Histopathological assessment of optic nerve invasion guided by radiological findings in enucleated globes with retinoblastoma.

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Abstract

Purpose: High-risk histopathological features in primary enucleated retinoblastoma globes affect the indication for neoadjuvant chemotherapy to avoid the increased risk of metastasis and to improve survival in such children. Optic nerve (ON) invasion is an important indicator of prognosis and we aim through this study to correlate the detected-ON invasion by imaging with the corresponding confirmed histopathological level of invasion. Methods: This is an approved retrospective study with collaborative agreement between the 2 centres. All enucleated globes with the diagnosis of retinoblastoma received in the histopathology department(s) from January 2015 to December 2016 (2 years) were collected for review by 2 pathologists and the charts were reviewed for basic demographic data. All patients underwent Magnetic resonance imaging (MRI) under sedation upon diagnosis and MRI reading was done by an experienced single neuroradiologist. Results: A total of 38 patients were included: 21 males and 17 females. 29 (77.3%) had unilateral involvement, 7 (18.4%) had bilateral involvement and 2 cases had trilateral disease. The overall mean age at diagnosis was 22.63 ±15.15 months. 28 cases (74%) had pathologically-proven ON invasion: prelaminar (31.6%), laminar (18.4%), and post-laminar (23.7%). Post-laminar ON invasion was identified in 8 cases (true positive), while another 8 were false positive. Only 1 case was missed on MRI (accuracy: 63.3%; sensitivity: 88.9%; specificity: 72.4%; Positive predictive value (PPV): 50%; Negative predictive value (NPV): 95.5%). Conclusions: MRI was found to be less sensitive in evaluating pre-laminar and laminar ON invasion (0.0 and 42.9%) compared to post-laminar invasion (88.9%) but had better specificity in detecting various levels of invasion (72.4 to 83.9%). Obtaining deeper histologic sections in some cases where there are mismatching ON level of invasion between MRI and histopathological examination is recommended to avoid misleading assessment of the high-risk histopathological features. There are no solid international protocols of how many sections should be obtained to evaluate the optic nerve invasion in these globes and this should be established for universal use especially in less developed countries where experienced pathologists might be lacking. Key words: Retinoblastoma; High-risk, Histopathology; Optic nerve invasion; Lamina cribrosa; Radiology; Magnetic resonance imaging; Chemotherapy.

Introduction

Retinoblastoma (RB) is the most common intraocular tumor in children and represents about 4% of all pediatrics malignancy. [1] It can present as unilateral, bilateral or trilateral (bilateral tumors with a third intracranial tumor). [2]

The former classification Reese–Ellsworth classification, created in 1960s, was used to predict globe salvage with external beam radiotherapy where this was the most popular non-surgical treatment (enucleation). [3] Many recommendations were proposed to update the classification to include the current treatment modalities and outcome. [4] Then a newer classification named International Classification of Retinoblastoma (ICRB) was finalized by a group of RB experts in April 2003, which is being used in this study. [5] The main goal of ICRB was being applicable to predict treatment success with current modalities such as chemo-reduction therapy. This classification, in contrary to the Reese-

Ellsworth classification, does not concentrate on the number, location or size of the tumor, because the chemo reduction (CRD) has been found effective despite these variables and is mainly based on the presence or absence of vitreous and subretinal seeds and whether they are localized or diffuse. [5]

Management of RB in general is tailored to each individual patient, but several factors play important roles in each case including: metastatic risk, second tumors' risk, systemic condition, laterality, size and location of the tumor/s and potential for vision. The priority is to detect and treat life-threatening conditions, then to save the globe and finally maintain vision. [1] Current management modalities include: intravenous chemo reduction, intra-arterial chemotherapy, thermotherapy, cryotherapy, laser photocoagulation, plaque radiotherapy, external beam radiotherapy, and enucleation. [1,3, 6]

