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Uses of Radiological Imaging in Retinoblastoma

Fahad Albader and Dalal Fatani

Abstract

Retinoblastoma is the most common primary ocular malignancy in children. Diagnosing retinoblastoma relies mainly on the clinical appearance of the lesion and not on histological description. Although histology still remains the gold standard in evaluation of tumor extension and progression risk factor, a tumor biopsy carries high risk of dissemination and is difficult to obtain. Retinoblastoma has characteristic clinical features of creamy-white mass associated with subretinal fluids and may be accompanied by retinal detachment and vitreous seeding. There are many factors contributing to metastatic risk factors like postlaminar optic nerve infiltration, scleral and choroidal invasion, and peribulbar fat invasion. Ancillary testing is necessary for any patient with a suspected retinoblastoma to assess the dimensions of the tumor as well as the tumor extension. An ultrasonography (B scan) will show the mass dimensions as well as the hyperechoic calcifications, which are commonly present with retinoblastoma. CT scan is not the modality of choice for diagnosis of retinoblastoma in children because of the radiation exposure. Magnetic resonance imaging is considered the examination of choice to assess the tumor extension as it has high soft tissue contrast. The use of MRI changed the accuracy of assessing metastatic risk factors as the results yielded before and after the use of MRI differed. This chapter will address the use of radiological imaging in retinoblastoma defining diagnostic characteristics and identifying parameters of metastatic risk factor assessment. This chapter will also include evidence-based review on the efficacy of radiological imaging of retinoblastoma and its impact on the choice of treatment and disease prognosis.

Keywords: magnetic resonance imaging, retinoblastoma, metastasis, optic nerve invasion, vitreous seeding, retinal detachment, calcification, prognosis

1. Introduction

Retinoblastoma is the most common primary ocular malignancy in children. It is usually unilateral but may be bilateral in one-third of cases. It presents in childhood as leukocoria or acute onset strabismus. Diagnosing retinoblastoma relies mainly on the clinical appearance of the lesion and not on histological description. Although histology still remains the gold standard in evaluation of tumors extension and progression risk factor, a tumor biopsy carries high risk of dissemination and is difficult to obtain. Retinoblastoma has characteristic

clinical features of creamy-white mass associated with sub retinal fluids and may be accompanied by retinal detachment. Endophytic tumors grow inwards towards the vitreous cavity which may result in vitreous seeding of the tumor cells. Exophytic tumors grow into the sub retinal space causing progressive retinal detachment and subretinal seeing. There are many factors contributing to metastatic risk factors like post laminar optic nerve infiltration, scleral and choroidal invasion, and peribulbar fat invasion. Ancillary testing is necessary for any patient with a suspected retinoblastoma to assess the dimensions of the tumor as well as the tumor extension.

The main ancillary tests that can be used with retinoblastoma are ultrasound imaging (US), computerized tomography (CT), and magnetic resonance imaging (MRI).

Ultrasonography (B scan) will show the mass dimensions as well the hyper-echoic calcifications which is commonly present with retinoblastoma. These imaging modalities and their uses in retinoblastoma detection will be discussed in this chapter with the main focus on MR imaging.

2. Ultrasonography imaging in retinoblastoma

Ultrasound imaging is a cost-effective widely available modality that is non-invasive and easy to perform. This modality is especially useful in patient when the ocular light-conducting media is opaque. It can detect tumor dimensions and characteristics as well as vitreous seeding. It is usually conducted at a 10 MHz high frequency probe. B scans can also visual the optic nerve which can be seen within the retrobulbar fat. The optic nerve is usually seen as a hypoechoic structure within the echogenic surrounding fat.

