ORIGINAL ARTICLE

TO ESTIMATE THE DIAGNOSTIC ACCURACY OF POST GADOLINIUM HIGH RESOLUTION MAGNETIC RESONANCE IMAGING (MRI) FOR EARLY DIAGNOSIS, OPTIC NERVE INVASION AND DETECTION OF INTRAOCULAR CALCIFICATION IN RETINOBLASTOMA USING EUROPEAN RETINOBLASTOMA IMAGING COLLABORATION (ERIC) GUIDELINES

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ABSTRACT

PURPOSE: To estimate the diagnostic accuracy of post gadolinium high resolution magnetic resonance images for early diagnosis, optic nerve invasion and detection of intraocular calcification in retinoblastoma using European Retinoblastoma Imaging Collaboration (ERIC) guidelines. **SUBJECT AND METHOD:** A total of forty five patients were included in this study all were less than 12 years of age and referred for the MRI of suspected retinoblastoma. Standard MRI technique of orbits and brain with contrast were obtained according to ERIC guidelines by Magneton Avanto 1.5 Tesla (SIEMENS) scanner at Dr. Ziauddin University Hospital Karachi. The results of MRI were compared with histopathological results obtained after surgery (enucleation) of the patients. **RESULTS:** Mean age of the patients was 19.98 ± 18.41 months. Sex distribution shows, 25 patients (55.6%) were male while remaining 20 patients (44.4%) were female. Duration of Symptoms was 33.6 ± 30.5 days. True positive cases were 39 and true negative cases were 4. Diagnostic accuracy of CE-MRI for the detection of RB was found to be 95.5% (43/45) (p value 0.0001), sensitivity and specificity was found to be 97.5% (32/32) and 80% (4/5) respectively. (p value 0.0001). For the detection of calcification high resolution MRI shows 82.2% accuracy while US/CT shows 84.4% accuracy for the detection of calcification. Optic nerve invasion was diagnosed with an accuracy of 55.5%. Out of 45 eyes, 30 eyes show retinal detachment which was diagnosed on MRI with 77.8% accuracy. 40% of RB shows exophytic growth pattern and 37.8% shows endophytic tumor growth while 11.1% showed mixed exo and endophytic growth pattern. **CONCLUSION:** High resolution MRI has superior contrast and spatial resolution compared to computed tomograph (CT) or other available imaging techniques. MRI is highly sensitive for the diagnosis of retinoblastoma as well as for the detection of optic nerve invasion which may be helpful in the treatment planning. MRI cannot substitute CT in detecting tumour calcification in retinoblastoma but with increasing experience and new techniques it should be possible to renounce CT scans in the majority of cases of retinoblastoma.

key words: Retinoblastoma, ERIC, Diagnostic Accuracy, MRI

Introduction

Retinoblastoma (RB) is the most common intraocular neoplasm of childhood and also highly malignant neoplastic lesion of the primitive neural retina. RB is one of the most challenging problems in paediatric ophthalmology, oncology and oncoradiology because it shows different patterns of growth, extension and recurrence.[1] According to international data RB

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accounts for 3% of all cancers occurring in children. It occurs in 1 out of 18000 to 30000 live births worldwide. The average age at diagnosis is 18 months with 80% of cases occurring before the age of 3–4 years old.[2,3] It has been observed that as many as one-half of all cases of childhood leukocoria are caused by RB.[4] Most patients present with leucocoria and ophthalmoscopic recognition of RB. A number of modalities including ultrasonography, CT and MRI are helpful in establishing the diagnosis of RB.[5]

