The potential of 3T high-resolution magnetic resonance imaging for diagnosis, staging and follow-up of retinoblastoma

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ABSTRACT

Radiological imaging is becoming increasingly important, as eye-saving treatments are performed more often. The objective of this article is to demonstrate the value of high-resolution magnetic resonance (MR) imaging in diagnosing, staging, and follow-up of retinoblastoma during eye-saving treatment. We have included informative retinoblastoma cases scanned on a 3T MR system from a retrospective retinoblastoma cohort from 2009 through 2013. We show that high-resolution MR has the potential to detect small intraocular seeds, hemorrhage, metastatic risk factors not visible with fundoscopy (e.g., optic nerve invasion and choroidal invasion), and treatment response. Unfortunately, however, the diagnostic accuracy of high-resolution MR imaging is not perfect, especially for subtle intraocular seeds or minimal postlaminar optic nerve invasion. The most important application of MR imaging is the detection of metastatic risk factors as these cannot be found by fundoscopy and ultrasound.
INTRODUCTION

Retinoblastoma is a malignant tumor of the retina and represents approximately 3% of all pediatric malignancies. The incidence is one in 17,000, typically presenting in the first five years of life.1

In most cases retinoblastoma can be distinguished accurately from other ocular lesions with fundoscopy and ultrasound. When there is still doubt about the diagnosis (intratumoral calcifications set retinoblastoma apart from other lesions) and/or in case of an unclear ocular medium (e.g., massive vitreous hemorrhage), magnetic resonance (MR) imaging can aid in diagnosing, staging, and follow-up of intraocular retinoblastoma. In staging, MR imaging plays an important role, as fundoscopy and ultrasound cannot assess tumor-extent beyond a certain point. Retinoblastoma can spread beyond the eye in different ways. The tumor can invade the highly vascularized choroid giving an increased risk of hematogenous spread. As the tumor continues to grow outwards, it can invade the sclera, carrying the risk of local recurrences. The tumor can also extend into the optic nerve through the lamina cribrosa, which may result in metastases in the brain and cerebrospinal fluid. Whether involvement of the anterior eye segment is also a risk factor for metastasis is still subject to discussion.2,3 Most commonly the International Classification of Retinoblastoma (ICRB) is used to classify the metastatic risk of intraocular retinoblastoma.4 For extraocular extension of retinoblastoma the International Retinoblastoma Staging System (IRSS) has been developed.5,6

Increasing use of eye-saving treatment strategies emphasize the importance of non-invasive diagnostic tools because often decisions cannot be confirmed by histopathologic analysis. The diagnostic accuracy of MR imaging in staging retinoblastoma tumor extent largely depends on image quality and resolution. False positives and false negatives are often borderline cases; for example optic nerve invasion posterior to the lamina cribrosa sclerae could be falsely diagnosed if the tumor has invaded the optic nerve pushing the lamina outwards, but has not actually passed it, that can give the impression of postlaminar invasion on MR imaging.7 The diagnostic accuracy of MR imaging will continue to increase as technology advances. Most modern hospitals have at least a 1.5T MR system. Such a system with a dedicated surface coil or a 3T system with a multi-channel head coil can produce high-resolution images of the eyes. We demonstrate the value of high-resolution MRI in diagnosing, staging and follow-up of retinoblastoma by showing high-resolution MR images of a wide spectrum of the disease.

METHODS

We evaluated MR images from 56 retinoblastoma patients between 2009 and 2013 who were scanned 119 times in total, ranging from one to ten scans per person. The median age at which the first MR imaging was performed was 25 months, ranging from 1–130 months. Forty percent (22/55) of the patients had unilateral disease. About a third (18/56) of the retinoblastoma patients underwent enucleation. All retinoblastoma patients were scanned on a 3T MR machine (Verio; Siemens, Erlangen, Germany) combined with a 32-channel receiver coil (running Syngo VB 15-17 software) at the University Hospital of Lausanne (CHUV). During the positioning of patients, the distance between the eyes and the coil was minimized by lifting the patient. All patients were scanned under general anesthesia. As contrast agent we used an intravenous injection of 0.1 mmol/kg of gadoteric acid (Dotarem; Guerbet, Villepinte,
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France). Details about the used high-resolution sequences for ocular and orbital imaging can be found in appendix A. Additionally routine brain imaging was performed in all patients. The Institutional Review Board approved the study with waiver of informed consent.