In case of retinoblastoma, the tumor is visualized as a hyperechoic tumor with irregular borders. It may present a diffuse lesion or a localized well-defined lesion (**Figure 1**). The calcium deposits are clearly visualized by ultrasonography as highly hyper-echoic and they are a pathognomonic feature [1]. Ultrasound imaging can also identify any associated retinal detachment or choroidal thickening (**Figure 2**). The vitreous surrounding the lesion may show hyper-reflective particles representing the calcified tumor seeding into the vitreous cavity.
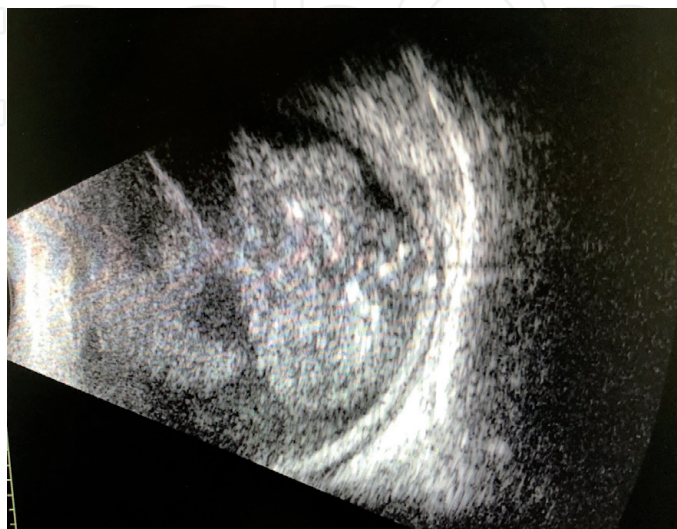

Figure 1.
B scan of an eye with diffuse pattern retinoblastoma showing areas of calcification.
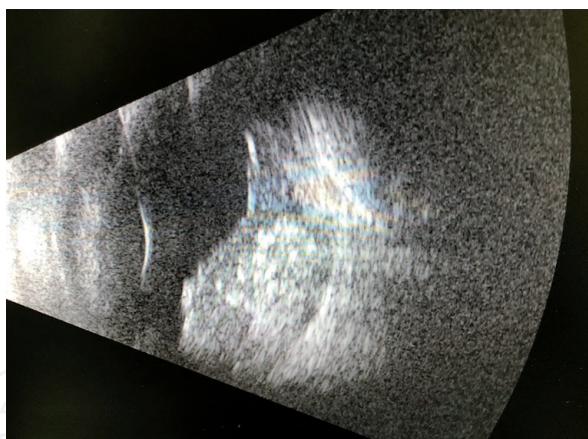
Figure 2.
B scan of an eye with retinoblastoma showing an exophytic growth pattern with an associated retinal detachment.

Extraocular invasion of the optic nerve can also be detected once the normal tubular hypo-echoic nature of it is altered.

3. Computerized tomography imaging in retinoblastoma

Computerized tomography (CT) is a combination of multiple X-ray images from different angles producing cross sectional images. Like standard X-ray, CT depends on relative the radio-density of different tissue structures. CT delivers ionization radiation reaching to 1–10 mSv per brain CT. Retinoblastoma appears as a hyperdense lesion on CT in relation to the surrounding hypodense ocular vitreous (**Figure 3**).

CT scan is also another beneficial tool in detecting calcification which may be seen in a non-homogenous pattern in most large tumors (**Figure 4**) or in a homogenous pattern in smaller tumors. In certain studies, CT scan has failed to show calcification in small retinoblastoma tumors [2–4] CT images can also be useful to detect any associated metastatic brain lesions (**Figure 5**).

CT scan is not the modality of choice for diagnosis and follow-up of children with retinoblastoma due to radiation exposure (ionizing radiation) and the high sensitivity of MRI for soft tissue. This reduces the implantation of CT in retinoblastoma cases especially in areas where MR studies are accessible [3].
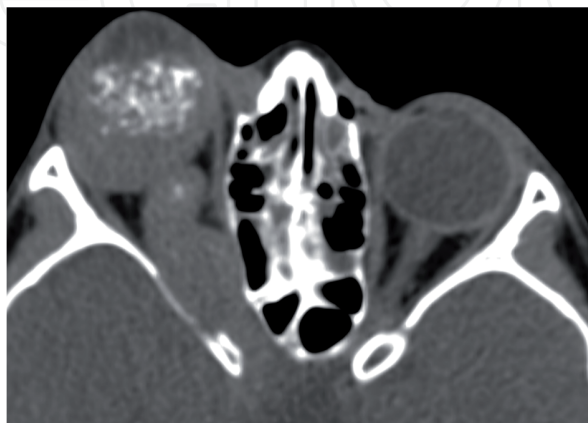

