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Optic Nerve Obscuration in Retinoblastoma: A Risk Factor for Optic Nerve Invasion?

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Keywords
Retinoblastoma · High-risk features · Optic nerve · Obscuration · Enucleation · Globe salvage

Abstract
Background: The objective of this study is to evaluate the risk of optic nerve invasion associated with optic nerve obscuration at diagnosis or persisting during treatment. ***Methods:*** Retrospective review from 2011–2016 of patients with advanced retinoblastoma (Group D/E) with complete obscuration of the nerve at diagnosis and a second group of patients with persistent, complete obscuration throughout treatment. ***Results:*** Advanced retinoblastoma was diagnosed in 102 eyes of 86 patients. The optic nerve was obscured in 69 eyes (68%) at diagnosis. Of these, 30 (43%) underwent salvage therapy and 39 (57%) primary enucleation. Histopathologic analysis of primarily enucleated eyes showed 41% prelaminar and 15% postlaminar invasion. Four eyes in the salvage group demonstrated persistent nerve obscuration; 2 were subsequently enucleated without evidence of nerve invasion. Average follow-up was 23.5 months (range 1–62 months). ***Conclusions and Relevance:*** Optic nerve obscuration at diagnosis may be associated with postlaminar optic nerve invasion. While persistent, complete obscuration of the optic nerve by retinoblastoma during treatment is a poor prognostic sign for both globe salvage and vision, it does not appear, in this small cohort, to increase the risk of optic nerve invasion. With appropriate control of the intraocular tumor, these eyes can be salvaged.

Introduction

Optic nerve involvement in retinoblastoma is a known risk factor for the development of metastatic disease; and the mortality risk rises with increasing depth of involvement [1]. Postlaminar optic nerve invasion alone carries a nearly 16% risk of metastatic disease [2]. If concomitant massive choroidal invasion is seen, the risk increases upwards of 30% [2]. There are clinical features present at diagnosis which have been correlated with postlaminar optic nerve invasion, including buphthalmos [3], neovascularization of the iris, and secondary glaucoma [4]. Secondary glaucoma may also be predictive of massive choroidal invasion [5]. The International Intraocular Retinoblastoma Classification of Retinoblastoma (IIRC) was

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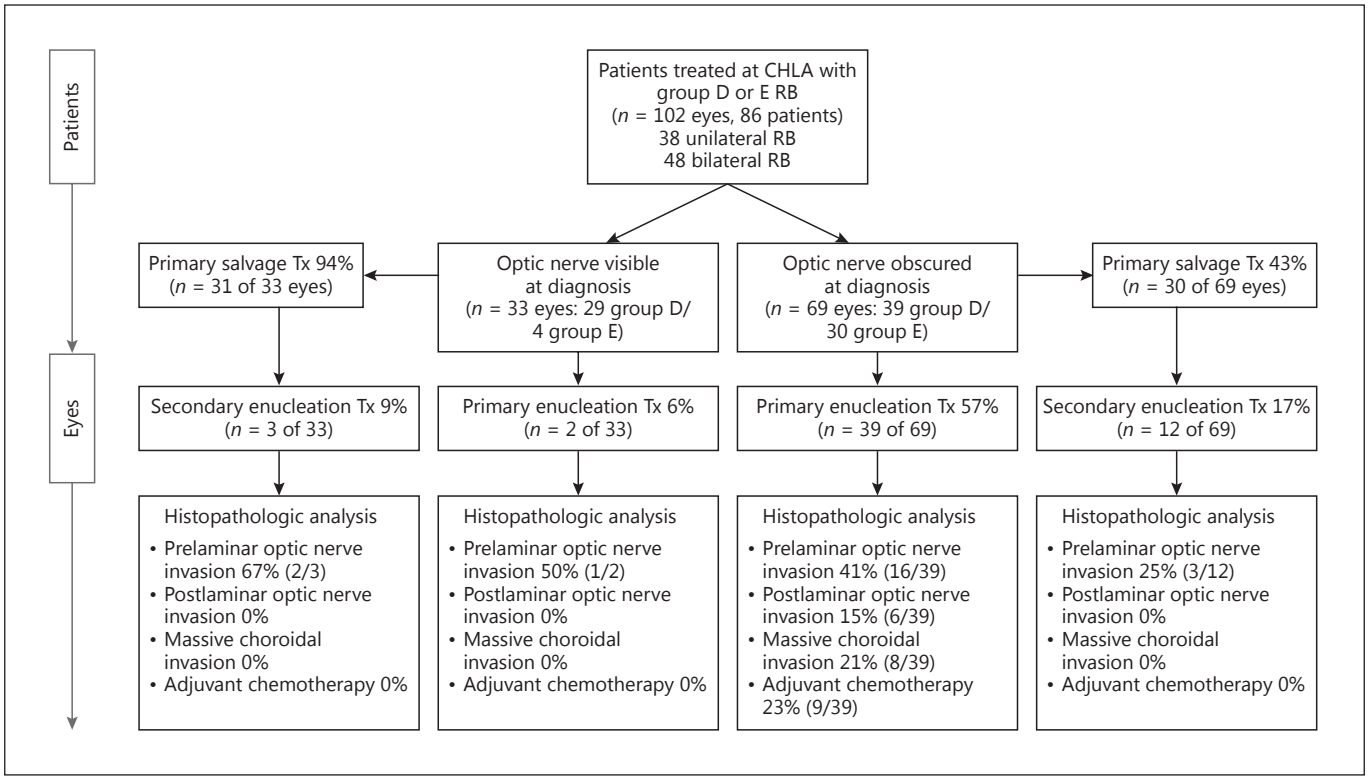