**Image evaluation**

During two consensus meetings in September 2012 and June 2013 of the European Retinoblastoma Imaging Collaboration (ERIC), five experienced radiologists (PM, PdG, HJB, PG and SG, all with more than 10 years’ experience in ocular MR imaging) made a selection from the available MR images to give an extensive overview of the retinoblastoma disease spectrum. We included detailed examples of various disease stages. In all patients the diagnosis of retinoblastoma was confirmed with fundoscopy and ultrasound.

Two radiologists (PG and SG) assessed the quality of the images (axial T1 and T2) independently on a scale from 1 (poor), 2 (average), 3 (good), to 4 (excellent). During the first ERIC consensus meeting images dating from January 2011 until September 2012 (73 out of 119 MR scans) were included in the quality scoring. Older images were excluded, because image quality improved over time.

**IMAGE QUALITY**

There were some differences in the quality scores between the two readers, but this was mostly due to differences between readers in terms of scoring 3 (good) or 4 (excellent). Appendix B shows that most of the images at least had a good quality.

**INTRAOCULAR RETINOBLASTOMA**

MRI has limited additional benefit to fundoscopy and ultrasound in assessing the appearance, diagnosis, and staging of intraocular retinoblastoma. In case of doubt, however, MR imaging may play an important additional role.

**Growth pattern**

In terms of growth pattern, retinoblastoma can be divided into four groups: endophytic tumors, exophytic tumors, a combination of endo- and exophytic growth patterns, and diffuse infiltrating tumors. Endophytic tumors develop in the intraretinal layers and have broken through the inner limiting membrane and hyaloid into the vitreous (figure 1A). Eventually vitreous seeding may develop when little chunks of cells break off the tumor mass and float in the vitreous. Exophytic tumors develop in the intraretinal layer and grow into the subretinal space and may result in subretinal fluid and retinal detachment (figure 1B). Retinoblastoma with an exophytic growth pattern has an increased probability of growing into the choroid. When chunks of cells break free in the subretinal space, we speak of subretinal seeding. Often retinoblastoma presents as a combination of an exophytic and endophytic growth pattern (figure 1C). Rarely retinoblastoma can also present as diffusely infiltrating patches in the retina, without a clear tumor mass, that often lack calcifications and present in older children.

**Tumor presentation**

Typically retinoblastoma presents as an area with moderately high signal intensity on T1-weighted images and low signal intensity on T2-weighted images compared to the vitreous body. On post-gadolinium T1-weighted images retinoblastoma usually shows
a heterogeneous enhancement pattern (visible on an image that is referenced later on for contrast enhancement of the iris: figure 3A).

Calcifications are a characteristic of the tumor, setting retinoblastoma apart from other intraocular lesions like Coats disease, persistent fetal vasculature and medulloepithelioma. MR imaging has not been considered sensitive for the detection of calcifications; however, two studies show that MR imaging has a good diagnostic accuracy with a sensitivity of 92%–93% and a specificity of 89%–100%. Calcifications show up as areas of low intensity on T2-weighted images (figure 1D).

As the tumor grows the risk of tumor extension increases, and as a result more aggressive and invasive treatment options will be necessary. Brisse et al. found a significant difference in maximum tumor diameter on MR imaging between eyes with (17.6 mm) and without (15.3 mm) histopathologically proven postlaminar optic nerve invasion (P=0.001). De Graaf et al. demonstrated that, on average, retinoblastoma eyes were slightly smaller than normal eyes and that tumor volume was negatively correlated with eye volume.

When diagnosed in a late stage retinoblastoma can present with increased intraocular pressure and buphthalmia. Figures 1E and F show an example of a normal sized left eye and an enlarged right eye, with globe deformation, a shallow anterior chamber and a tumor induced impairment of the aqueous humor drainage. In a late stage or (more commonly) after extensive conservative treatment, the affected eye can start to shrink leading to a non-functional shrunken eye (phthisis bulbi; figures 1G and H).