Figure 3.
CT (soft tissue window image) showing right globe hyperdense vitreous, retrolental intraocular solid mass with dystrophic calcification and proximal calcified optic nerve local invasion.
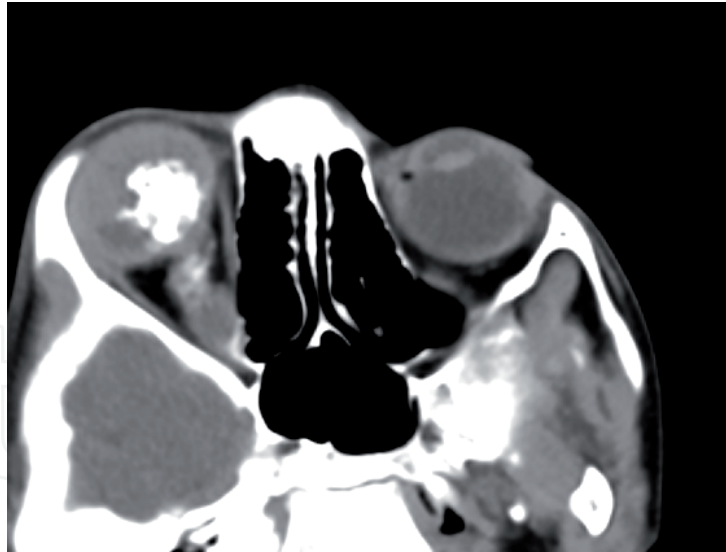
Figure 4.
CT (bone window image) showing right globe enlargement, hyperdense vitreous due to hemorrhage, retrolental intraocular solid mass with central large dystrophic calcification and an enlarged proximal calcified optic nerve due to local invasion.
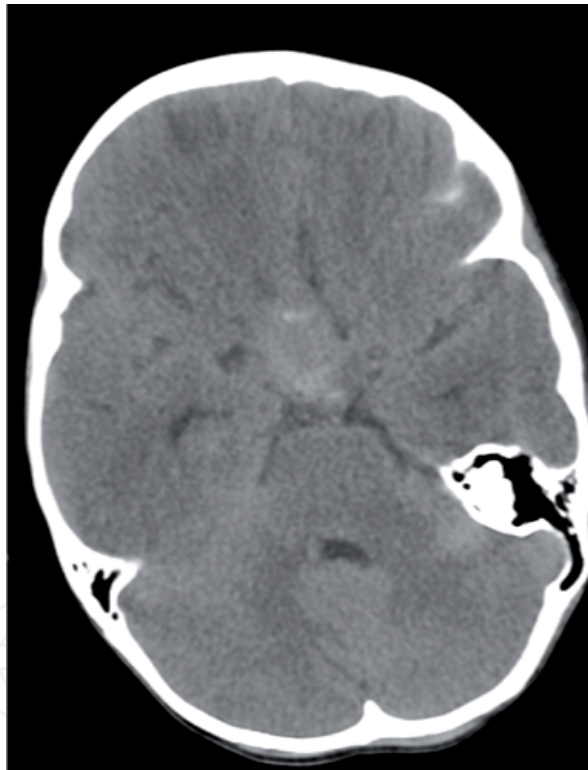

Figure 5.
A non-contrast brain CT for follow up of retinoblastoma patient, showed solid suprasellar mass with faint calcification suggestive of metastasis.

4. Magnetic resonance imaging in retinoblastoma

Magnetic resonance imaging is a type of imaging that use strong magnetic fields and magnetic field gradients to generate anatomical images without the use of ionization radiation.

Magnetic resonance imaging is considered the examination of choice to assess the retinoblastoma tumor extension extraocularly as it has high soft tissue contrast. Although retinoblastoma is usually diagnosed clinically by fundoscopy examination; in cases of unclear ocular medium, MRI can even be used in diagnosing retinoblastoma.

