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An Intraocular Pressure Predictive of High-risk Histopathologic Features in Group E Retinoblastoma Eyes

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Introduction

Postlaminar optic nerve invasion, massive choroidal invasion, and extrascleral invasion are histopathologic features that, when present in enucleated retinoblastoma (Rb) eyes, suggest a worse prognosis due to an increased risk for development of metastatic disease.^{1–6} Patients with eyes displaying these features upon postoperative histopathologic evaluation are generally recommended adjuvant chemotherapy to prevent metastasis and death.^{7,8} Efforts have been made to identify clinical and radiographic features associated with the presence of high-risk histopathology, which can be recognized at time of diagnosis rather than after enucleation. This gives clinicians the opportunity to recommend prompt enucleation to prevent additional growth/spread of the tumor or to suggest administration of preoperative neoadjuvant chemotherapy to achieve tumor regression and support a more targeted treatment plan.^{9,10} Optic nerve enhancement on magnetic resonance imaging (MRI) is a preoperative imaging finding that may be suggestive of high-risk pathology; however, thickening is more specific.^{10–12} In terms of clinical features, Rb eyes with glaucoma, buphthalmos, neovascularization of the iris (NVI), and an increased intraocular pressure (IOP) at diagnosis are associated with high-risk histopathologic features upon enucleation.^{11,13–16}

Although increased IOP is already recognized as an indicator of advanced disease with high-risk pathology, it is not a clinical factor of high specificity, as many Rb patients present with elevated IOP at diagnosis, but do not display high-risk features upon enucleation. In addition, the numeric level of “elevation” is infrequently discussed in other studies; therefore, the impact of this variable is not entirely known.

Secondarily, we were interested in stratifying risk for eyes with an elevated IOP based on the presence or absence of NVI. Increased IOP in Rb eyes at diagnosis can be seen with or without NVI, as the 2 most common mechanisms causing ocular hypertension in Rb are peripheral anterior synechiae formation secondary to NVI and NVI-independent angle closure due to massive exudative retinal detachment.^{17,18} Thus, we wanted to establish if the presence of NVI is a significant additional variable when determining an IOP cutoff value most predictive of high-risk pathology.

While Group E eyes are often considered unsalvageable, there is a growing trend toward attempts at conservative treatment.¹⁹ As Group E Rb eyes have the greatest prevalence of high-risk histopathologic features,^{14,20–22} it is critical to stratify clinical risk for them at time of diagnosis. Therefore, this study was limited to Group E eyes at diagnosis. We hope to elucidate if there is a specific IOP value above which Rb eyes are more likely to display high-risk histopathologic features in order to equip clinicians with the most precise prognostic clinical criteria possible.

Materials and Methods

We conducted a retrospective chart review of patients diagnosed with Group E Rb [using the Intraocular International Rb Classification (IIRC) System outlined by Murphree²³] in at least 1 eye from January 1, 1995 to December 31, 2017 that had histopathology for review and a documented numerical IOP at diagnosis taken during staging examination under anesthesia (EUA). The Institutional Review board at Children's Hospital Los Angeles approved this study, and it conformed to the requirements of the United States Health Insurance Portability and Privacy Act.

Treatment

Primary enucleation is the standard treatment for unilateral Group E Rb at Children's Hospital Los Angeles.²² In the setting of bilaterally advanced Rb, salvage is attempted such that the patient does not become bilaterally anophthalmic. While children with bilateral Rb are the subset of patients for which the results of this study are most applicable, given the recent trends toward salvage for more advanced eyes, the results can be applied to any Group E eye. In these cases, correctly stratifying the risk for metastasis is critical because salvage should not be attempted on an eye if there is considerable risk to the child's life.

When there is evidence of tumor extension on preoperative MRI, some clinicians postpone enucleation and recommend neoadjuvant chemotherapy, consisting of 1 to 5 cycles of a combination drug which includes platinum-based chemotherapy and etoposide with the goal of achieving extraocular tumor regression.^{9,10} Other clinicians who are confidently able to resect a longer length (> 10 mm) of optic nerve recommend immediate enucleation if there is suggestion of high-risk pathology either via MRI optic nerve enhancement or clinical features to prevent further invasion of the tumor posteriorly.²⁴ These 2 treatment options were not directly evaluated in this study.

Patients with eyes found to display high-risk features postoperatively upon pathologic examination are usually treated with 6 cycles of systemic carboplatin, etoposide phosphate, and vincristine sulfate (CEV) adjuvant chemotherapy to reduce the likelihood for metastasis.⁸ Briefly, this treatment course consists of intravenous carboplatin 560 mg/m² (18.6 mg/kg for children below 36 mo) for 1 day, etoposide 150 mg/m² (5 mg/kg for children below 36 mo) each day for 2 days, and vincristine 1.5 mg/m² (0.05 mg/kg for children below 36 mo) for 1 day for 6 cycles every 28 days.