Fig. 1. Consort diagram showing clinical and pathologic features of advanced retinoblastoma eyes with and without obscuration of the optic nerve at diagnosis. CHLA, Children's Hospital Los Angeles; RB, retinoblastoma; Tx, therapy.

intended to predict success of systemic chemotherapy treatment, and Group D and E are the most advanced eyes in the classification system [6, 7]. These advanced eyes may also harbor high-risk features 17–24% of the time [8]. While these clinical features such as buphthalmos may be helpful to the ocular oncologist in making the decision between enucleation and eye salvaging treatment, obscuration of the optic nerve has not been previously studied. In addition, there is limited information regarding clinical factors that may predispose to persistent or the subsequent development of optic nerve infiltration during the course of treatment. While recurrence and persistence of disease in retinoblastoma is common, a dreaded consequence of attempted ocular salvage is subsequent optic nerve invasion (and/or choroidal invasion), the need for adjuvant chemotherapy (often as a second course of chemotherapy), and the increased risk to the child of the development of metastatic disease. Thus, it would be helpful to identify clinical factors that may predispose to optic nerve invasion in secondarily enucleated eyes that have failed salvage attempts.

While it is common at diagnosis in advanced Group D and E retinoblastoma eyes to be unable to visualize the optic nerve secondary to the tumor and/or a complete retinal detachment, the ability to evaluate the nerve is often restored early in the course of therapy. Herein we evaluate the clinical finding of optic nerve obscuration and its risk for optic nerve invasion. In addition, we present a case series of 4 patients with advanced retinoblastoma and complete obscuration of the optic nerve by tumor that persisted throughout treatment.

Materials and Methods

A retrospective, Institutional Review Board-approved study was conducted at Children's Hospital Los Angeles (CHLA). The Institutional Review Board at CHLA approved this study. Patients diagnosed at CHLA with advanced IIRC Group D or E retinoblastoma between 2011 and 2016 were evaluated for this study. RetCam photographs from examination under anesthesia (EUA) at diagnosis and each subsequent EUA were evaluated for completed obscuration of the optic nerve by the tumor.

Table 1. Demographics, clinical and pathologic features of advanced retinoblastoma eyes with and without obscuration of the optic nerve at diagnosis