High resolution post gadolinium Magnetic Resonance Imaging (MRI) is the technique of choice and proved to be the most sensitive technique for evaluating RB, principally regarding tumor infiltration of the optic nerve, extra ocular infiltration and intracranial extension. Calcification is present in approximately 95% of tumors in histological specimens. Computed Tomography (CT) and MRI are the mainstay for imaging of head and neck tumors in children. MRI is more applicable than CT for preoperative detection of optic nerve invasion.[6] The disadvantages of CT are reduced soft tissue contrast, iodine based contrast agent, exposure to ionizing radiation especially in hereditary pattern of disease, who have elevated radiosensitivities.[7] Ultrasound (US) is not the imaging modality of choice because of shadowing artifact from intraocular intratumoral calcification which hinders complete visualization of the lesion. US also had limited role because it cannot assess extra ocular tumor extension.[4,8] Early and accurate diagnosis is required in patients suffering from RB as it is crucial to salvage the eye and the life of the child. Suspected patients of RB are usually investigated by ophthalmoscopy and CT scan. MRI is not only required for early and accurate diagnosis, it also helpful in determining extension of the disease, staging, associated developmental malformations of the brain, trilateral retinoblastoma and postoperative assessment of the patient.[1,6] If the tumor is confined to the globe, 5 years survival is over 90%, where as if the tumor extends outside the globe, the mortality is over 90%.[1] It is also valuable in differentiating retinoblastoma from lesions that simulate it.[7] Coat's disease, persistent hyperplastic primary vitreous, retinopathy of prematurity and toxocariasis are a few diseases which are included in the differential diagnosis of retinoblastoma.[4] MRI is the best modality of choice in detection of retinoblastoma. In one study researcher calculated the sensitivity, specificity and diagnostic accuracy of 60%, 95% and 91% respectively.[8] MRI also showed high sensitivity 91.7% and specificity 88.9% in detecting a marked amount of intraocular calcification.[9]

Previously RB was diagnosed on the basis of calcification in the tumor, which is easily and accurately seen with the help of CT scan. Since these patients may have to be repeatedly imaged for disease progression and response to treatment, it is also important to decrease the radiation burden and subsequently the risk of developing other primary tumors. RB is the most important childhood malignant neoplasm and by early diagnosis with MRI by using ERIC guidelines we can help in the treat of the disease in initial stages as well as by knowing the accurate disease extent we can prevent unnecessary treatment options for the patients. The aim of this study is to provide supportive data in early detection and treatment of retinoblastoma in our setup to reduce the radiation burden to the patients who are still undergoing CT scan for the diagnosis of RB where MRI facilities are available.

Imaging Features

ULTRASOUND:

US demonstrates an irregular mass, more echogenic than the vitreous body, with fine calcifications (highly reflective foci mostly with characteristic acoustic shadowing.[10]

CT SCAN:

On CT, retinoblastoma is typically a mass of high density compared with the vitreous body, usually calcified and moderately enhancing after iodinated contrast medium administration. CT detection of calcifications in retinoblastoma has a sensitivity of 81–96%, and an even higher specificity. However, delineation of intraocular soft-tissue detail is limited. The evidence from surveys suggests that CT is still regarded an obligatory imaging tool for evaluation of leukocoria, primarily because CT is supposed to be the best imaging modality for detection of intraocular calcifications.[11,12,4]

MRI:
MRI has proved to be the most sensitive technique for evaluating retinoblastoma, especially regarding tumor infiltration of the optic nerve, extraocular extension and intracranial disease.[6,8,9,13,14]

MRI FINDINGS:
Compared to the vitreous body, retinoblastoma has moderately higher signal intensity on T1- and lower on T2-weighted images. Increased size of the globe, globe deformation and reduced anterior chamber depth are signs of increased intraocular pressure and are usually associated with buphthalmia. In normal-size optic nerves, the direct radiological criterion used to diagnose postlaminar nerve invasion is the presence of abnormal contrast enhancement (enhancement ≥ 2mmin diameter) in the distal nerve. Interruption of the normal linear enhancement at the optic nerve disk (choroidoretinal complex) supports a suggestion of optic nerve invasion. Postlaminar optic nerve or optic nerve meningeal sheath invasion should raise suspicion of leptomeningeal metastases. In such situations, additional contrast-enhanced sagittal T1-weighted imaging of the whole spine is recommended. Ocular wall invasion and extraocular extension Discontinuity of the normal choroidal enhancement is the leading criterion for infiltration. Massive choroidal invasion presents as focal choroidal thickening. Increased enhancement and thickening of the entire uveal tract (choroid, ciliary body, iris) is a sign of uveitis, usually secondary to massive (sub) total tumor necrosis. Protrusion of enhancing tissue through the thickened choroid into the (low signal-intensity) sclera or beyond is a sign of scleral invasion or extraocular extension, respectively.[6, 8,15]

