Original Article

Accuracy of preoperative imaging in predicting optic nerve invasion in retinoblastoma: A retrospective study

Usha Kim, Gunjan Rathi, Gunja Chowdhary, K G Srinavasan, R Shanthi, R S Prabhu Krishna

Purpose: Optic nerve invasion is an important cause of mortality in retinoblastoma. We aimed correlate preoperative imaging and surgical histopathology findings in enucleated eyes with retinoblastoma to determine the efficacy of preoperative imaging in predicting optic nerve invasion in retinoblastoma. **Methods:** A retrospective review of records of all patients undergoing primary enucleation for retinoblastoma at a tertiary eyecare system between March 2013 and December 2017 with all patients having undergone preoperative imaging, either CT scan or MRI. Data was analyzed statistically to determine the correlation between preoperative CT scan/MRI and histopathology. **Results:** Totally, 97 eyes of 97 patients were included in the study who underwent primary enucleation for unilateral retinoblastoma. The average age at presentation was 27.8 months with the chief complaint being leukocoria in all the cases. 14 patients (14.43%) had evidence of optic nerve involvement in preoperative imaging. 30 patients had optic nerve invasion on histopathology (laminar and retrolaminar). Spearman's rank correlation test revealed a significant correlation between MRI findings and HP and an insignficant correlation between CT findings and HP. The CT scan had a sensitivity of 20%, specificity of 88.89%, 50% positive predictive value and 66.67% negative predictive value. MRI had a sensitivity of 40%, specificity of 93.55%, positive predictive value of 66.67% and a negative predictive value of 82.86%. **Conclusion:** MRI showed significant moderate correlation with surgical histopathology for predicting optic nerve invasion in retinoblastoma whereas CT shows insignificant correlation with HPE. Therefore, we recommend MRI for predicting optic nerve invasion in cases of retinoblastoma.

Access this article online

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_1611_18

Quick Response Code:

Key words: Optic nerve invasion, preoperative imaging, retinoblastoma

Retinoblastoma is the most common intraocular tumor in children, accounting for 4% of all pediatric malignancies.[1] The disease may be familial or sporadic, and arises following a "two-hit" insult to the tumor-suppressing retinoblastoma (RB) gene of chromosome 13.[2,3] Mortality from retinoblastoma occurs subsequent to central nervous system metastasis, most commonly by way of the optic nerve. Accordingly, optic nerve invasion has been found to be correlated with worse survival rate.[4]

Optic nerve infiltration in retinoblastoma is histopathologically confirmed in 29.5–48.6% of enucleated eyes[4] Preoperative assessment for extraocular disease is performed using magnetic resonance imaging and computed tomography, with findings routinely used to guide management. While enucleation remains the standard of care for advanced intraocular tumors, conservative treatment which can result in globe salvage and preservation of useful vision is being successfully used for less-advanced disease (Groups A-D, International Classification System). These therapies include systemic chemotherapy, focal consolidation with transpupillary thermotherapy, laser photocoagulation and cryotherapy, radiation treatment with plaque brachytherapy or EBRT, and local injections of chemotherapeutic agents through the subtenon or subconjunctival routes as an adjunct to systemic chemotherapy.[5] In this study, we aim to correlate preoperative imaging (CT scan and MRI) and surgical histopathology findings in primarily enucleated eyes with retinoblastoma for determining the efficacy of preoperative imaging in predicting optic nerve invasion in retinoblastoma.

Methods

A retrospective chart review was performed of patients who presented to a tertiary eye care system between March 2013 and December 2017 and underwent primary enucleation for unilateral retinoblastoma. All patients underwent preoperative imaging to evaluate the extent of disease. The study was approved by the local institutional ethics committee and was conducted as per the tenets of the Declaration of Helsinki. Informed consent for surgery was obtained from the parents of all the participants as part of the procedures for undergoing enucleation surgery.