		Optic nerve visible at diagnosis	Optic nerve obscured at diagnosis	*p* value
Patients	86			
Unilateral	38 (44)			
Bilateral	48 (66)			
Eyes	102	33 (32)	69 (68)	
Right eye	55 (54)	19 (58)	36 (52)	
Left eye	47 (46)	14 (42)	33 (48)	
Group D	68 (67)	29 (88)	39 (57)	
Group E	34 (33)	4 (12)	30 (43)	0.0016
Primary salvage	61 (60)	31 (94)	30 (43)	
Primary enucleation	41 (40)	2 (6)	39 (57)	
Secondary enucleation	15 (15)	3 (9)	12 (17)	
All enucleated eyes	56	5	51	
Prelaminar optic nerve invasion	22 (56)	3 (60)	19 (37)	0.37
Postlaminar optic nerve invasion	6 (11)	0 (0)	6 (12)	1.0
Massive choroidal invasion	9 (16)	0 (0)	8 (16)	0.58
Required adjuvant chemotherapy	9 (16)	0 (0)	9 (18)	0.58
After primary enucleation	41	2	39	
Prelaminar optic nerve invasion	17 (42)	1 (50)	16 (41)	1.0
Postlaminar optic nerve invasion	6 (15)	0 (0)	6 (15)	1.0
Choroid without optic nerve	8 (20)	0 (0)	8 (21)	1.0
Required secondary adjuvant chemotherapy	9 (22)	0 (0)	9 (23)	1.0
After secondary enucleation	15	3	12	
Prelaminar optic nerve invasion	5 (33)	2 (67)	3 (25)	0.24
Postlaminar optic nerve invasion	0 (0)	0 (0)	0 (0)	
Choroid without optic nerve	0 (0)	0 (0)	0 (0)	
Required secondary adjuvant chemotherapy	0 (0)	0 (0)	0 (0)	

Values are presented as *n* (%).

Treatment

The treatment protocol for advanced (Group D/E) retinoblastoma eyes at CHLA depends on several clinical features including the age of the patient, the laterality of disease, and the staging of the contralateral eye. Enucleation is offered to parents as a treatment option for advanced unilateral retinoblastoma (Group D or E). Globe salvaging treatment is offered to parents with unilateral Group D disease. Globe salvaging treatment for Group E retinoblastoma is done only if the patient has bilateral disease wherein the contralateral eye will also require systemic therapy for salvage. The treatment paradigms at our center have been described previously [9–11].

Gadolinium-enhanced magnetic resonance imaging (MRI) is performed with standard multiplanar sequences for the brain and orbit on a 1.5- or 3-Tesla MRI scanner. At our institution, 6 board-certified radiologists are available for neuroimaging evaluation. Additionally, each scan has an initial radiologist evaluation, which is subsequently verified by a second, separate radiologist so that each scan is evaluated twice in consensus. MRI is routinely performed at diagnosis as part of staging for all new patients diagnosed with retinoblastoma in order to evaluate for intracranial disease and/or the presence of optic nerve thickening or enhancement on MRI concerning for optic nerve infiltration. In general, optic nerve involvement of less than 5 mm on MRI is treated with primary enucleation with a long nerve stump; if the optic nerve involvement is too extensive to be cleared surgically, neoadjuvant chemotherapy is given followed by enucleation [12].

Chart Review

Medical records from eligible patients were reviewed during the course of the study to record chemotherapy regimen, age at diagnosis, laterality, and globe salvage. Pathology and MRI results were also evaluated.

Images

Ocular images for each patient were obtained using a wide-angle contact fundus camera (RetCam3, Clarity Medical Systems, Inc., Pleasanton, CA, USA, December 2011) during EUA. Fundus

Table 2. Clinical course of 4 patients with advanced retinoblastoma with persistent obscuration of the optic nerve through the course of therapy

	Patient 1	Patient 2	Patient 3	Patient 4
Sex	male	male	male	male
Age at diagnosis	11 months	7 months	21 months	20 months
Laterality	bilateral	bilateral	bilateral	unilateral
Classification				
OD	Group D	Group D2	Group D2	
OS	Group D	Group D2	Group D2	Group D2
Treatment	CEV × 6 cycles + local consolidation	CEV × 6 cycles + local consolidation	CEV × 4 cycles + local consolidation	CEV × 6 cycles + local consolidation
Age at enucleation	n/a	18 months	25 months	n/a
Reason for enucleation	n/a	neovascular glaucoma (OS)	poor response to chemotherapy (OD)	n/a
Pathology	n/a	– marked optic nerve atrophy – retinal gliosis – thick neovascular membrane without evidence of active retinoblastoma	– subretinal and vitreous seeds – tumor covering an atrophic optic nerve – no proliferating tumor at lamina cribosa or beyond – no massive choroidal invasion or other high-risk features	n/a
MRI at diagnosis	no optic nerve or extraocular disease	no optic nerve enhancement or enlargement	no optic nerve enhancement or enlargement	no optic nerve or extraocular disease
Final MRI	no optic nerve enhancement or enlargement	no optic nerve enhancement or enlargement	no optic nerve enhancement or enlargement	no optic nerve or extraocular disease
Follow-up	14 months	37 months	36 months	14 months
Final visual acuity	poor fix and follow	n/a	n/a	poor fix and follow

photos imaged on the date of diagnosis, second EUA, and last EUA were examined. For the eyes that were secondarily enucleated, fundus photos taken immediately prior to enucleation were used.

