

Take Good Care of My Baby: Evolving Standards of Care for Retinopathy of Prematurity

The current issue of *Ophthalmology* includes two articles by Tasman et al (*Ophthalmology* 2002;109:928–41) regarding advantages of laser versus cryotherapy for peripheral retinal ablation of stage 3 threshold retinopathy of prematurity (ROP). Ten-year data from the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) on ophthalmologic outcome,¹ perimetry,² and contrast sensitivity³ have recently been published, as well. Despite such advances, ROP remains a leading cause of childhood blindness. With more than a decade of experience with peripheral retinal ablation behind us, it is timely to reflect on ROP management and ask: How can we do better?

Survival of extremely premature infants has improved, with profound impact on the ophthalmic community. Ophthalmologists in urban centers are encountering increasingly premature infants with greater frequency, whereas those in community hospitals may be pressed to examine premature infants for the first time. In both scenarios experience with ROP, particularly that located in zone 1, may be limited.

Because most eyes in the CRYO-ROP study developed ROP in zone 2, the features and course of zone 2 ROP are those with which clinicians are most familiar. Eyes with minimal ROP located in zone 1 frequently behave like eyes with zone 2 ROP. However, ROP may appear and behave quite differently when located mostly (> 6 clock-hours) in zone 1. Progression to stage 3 may proceed directly from immature retina without passing through intervening stages. The absence of a demarcation line or ridge may render it difficult to discern the interface between vascular and avascular retina. Stage 3 ROP in zone 1 may appear flat and velvety, with little fibrous component. Choroidal vascular prominence through the pale retinal pigment epithelium of prematurity may convey a false sense that retinal vascularization is complete.

The determination of “threshold ROP” in the CRYO-ROP sought to define that severity of ROP for which a given eye had an equal chance of spontaneous regression or progression to untoward outcome. For eyes with zone 2 ROP, this estimation proved quite precise: 62% of untreated eyes with threshold ROP went on to an untoward visual outcome.¹ However, the estimation of a 50/50 threshold for eyes with zone 1 ROP was off the mark: untreated threshold zone 1 eyes had a 90% chance of untoward outcome.⁴ That approximately 44% of eyes with zone 2 ROP in the CRYO-ROP had an untoward outcome despite treatment,¹ is also well short of ideal. Because zone 1 eyes almost always progress to threshold,⁵ the question for such eyes and high-risk zone 2 eyes would seem to be not whether to treat earlier, but when. This issue is under investigation in the multicenter study of Early Treatment for Retinopathy of Prematurity (ETROP).⁶ Comparison between untreated eyes, high-risk eyes treated early, and high-risk eyes treated at threshold should provide guidelines regarding early intervention.

Laser has become the instrument of choice by ophthalmologists throughout the world, although the benefits of treatment with cryopexy versus laser continue to be debated. Tasman et al report long-term structural and functional outcomes with laser superior to those obtained with cryotherapy. The superiority of laser over cryopexy should be no surprise. Laser has long been the standard of treatment in the management of other vasoproliferative retinopathies associated with diabetes, sickle cell disease, and retinal vascular occlusion. Few indications remain for using cryopexy over laser in the management of ROP: poor fundus visibility, lack of availability of laser, and lack of treating physician familiarity with indirect laser retinopexy techniques.

The CRYO-ROP study unquestionably demonstrated the value of screening at-risk infants in preserving vision. Manpower issues, transport costs, and medicolegal liability associated with ROP are but a few of the barriers to universal screening. Telemedicine offers an opportunity to conquer some of these barriers. One can imagine a trained technician acquiring digital fundus images from at-risk infants in a neonatal intensive care unit, followed by transmission to a regional Reading Center. Certified graders could provide timely and cost-effective input for ROP management, identifying infants requiring on-site examination or treatment. Although technology enabling complete imaging of both the peripheral retina and posterior pole of infants is currently lacking, interval technologies are available. Pursuant to a successful proof-of-principle project,⁷ a multicenter study is underway to evaluate whether digital fundus images, evaluated remotely, effectively complement on-site management of ROP (Coats DK. *Invest Ophthalmol Vis Sci* 2001;42 [Suppl]:681.)

Digital fundus imaging also would impact ROP clinical trials. The paradigm of a dedicated Reading Center with dedicated image graders is the “gold standard” for ophthalmic clinical trials. To date, however, all large ROP trials have gathered data by requiring examiners to draw retinal findings. Neither the examiner nor study center has an opportunity to study a fundus image. Although simplicity is an advantage to this approach, image grading by dedicated graders is superior to observations of busy clinicians. Photographic documentation of treatment is also essential to distinguish true therapeutic failure from poor outcome because of incomplete treatment.