On fundoscopy retinoblastoma sometimes presents with cavitary spaces in the tumor (figure 1I). There is some evidence that cavitary retinoblastoma is an indication of a more differentiated tumor that responds less well to chemotherapy, but long-term outcomes don't seem to be worse.

**Vitreous and subretinal seeding, and retinal detachment**

Intra-arterial chemotherapy may be effective for the treatment of subretinal seeding, and with the introduction of intravitreal injection of chemotherapy, vitreous seeds can also be treated, avoiding external beam radiotherapy. Tumor seeding can often easily be seen at fundoscopy and was usually missed by MR imaging. Several studies showed that the diagnostic accuracy of MRI in detecting vitreous seeding compared with histopathologic analysis was not much better than a coin flip. Histopathologic analysis is not, however, an ideal method to detect seeding. Sometimes part of the vitreous is lost during histopathological preparation and harvesting of fresh tumor tissue for DNA-mutation analysis.

As image quality of MR imaging continuously improves over time, these numbers underestimate the current diagnostic accuracy for the detection of seeding. To be able to detect small subretinal or vitreous tumor seeds, the in-plane resolution of the images needs to be high enough and the slice thickness small enough. Figure 2A shows an example of a small vitreous seeds directly posterior to an artificial lens. Figure 2B shows a small seed in the anterior chamber. Fundoscopy confirmed the presence of tumor seeding in these two examples. In case seeding cannot be seen with fundoscopy (e.g., an unclear ocular medium due to massive hemorrhage), high-resolution MRI could be a useful addition. Optical coherence tomography has also shown promising results with regards to imaging of tumor seeding.
Exophytic tumors combined with subretinal fluid accumulation can cause the retina to detach. Seeding can then develop in the subretinal space (figure 1D). Three studies have reported sensitivities of 50–89% and specificities of 88–100% on the diagnostic accuracy of MR imaging at detecting retinal detachment compared to clinical findings or histopathologic analysis.\textsuperscript{21,22,25} Retinal detachment shows up as a distinct hypointense line on T2-weighted images and can be seen in figures 2C–E. Detachment of the retina may be focally around the tumor, but can eventually evolve into a total retinal detachment, with a typical V-shaped appearance.

\textbf{Figure 1.} Axial T2 weighted images showing a small endophytic tumor (A) that can freely grow into the vitreous unconstrained by the retina, an exophytic tumor (B) constrained by the retina giving the tumor a more lens-like shape, and a combined endophytic (arrow on C) and exophytic tumor (arrowhead on C). Calcification shows up as dark areas in this exophytic tumor (arrow on D); this image also shows extensive retinal detachment with subretinal seeding (arrowhead on D). A buphthalmic right eye (E) compared to a normal sized left eye (F) in the same patient. Images G and H depict the shrinkage of an eye before and 1 year after conservative eye-salvage treatment. A tumor with cavitary changes presents as clearly delineated hyperintense areas within the tumor (arrows on I).
Hemorrhage

Besides intratumoral hemorrhage that can cause false-positive diagnoses of tumor calcification, hemorrhage also may occur in the vitreous, subretinal space, or the anterior chamber. Hemorrhage in any of these spaces is a predictor of a worse outcome for eye salvage. Intraocular hemorrhage can be identified on MR images as fluid-fluid levels. Figure 2F shows subretinal hemorrhage in an eye with total retinal detachment. Figures 2G and H show an example of an eye initially with vitreous hemorrhage, but with subretinal hemorrhage after ten months.
Anterior eye chamber involvement