Statistical Analysis

The data analysis for this paper was generated using SAS/STAT© software, version 9.2 of the SAS System for Unix (SAS Institute Inc., Cary, NC, USA).

Results

Advanced retinoblastoma was diagnosed in 102 eyes of 86 patients. Sixty-eight eyes (67%) were designated IIRC Group D and 34 eyes (33%) were Group E. The optic nerve was visible in 33 eyes (32%; 29 Group D and 4 Group E) and obscured in 69 eyes (68%; 39 Group D and 30 Group E) at diagnosis (Table 1; Fig. 1). Thirty of the 34 Group E eyes included in this analysis demonstrated obscuration of the optic nerve at diagnosis ($p = 0.0016$). Of the 69 Group D and Group E eyes with optic nerve obscuration at diagnosis, 30 (43%) underwent salvage therapy and 39 (57%) primary enucleation. Among the 69 eyes with optic nerve obscuration, 4 patients (6%) had optic nerve enhancement on the pretreatment MRI scan compared to 0 patients (0%) without optic nerve obscuration at diagnosis. All 4 of these patients were treated with primary enucleation.

After primary enucleation, 16 of 39 eyes (41%) with optic nerve obscuration showed prelaminar optic nerve invasion and 6 (15%) demonstrated postlaminar optic nerve invasion. While statistical significance could not be achieved due to the small numbers in each cohort, this is compared to 1 of 2 patients (50%) with prelaminar optic nerve invasion and 0 patients with postlaminar invasion in the eyes without obscuration of the optic nerve at diagnosis. MRI evaluation at diagnosis did not show enhancement of the optic nerve in any case which subsequently had prelaminar optic nerve invasion, and demonstrated enhancement only in 50% (3/6) of those with postlaminar optic nerve invasion confirmed by pathology. Among the 39 eyes with nerve obscuration at diagnosis that were primarily enucleated, 9 (23%) patients were recommended adjuvant chemotherapy and 8 patients completed treatment (1 did not accept the recommendation). No patient with a visible optic nerve at diagnosis required adjuvant chemotherapy. There were no cases of metastatic disease at an average follow-up of 23.5 months (range 1–62 months). Of the 102 eyes, 29