Uniform consensus as to what constitutes high-risk pathology has not been reached and high-risk pathological features have been described with few debates in the literature. [7,8,9] However, it has been agreed among many experts that the high-risk features should include: post-laminar optic nerve (ON) invasion, massive choroidal invasion, combined ON and choroidal invasion (of any type) or anterior segment invasion (including anterior chamber seeding and infiltration of anterior uveal stroma). [9,10]

The presence of high-risk histopathological features after primary enucleation is an indication for neoadjuvant chemotherapy in view of increased risk of metastasis. Survival in these children increased significantly because of neoadjuvant chemotherapy. [11]

Based on the international RB staging work group for histopathological studying and globe preparation, ON invasion level has been classified as being prelaminar, laminar (intralaminar), post-laminar and involving surgical margin. Consensus on choroidal invasion has been also reached, where this can be focal or massive (massive choroidal invasion is defined as having diameter of 3 mm or more in any tumor dimension). [12] Magnetic resonance imaging (MRI) is now becoming the most widely used modality in the workup for RB staging and assessment prior to primary enucleation. [13] To detect risk factors for metastasis, MRI is a helpful tool but not as reliable as histopathology, where microscopic infiltration is best detected. [11] Generally, the role of MRI in RB assessment includes: determination of the growth pattern, extension of the ON involvement, detection of orbital and/or meningeal extension, and the presence of second tumors. [14] Additionally, detection of ON invasion on MRI in children treated with primary enucleation might have a role in helping the surgeons to ensure free resection margin. [15]

The aim of this study is to correlate the detected-ON invasion by imaging with the corresponding histopathological level of invasion. The cases where MRI showed more advanced level of ON invasion than what detected on histopathology were further subjected to more sectioning either by obtaining deeper levels or by sectioning the globes after rotating the blocks.

Methods

This is an approved retrospective study on an expedited basis by the HEC/IRB at King Khaled Eye Specialist Hospital (KKESH) with collaborative agreement with King Saud University.

The histologic slides of all retinoblastoma enucleated globes received in the histopathology department(s) from January 2015 to December 2016 (2 years) were collected for review by 2 pathologists and the charts were reviewed for basic demographic data including: age at the time of study, age of presentation, gender, timing of enucleation, laterality, family history and previous treatment modalities if present. All patients underwent MRI under sedation upon diagnosis with sonography.

MRI reading was done by an experienced neuroradiologist (SE). All patients underwent MRI of the orbit and brain with a 3.0-T system (Signa HDxt, GE Medical System) by using an eight-channel head coil under sedation. Sedation with oral chloral hydrate used for infants and children 5 years of age. The conventional ocular MR imaging protocol comprised axial unenhanced T1-weighted spin-echo images (TR/TE, 500/11ms) and fat suppressed axial T2-weighted images (TR/TE, 3450/90 ms). Pre- and post-contrast axial T1weighted MRIs with and without fat suppression are obtained. Contrast-enhanced fat suppression T1 weighted MRI after intravenous injection of 0.1 mmol kg21gadopentate dimeglumine is done in axial and coronal planes as well as the parasagittal plane parallel to the long axis of the optic nerve (TR/TE, 560/11ms) after intravenous injection of Gd-DTPA (Magnevist; Bayer-Schering Pharma AG, Berlin, Germany) with 0.2 mL/ kg of body weight). High-resolution three-dimensional (3D) FIESTA (Fast Imaging Employing Steady-state Acquisition) allows thin sections (0.4 mm) with high SNR sequence allow performance of multiplanar reconstruction to better demonstrate tumor extension. Slice thickness was 3 mm, with an inter- section gap of 0.5 mm. The FOV was 18 cm with a matrix of 256 × 160. Additionally, images covered the whole brain including axial T2-weighted images, as well as axial post-contrast T1-weighted images with a slice thickness of 5 mm, were obtained to check for intracranial lesions including pineal gland and suprasellar assessment (trilateral retinoblastoma) as well as abnormal meningeal enhancement. Diffusion-weighted MRI was acquired in the axial plane using a single-shot echo-planar imaging sequence (TR/TE, 8000/70 s; slice thickness, 3 mm; intersection gap, 0.5 mm; FOV, 18 cm; and matrix, 128 × 128. excitation, 2). A b value of 0 and of 1000 s/mm2 was also applied in three orthogonal (z, y and x) directions. The time interval between MRI and enucleation operation was measured and varied from 1 to 128 days (Average of 4.0 days).