Department of Orbit and Oculoplasty, Aravind Eye Hospital, Madurai, Tamil Nadu, India

Correspondence to: Dr. Usha Kim, Department of Orbit and Oculoplasty, Aravind Eye Hospital, Madurai - 625 020, Tamil Nadu, India. E-mail: Usha@aravind.org

Received: 06-Dec-2018 Revision: 21-May-2019
Accepted: 29-Aug-2019 Published: 22-Nov-2019

Cite this article as: Kim U, Rathi G, Chowdhary G, Srinavasan KG, Shanthi R, Krishna RS. Accuracy of preoperative imaging in predicting optic nerve invasion in retinoblastoma: A retrospective study. Indian J Ophthalmol 2019;67:2019-22.

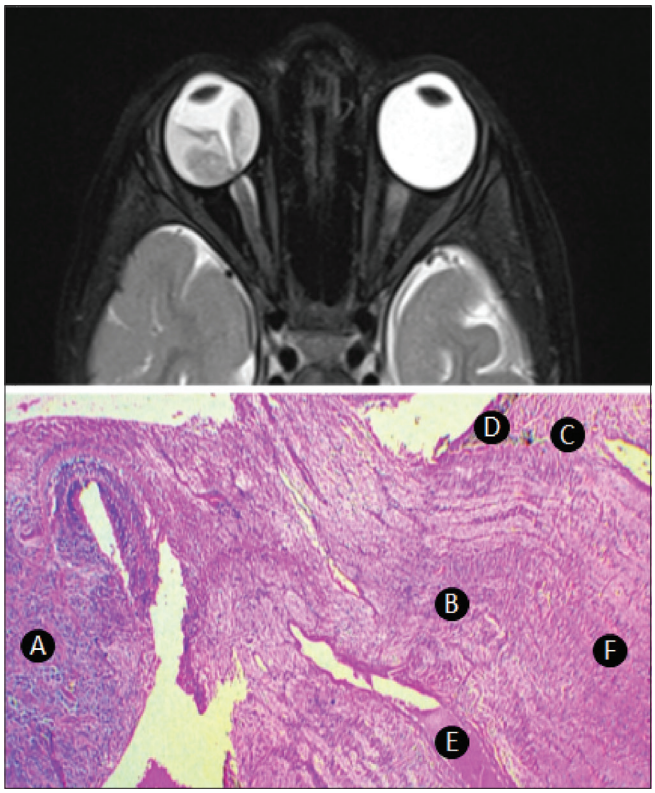

Figure 1: Trans axial T2 weighted MRI of exophytically growing retinoblastoma with secondary retinal detachment of right eye. No optic nerve infiltration seen on right side. Left eye appears normal. Histopathological analysis of the same patient showing retinoblastoma without optic nerve infiltration. Image shows (A) intraocular retinoblastoma (B) lamina cribrosa (C) sclera (D) choroid (E) central retinal artery (F) optic nerve