Subject and Methods

Over a period of 2 years, 60 patients under the age of 12 years who referred for MRI orbits and brain at Department of Radiology and Imaging Dr. Ziauddin University Hospital Karachi with the clinical suspicion of RB or having signs/symptoms of leukocoria, strabismus or retinal detachment were initially involved in this study. Informed consent was taken after explaining the study's purpose, procedure, risk-benefit ratio to the patient. Approval of the hospital's ethical committee was acquired. History and physical examination was performed in each case by the researcher and it was especially focused on the laterality, the duration of symptoms, family history or numbers of affected family members.

To remove the confounding variables, patients that were already diagnosed RB or those who were presented after chemotherapy for disease reassessment or follow up were not included in this study. 7 patients were excluded from this study because they were already diagnosed as having RB and undergone imaging from other institutes. 3 patients were excluded from the study because they have contraindication for Gadolinium (serum creatinine > 1.5mg/dl) and 5 patients cannot undergone post gadolinium MRI cannot be done due to restlessness and excessive crying and these patients were not giving consent for sedation. Remaining 45 patients were finally fulfilled the inclusion criteria.

There were 25 (55.6%) males while remaining 20 patients (44.4%) were females. Mean age of the patients was 19.98 ± 18.41 months. This was a cross-sectional, validational study. The sample technique used was non-probability, purposive type. The MRI Orbit and brain were performed in these 45 patients before and after administration of gadolinium in Magneton Avanto 1.5 Tesla (SIEMENS) scanner at MRI department. The MRI protocols which were followed were standard protocol for the workup of RB according to ERIC guidelines. (Tab.1). A typical MR imaging protocol for RB should always include high-resolution imaging of the affected eye(s) and imaging of the entire brain. Images of the MRI were interpreted by the experienced radiologist (at least 5 years of experience). The findings were recorded according to already designed imaging check list by the ERIC. (Tab. 2). The relevant findings were notified in the Performa by the researcher. Patients that are diagnosed as having RB on MRI basis or on clinical grounds and were undergone surgery (enucleation) were followed for histopathology results. Enucleated globes were examined for histopathological analysis for extra ocular tumor extension into the optic nerve or brain/

MRI protocol in Retinoblastoma

Requirements
Scanner and coils Field strength above 1 T 1.5 T system combined with one or two small surface coils (diameter <5 cm)
Sequences
Orbits Transaxial T2-W(slice thickness < 2 mm)
Eye(s) and optic nerve(s) Unilateral disease Precontrast T1-W; at least one plane: transaxial or sagittal oblique T2-W; at least one plane: transaxial or sagittal oblique Post contrast T1-W, no FS; transaxial and sagittal oblique Bilateral disease Precontrast T1-W (transaxial) T2-W; (transaxial) Post contrast T1-W, no FS; sagittal oblique of both eyes and transaxial Brain Transaxial T2-W (Slice thickness ≤ 4 mm) Post contrast T1-W (2D SE with slice thickness ≤ 3 mm or 3D GRE ≤ 1mm))
FS= Fat saturation, SE= Spin-echo, GRE= gradient-echo

Table 1: Shows the standard protocol for MRI of the patient for the workup of retinoblastoma according to European retinoblastoma imaging collaboration (ERIC)[6]