The European Retinoblastoma Imaging Collaboration (ERIC) released a recommended guideline protocol for MR imaging in retinoblastoma. This MR retinoblastoma protocol uses a 1.5 T in T_1 weighted images scout view and turbo spin-echo T_2 and PD images if the brain as well as 2 mm thick T_2 images of the eye in sagittal cuts. Later axial T_1 images and T_2 with fat suppression of the orbit with contrast medium of 0.1 mmol/kg gadopentetate dimeglumine are obtained. The advanced use of high resolution three-dimensional T_2 weighted imaging allows for then 0.4 mm sections with high SNR that is sensitive to detect calcification.

In this guideline a post laminar optic nerve invasion is characterized by abnormal contrast enhancement of the optic nerve that is > = 2 mm length or any asymmetrical thickening [5].

Sagittal and axial T_1-weighted images: repetition time (TR) = 475 ms; echo time (TE) = 10 ms; slice thickness = 2 mm; field of view (FOV) = 150 × 150 mm; matrix = 256 × 179; number of excitations = 1].

Axial T_2-weighted fat sat images: TR = 3600 ms; TE = 95 ms; echo train length = 15; slice thickness = 2.5 mm; FOV = 150 × 150 mm; matrix = 320 × 240; number of excitations = 2].

When approaching MRI images of an intraocular lesion, one of the first parameters to be assessed is the axial length and eye volume as well as the laterality of the disease. Thorough examination of the brain images is also a major step for the detection of any syndromic associations or intracranial metastasis. These parameters are very beneficial in the differentiation of similar intraocular lesions. In cases of persistent fetal vasculature (PFV), they can present with leukocoria or strabismus as well. However, the globe size is markedly smaller in PFV cases (**Figure 6**).

On MRI the retinoblastoma tumor borders usually exhibit an irregular lobulated pattern.

The eye parameters are relatively smaller in eyes with retinoblastoma with the size of the tumor volume inversely proportional to the size of the globe [6].

Retinoblastoma can also be associated with retinal detachment which can be clearly detectable on MR images (**Figure 7**).

Retinoblastoma on T_1 weighted MR imaging appears as relatively hyper-intense compared to the adjacent normal vitreous. It also contains areas of low signal intensity within the hyper-intense tumor that reflects the areas of calcification (**Figure 8**).
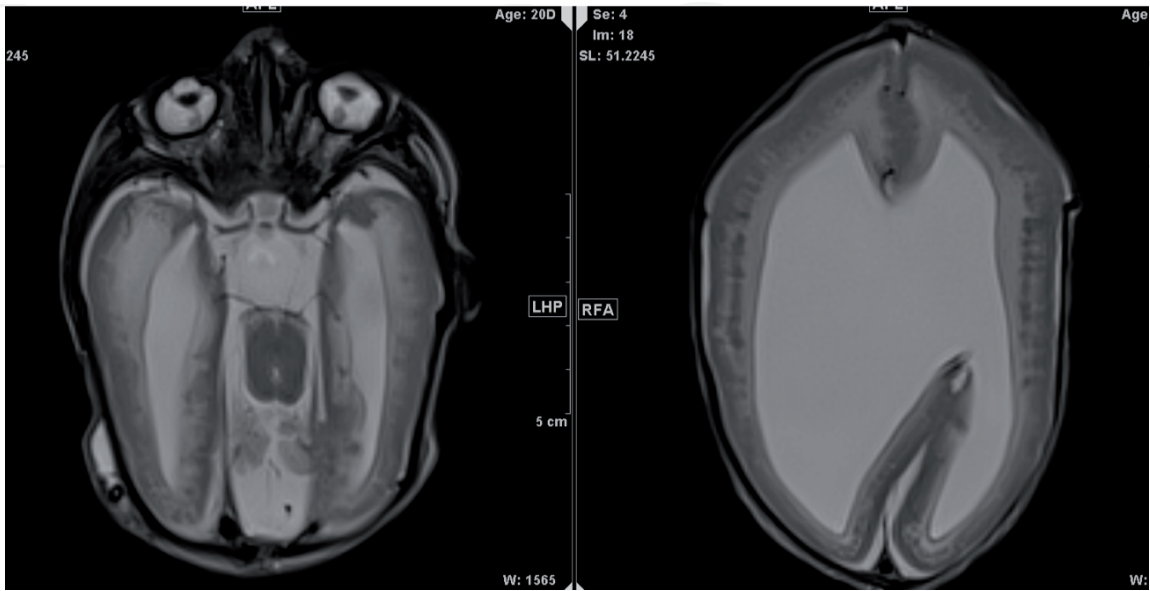