The histopathological results of the enucleated eyes utilizing the examination of the routine 3 Hematoxylin and eosin (H&E) slides and a single Periodic Acid-Schiff (PAS) stained slide prepared from all 4 blocks: the pupil-optic nerve (PO) globe section, the 2 calottes (each one in a separate block) and the ON surgical margin of excision were reviewed for the following features: tumor differentiation and high risk features including invasion of the optic nerve (none, prelaminar, laminar, or post-laminar, transection end). The first stage of this study involved basic review of all histopathology and radiology reports in the charts aiming at the demonstration of basic demographic data with simple analysis of our RB histopathological cases data-base over the study period.

The second stage was to extract our targeted sample using the following inclusion criteria: cases where the level of ON invasion histopathologically (based on the IRSWG Consensus) did not match the corresponding pre-operative MRI reported level. We have excluded cases, in which the level of ON invasion was identical by both histopathological study and MRI. The cases with discrepancy of the level

of ON invasion with MRI study showing deeper level than the initial histopathology where re-evaluated by further serial sections from the PO tissue block. In some cases, flipping of the PO block was tried to re-examine the ON from the other side.

We also determined the accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of MRI in predicting ON tumor invasion.

All data was entered in an excel sheet (Microsoft office excel 2011 for Mac). Statistical analysis was performed with SPSS version for Microsoft Windows (SPSS, Inc., Chicago, IL, USA). Sensitivity was calculated as a percentage by dividing true-positive findings by the sum of true-positive and false-negative findings. Specificity was calculated as a percentage by dividing true-negative findings by the sum of true-negative and false-positive findings. Accuracy was also calculated.

Results

A total of 44 cases were initially identified, out of which, 6 patients were excluded because of prior treatment pre-enucleation. A total of 38 patients were included: 21 males and 17 females. Out of these patients, 29 (77.3%) had unilateral involvement, 7 (18.4%) had bilateral involvement and 2 cases had trilateral disease. The overall mean age at diagnosis was 22.63 ±15.15 months. (Table 1)

Pathologically-proven ON invasion was found in 28 cases (74%). 12 eyes had prelaminar invasion (31.6%), 7 eyes had laminar invasion (18.4%), and 9 (23.7%) had post-laminar invasion (including 1 patient with surgical margin involvement). On MRI, ON invasion was predicted in 30 patients (78%). 6 (15.8%) eyes were labeled as pre-laminar type of invasion, 8 (21.1%) had laminar invasion, and 16 (42.1%) had post-laminar (including 1 patient with surgical margin involvement). Post-laminar ON invasion was correctly identified in 8 cases (true positive), while another 8 were false positive. Only 1 case was missed on MRI (accuracy: 63.3%; sensitivity: 88.9%; specificity: 72.4%; Positive predictive value (PPV): 50%; Negative predictive value (NPV): 95.5%). MRI was found to be less sensitive in evaluating prelaminar and laminar ON invasion (0.0 and 42.9%) compared to post-laminar invasion (88.9%) but had better specificity in detecting various levels of invasion (72.4 to 83.9%). (Table 2) Out of these patients, 15 (39.5%) had identical level of ON invasion by both modalities, and 23 cases showed non-matching results. 18 cases (47.4%) demonstrated less depth of invasion histopathologically, and when these were sectioned further in the second stage of the study, the level of ON invasion was not altered in 11 (61.1%), while the remaining 7 (40%) cases showed deeper levels of invasion (Figures 1-3).