The advanced stages of ROP (stages 4A, 4B, and 5) are poorly understood. Common misconceptions are that macula-sparing (stage 4A) partial retinal detachments are largely benign, that surgery should be deferred until the macula is detached, that scleral buckle is the preferred retinal reattachment procedure, and that useful vision cannot be obtained in eyes with total (stage 5) detachments. ROP-related detachments may seem stable in the first few weeks or months after peripheral retinal ablation. Yet neither the stability of partial detachment⁸ nor visual acuity⁹ is predictable from retinal appearance in infants with ROP. This is particularly true for untreated eyes¹ or those with incomplete peripheral retinal ablation. Visual outcome of eyes with even partial ROP-related retinal detachment is generally poor by 4.5 years of age.⁸

The goal of intervention for ROP-related retinal detachments varies with the severity of the detachment. The goal for extramacular retinal detachment (stage 4A ROP) is an undistorted/minimally distorted posterior pole, total retinal reattachment, and preservation of the lens and central fixation vision. Scleral buckle and vitrectomy have been used to manage stage 4A ROP. Vitreous surgery can interrupt progression of ROP from stage 4A to stages 4B or 5 by directly addressing transvitreal traction resulting from fibrous proliferation.¹⁰ Disadvantages of scleral buckle for stage 4A ROP are the dramatic anisometropic myopia and the second intervention required for transection or removal, so that the eye may continue to grow.

Surgery for traction retinal detachments involving the macula (stage 4B ROP) is performed to minimize retinal distortion and prevent total detachment (stage 5). The functional goal is ambulatory vision. In earlier studies, visual outcome for retinal detachment beyond stage 4A was quite poor. More recent reports demonstrate that form-vision can be obtained by vitrectomy for stage 5 ROP.¹¹ Maximal recovery of vision after the insult of macula-off retinal detachment and interruption of visual development in infants may take years.

ROP has changed in the last decade and so should our approach to its management. Digital fundus imaging has the potential to revolutionize both ROP-screening efforts and the conduct of ROP-related clinical trials. We look to prospective studies for guidance as to whether ROP should be treated earlier in zone 1 and high-risk zone 2 eyes. The sum of clinical experience to date supports the contention that laser is the preferred method of peripheral retinal ablation for ROP. Surgical intervention offers the potential for preservation of vision for eyes with ROP-related retinal detachment, particularly if addressed before macular distortion or detachment.

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Radiation for Optic Nerve Meningiomas: Is This the Answer?

The management of optic nerve sheath meningiomas has been a controversial and sometimes contentious issue for a number of reasons. In the first place, these tumors are not associated with any mortality or significant neurologic morbidity. In the second place, despite their potential for spread across the planum sphenoidale, these tumors rarely cause loss of vision in the opposite eye. Thus, the major manifestation of optic nerve sheath meningiomas is monocular visual loss, and their management must reflect these issues.

Because primary optic nerve sheath meningiomas arise from the arachnoid cap cells surrounding the intracanalicular or intraorbital portions of the nerve, they almost always are intimately associated with the nerve and tend to surround the nerve by the time they become clinically apparent. Similarly, secondary optic nerve sheath meningiomas extend from the planum sphenoidale into the subdural or subarachnoid spaces (or both) surrounding the nerve within the optic canal and, ultimately, within the orbit. As if that were not enough, many optic nerve sheath meningiomas involve the portion of the optic nerve at the apex of the orbit within the annulus of Zinn, a surgical “no-man’s land,” if you will. Thus, despite a few reports indicating preservation of vision after removal of an optic nerve sheath meningioma, attempts to cure this tumor surgically almost always produce blindness in the affected eye—precisely what one is trying to avoid in the first place. If the optic nerve is removed along with the tumor, the tumor may be eradicated, but the procedure will, of course, cause blindness in an eye that may have had useful vision and that may have retained that level of visual function for several years without intervention.

Although the potential for hormone therapy for meningiomas, the cells of which usually possess both estrogen and progesterone receptors, has received considerable attention, initial studies using tamoxifen (an antiestrogen agent) and mifepristone (an antiprogestosterone agent), have been disappointing. Thus, the most popular treatment options for optic nerve sheath meningiomas have been surgical excision of the tumor along with the nerve, or follow-up without intervention.

In this issue of *Ophthalmology*, Turbin et al (*Ophthalmology* 2002;109:890–99) provide substantial data indicating that conventional radiation therapy is the optimum treatment for these tumors, at least until a better option is available. To be sure, this is not the first article to suggest a major role for radiation therapy in the treatment of intracranial meningiomas in general and optic nerve sheath meningiomas in particular. In 1975, Wara et al¹ emphasized the potential role of radiation therapy for intracranial meningiomas in what many consider a landmark article. Six years later, in 1981, Smith et al² reported five cases of optic nerve sheath meningioma in which radiation therapy was followed by stabilization or improvement in visual function in the affected eye. The follow-up in these cases ranged from 6 months to 5 years. Despite these reports, as well as several others that described improvement in vision after radiation therapy for intracranial and optic nerve sheath meningiomas, radiation therapy was used only sparingly for meningiomas until 1987, when Kupersmith et al³ presented impressive evidence that both primary and secondary (i.e., after subtotal resection of the tumor) irradiation of intracranial meningiomas that damage the optic nerves, optic chiasm, or both can result in stabilization or