Figure 6.
Axial T_2 WI image of brain and orbit showing bilateral microphthalmia, hyaloid canal, a characteristic finding of PFV. Images of brain cortex are characteristic of type II cobblestone lissencephaly, hydrocephaly with dysplastic white matter, over all finding are of Walker-Warburg syndrome.

Figure 7.
MRI orbit T$_1$ weighted fat saturated with contrast imaging showing bilateral faintly enhanced retrolental retinal based mass with right retinal detachment.
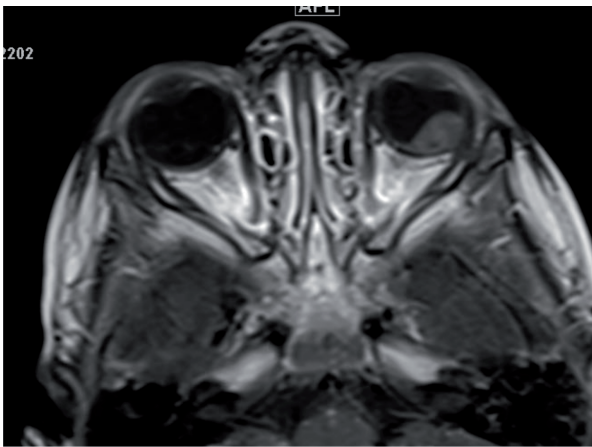

Figure 8.
MRI T$_1$ weighted image with contrast, faintly enhanced retrolental mass at left globe corresponding to retinoblastoma tumor core.
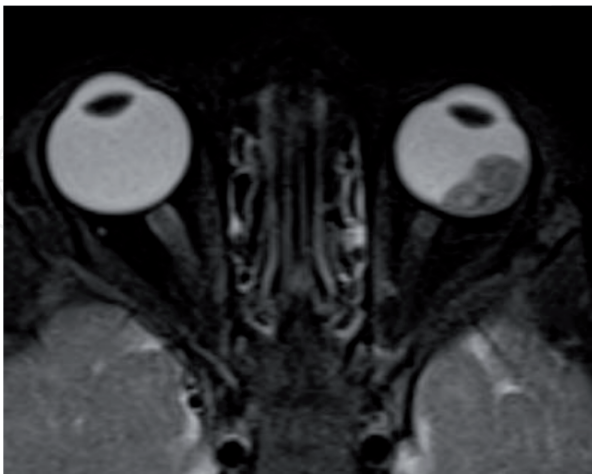

Figure 9.
MRI T$_2$ weighted fat saturated image of the orbits showing low signal of retrolental mass corresponding to retinoblastoma tumor at left globe with mild reduction of size of globe.

A study compared the efficacy of MRI in calcification detection by comparing in vivo T$_2$ weight MRI with ex vivo high-resolution CT. It has found the T$_2$WI correlated well with CT findings. Therefore, combining examination with

Figure 10.
Axial T$_2$ weighed MRI of the brain and orbit showing a hypointense tumor of the right globe, filling 80% if the globe with areas of hypo-intensity representing calcification or retinoblastoma tumor core.

ultrasonography and MRI with gradient-echo sequence is thought to be the standard diagnostic approach for any patient with retinoblastoma [4].

On T$_2$ weighted imaging, the retinoblastoma tumor is usually darker than the vitreous resulting in a relative hypo-intense lesion within the vitreous with further patches of hypointensity within corresponding to calcification area (**Figures 9** and **10**).