Parameters
Tumor characterstics SI relative to the vitreous body; moderately high on T1-W and low on T2-W Laterality
Growth pattern Tumor size and location; in contact with optic nerve Buphalmia
Tumor extension Optic nerve and meningeal sheath invasion Ocular wall invasion (choroid and sclera) Extraocular extension Anterior eye segment Anterior chamber depth Enhancement Tumor invasion; ciliary body Brain Trilateral retinoblastoma; pineal gland and supra or parasellar region Leptomeningeal metastasis Malformations
SI= signal intensity

Table 2: Retinoblastoma: table showing check list for MRI radiology reports[6]

meninges. It is imperative that the enucleating surgeon take a long (10-cm) piece of optic nerve as tumor at the cut margin of the nerve imparts a poor prognosis. Finding tumor cells past the lamina cribrosa of the nerve (the exit point of the nerve from the globe) is an indication for prophylactic chemotherapy. Data obtained from laboratory was also recorded in the Performa.

The data is then shifted to Statistical Package for the Social Sciences (SPSS). Statistical analysis was performed with SPSS software (IBM SPSS statistics v 22; SPSS, Inc, Chicago, IL). Descriptive analysis were conducted i.e. frequencies and percentage for categorical variables like gender, mean and standard deviation for the continuous variables like age, duration of symptoms. Results were calculated in terms of presence/absence of RB on pre and post contrast MRI out of total cases correlated with histopathological analysis, sensitivity, specificity, positive value, negative predictive value and accuracy of MRI in detecting RB will be calcu-

Figure 1: MRI images of orbit including brain of 7 months old male child showing retinoblastoma in right globe. a. T1W axial b. T2W axial c & d.T1W post gadolinium axial and sagittal images. It is showing isointense endophytic plaque like mass on T1W which appear hypointense to vitreous on T2W. The lesion shows homogenous significant post contrast enhancement. Both optic nerves appear normal. Bilateral ethmoid sinusitis is incidentally noted.

Figure 2: MRI brain and orbit of 4 years old female patient showing left eye retinoblastoma with optic nerve and suprasellar extension. a. T2W axial b,c & d. Post gadolinium T1W axial and sagittal images. Intensely enhancing left globe mass noted causing its enlargement. Left optic nerve and optic chiasm is markedly thickened and enhancing represents infiltration by the tumor. MRI brain shows large sellar and suprasellar mass representing intracranial extension of the primary tumor which is causing obstructive hydrocephalus. Normal right globe and optic nerve.

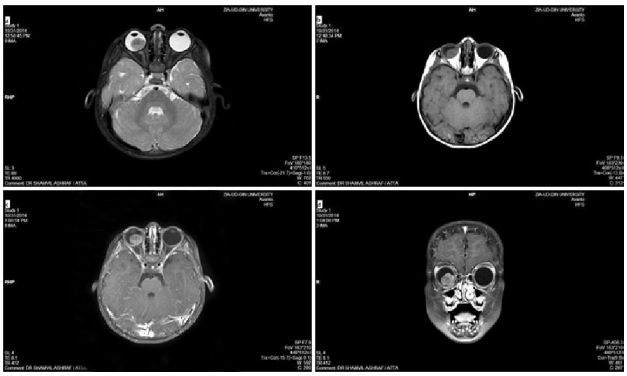

Figure 3: MRI brain and orbit of 2 years old female patient a.T2W axial b. T1W axial c & d. T1W axial and sagittal post gadolinium images. There is a polypoid inhomogeneously enhancing mass occupying the posterior chamber right globe. The central area is low intensity on all sequences represent tumor calcification. Normal both optic nerves and left globe.