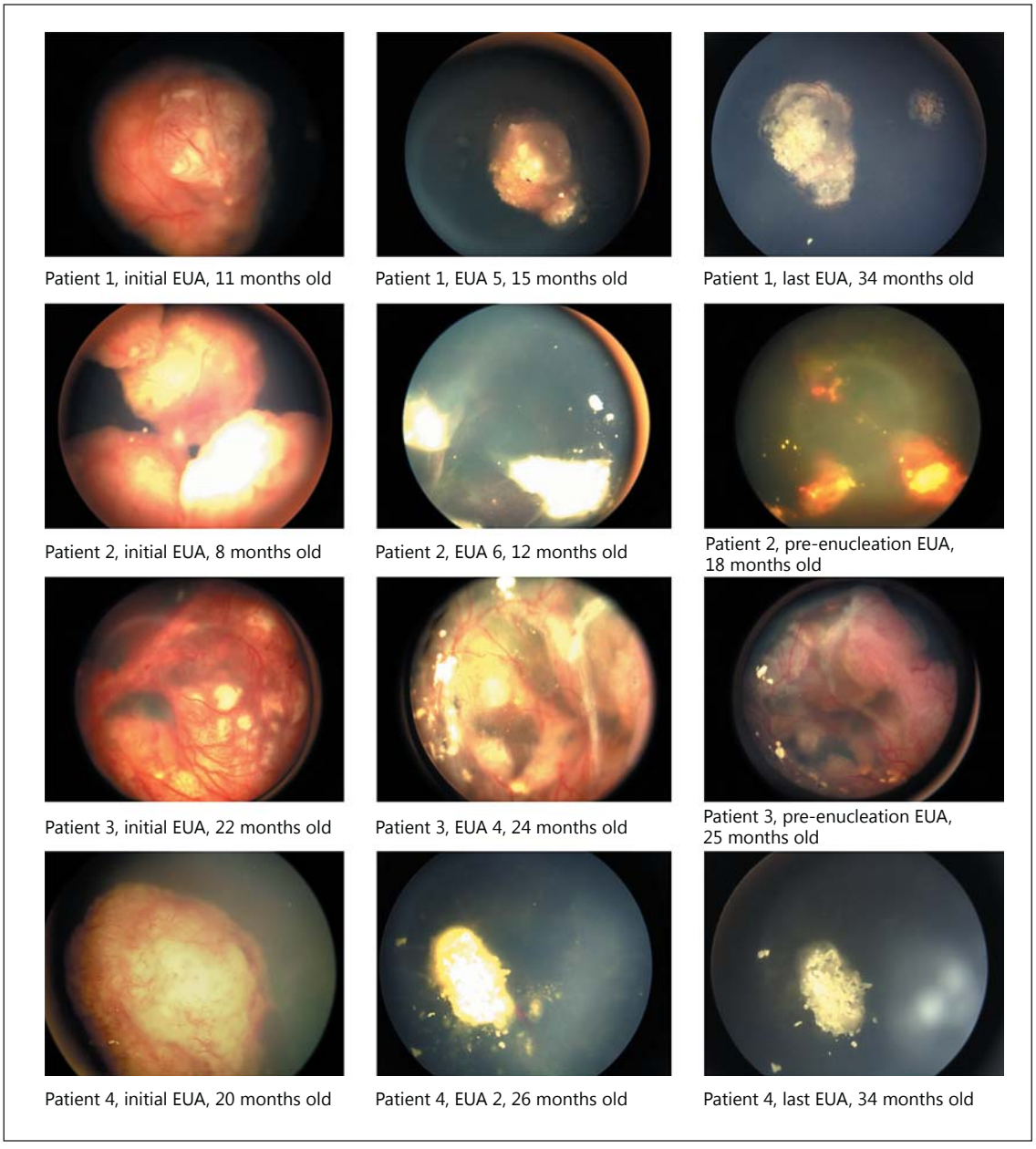

Fig. 2. Fundus photos of 4 patients with advanced retinoblastoma with persistent obscuration of the optic nerve through the course of therapy. Patients 2 and 3 were enucleated; patients 1 and 4 were salvaged with full control of the intraocular disease. EUA, examination under anesthesia.

had follow-up of less than 1 year; however, these were enucleated eyes and the results of histopathologic analysis is known. After treatment, 4 eyes of 4 patients demonstrated complete and persistent lack of visibility of the optic nerve during chemoreduction due to direct obscuration by the tumor and were included in the following case series.

Clinical Summary of 4 Patients (Table 2; Fig. 2)

Patient 1 is an 11-month-old male with bilateral sporadic retinoblastoma, IIRC Group D for both eyes, with no view of the optic nerve in the right eye at the time of diagnosis. The right eye was included in this case series. The MRI performed at diagnosis showed no evidence of extraocular retinoblastoma or optic nerve invasion. He

was treated with 6 cycles of systemic 3-drug chemoreduction according to the CHLA protocol with concomitant local consolidation. At no point in time was the optic nerve visible during EUA (Fig. 2). However, the intraocular tumor had responded well to the treatment and the eye was stable without evidence of active disease. The last MRI performed at 31 months of age had no signs of optic nerve enhancement or optic nerve enlargement. The follow-up for this patient is 14 months and last visual acuity is recorded as "poor fix and follow."

Patient 2 is a 7-month-old male with bilateral retinoblastoma with IIRC D in the right eye and Group D in the left eye. The child was treated with 6 cycles of systemic 3-drug chemoreduction according to the CHLA protocol. The left eye demonstrated obscuration of the optic nerve at diagnosis, which persisted through treatment and was included in this series. Both eyes showed impressive response to chemoreduction and local consolidation as shown in Figure 2. However, the left eye was enucleated, approximately 11 months after being diagnosed with retinoblastoma, due to neovascular glaucoma and not persistent/recurrent intraocular disease. Pathology showed marked optic nerve atrophy, retinal gliosis, and a thick neovascular membrane without evidence of active retinoblastoma. The first MRI at 7 months of age (at diagnosis) and the last MRI at 35 months of age lacked clinical findings of optic nerve enhancement and/or enlargement. The follow-up for this patient is 37 months and last visual acuity is recorded as "poor fix and follow."