IOP Measurement

IOP was measured as a routine part of the staging EUA, as an initial step in the case. All measurements were performed under anesthesia and not in the office. A tonopen (Reichert technologies, Depew, NY) was used for measurement without a lid speculum in place.

Chart Review

We classified eyes according to the IIRC System outlined by Murphree.²³ We also classified eyes as having high-risk pathology if they displayed one or more of the following features upon postoperative pathologic examination: postlaminar optic nerve invasion, massive choroidal invasion, and extrascleral invasion.^{1–6} Lastly, outcomes included primary enucleation, attempted salvage+ultimate enucleation, and ultimate successful salvage.

A retrospective chart review was done to obtain the following information: age at diagnosis, sex, laterality of Rb, genetic testing status, length of follow-up, percent invasion of macula, presence of NVI, IOP at diagnosis, tumor margins, presence of high-risk histopathology as noted above, initial treatment approach, details of systemic or local chemotherapy/radiation/laser/cryotherapy when applicable, and ultimate globe salvage outcome.

Statistical Analysis

We compared differences in IOP at baseline using the Student *t* test, grouping eyes according to whether high-risk histopathology was present, as well as whether enucleation was the primary therapeutic choice.

To examine the predictive nature of IOP with or without NVI on the presence of high-risk histopathology, we used logistic regression with receiver operating characteristic (ROC) curve analysis. This analysis suggested that 2 values of IOP could serve as useful cutpoints for predicting the presence of high-risk histopathology—around 22 mm Hg, the widely accepted upper bound of normal IOP, which optimized model sensitivity; and around 34 mm Hg, a value that optimized model specificity. Next, we trichotomized patients into groups based on IOP at diagnosis—low or normal (IOP<22 mm Hg), high (22 mm Hg<IOP<34 mm Hg), and very high (IOP ≥ 34 mm Hg)—and utilized this to assess the relative odds of the presence of high-risk features, with or without NVI.

We conducted all analyses using Stata/SE 14.2 (StataCorp LLC, College Station, TX).

Results

A retrospective review was performed on patients diagnosed with IIRC Group E Rb that had a documented numerical IOP at diagnosis from January 1, 1995 to December 31, 2017. The inclusion criteria were met in 126 eyes of 123 patients. In our cohort, 8 eyes of 8 patients showed significant optic nerve enhancement on preoperative MRI and were treated with neoadjuvant chemotherapy before enucleation¹⁰; these eyes were excluded from the analysis because although MRI enhancement is suggestive of optic nerve invasion and the patients were treated with neoadjuvant chemo as such, histopathologic evidence of invasion was used as the gold standard for classifying a high-risk eye in this study.¹³ Thus, 118 eyes of 115

patients were included in the analysis. Please see Table 1 for detailed demographic information.

Primary enucleation was the treatment option for 96 eyes (81%) due to a diagnosis of unilateral Group E Rb. Fifty-one of these eyes (53%) showed no high-risk pathologic features, and no further treatment was pursued. Forty-five of these eyes (47%) showed high-risk pathologic features, with 20 eyes showing postlaminar optic nerve invasion, 10 eyes showing massive choroidal invasion, 10 eyes showing postlaminar optic nerve invasion and massive choroidal invasion, 2 eyes showing massive choroidal invasion and extrascleral invasion, and 3 eyes showing all 3 high-risk pathologic features. These 45 patients were, therefore, recommended 6 cycles of adjuvant CEV chemotherapy. Forty-four patients (98%) received adjuvant CEV chemotherapy, while 1 patient (2%) refused the recommendation.

The other 22 eyes (19%) underwent attempted salvage due to a diagnosis of bilateral Rb. Of the 22 attempted salvage eyes, 15 eyes (68%) were ultimately enucleated and 7 eyes (32%) were salvaged; secondarily enucleated eye (7%) showed postlaminar optic nerve invasion.

None of the patients in our study developed orbital recurrences or metastases during the follow-up period of median 63.9 months (SD, 52.5 mo). Please see Figure 1 for a modified CONSORT diagram. It should be noted that 2 Group E patients developed metastatic disease during this time at our institution; they did not meet the inclusion criteria due to no documented numerical IOP at diagnosis (documented rather as “elevated” IOP); however, this information has been published previously.²⁵

IOP as a Predictor of High-risk Histopathologic Features

Analysis was performed on primarily enucleated eyes only, as these eyes received no chemotherapy before pathologic examination that could confound the results. The mean IOP at diagnosis for the 45 eyes with high-risk pathology was 31.8 mm Hg (± 11.1), whereas the mean IOP at diagnosis for the 51 eyes without high-risk pathology was 24.5 mm Hg (± 12.2). This difference was statistically significant (t test, $P = 0.0031$).