5. Diffusion weighted imaging in retinoblastoma

Diffusion-weighted imaging (DWI) is a type of MR imaging that depends on the motion of water molecule within the tissue. Highly cellular tissue exhibits lower diffusion coefficients making this modality useful for tumor characterization. DWI is wisely wised for orbital disease as well as brain malignancy. On diffusion weighted imaging (*P* value 1000) the retinoblastoma tumor shows diffuse restriction.

A pulse sequence form of DWI that generates various imaging is referred to as ADC images (apparent diffusion coefficient) which measures the magnitude of diffusion resulting a numerical value. The mean ADC value of retinoblastoma was $0.49 \pm 0.12 \times 10^{-3}$ mm^2/s.

The low ADC values of retinoblastoma tumors are attributed to the tightly packed nature of high nuclear cytoplasmic ratio of the tumor (**Figure 11**).

The use of ADC value images has shown to be well correlated with the degree of tumor differentiation in a study conducted in Saudi Arabia. The ADC value was analyzed in different sized tumors and was shown to be significantly different with various sized tumors. It demonstrates an inverse correlation of the ADC value with the tumor size. The ADC value of small tumors (<10 mm) was $0.55 \pm 0.09 \times 10^{-3}$ mm^2/s, medium tumors (>10–15 mm) was $0.48 \pm 0.09 \times 10^{-3}$ mm^2/s, and large tumors (>15 mm) was of $0.38 \pm 0.11 \times 10^{-3}$ mm^2/s value.

In addition, the ADC value was lower in tumors with optic nerve invasion which may correlate with the tumor's likelihood to be poorly differentiated and
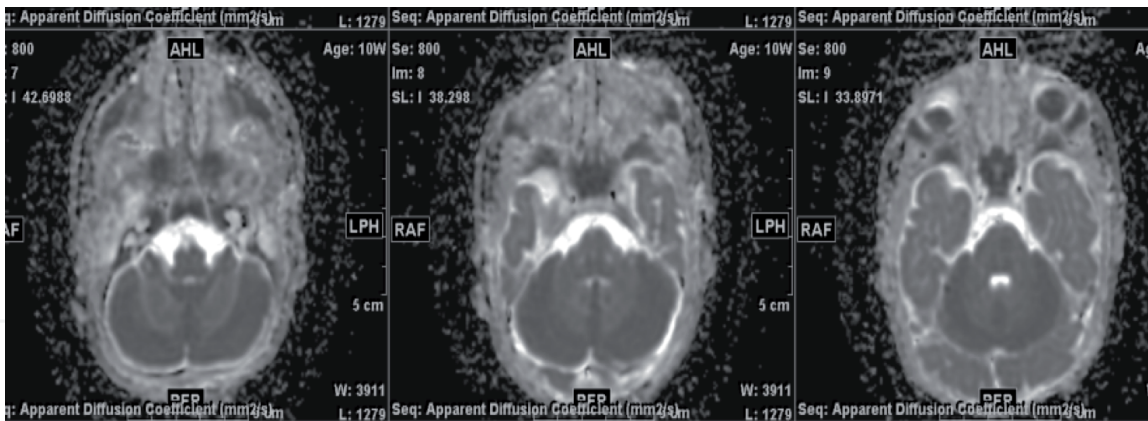
Figure 11.
ADC (apparent diffusion coefficient) MR image of the brain and orbit showing bilateral ocular lesions with low ADC values represented tumor core representing bilateral retinoblastoma.

aggressive [7]. *Axial diffusion weighted images: TR = 5000 ms; TE = 74 ms; number of diffusion matrix = 200 – 162; number of excitations = 1 with reconstruction of the ADC map.*

6. Metastasis of retinoblastoma on MRI

Retinoblastoma tumor grows with an endophytic and/or an exophytic pattern. Endophytic growth starts from the inner layers of the retina progressing into the vitreous cavity. As the tumor cells detach from the main tumor, they can float into the vitreous and cause what is known as vitreous seeding. Detection of vitreous seeding is crucial in the staging of retinoblastoma and is considered a main prognostic indicator. Although detection of vitreous seeding by ophthalmoscopy examination is superior to MR imaging, it can be clearly identified in 63% of patient on MRI. It is usually identified as bright patches on T_1 weighted imaging and dark patches on T_2 weighted imaging within the vitreous cavity [5, 8] (**Figure 12**).