Discussion

Many studies worked at correlating clinical and MRI features that might indicate high risk features. [7,14,15] In the era of targeted therapy like intra-arterial chemotherapy (IAC), these features are important because many eyes with advanced diseases are salvaged with non-surgical treatment. [6] The combined

clinical and MRI features can predict high-risk RB, while ICRB and/or Reese-Ellworth classifications can provide limited correlation with high-risk RB. [10]

MRI works without the use of ionizing radiation, preventing the occurrence of the potential risk of secondary tumors and has a high soft tissue contrast. [2] Using special surface coils with small diameter and a short penetration depth have raised the potential use of MRI in ophthalmic pathologies. [2, 16] Results from many studies showed that preoperative MRI is more relevant in showing and detecting ON invasion. [15] Others have shown different sensitivity and specificity of MRI in detecting the level of ON invasion. [17] Moreover, some investigators advocated neoadjuvant chemotherapy before enucleation in cases with extensive unilateral disease based on MRI detection of post-laminar ON invasion. [11,18,19) Decision in favor of neoadjuvant chemotherapy based on MRI alone with no histopathological confirmation is not justified -at least until this moment - based on lack of sufficient evidence. [11]

In 2007, Lemke in a prospective clinical trial showed that MRI sensitivity for the detection of ON infiltrations (prelaminar and post-laminar together) was 53.8% and the specificity was 82.3%. ON infiltrations were correctly recognized in seven out of 10 cases (true positive) and excluded in 14 cases out of 20 cases (true negative). The histopathological findings showed six cases of prelaminar ON infiltration with false negative results on MRI. Three cases were incorrectly diagnosed as prelaminar infiltration in MRI. Importantly, no post-laminar ON infiltration was missed. This might suggest a better ability of MRI to diagnose post-laminar ON invasion, which would be expected. [2, 20] Brisse and colleagues found that MRI sensitivity is 60% in detection of post-laminar invasion in normal-size ONs, and they compared their results with previous studies. [15] Sensitivities were variable for post-laminar invasion and varied significantly, but true negative rates (specificity) and negative predictive values (NPV) were 87% and 93% respectively. Wilson in 2009, concluded that limited correlation was found between MRI and histologic results in assessing ON invasion in eyes with RB. [17] Chawla in 2012 showed that because MRI has limitations in reliably predicting microscopic infiltration of the choroid and optic nerve, decision in favor of neoadjuvant chemotherapy on the basis of suspected post-laminar invasion on MRI is not justified in the absence of histopathologic evidence of disease. [11]

More recently, in 2018 Cui and colleagues published a retrospective review on 63 primary enucleated eyes with advanced RB and their histopathological examination showed proven ON invasion in 26 cases (41%). MRI had failed to predict prelaminar and laminar ON invasion indicating its low sensitivity and PPV (42.9% and 37.5% for prelaminar, 50.0% and 40.0% for laminar invasion, respectively). However, on MRI, post-laminar ON invasion was diagnosed in 16 cases (25.4%), of which 11 eyes (17.5%) were truly positive and 5 (7.9%) were falsely positive. Only 4 cases were missed on MRI (accuracy, 85.7%; sensitivity, 73.3%; specificity, 89.6%; PPV, 68.8%; NPV, 91.5%). [21] Li evaluated the value of MRI as a useful diagnostic tool for post-laminar optic nerve invasion with a measured sensitivity of 82%, specificity of 73% and accuracy of 77%. [22] Similarly, in our series, pathologically proven ON invasion was found in 28 cases (74%). 12 eyes had prelaminar invasion (31.6%), 7 eyes had laminar invasion (18.4%), and 9 (23.7%) had post-laminar invasion (including 1 patient with surgical margin involvement). On MRI images, ON invasion was predicted in 30 (78%) patients. 6 (15.8%) eyes labeled pre-laminar, 8 (21.1%)