Patient 3 is a 21-month-old male diagnosed with bilateral IIRC Group D retinoblastoma. The right eye was included in this series due to persistent obscuration of the optic nerve by the intraocular tumor (Fig. 2). He was treated with 4 cycles of 3-drug CEV chemoreduction with poor response and the right eye was subsequently enucleated 4 months after diagnosis. Pathology showed retinoblastoma with subretinal and vitreous seeds, tumor covering an atrophic optic nerve, no proliferating tumor at the lamina cribrosa or beyond, and no massive choroidal invasion or other high-risk features. MRI was done at diagnosis and indicated no findings of either optic nerve enhancement or optic nerve enlargement. The patient remained stable without evidence of extraocular disease at last screening MRI done at 36 months of age. The follow-up for this patient is 36 months and last visual acuity is recorded as "poor fix and follow."

Patient 4 was diagnosed with left unilateral retinoblastoma IIRC Group D2 at 20 months of age. MRI at diagnosis did not demonstrate signs of extraocular disease. The patient was treated with 6 cycles of standard CEV chemotherapy. The intraocular tumor continued to obscure the optic nerve throughout the course of chemotherapy; however, the tumor responded well to treatment and the eye was successfully salvaged. The last MRI was done at 34 months of age and was stable without radiographic signs of optic nerve involvement or extraocular disease. The follow-up for this patient is 14 months and last visual acuity is recorded as "poor fix and follow."

Discussion

Optic nerve invasion is a known consequence of untreated retinoblastoma. It is one of the most significant risk factors for mortality in retinoblastoma given the increased risk of developing orbital relapse and/or metastatic disease [2]. Choroidal invasion [13] and other high-risk histopathologic features may increase the risk; however, the most salient feature appears to be invasion of active proliferating tumor into the optic nerve. This risk also increases with increasing optic nerve involvement, with the greatest risk being involvement at the surgical margin [1]. Despite this known relationship, estimating the risk of optic nerve invasion remains difficult for the treating physician, and furthermore, it is even more difficult to predict the development of nerve invasion during treatment. In this review, we aimed to evaluate the effect of (1) optic nerve obscuration at diagnosis and (2) persistent obscuration of the optic nerve during treatment on the risk for optic nerve infiltration.

At diagnosis, in advanced Group D and E retinoblastoma eyes, it is very common for visualization of the optic nerve to be impeded either from direct obscuration by the tumor or secondary to a significant retinal detachment. A retrospective review from our center showed that 80% of Group D eyes demonstrate subretinal fluid at diagnosis [14], and in this review, similarly, 68% of eyes (Group D and E) demonstrated obscuration of the optic nerve at initial presentation. Of these, 30 (43%) underwent salvage therapy and 39 (57%) primary enucleation. On histopathologic analysis of primarily enucleated eyes with optic nerve obscuration at diagnosis, 41% had prelaminar invasion and 15% postlaminar invasion. In comparison, 50% (1 of 2 eyes) and 0% of eyes with a visible optic nerve that were primarily enucleated demonstrated pre- and postlaminar invasion, re-

spectively (Fig. 1). It should be mentioned that 43% of eyes with optic nerve obscuration at diagnosis were not enucleated primarily. Therefore, the incidence of optic nerve invasion for this clinical feature may be lower since we cannot discount the possibility of selection bias in enucleating the more advanced eyes. While statistical significance could not be achieved due to the small numbers in each cohort, particularly the eyes without optic nerve obscuration, this suggests that there may be an association between this clinical feature and optic nerve infiltration. Further investigation with a larger number of patients is warranted to better understand this association.

It is also not known what risk, if any, persistent optic nerve obscuration during treatment portends. While obscuration at diagnosis is common in advanced eyes, after the first few cycles of chemotherapy, there is generally a response to treatment so that the overall tumor shrinks and there is secondary resolution of subretinal fluid, both of which allow for improved visibility of the optic nerve. Persistent, complete obscuration of the optic nerve due to the tumor is rare. In this review of 102 patients with advanced Group D and E eyes, only 4 (4%) demonstrated persistent obscuration throughout treatment with a range of follow-up of 14–37 months (average 25.2 months for these 4 patients). Of these 4 eyes, all were classified per the IIRC as Group D [15], and further subclassified as Group D2 [16]. Two eyes were salvaged with complete control of intraocular disease and no clinical or radiographic signs of relapse at a follow-up of 14 months (same time for both patients). The vision in both of these eyes is poor; however, it cannot be precisely quantified due to the age of the patients. For the 2 eyes that required enucleation, only 1 was for progression of disease. The other eye was enucleated due to the development of neovascular glaucoma and no active tumor was appreciated on clinical or pathologic examination. Optic nerve infiltration was not found on histopathologic evaluation of either globe. The average follow-up for the 2 patients who required enucleation is 36.5 months (36–37 months) and there have been no signs of orbital relapse or metastatic disease during that time.