Exophytic growth pattern starts at the outer retinal layers and progress into the sub-retinal space causing a retinal detachment and sub-retinal tumor seeding [9].

MR imaging can detect choroidal invasion of retinoblastoma tumor at a sensitivity of 74% and a specificity of 72%. (Brisse relevance) Scleral invasion of retinoblastoma tumor can also be assessed by MR imaging with 88% sensitivity and 99% specificity [2] (**Figure** 7).

Another more aggressive pattern of retinoblastoma tumor growth is diffuse infiltrating growth pattern. In this pattern, the tumor grows along the retina as a placoid mass which subsequently results in ocular inflammation and hemorrhages. This may be seen as severe AS inflammation and a pseudohypopyon. MR images can help assess the anterior segment for the presenter absence if abnormal enhancement.

Diffuse infiltrative growth pattern is very rare (1–2%) and occurs with older age children with a male predilection of 8:1. It is usually difficult to diagnose as there are no discrete mass borders and it usually lacks the characteristic retinoblastoma calcification. A retinal detachment is commonly associated and is often evident on MRI especially on FLAIR sequence (Fluid attenuated inversion recovery) [10].

Figure 12.
MRI of the spine showing areas of diffuse leptomeningeal enhancement of the spinal cord representing areas of CSF seeding.

7. MRI's uses in the staging and prognosis of retinoblastoma

Although MRI can aid in the diagnosis of retinoblastoma by the aforementioned characteristics, it is more widely used for the staging of retinoblastoma. Like all other malignancies, tumor staging in retinoblastoma is essential for the prognosis predictions.

The use of MRI has changed the accuracy of assessing metastatic risk factors as the initial retinoblastoma staging of patients before the use of MRI varied after MR imaging were obtained.

The extension of retinoblastoma is usually by direct extension into adjacent structures. Intraocular extension of the tumor can easily be visualized during examination in patients with good posterior pole visualization. MR imaging has

been widely used to evaluate the extra-ocular and intracranial extension and can also aid in the evaluation of intraocular tumor extension [11].

Intraocular extension can be detected by choroidal irregularities. Choroidal invasion identification is important in the prognosis of the disease. It changes the prognosis of retinoblastoma by increasing the mortality rate up to 24–65% depending on the severity of invasion [12].

In the assessment of extra-ocular retinoblastoma extension, the most important structure to evaluate is the optic nerve. Involvement of the optic nerve in retinoblastoma alters the prognosis and the management of the disease. The overall mortality rate of retinoblastoma without optic nerve invasion is 10%. If the invasion of the optic nerve reaches through the lamina cribrosa, the mortality may rise up to 15%. Moreover, if the extension is posterior to the lamina cribrosa the mortality rises up to 44%. This makes the optic nerve assessment by MR imaging crucial in any retinoblastoma case with proper identification of the level of optic nerve invasion. On MRI, the affected optic nerve appears thickened and irregular with high enhancement of the nerve itself and the area surrounding it [11].

A study showed that the specificity of MRI in detecting optic nerve invasion past the lamina cribrosa to reach up to 80% and a sensitivity of 74%. This makes MR imaging the most superior non-invasive method in the detection of retinoblastoma optic nerve invasion [13] (**Figures 13** and **14**).

