ABSTRACT
A 5-month-old infant with bilateral advanced retinoblastoma underwent six cycles of systemic chemotherapy. In an attempt to salvage the second eye, three serial injections of periocular carboplatin were given for persistent vitreous seeding. Following the third injection, the patient developed periorbital ecchymosis and magnetic resonance imaging demonstrated abnormal signal characteristics at the site of injection. An orbital biopsy did not demonstrate extraocular tumor extension, but histopathologic examination revealed severe orbital fibrosis and fat necrosis. Following the biopsy, the patient developed an intraocular tumor recurrence at the same location where the carboplatin injections had been given and enucleation was performed to prevent tumor spread. In this case, a child developed periorbital scarring and intraocular tumor recurrence at the site of injection following treatment with periocular carboplatin.

INTRODUCTION
Periocular carboplatin has been used by clinicians to treat advanced intraocular retinoblastoma, often as a method for salvaging eyes following unsuccessful chemoreduction. In an animal model, periocular delivery of carboplatin has been shown to achieve higher drug levels in the vitreous compared with intravenous administration. However, the clinical efficacy of periocular carboplatin has been rather disappointing. One group reported an approximate 50% success rate in treating eyes with vitreous and subretinal seeding not responsive to systemic chemotherapy. Recently, local complications in patients receiving periocular carboplatin have been reported, ranging from periorbital cellulitis to ischemic optic neuropathy. We describe a case of periorbital scarring and intraocular tumor recurrence of retinoblastoma after three serial injections of subconjunctival carboplatin.

CASE REPORT
A 5-month-old infant was diagnosed as having retinoblastoma after presenting with bilateral leukocoria in September 2007. Initial examination revealed a visual acuity of light perception, total exudative retinal detachments, and large intraocular masses with foci of calcification in both eyes. Computed tomography scan showed calcified intraocular masses measuring 1.4 × 1.4 cm in the right eye and 1.8 × 1.2 cm in the left eye. A diagnosis of bilateral retinoblastoma was made, International Classification Retinoblastoma group E. Systemic chemotherapy was initiated according to the Children’s Oncology Group study protocol: carboplatin, etoposide, and vincristine, administered in six 28-day cycles. After the first session of chemotherapy in October 2007, the right eye developed secondary angle-closure glaucoma due to tumor involvement of the iris and anterior chamber, necessitating enucleation.

During the next year, the infant maintained a visual acuity of light perception in the left eye. He completed six courses of chemotherapy, with a 50%
to 60% reduction in overall tumor size. The patient never received focal treatment modalities such as laser or cryotherapy. Following the completion of systemic chemotherapy, an examination revealed persistent retinal detachment with both vitreous and subretinal seeding. Due to concerns regarding persistent vitreous seeding, the patient received three serial injections of periocular carboplatin. The treatments were given 2 months apart due to scheduling issues related to ongoing chemoreduction. The technique used for the injections included giving 2 cc of 10 mg/cc of carboplatin with a 25-gauge needle into the sub-Tenon’s space without creating a conjunctival incision. The third injection was given in April 2008 and no unusual findings were noted during the procedure. There was mild eyelid edema but no evidence of hemorrhage when the patient was discharged. However, 3 weeks after the injection in May 2008, the patient presented with lower eyelid swelling and ecchymosis (Fig. 1). Brain and orbit magnetic resonance imaging showed signal abnormalities at the site of injection: the inferotemporal quadrant of the orbit demonstrated hypointensity on T2-weighted scans and diffuse enhancement (with contrast) (Fig. 2). Surgical exploration and orbital biopsy demonstrated dense, avascular fibrosis and fat necrosis (Fig. 3) but no evidence of tumor recurrence.

By October 2008, an area of increased vascularity was noted at the anterior edge of the main calcified tumor mass near the inferotemporal quadrant where the injections had been given (Figs. 4A and 4B). Persistent vitreous seeding was also noted, essentially unchanged by the carboplatin injections. By December 2008, definite tumor recurrence was diagnosed in the same location (Fig. 4C). Brachytherapy was considered, but given the likelihood of other active seeding foci, a consensus was reached by the treatment team to recommend enucleation. The left eye was enucleated in January 2009, 15 months after the initiation of systemic chemotherapy. Pathologic examination showed the main necrotic tumor mass and two areas of tumor recurrence: a 5 × 5 mm mass of poorly differentiated retinoblastoma cells arising from the anterior retina (Fig. 5) and a smaller 1 × 1 mm focus of subretinal tumor cells, just nasal to the optic nerve. Both areas of tumor recurrence contained Ki-67 positive cells.
DISCUSSION

In 1999, Abramson et al. reported using subconjunctival injections of carboplatin, a platinum-based alkylating agent, to treat patients with retinoblastoma with vitreous and subretinal seeding. This protocol used a total of 20 mg of carboplatin per injection at a concentration of 10 mg/cc, the highest stable concentration of drug recommended by the manufacturer. Despite some evidence of clinical success, recent reports of local complications associated with periocular carboplatin injections have raised serious concerns regarding the safety of this dose and delivery method. In one case series, histopathologic evaluation of four globes enucleated after three to seven carboplatin injections demonstrated circumscribed areas of ischemic necrosis and atrophy of the optic nerve adjacent to the site of injection. Ocular motility abnormalities in children receiving periocular carboplatin injections have been attributed to a severe, local inflammatory reaction, ultimately causing orbital fibrosis, enophthalmos, and restriction of extraocular movements. Histological findings in these cases have included ischemic necrosis or atrophy of the optic nerve, dystrophic calcification, astrocytic proliferation, and mild inflammation in the surrounding fibrovascular adipose tissue. Due to concerns regarding local toxicity, a decrease in the dosage or alternative vehicles for delivering carboplatin have been suggested to decrease peak drug levels at the site of injection.

Our patient demonstrated histopathologic and radiographic evidence of periocular scarring following three serial injections of carboplatin at the standard dose of 20 mg per treatment. The patient developed clinical signs of toxicity (eg, ecchymo-
sis) and a biopsy specimen from the inferotemporal quadrant of the orbit demonstrated severe fibrosis and fat atrophy. Post-treatment magnetic resonance imaging scan showed abnormal signal characteristics at the site of injection, suggesting the possibility of extrascleral tumor extension but ultimately shown to be the result of severe orbital scarring. Furthermore, the recurrence of intraocular retinoblastoma in a location adjacent to the injection site (ie, inferotemporal quadrant) suggests an inability to control tumor regrowth despite three serial treatments with carboplatin. The unfavorable “therapeutic index” of periocular carboplatin demonstrated in this case report provides further evidence that more effective treatment options are needed to treat eyes with advanced intraocular retinoblastoma.

REFERENCES