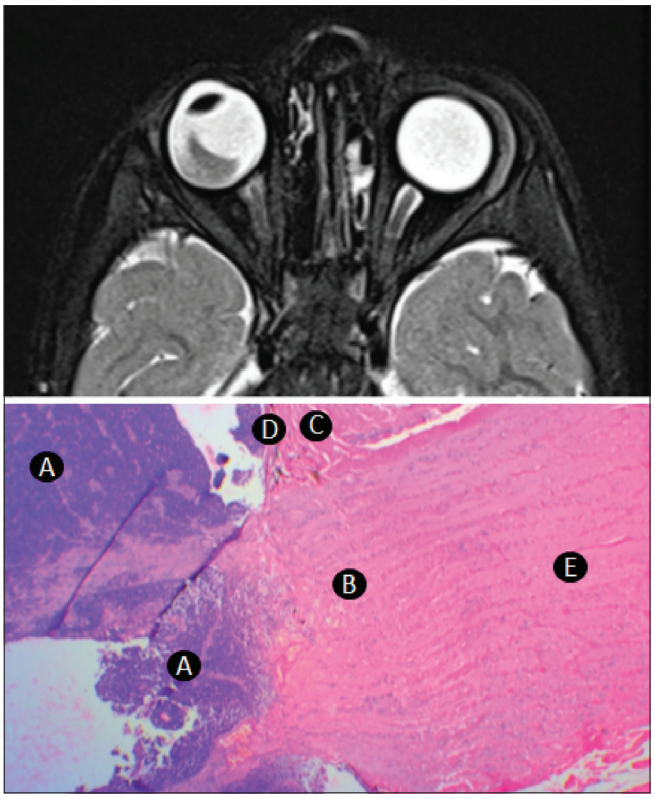

Figure 2: Trans axial T2 weighted MRI of exophytically growing retinoblastoma without optic nerve infiltration of the right eye. Left eye appears normal. Histopathological analysis of the same patient showing retinoblastoma cells infiltrating the optic nerve upto the level of lamina cribrosa . Image shows (A) retinoblastoma cells (B) lamina cribrosa (C) sclera (D) choroid and (E) optic nerve

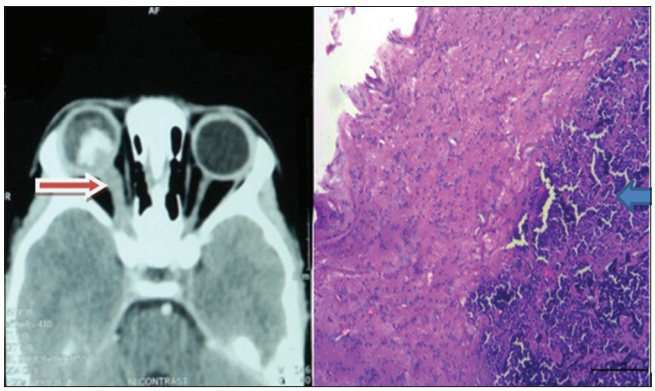

Figure 3: Both imaging and histology showing optic nerve invasion

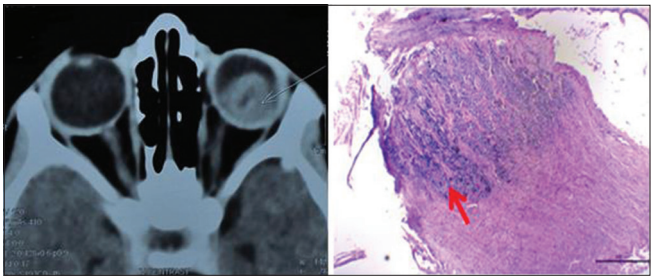

Figure 4: Imaging showing retinoblastoma with no optic nerve invasion but histology showing retrolaminar optic nerve involvement

The chosen imaging modality was selected according to age, consistent with standard country protocols. Those patients less than one year of age, or with clinical suspicion for metastatic central nervous system disease, underwent diffusion weighted, 3 Tesla strength MRI of the brain and orbits using head coils with and without contrast and a slice thickness of 1 mm. Patients more than one year of age underwent spiral CT with and without contrast and a slice thickness of 1mm. Optic nerve invasion was diagnosed by thickened or assymetric optic nerves. Optic nerve invasion was diagnosed by enhancement or irregularity of optic nerves. All orbital images were reviewed both by the head radiologist and the chief of the Orbit department at the eye hospital and interpretation was made in consensus. Metastatic work-up also included bone marrow and cerebrospinal fluid evaluation, as well as chest and abdominal CT imaging. Only patients without evidence of metastatic disease proceeded with enucleation.

All patients reviewed underwent primary enucleation of the globe with inclusion of a long optic nerve stump. Enucleation specimens were histopathologically evaluated at the pathology department of the eye hospital.