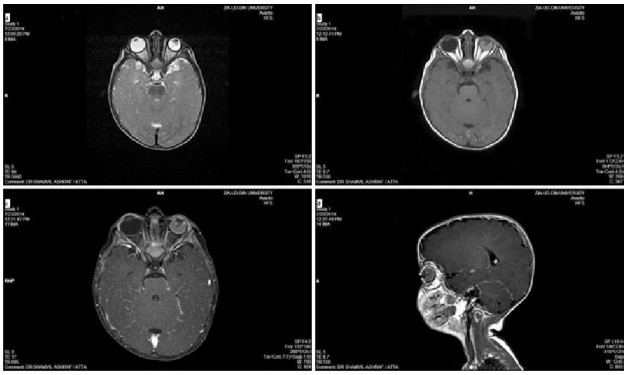

Figure 4: MRI brain and orbit of 12 months old male patient a.T2W axial b. T1W axial c & d. T1W axial and sagittal post gadolinium images. There is Extensive disease in left eye; small left globe identified showing enhancing mass occupying almost complete left globe. There is associated left sided retinal detachment conspicuous on T2W image. Normal both optic nerves and right globe seen.

lated by using histopathology analysis as "Gold Standard" and followed by using 2x2 table stratification with regards of age, gender and duration of symptoms to see their effect on outcome. Chi-square test were applied taken $P \leq 0.05$ as significant.

Results

A total of 45 patients who fulfilled the inclusion criteria were included in the study. Diagnostic accuracy of contrast-enhanced high resolution MRI was calculated for early diagnosis, optic nerve invasion and detection of intraocular calcification in retinoblastoma by using ERIC guidelines.

Mean age of the patients was 19.98 + 18.41 months. Sex distribution shows, 25 patients (55.6%) were male while remaining 20 patients (44.4%) were female. Duration of Symptoms was 33.6 + 30.5 days. (Tab. 3) True positive cases were 39 and true

Age	19.98 ± 18.41 months
Gender	Male = 25 (55.6%), Female = 20 (44.4)
Family History	Positive = 19 (42.2), Negative = 26 (57.8)
Duration of Symptoms	33.6 ± 30.5 days

Table 3: Shows descriptive statistics on this study

negative cases were 4. Diagnostic accuracy of CE-MRI for the detection of RB was found to be 95.5% (43/45) (p value 0.0001), sensitivity and specificity was found to be 97.5% (32/32) and 80% (4/5) respectively. (p value 0.0001). (Tab. 4 & Chart 1)

Variable	No. of patient	TP	FP	TN	FN	Accuracy (%)	Sensitivity (%)	Specificity (%)	P-value
RB Histopath versus Laterality	45	40	0	3	2	95.5 (43/45)	95.2 (40/42)	100 (3/3)	0.0001
RBMRI versus RB Histopath	45	39	1	4	1	95.5 (43/45)	97.5 (39/40)	80 (4/5)	0.0001
RBMRI versus Ca on US	45	33	7	5	0	84.4 (38/45)	100 (33/33)	41.7 (5/12)	0.0001
RBMRI versus Ca on CT	45	33	7	5	0	84.4 (38/45)	100 (33/33)	41.7 (5/12)	0.0001
RBMRI with RD	45	30	10	5	0	77.8 (35/45)	100 (30/30)	33.3 (5/15)	0.001
RBMRI with Optic Nerve Invasion	45	20	20	5	0	55.5 (25/45)	100 (20/20)	20 (5/25)	0.034
RBMRI with Ca on MRI	45	32	8	5	0	82.2 (37/45)	100 (32/32)	38.5 (5/13)	0.0001

Ca=calcification RD= retinal detachment

Table 4: table showing variables taken in this study and their results obtained after analysis of the data.

For the detection of calcification high resolution MRI shows 82.2% accuracy while US/CT shows 84.4% accuracy for the detection of calcification. Optic nerve invasion was diagnosed with an accuracy of 55.5%. Out of 45 eyes, 30 eyes show retinal detachment which was diagnosed on MRI with 77.8% accuracy. 40% of RB shows exophytic growth pattern and 37.8% shows endophytic tumor growth while 11.1% showed mixed exo and endophytic growth pattern (Tab. 5 & Chart 1).