Knowing that IOP can be used as a predictor of high-risk pathology, we ran a ROC curve analysis to determine IOP values that most accurately predicts eyes with high-risk features. An IOP cutoff value of 34 mm Hg at diagnosis optimizes specificity in predicting the presence of high-risk features (45.6% sensitivity, 82.4% specificity, 65% of patients correctly classified). Because we are not trying to capture all patients with high-risk pathology but rather identify an IOP cutoff value above which clinicians should be especially concerned about the almost definite presence of high-risk pathology, we chose to optimize specificity over sensitivity in the ROC curve analysis. For example, using a cutoff value of 30 mm Hg at diagnosis results in an increased sensitivity but decreased specificity and correct classification of fewer patients (58.7% sensitivity, 66.7% specificity, 62.9% of patients correctly classified).

Using this cutoff value, eyes with an IOP ≥ 34 mm Hg at diagnosis are 5.91 times more likely to have high-risk pathology than all eyes with a pressure < 22 mm Hg at diagnosis. In

comparison, eyes with an IOP > 22 mm Hg but <34 mm Hg are only 3.80 times more likely to have high-risk pathology than all eyes with a pressure <22 mm Hg at diagnosis.

The Effect of NVI

The presence of NVI alone was associated with increased odds (OR = 2.62; 95% CI = 0.87–7.86) of displaying high-risk histopathology upon enucleation compared with the odds for those without NVI. This association trended toward significance in our study ($P = 0.09$), and has been previously demonstrated as significant in the literature.^{4,13,15,16}

Acknowledging the association between IOP and NVI (ie, NVI may produce higher IOP), we also examined the effects of NVI after removing overlapping variance with our IOP data.

Although both NVI and an IOP ≥ 34 mm Hg at diagnosis are independently predictive of high-risk features, having both NVI and an IOP ≥ 34 mm Hg at diagnosis does not confer a significantly greater risk for high-risk features upon enucleation than high IOP alone ($P = 0.34$). Eyes with an IOP ≥ 34 mm Hg at diagnosis and with NVI have 2.29 times greater odds of high-risk pathology compared with all other eyes examined, while eyes with an IOP ≥ 34 mm Hg at diagnosis and without NVI have 2.5 times greater odds of high-risk pathology compared with all other eyes examined. Thus, we conclude that having an IOP ≥ 34 mm Hg at diagnosis is an independent risk factor for high-risk histopathologic features, regardless of the presence of NVI.

IOP as a Predictor of Globe Salvage

Ultimately salvaged eyes had a mean IOP of 21.4 mm Hg (± 15.1) at diagnosis, while enucleated eyes had a mean IOP of 27.7 mm Hg (± 12.0) at diagnosis. This difference approached significance ($P = 0.19$). There was no statistically significant difference in the mean IOP at diagnosis between eyes that were primarily enucleated and eyes that underwent attempted salvage before ultimate enucleation ($P = 0.53$).

Discussion

In patients diagnosed with Group E Rb, an important concern for clinicians is the presence of high-risk histopathologic features compared with eyes with less advanced disease.^{14,20–22} Postlaminar optic nerve invasion, massive choroidal invasion, and extrascleral invasion by the tumor are histopathologic features that suggest a higher risk for metastasis when present; without adjuvant chemotherapy, these patients have a worse prognosis and increased risk of death from metastatic disease when compared with patients without any high-risk histopathology.^{1–6} It is paramount for clinicians to note features at diagnosis that are associated with high-risk pathology, and thus create a treatment plan tailored to these features including primary enucleation in most Group E cases. A variety of clinical factors that predispose patients to display these high-risk features have already been identified, including glaucoma, buphthalmos, NVI, and increased IOP (> 22 mm Hg), among others.^{11,13–16} Of particular interest to us was increased IOP, which may be caused via 2 mechanisms in Rb eyes. Firstly, massive exudative retinal detachment from tumor or direct tumor invasion of the anterior chamber can cause consequent angle closure.^{17,18} In addition,

advanced tumors lead to general ocular ischemia which promotes NVI growth that results in secondary peripheral anterior synechiae formation.^{17,18}

Many patients with advanced Rb present with an elevated IOP at diagnosis, but not all of them display high-risk histopathologic features upon enucleation; thus, increased IOP > 22 mm Hg alone is not a clinical factor of high specificity. Therefore, we were interested in more specifically exploring the relationship between increased IOP and high-risk histopathologic features. Further, we wanted to determine whether there exists an IOP cutoff point above which eyes should be considered at particularly increased risk for having high-risk pathologic features. We found that the mean IOP at diagnosis for eyes with high-risk pathology (31.8 mm Hg) was significantly higher than the mean IOP at diagnosis for eyes without high-risk pathology (24.5 mm Hg) ($P = 0.0031$). We identified that an IOP value of 34 mm Hg optimizes specificity (82.4%) in predicting the presence of high-risk histopathologic features. Specifically, eyes with an IOP ≥ 34 mm Hg at diagnosis are 5.91 times more likely to have high-risk pathology than eyes with an IOP < 22 mm Hg.