Tumor invasion into the anterior eye segment is considered by some to be a risk factor for extraocular relapse, but this is still debated.\(^2\) Besides tumor invasion, other tumor related changes in the anterior eye segment can be depicted on MR images. An increase in contrast enhancement on T1-weighted images has been correlated with rubeosis iridis (iris neoangiogenesis), with a sensitivity ranging from 68%–93% and a specificity ranging from 43%–82%\(^{26}\). Figure 3A shows an example of clinically and histopathologically confirmed rubeosis iridis. Rarely advanced intraocular retinoblastoma can cause a dislocated lens, which usually occurs in the presence of massive tumor necrosis (figure 3B). Vitreous tumor seeding can eventually also invade the anterior eye segment and from there the seeds can end up in the trabecular meshwork of the anterior chamber angle. The diagnostic accuracy of MR imaging compared to histopathologic analysis at detecting ciliary body invasion has a sensitivity ranging from 71%–100% and a specificity ranging from 65%–100%.\(^{26}\) Recently, the use of ultrasound biomicroscopy has demonstrated a sensitivity of 81% and specificity of 100% in the assessment of anterior eye segment invasion compared to histopathology.\(^{27}\)

METASTATIC RISK FACTORS

Cross-sectional imaging, like MRI, is essential for the evaluation of tumor invasion into the ocular wall or optic nerve, as fundoscopy and ultrasound are of little value.\(^{28}\)

Optic nerve invasion

Patients with postlaminar optic nerve tumor invasion without adjuvant systemic chemotherapy are at great risk of regional extraocular recurrences or distant metastases.\(^{29}\) Optic nerve invasion can be seen as contrast enhancement on T1-weighted images (figures 3C and E). Histopathologic analysis showed postlaminar optic nerve invasion (2.2 mm) in the first example (figure 3D). Histopathologically, the second example also proved to be a postlaminar optic nerve invasion (figure 3F), and depending on the assessment of the dubious postlaminar enhancement pattern in second MR image (figure 3E) this case could either be classified as a false negative or a true positive.

Appendix C shows an example of extensive postlaminar optic nerve invasion and the effect of subsequent chemotherapy (4 cycles of etoposide and carboplatin) over the course of 3.5 months. Ten months prior to this, this patient was diagnosed with unilateral retinoblastoma (left eye was classified as group E) in another institution for which the patient had been treated with intra-arterial melphalan.

In a recent meta-analysis with histopathology as the gold standard, De Jong et al.\(^{26}\) (chapter 1) showed that MRI could detect postlaminar optic nerve invasion with a sensitivity of 59% (95% confidence interval [CI]: 37–78) and a specificity of 94% (95% CI: 84–98). Metaregression showed no difference between low- and high-quality MR images. After exclusion of one potential outlier, the sensitivity of high-quality MR rose from 58% (27–84) to 76% (45–93). This was not, however, statistically different from a sensitivity of 59% (32–82) for low-quality MRI (P=0.26). This raises the question whether the resolution of the images is the only problem of test sensitivity, or it may be depiction of tumor-extension by gadolinium contrast enhancement is not an ideal marker for optic nerve invasion, i.e., tumor invasion does not always show contrast enhancement. Contrast enhancement also is not 100% specific for tumor invasion, with reactive inflammation being the main cause of false-positive findings.\(^{30}\)
On the other hand – emphasizing the importance of high-resolution imaging – Brisse et al.\textsuperscript{7} showed that false-positive and false-negative findings were often borderline cases. Before the tumor invades the optic nerve beyond the lamina cribrosa, it can cause bulging of the lamina resulting in contrast enhancement on MR images to reach beyond where the lamina cribrosa is expected to be producing a false positive. A false-negative result can be caused by minimal postlaminar invasion (only a few cells on histopathologic analysis; figure 3F), which is still without the tumor neovascularization that causes the typical contrast enhancement visible on MR images.