Results

A total of 97 eyes of 97 patients who underwent primary enucleation for unilateral retinoblastoma were identified. The average age at presentation was 27.8 months (3–63 months). All patients presented with a chief complaint of leukocoria noticed by their caregiver.

All patients underwent preoperative imaging (CT scan or MRI), with modality dependent on age. During initial presentation, 14 patients (14.43%) had evidence of optic nerve involvement on imaging. Enucleation was performed within one month of imaging.

On histopathologic analysis of the enucleation tissue, 55 patients (56.7%) had evidence of prelaminar, laminar, or retrolaminar optic nerve tumor involvement. All but one patient had no evidence of disease at the proximal cut-end optic nerve margin. Those with prelaminar infiltration were not taken into consideration for statistical analysis as there is no clinical significance of diagnosing prelaminar invasion from the treatment point of view. Also, since it is not seen on imaging, it will lead to incorrectly high false negative values. Therefore, if cases with laminar and retrolaminar invasion alone are taken into consideration, there were 30 patients (30.93%). The Spearman's rank correlation test revealed a significant correlation between MRI findings and HP (0.4076; $P < 0.05$) [Figs. 1 and 2] and an insignificant correlation between CT findings and HP (0.1217; $P < 0.05$) [Figs. 3 and 4; Table 1]. The CT scan had a sensitivity of 20%, specificity of 88.89%, a positive predictive value, presence of optic nerve invasion on both CT and HPE, of 50%, and a negative predictive value, absence of optic nerve invasion on CT and HPE, of 66.67% [Table 2]. MRI had a sensitivity of 40%, specificity of 93.55%, a positive predictive value of 66.67%, and a negative predictive value of 82.86% [Table 3].

Upon histologic analysis, 46 lesions (47.5%) were well-differentiated, 2 (1.9%) were moderately differentiated, 39 (40%) were poorly differentiated, and 11 (10.6%) were calcified and regressed in response to chemotherapy. Tumor differentiation and histologic grade did show moderate correlation with accuracy of MR imaging results.

The data was statistically analyzed using STATA Ver. 14 (Texas, USA).

Table 1: Correlation table

Parameters	No. of observations	Correlation value (*r*)	*P**
MRI scan findings vs histopathology findings	41	0.4076	0.0082 (S)
CT scan findings vs histopathology findings	56	0.1217	0.3715 (NS)
Scan findings vs histopathology findings	97	0.2329	0.0217 (S)

*Spearman's Rank Correlation ; S-Significant ; NS-Not significant

Table 2: Tables of CT scan

Result	Percentage
Sensitivity	20
Specificity	88.89
Positive predictive value	50
Negative predictive value	66.67

Table 3: Tables of MRI scan

Result	Percentage
Sensitivity	40
Specificity	93.55
Positive predictive value	66.67
Negative predictive value	82.86

Discussion

We have found that preoperative imaging does not accurately predict optic nerve invasion in retinoblastoma. Prior studies have similarly shown poor reliability of preoperative imaging in detecting optic nerve invasion in patients with retinoblastoma, though many called for large-scale confirmatory studies.[6-9] We believe our study to be the largest to-date to assess this correlation. Our sensitivity results for both CT scan and MRI for optic nerve imaging were lower than that previously reported. De Graaf *et al*. found 66% sensitivity and 96% sensitivity in predicting prelaminar optic nerve invasion, and 50% sensitivity and 100% specificity in predicting ON infiltration in MRI.[10] Lee *et al*. found sensitivity and specificity rates to be 35.7–42.9% and 92.6–96.3%, respectively, when assessing 5 mm-section images of brain MRI.[7] Wilson *et al*. additionally determined poor agreement between neuroradiology assessment and histologic optic nerve disease, and concluded that preoperative imaging should not be used in isolation to justify delay in enucleation for neoadjuvant chemotherapy.[8]