had laminar, and 16 (42.1%) had post-laminar (including 1 patient with surgical margin involvement). Post-laminar optic nerve invasion was correctly identified in 8 cases (true positive), 8 were false positive. Only 1 case was missed on MRI (sensitivity, 88.9%; specificity, 72.4%; accuracy, 63.3%; PPV, 50%; and NPV, 95.5%). In our series, MRI did not also predict ON invasion reliably and accurately in cases of prelaminar and laminar ON invasion. This is again somehow similar to previous published findings. [23]

Since MRI has been recently proven to be useful in predicting post-laminar ON invasion with a better sensitivity, specificity and accuracy, care should be taken when routine histopathological sections show less depth of ON invasion in tissue than what has been shown radiologically.

Conclusions

Our demographic data and the value of the MRI in detecting various levels of ON invasion in enucleated globes with RB with a better specificity, sensitivity and accuracy in cases of post-laminar invasion have been similar to more recent reports. However, this is the first study demonstrating that routine histopathological sections of RB enucleated globes submitted to a pathologist might not match the MRI findings because there are no standard numbers of sections to be submitted and routine sections examined by a pathologist vary from one center to the other, which is of paramount significance. Correlating the MRI findings in such cases is extremely essential for possibly obtaining further histopathological deeper sections thus avoiding misleading assessment of this high-risk histopathological feature. Therefore, we strongly recommend an internationally used pathway for the use of deeper histopathological sections in parallel to the radiological MRI findings with special attention in cases when post-laminar ON invasion by MRI fails to be proven by tissue diagnosis.

Declarations

Ethics and Consent to participate: The study was prepared in accordance with the ethical standards of the Human Ethics Committee at KKESH and was approved by the Research Department (HEC/IRB) in accordance with the Helsinki Declaration. This implies a written “Informed Consent to participate in Research” to be placed in the patient(s) medical records with the project title, number and the name of the principal investigator. All patients (and guardians) are also provided with a copy of the approved patient information sheet in their preferred language: Arabic and/or English.

Consent for publication: A general informed written consent was obtained from the guardians of all participants included in the study for the publication of patient/clinical data and identifying images (if any).

Availability of data: The data for this study is stored at the institution where HEC/IRB approval has been obtained and can be made available upon request from the journal otherwise the necessary data is shown in this manuscript.

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Authors' Contributions:

First author: Data collection, literature review and drafting of the manuscript.

Second author: Histopathological review of cases, critical revision and final preparation of the manuscript for submission including an update of the literature.

Third author: Histopathological review of cases and data correction.

Forth author: Imaging studies and interpretation of the radiological data for all cases.

Fifth author: Clinical data and review of cases.

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Tables

Table 1: Descriptive analysis of our RB cases (n=38)

Characteristic	N (%)
Gender	
Male	21 (55.3)
Female	17 (44.7)
Family history	
Positive	2 (5.3)
Negative	36 (94.7)
Laterality	
Unilateral	29 (76.3)
Bilateral	7 (18.4)
Trilateral	2 (5.3)
Studied eye	
Right	19 (50.0)
Left	19 (50.0)
Age at presentation (months)	
Overall (n=38) mean ±SD [Range]	22.6 ±15.2 [2-72]
Unilateral (n=29) mean ±SD [Range]	26.6 ±15.0 [2-72]
Bilateral (n=7) mean ±SD [Range]	8.0 ±5.1 [2-17]
Trilateral (n=2) mean ±SD [Range]	17.0 ±1.4 [16-18]
Age at enucleation (months)	
Overall (n=38) mean ±SD [Range]	22.9 ±15.3 [2-72]
Unilateral (n=29) mean ±SD [Range]	26.9 ±15.2 [2-72]
Bilateral (n=7) mean ±SD [Range]	8.1 ±5.0 [2-17]
Trilateral (n=2) mean ±SD [Range]	17.0 ±1.4 [16-18]
Radiological evidence	
None	8 (21.1)
Pre-laminar	6 (15.8)
Laminar	8 (21.1)
Post-laminar	16 (42.1)
Histopathological evidence	
None	10 (26.3)
Pre-laminar	12 (31.6)
Laminar	7 (18.4)
Post-laminar	9 (23.7)
Radio-Histopathological agreement	
Equal	15 (39.4)
R<P	5 (13.2)
R>P	18 (47.4)
Final decision for the R>P (n=18)	
No change	11 (61.1)
Pre-laminar	1 (5.6)
Laminar	1 (5.6)
Post-laminar	5 (27.8)
Histopathological evidence of choroidal invasion	
None	20 (52.6)
Focal	6 (15.8)
Massive	12 (31.6)
Diagnostic US findings	
No calcification	3 (7.9)
Calcification	35 (92.1)