Ophthalmic surgeons require extra measurements of the invasion to take extra precautions during the enucleation of the affected eye. It is important for the MR image to demonstrate if the retrolaminar optic nerve invasion extends more than 5 mm posteriorly. This is particularly crucial to identify prior to surgical intervention as the tumor may be cut through during the enucleation. If such complication happens, the distal part of the tumor that remains is connected to the brain and may progress to brain metastasis. In such cases, the surgeon might consider doing an orbitotomy to be able to reach further posterior and dissect at least 10 mm from

Figure 13.
MRI T$_2$ weighted image of brain and orbit showing right globe retrolental hypo-intense tumor core, retro bulbar extension and extensive long segment right optic nerve invasion resulting in right globe proptosis.
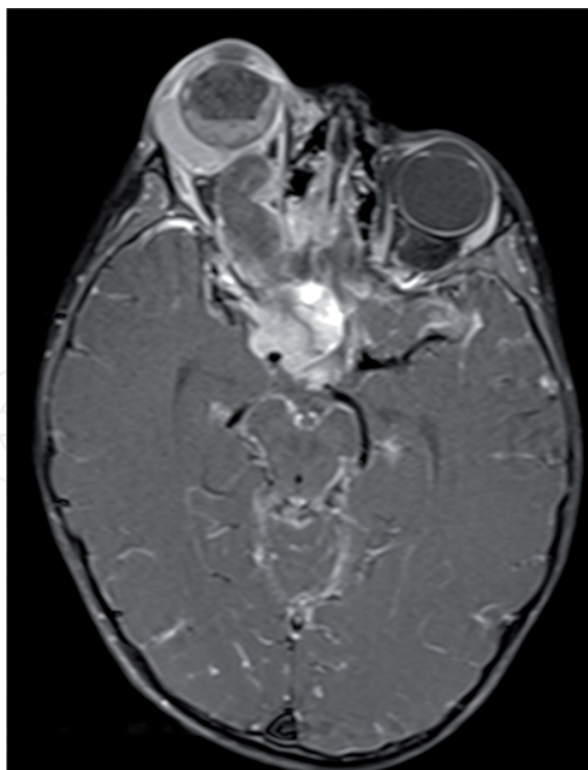
Figure 14.
MRI T$_1$ weighted image with contrast of the same patient delineating the retrobulbar extension, enhanced and enlarged right optic nerve, leptomeningeal enhancement due to direct extension and CSF seeding of retinoblastoma.

the suggested tumor margin. Despite the advancement of MRI, it has limitations in detecting microscopic optic nerve invasion. Studies have shown a discrepancy between histological results in optic nerve assessment (gold standard) and MRI results [14]. This dictates the need for thorough histopathological assessment of the optic nerve regardless of MR findings.

An important disease entity in retinoblastoma is the trilateral retinoblastoma disease. It refers to rare disease that is characterized by bilateral ocular RB and a primitive midline neuroectodermal tumor in the pineal region or the suprasellar cistern. It represents 1.5–5% of all RB patients [15].

8. Conclusion

Retinoblastoma is the most common primary ocular malignancy in children. Diagnostic imaging has changed the accuracy of diagnosing and staging retinoblastoma. There are many imaging modalities that are currently in use for retinoblastoma tumor like ultrasonography, computerized tomography and magnetic resonance imaging. MR images of the brain and spinal cord need to be obtained routinely in retinoblastoma patients in institutes where MRI is accessible. They aid in the diagnosis and prognosis of the disease. As the retinoblastoma tumor seeding may spread via cerebrospinal fluid and reach the intracranial resulting in brain metastasis, MRI can clearly delineate these metastatic lesions, which eventually alters the management plan.

MRI can show retrolaminar optic nerve and choroidoscleral infiltration and spread of tumor into the brain and spine more accurately than other diagnostic imaging.

A purely ocular tumor confined within the globe reaches a survival rate of 90% AT 5-years whereas a tumor that has extended outside the globe has a mortality rate of over 90%.

This drastic difference makes staging and the use of ancillary testing vital for the prognosis and survival rate estimation which further guides the treatment decision.

It is now currently recommended for any newly diagnosed patient with retinoblastoma to undergo an MRI [13].

MRI can also offer hope for future advancement of early diagnosis. It has recently shown to aid in very early fetal diagnosis of retinoblastoma in a fetus with high-risk of RB and may be implemented as a part of future screening protocol in high risk population [16].

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Conflict of interest

There is no financial interest to disclose.

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