RBMRI * growth pattern Cross tabulation							
			growth pattern				Total
			exophytic	endophytic	both	negative	
RBMRI	Present	Count	18	17	5	0	40
		% of Total	40.0%	37.8%	11.1%	.0%	88.9%
	Absent	Count	0	0	0	5	5
		% of Total	.0%	.0%	.0%	11.1%	11.1%
Total		Count	18	17	5	5	45
		% of Total	40.0%	37.8%	11.1%	11.1%	100.0%

P - Value 0.0001

Table 5: Table showing growth pattern of retinoblastoma on MRI

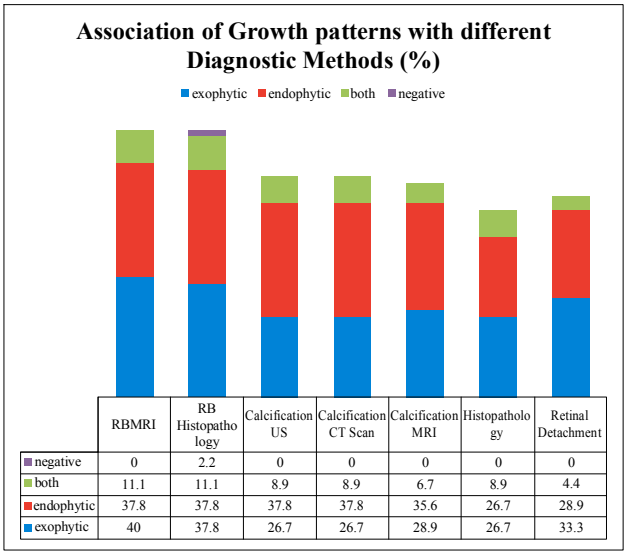

Chart 1: Bar chart showing association of growth patterns with different diagnostic methods

Discussion

Exact knowledge of tumour infiltration is essential for the treatment of RB and imaging is required to exclude extraocular extension in particular at the posterior pole of the eye. In clinical routine, ultrasound is used to determine tumour size and location within the eye. The resolution of ultrasound examination is too low to detect choroidal infiltration or to exclude a limited infiltration of the optic disc or optic nerve.[16]

Since its arrival the CT scanning has been the standard imaging technique in the diagnosis of RB because of the sensitivity in detecting the typical calcification occurring in about 80%. The presence of calcification in the tumour by CT scan is virtually diagnostic.[17-20] At present, MR imaging with its superior contrast resolution is generally recommended as an additional diagnostic method to CT scan in cases of suspected RB.[19,21-24] Special coils for the examination of the eye which allow imaging with a field of view as small as 60 mm are just becoming available.[25] With these new coils spatial resolution of MRI could be markedly increased. However, a few problems like the presence of motion artifacts, which sometimes occur with long scanning times and low capacity for detecting calcification, are still encountered with this technique.[26] MR imaging has become a very useful diagnostic tool for clinicians to rely on in evaluation of these patients. Although ophthalmoscopy and US are of great value in the diagnosis of and the determination of the status of intraocular disease, MR imaging with high soft-tissue contrast resolution and multiplanar capabilities enables pretreatment intraocular and extraocular tumor staging with rather high diagnostic accuracy.[27]

The results of this study were compared with that of de Graaf et al[27] and Schueler et al.[16]

In all three studies, MR imaging depicted lesions with characteristic SI: hyperintense with respect to the vitreous on T1-weighted MR images and hypointense onT2-weighted MR images. After intravenous administration of gadolinium, all tumors showed enhancement. 45 patients were included in this study while 56 and 21 patients were included in de Graaf et al and Schueler et al studies respectively. Mean age of the patients was 19.98 ± 18.41 months. Sex distribution shows, 25 patients (55.6%) were male while remaining 20 patients (44.4%) were female. Duration of Symptoms was 33.6 ± 30.5 days. True positive cases were 39 and true negative cases were 4. Diagnostic accuracy of CE-MRI for the detection of RB was found to be 95.5% (43/45), sensitivity and specificity was found to be 97.5% (32/32) and 80% (4/5) respectively.

