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Clinical Significance of Optic Nerve Enhancement on Magnetic Resonance Imaging in Enucleated Retinoblastoma Patients

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Purpose: The aim of this 8-year retrospective review was to determine the clinical significance of gadolinium-enhanced magnetic resonance imaging (MRI) findings in retinoblastoma patients after enucleation, particularly the presence of abnormal contrast enhancement of the transected optic nerve.

Design: Retrospective chart review.

Subjects: A review was done on 88 patients with retinoblastoma undergoing 90 enucleations between January 2008 and December 2015.

Methods: These patients underwent 233 MRI scans: 90 preoperative and 143 postoperative that were included for review.

Main Outcome Measure: The primary outcome measure assessed was abnormal MRI findings in the preoperative and postoperative MRI scans, specifically enhancement of the optic nerve and correlations between abnormal MRI findings and clinical outcomes for the 88 patients.

Results: On the preoperative MRI, 4 optic nerves out of 90 scans showed positive enhancement. Fifty orbits had $\geq$1 postoperative MRI. Overall, 41 of 50 orbits (82%) of enucleated patients demonstrated postoperative contrast enhancement on MRI after enucleation, at a mean interval of 10 months after surgery. The percentage of MRI scans with optic nerve enhancement was 77% from 0 to 6 months after enucleation and 68% at >24 months after surgery. Postenucleation optic nerve enhancement did not correlate with preoperative optic nerve enhancement, chemotherapy administration, or the presence of optic nerve invasion on histopathology. No child required an orbital biopsy. None of the 88 patients were found to have subsequent orbital or metastatic disease at the last clinical follow-up visit (average, 29 months; range, 1–71).

Conclusion: Optic nerve contrast enhancement on follow-up MRI after enucleation for retinoblastoma seems to be a common, benign radiographic finding; none of the patients in this series developed extraocular tumor relapse. The presence of postenucleation enhancement on MRI did not correlate with preoperative chemotherapy or the presence of optic nerve invasion on histopathology. Based on our findings, intervention for isolated optic nerve enhancement on MRI is not indicated in the absence of other abnormal clinical or radiographic signs. A prospective trial with a validated radiographic grading system would be helpful to clarify the MRI features to differentiate orbital recurrence from benign postoperative enhancement. *Ophthalmology Retina 2017;■:1–6 © 2017 by the American Academy of Ophthalmology*

Retinoblastoma (Rb) is the most common primary intraocular malignancy in children, with an estimated incidence of 11.8 cases per million children aged 0–4 years.[1] Ocular salvage rates for treated eyes have been reported to be >90% in developed countries using various treatment options such as systemic chemotherapy, intra-arterial chemotherapy, and intravitreal chemotherapy injections.[2–14] However, enucleation remains the most common treatment for Rb patients worldwide and is thought to be curative in 96% to 100% of cases.[15,16] Tumor relapse after enucleation is an unlikely but feared event, and may occur through hematogenous dissemination, postlaminar invasion into the optic nerve, or direct extension into the orbit through the sclera.[15] High-risk pathologic features such as postlaminar optic nerve invasion, massive choroidal invasion, and scleral invasion have been correlated with an increased risk for orbital recurrence and/or distant metastasis.[17–20] Orbital tumor recurrence of Rb after enucleation has an estimated incidence of 4.2%, with the majority of these patients occurring within 12 months of surgery and having evidence of concomitant systemic metastasis.[15,21] Therefore, any clinical or radiographic evidence of tumor recurrence after enucleation requires immediate intervention, including tissue biopsy, systemic metastasis workup, and often multimodal therapy if the diagnosis is confirmed.

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Magnetic resonance imaging (MRI) is the preferred neuroimaging modality for Rb patients given its excellent tissue resolution and the absence of potentially mutagenic radiation 0.[22,23] Recent studies have shown that MRI is useful for staging Rb patients and for patients during and after treatment.[22,24] At diagnosis, MRI scans have been used to assess patients for possible postlaminar optic nerve invasion and its high sensitivity for detecting this feature has been confirmed in several studies.[23,25,26] Sirin et al[24] recently published an analysis of MRI findings after enucleation in children with Rb, which included 3 patients with orbital masses on MRI scans who were biopsy confirmed as Rb. The authors also strongly recommended routine MRI surveillance for all Rb patients for orbital relapse for 2 years after enucleation.[24] The aim of this retrospective review was to evaluate gadolinium-enhanced MRI findings of the orbit after enucleation. Our hypothesis was that enhancement of the transected end of the optic nerve on postoperative MRI scans represents a common, benign finding not associated with tumor relapse.

