean of 8.5 years follow-up, the anatomic and visual success rates following vitreoretinal surgery for ROP stage 4B and 5 were encouraging for an interventional approach. Retinal reattachment allowed an achievement of better visual outcome as compared to the untreated natural history of advanced ROP related RD.

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