Eighteen (32%) patients had bilateral disease in de Graaf study while ten (22.22%) patients had bilateral disease in our study. Regarding optic nerve infiltration Schueler et al showed sensitivity of 75% with a specificity of 38%. The positive predictive value was 43% with a negative predictive value of 71%, with a 38% prevalence of optic nerve infiltration. These researchers found overall accuracy for excluding extraocular tumour extension

by MRI scans was 95%.

De Graaf study showed the sensitivity of MR imaging in detection of optic nerve infiltration was 66%, with a specificity of 96% and an accuracy of 79%. However, in our study optic nerve infiltration was detected with accuracy of 55.5 %, sensitivity of 100% and specificity of 20%.

At MR imaging, detachment of the retina was diagnosed with sensitivity of 89% in de Graaf study and 77.8% sensitivity was observed in our study. (Tab. 6 & Chart 2) For the detection of calcification high resolution MRI shows 82.2% accuracy while

	This study	de Graaf et al[27]	Schueler et al[16]
No. of patients	45	56	21
Bilateral disease (no. of patients)	10	18	-
Optic nerve invasion			
Sensitivity	100%	66%	75%
Specificity	20%	96%	38%
Retinal detachment diagnosis (Sensitivity)	77.8%	89%	-
Growth pattern			
Endophytic	40%	42%	-
Exophytic	37.8%	46%	-
Mixed	11.1%	12%	-

Table 6: Comparison between this study, de Graaf et al and Schueler et al

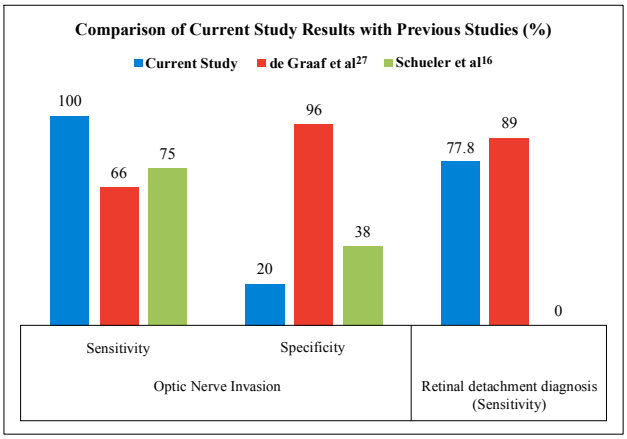

Chart 2: Bar chart showing comparison between this study, de Graaf et al and Schueler et al.

US/CT shows 84.4% accuracy for the detection of calcification. In the study done by de Graaf tumor growth pattern was endophytic in 42% and exophytic in 46%; in 12% eyes, both exophytic and endophytic tumor growth patterns coexisted simultaneously. In our study 40% of RB shows exophytic growth pattern and 37.8% shows endophytic tumor growth while 11.1% showed mixed exo and endophytic growth pattern. (Chart 1) No correlation of the tumor location was found with the risk of optic nerve infiltration in this study as well as de graaf's study. De graaf et al compared mean tumor volume with pre-laminar optic nerve infiltration and found a strong association between increase in tumor volume and risk of prelaminar optic nerve invasion (P=.001). Several studies focused on clinical features that may be used to predict the presence of metastatic disease and extraocular recurrence. However we were not able to correlate tumor volume with optic nerve infiltration.

Conclusion

High resolution MRI has superior contrast and spatial resolution compared to computed tomograph (CT) or other available imaging techniques. MRI is highly sensitive for the diagnosis of retinoblastoma as well as for the detection of optic nerve invasion which may be helpful in the treatment planning. MRI cannot substitute CT in detecting tumour calcification in retinoblastoma but with increasing experience and new techniques it should be possible to renounce CT scans in the majority of cases of retinoblastoma.

Disclosure: The authors declare no conflicts of interest in relation to this work.

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