There is little to no information in the literature to guide clinicians on what, if any, factors during globe salvaging treatment for retinoblastoma may predispose to the development of optic nerve infiltration. Additionally, to our knowledge, there is nothing in the literature describing the management of retinoblastoma with persistent, complete obscuration of the optic nerve. We hypothesized that obscuration of the nerve during treatment was a potential risk factor for the development of optic nerve infiltration; however, in this very small cohort of patients, this was not found. It also does not appear to be a significant risk factor for orbital relapse or metastatic disease during an average follow-up of 25.2 months. However, it should be mentioned that the rate of metastasis for intraocular retinoblastoma in developed countries is probably too low to demonstrate a difference when comparing retrospective studies. Additionally, the majority of Group E eyes will present with optic nerve obscuration and likely undergo enucleation; therefore, the findings of this study may be more important when managing the subset of Group D eyes with this clinical feature at diagnosis. Persistent obscuration does, however, remain a poor prognostic sign both for globe salvage (50%, on par with salvage rates for Group D eyes treated with chemoreduction [11]) and for vision in the salvaged eye. While there are no clear guidelines for management in these rare cases, there are reports of stereotactic radiation for peripapillary tumors [17]. While successful, we recommend radiation therapy only if there is some visual potential to the eye and the child is older than 12 months of age. We do recommend radiographic visualization of the optic nerve at each EUA with B-scan ultrasound and further with MRI screening at 6-month intervals. We do not routinely recommend screening MRI scans of the brain and orbit simply for evaluation of the optic nerve and/or orbit after diagnosis unless there is the risk of trilateral disease development in a genetically predisposed patient. However, in any instance where the optic nerve cannot be directly evaluated, we do recommend screening. Otherwise we would repeat imaging only if the patient develops changes concerning for an orbital lesion. While the sensitivity for detecting postlaminar disease is variable (50% in this study), it has been shown to improve with fat saturation [18] and surface coils [19], and MRI can reliably detect larger levels of invasion and orbital disease [20]. We found that in this very small cohort, there is no need to enucleate these patients if the intraocular disease can be controlled with therapy, and the nerve can be adequately and routinely imaged with B-scan ultrasound and MRI. However, given the low vision in these eyes, we also recommend a lower threshold for enucleation for relapsed or persistently active disease without pursuing intensive measures for globe salvage. There is one case report in the literature of a peripapillary retinoblastoma, with initial optic nerve obscuration, which subsequently cleared with normal-appearing papillae followed by a large recurrence with retinal detachment. Enucleation

was performed and demonstrated cryptic postlaminar optic nerve despite a clinically, ultrasonographically, and histopathologically tumor-free prelaminar area [21]. This case, while rare, highlights the difficulty in managing patients with complete and partial optic nerve obscuration. Finally, there may be subgroups of patients with optic nerve obscuration that may be at lower risk than others, such as those with a total retinal detachment versus those with a large nasal tumor growing directly over the optic nerve. However, whenever the optic nerve cannot be visualized on fundoscopy, the clinician cannot rule out the possibility of optic nerve tumor infiltration. The current study provides some data on the likely histopathologic and clinical outcomes in that setting.

In conclusion, this is the first paper to discuss obscuration of the optic nerve in retinoblastoma. This is a common finding in advanced eyes at diagnosis and it may increase the risk of optic nerve invasion, particularly the more worrisome postlaminar invasion. While optic nerve obscuration is common at diagnosis, it is very rare to persist during the course of treatment. It is generally a poor prognostic sign, however, that persistent obscuration did not, at least in this small cohort of patients, appear to indicate an increased risk of optic nerve infiltration. Further research is required to understand if all these findings persist with a larger subset of patients given the limitation with a small sample size. Furthermore, while features at diagnosis associated with high-risk pathology have been identified, there remains a need to better understand whether certain clinical features present during treatment may portend a risk of developing optic nerve infiltration during attempted globe salvaging therapy.

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Statement of Ethics

The Institutional Review Board at CHLA approved this study.

Disclosure Statement

No conflicting relationship exists for any author.

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