The drawback of completely relying on imaging is present in some cases where the invasion might not be shown on preoperative imaging and might need chemoreduction instead of primary enucleation. It is possible that preoperative chemoreduction may aid in tumor size augmentation and may allow for improved assessment of tumor extent. However, the converse may also be true, that chemotherapy distorts tumor anatomy and induces inflammation that may mimic optic nerve enhancement. De Graaf *et al*. described a case of MRI optic nerve enhancement in a patient with retinoblastoma, initially believed to be evidence of infiltration, though found to have negative pathology. Nerve enhancement was later attributed to secondary inflammation and endothelial proliferation following neoadjuvant chemotherapy.[9]

Failure to identify high-risk patients with optic nerve involvement on imaging may have devastating implications. As invasion of the optic nerve is correlated with higher rates of metastasis and mortality, this low sensitivity of detection may lead to delay in aggressive treatment for these high-risk patients. We also found that neuroradiologic studies falsely identify patients as having optic nerve involvement in 7.7% of our patients. This improper identification of optic nerve involvement may unnecessarily deter globe-sparing treatment in these patients. For these reasons, we believe preoperative CT and MRI imaging should not be profoundly relied upon to guide management in patients with retinoblastoma.

The strength of our study was the large sample size. Also, this study compares the two imaging modalities, i.e., computed tomography and diffusion weighted MRI and has been the first study to do so in our knowledge. The results show that DW MRI is superior to CT scan and hence MRI should be the preferred imaging modality for predicting the status of optic nerve invasion in cases of retinoblastoma. This study could have been better if the sample size undergoing DW MRI was greater. Further studies with larger subset of patients could give us a better idea about the accuracy of identification of optic nerve involvement by DW MRI.

Conclusion

Optic nerve infiltration in retinoblastoma is significantly associated with mortality. Imaging studies are often relied upon to assess the presence of optic nerve involvement and guide management. We have found a significant correlation between MR imaging and histopathologic findings. Since, CT scan does not corelate with histopathology when considering optic nerve invasion, we advocate the use of MRI scan for predicting optic nerve invasion.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Shields CL, Shields JA. Diagnosis and management of retinoblastoma. Cancer Control 2004;11:317-27.
2. Wiman KG. The retinoblastoma gene: Role in cell cycle control and cell differentiation. FASEB J 1993;7:841-5.
3. Knudson AG, Meadows AT, Nichols WW, Hill R. Chromosomal deletion and retinoblastoma. N Engl J Med 197611;295:1120-3.
4. Magramm I, Abramson DH, Ellsworth RM. Optic nerve involvement in retinoblastoma. Ophthalmology 1989;96:217-22.
5. Chawla B, Singh R. Recent advances and challenges in the management of retinoblastoma. Indian J Ophthalmol 2017;65:133-9.
6. Lee BJ, Kim JH, Kim DH, Park S-H, Yu YS. The validity of routine brain MRI in detecting post-laminar optic nerve involvement in retinoblastoma. Br J Ophthalmol 2012;96:1237-41.
7. Wilson MW, Rodriguez-Galindo C, Billups C, Haik BG, Laningham F, Patay Z. Lack of correlation between the histologic and magnetic resonance imaging results of optic nerve involvement in eyes primarily enucleated for retinoblastoma. Ophthalmology 2009;116:1558-63.
8. Song KD, Eo H, Kim JH, Yoo S-Y, Jeon TY. Can preoperative MR imaging predict optic nerve invasion of retinoblastoma? Eur J Radiol 2012;81:4041-5.
9. de Graaf P, Moll AC, Imhof SM, van der Valk P, Castelijns JA. Retinoblastoma and optic nerve enhancement on MRI: Not always extraocular tumour extension. Br J Ophthalmol 2006;90:800-1.
10. de Graaf P, Barkhof F, Moll AC, Imhof SM, Knol DL, van der Valk P, *et al*. Retinoblastoma: MR imaging parameters in detection of tumor extent. Radiology 2005;235:197-207.