We recognize that this is not a cutoff definitive of the presence or absence of high-risk features, but rather a guideline by which clinicians should increase their level of concern and propose an appropriate treatment plan guided by this information even in unilateral cases.¹⁹ For these patients, the 34 mm Hg IOP cutoff is another method that can be used in conjunction with other clinical and radiographic features to predict if an eye has high-risk histopathology and is safe to attempt conservative treatment. A better understanding of the likelihood of an eye to display high-risk histopathology at diagnosis allows for a more informed and appropriate discussion with the family regarding the potential for metastatic disease. This information allows clinicians the opportunity to provide the most effective care possible.

Of note, IOP was recorded via Tonopen as an early part of the staging EUA. While IOP during EUA can be impacted by various factors including intubation and anesthesia, it is similarly affected for all children with Rb undergoing a staging EUA. Thus, we hope that these guidelines will remain a useful prognostic factor in conjunction with other clinical and imaging evidence in predicting the presence of high-risk pathology. IOP measurements on a young, awake child are often unreliable; we do not recommend that clinical IOP measurements be used to stratify risk with the guidelines proposed by this study.

Increased IOP in a Rb eye can arise from both NVI-dependent and NVI-independent mechanisms. Further, NVI is a known risk factor for high-risk pathology.^{4,13,15,16} Thus, we were also interested in exploring the relationship between increased IOP and NVI as it is associated with high-risk histopathologic features.^{17,18} Although both NVI and an IOP ≥ 34 mm Hg at diagnosis are independently predictive of high-risk features, having both NVI and an IOP ≥ 34 mm Hg at diagnosis does not confer a significantly greater risk for displaying high-risk features upon enucleation ($P = 0.34$). While we are trying to define the role that NVI and increased IOP play separately in predicting high-risk features, we understand that the 2 are integrally related. However, in this retrospective analysis, it seems that an IOP ≥ 34 mm Hg at diagnosis is most predictive of high-risk histopathology, and is an independent risk factor regardless of the presence of NVI. Of note, the only odds ratio that cleared our

threshold for statistical significance was the one predicting high-risk pathology given an IOP ≥ 34 mm Hg at diagnosis. Clinicians should be concerned about an eye with an IOP ≥ 34 mm Hg regardless of the presence of NVI. At lower pressures, NVI remains a high-risk clinical trait.

To conclude, whether or not NVI occurs, eyes with an IOP ≥ 34 mm Hg at diagnosis are 5.91 times more likely to have high-risk histopathologic features than eyes below this value. Thus, any attempts at salvage or unnecessary delay in enucleation for these eyes may predispose the child to unnecessary metastatic risk. This quantitative IOP cutoff is by no means definitive of high-risk histopathology, but rather a guideline that clinicians should use along with other diagnostic features to recommend the best course of treatment for each and every patient.

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Figure 1. Modified CONSORT (Consolidated Standards of Reporting Trials) diagram. EUA indicates examination under anesthesia; IOP, intraocular pressure; m F/U, median follow-up time; MRI, magnetic resonance imaging; Rb, retinoblastoma.

Table 1.**Demographics**

All patients included	115
No. eyes	118
Sex	
Female	57
Male	58
Age	
Median age at dx (range)	17 mo (1–99)
Laterality	
Left eye	55
Right eye	63
Follow-up time	
Median (SD)	63.9 mo (52.5)
Outcome	
Primarily enucleated	96
Treatment due to bilateral Rb, ultimate enucleation	15
Treatment due to bilateral Rb, successful salvage	7
IOP (mm Hg)	
Median (SD)	27 (12.2)
NVI	
Eyes with NVI	81
Eyes without NVI	37
HRF	
Eyes without HRF	72
Eyes with HRF	46
Count of HRF	
Postlaminar optic nerve invasion only	21
Massive choroidal invasion only	10
> 1 HRF	15

HRF indicates high-risk histopathologic features; IOP, intraocular pressure; NVI, neovascularization of the iris; Rb, retinoblastoma.