Materials and Methods

The Institutional Review Board at Children's Hospital Los Angeles approved this retrospective study. Patients eligible for this review underwent enucleation for Rb between January 2008 and December 2015 and had MRI reports available for review; subsequent histopathology reports confirmed the diagnosis of Rb in all cases and assayed for high-risk features. Gadolinium-enhanced MRI was performed routinely at diagnosis and often postoperatively as a part of our normal clinical protocol, which includes MRI evaluations every 6 months until the age of 3 for all patients with bilateral Rb or a known Rb tumor suppressor gene (*RB1*) mutation as screening for central nervous system disease. Primarily enucleated unilateral patients are not screened routinely unless there are significant high-risk pathologic features or clinical presentation warrants evaluation. At our institution, 6 board-certified radiologists with significant experience in pediatric neuroimaging evaluation read neuroimaging studies, including brain and imaging MRIs. Additionally, each scan has an initial radiologist evaluation, which is subsequently verified by a second, separate radiologist so that each scan is evaluated twice with consensus. Our institutional protocol for extensive optic nerve involvement on MR imaging has been described previously; we currently treat optic nerve involvement of <5 mm on MRI with primary enucleation and those with >5 mm of involvement with intensive pre-enucleation chemotherapy. No child in this study was treated with this pre-enucleation protocol.

All MRI reports were reviewed and the following outcome measures were assessed: (1) pretreatment contrast enhancement (and/or thickening) of the optic nerve and its sheath, (2) enhancement along the transected end of the optic nerve after enucleation, (3) evidence of other areas of abnormal enhancement or masses in the orbit (before or after treatment), and (4) evidence of trilateral Rb both before and after treatment. On histopathology, tumor extension into the optic nerve was categorized with reference to the lamina cribrosa as pre or post laminar.

Other pathologic features such as choroidal invasion and scleral invasion were also assessed. Clinical data collected from the patient medical records included unilateral or bilateral disease, international intraocular classification Rb, age at diagnosis, age at enucleation, and clinical and tumor status at the time of the last follow-up examination. MRI scans were performed according to standard neuroimaging protocols for the brain and orbit using gadolinium contrast agent in all patients with 1.5 or 3.0 Tesla MRI scanners (Siemens Health Care Sector, Erlangen, Germany). A dose of 0.1 mmol/kg body weight of gadolinium chelate was injected intravenously during the scans. All MRI examinations were performed under general anesthesia due to the age of the patients.

Statistical analysis was performed with GraphPad (La Jolla, CA). Chi-square testing was performed to evaluate for significance; $P < 0.05$ was considered significant.

A literature review was performed on PubMed search using terms "retinoblastoma" and "MRI" and "enucleation" from 1990 to 2016.

Table 1. Preoperative and Postoperative MRI Demographics

Demographic	n
Total number of orbits	90
Total number of patients	88
Total number of MRI scans	233
Number of preoperative MRI scans	90
Preoperative optic nerve enhancement	4
Number of postoperative MRI scans	143
Orbits with postoperative MRI scans	50
Orbits that showed post operative enhancement	41
Patients treated with CEV	38
Positive optic nerve enhancement in patients treated with CEV	20
No optic nerve enhancement in patients treated with CEV	9
Postlaminar optic nerve invasion	6
Postlaminar optic nerve invasion with preoperative enhancement	3
Postlaminar optic nerve invasion without preoperative enhancement	3
Median follow-up to first MRI scans, mo (range)	10 (2–65)
Average clinical follow-up, mo (range)	29 (1–71)

CEV = carboplatin, etoposide, and vincristine; MRI = magnetic resonance imaging.

Results

A total of 90 enucleations were performed in 88 Rb patients between January 2008 and December 2015. Sixty eyes (67%) were designated International Classification of Retinoblastoma group D and 30 eyes (33%) were group E. Fifty-three patients (60%) had unilateral disease and 35 patients had bilateral disease (40%). The average age at diagnosis was 21.7 months (range, 0–111) and average age at enucleation 24.9 months (range, 0–127). Primary enucleation was done as treatment for intraocular Rb in 56 eyes.

There were a total of 90 preoperative MRI reports and 143 postoperative MRI reports available for review. Preoperative optic nerve enhancement on MRI was detected in 4 orbits (Table 1, Fig 1); one demonstrated concomitant thickening. On histopathology, 3 of the 4 globes with this preoperative finding demonstrated postlaminar optic nerve invasion. There were 3 other globes that did not demonstrate preoperative optic nerve enhancement on MRI but were found to have postlaminar optic nerve invasion on histopathology. No case was found to have tumor involvement to the cut end of the optic nerve. All 6 cases with postlaminar optic nerve invasion received 6 cycles of adjuvant systemic chemotherapy (carboplatin, etoposide, and