Table 2: Sensitivity, specificity, accuracy, PPV and NPV of MRI compared to histopathology detection of ON invasion level (n=38) excluding 6 cases that had treatment before

enucleation.

Optic nerve invasion	TP (n)	FP (n)	TN (n)	FN (n)	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
None	4	4	24	6	67.2	40.0	85.7	50.0	80.0
Prelaminar	0	6	20	12	52.6	0.0	76.9	0.0	62.5
Laminar	3	5	26	4	71.4	42.9	83.9	37.5	86.7
Postlaminar	8	8	21	1	63.3	88.9	72.4	50.0	95.5

TP: Total positive, FP: False positive, TN: Total negative, FN: False negative, PPV: Positive predictive value, NPV: Negative predictive value.

Figures

Figure 1

A and B: High resolution Sagittal (A) and Axial T1 orbital Constructive Interference in Steady State (CISS) magnetic resonance imaging (B) prior to enucleation of left globe in a case with bilateral retinoblastoma showing a tumor mass with hemorrhage filling the posterior cavity, pushing the lens anteriorly, with optic nerve invasion beyond the lamina cribrosa. C and D: Early Histopathological appearance of the optic nerve (ON) in the early initially submitted routine sections with tumor cells level of ON invasion (Dotted curve line) anterior to the lamina cribrosa (C) while deeper sections obtained were showing islands of tumor cells (black arrows) invading the ON posterior to the lamina cribrosa (D) (Original magnification x200 Hematoxylin and eosin).

Figure 2

A and B: High resolution Sagittal and Axial orbital Constructive Interference in Steady State (CISS) and post contrast fat suppressed magnetic resonance imaging (A) showing invasion of the optic nerve (ON) up to 3 mm post lamina cribrosa (white arrow). Sagittal oblique magnetic resonance imaging view of the orbit (B) showing the posterior cavity is almost totally filled by tumor with interruption of the choroidal-retinal interface line (white arrow). C and D: Deeper histopathological sections of the ON at the level of central artery (indicated by CR) with superficial invasion by retinoblastoma (RB) tumor cells (C). Histological sections (D) obtained after flipping of the tissue block showing tumor cells invading the ON (black arrows) and extending posterior to the lamina cribrosa (arrow head) (Original magnification x200 Hematoxylin and eosin).

Figure 3

A and B: Post-contrast fat suppressed Sagittal oblique and Axial magnetic resonance imaging of the orbit showing tumor with interruption of the choriodal-retinal interface line in (A) and optic nerve (ON) invasion of the lamina cribrosa extending for 1.5 mm within the ON beyond the lamina (B) (white arrows). C and D: Initial histological sections at the level of central artery (CR) with No ON invasion detected in (C) while further deeper sections have shown tumor cells (black arrow) filling the glaucomatous ON cup and reaching to the lamina cribrosa (Original magnification x200 Hematoxylin and eosin).