Figure 3. A contrast-enhanced fat-suppressed axial T1 weighted image (A) shows a heterogeneously enhancing tumor and enhancement of the iris (arrows), indicative of neoangiogenesis in the iris. A dislocated lens depicted on a T2 weighted image (arrow in B). This contrast-enhanced axial fat-suppressed T1 weighted image (C) shows focal enhancement in the distal optic nerve (arrow) suggestive of postlaminar optic nerve invasion and a sagittal subtraction image (E) of a T1 weighted image with and without contrast enhancement shows dubious contrast enhancement of the distal optic nerve; the arrow indicates an area of enhancement that matches bulging of the lamina cribrosa on histologic examination and the arrowhead indicates dubious postlaminar optic nerve enhancement; histopathologically both patients had postlaminar invasion indicated by hyperchromatic cells posterior to the lamina cribrosa (D and F; arrowheads show the prelaminar tumor mass and the arrows point at postlaminar tumor cells). A coronal T2 weighted image (G) and a coronal reconstruction of axial VIBE (volumetric interpolated brain examination) images (H) show multifocal irregular thickening and enhancement of the choroid suspicious of choroidal invasion; massive choroidal invasion in the nasal part was confirmed (arrow on I, corresponding with arrows on G and H).
The only alternative to MR for the detection of optic nerve invasion is computed tomography (CT), but this appears to have a low diagnostic value.26

**Choroidal and scleral invasion**
Massive choroidal and scleral invasion are seen as risk factors for local retinoblastoma recurrence and distant metastases. According to Sastre et al., choroidal invasion of more than 3 mm or reaching the sclera should be classified as massive choroidal invasion. On T1-weighted contrast-enhanced MRI, choroidal invasion can be identified as a focal inhomogeneous enhancement and/or choroidal thickening. Figures 3G and H show an example of irregular thickening and abnormal enhancement of the choroid on MR images that correspond with massive choroidal invasion on histopathology (figure 3I). In case of scleral invasion, the contrast-enhanced area extends beyond the choroid into the normally unenhanced sclera. De Jong et al. (chapter 1) found a sensitivity of 74% (95% CI: 52–88) and a specificity 72% (31–94) for choroidal invasion and a sensitivity 88% (20–100), and a specificity 99% (86–100) for scleral invasion. Sensitivity and specificity were higher for higher-quality MRI, but these differences were not statistically significant. These numbers are in line with expectations, as choroidal invasion is visible as subtle changes on MRI, whereas scleral invasion is more manifest.

No studies evaluated the diagnostic accuracy of CT for the detection of choroidal invasion and only one study looked at scleral invasion, showing a reasonable sensitivity of 71% (42–92) and specificity of 98% (9–100) for the ability of CT to diagnose scleral invasion.

**Extraocular spread**
When the tumor passes through the ocular wall or into the postlaminar optic nerve, it can extend directly into the orbit or spread via the leptomeninges and cerebrospinal fluid. Appendix D shows an example of extensive invasion of the optic nerve that, because the parents refused any treatment, developed into a large intracranial mass within four months. As these lesions are large and therefore usually clearly visible on MR images, diagnostic accuracy of MRI of extrascleral growth in retinoblastoma patients is expected to be high.31 There only is one study with a small sample size presenting a sensitivity of 100% for MR imaging and one study showing a sensitivity of 100% for CT. According to three studies specificity of MR imaging ranged from 94%–100%.26

**POST-TREATMENT STATUS AND TREATMENT RESPONSE**
Post-treatment follow-up with MRI is a rapidly developing discipline and shows promising results providing additional information to fundoscopy and ultrasound. As mentioned in the introduction, there are a number of conservative treatment options for retinoblastoma. External beam radiotherapy is falling out of favor, because it causes orbital bone growth restrictions and cosmetic problems on the face. Furthermore it increases the risk of second
primary tumors within the radiation field later in life in hereditary retinoblastoma patients. Depending on tumor size, location, and shape, local treatment (laser therapy, cryotherapy, and radioactive plaque therapy), intra-arterial, intravitreal and peribulbar chemotherapy, and systemic chemotherapy are currently the conservative treatment options of choice. Appendix E shows a number of post-treatment findings on MRI. Appendix F shows the tumor response to chemotherapy over the course of a year. Choroidal ischemia is a known complication of intra-arterial chemotherapy, which can be seen on MRI as the lack of choroidal contrast enhancement. Figures 4A–C show the fundoscopic and fluorescent angiography and MRI findings of a patient with treatment-induced choroidal ischemia. Over the course of 6 months, this patient underwent multiple melphalan and topotecan injections. Perfusion and diffusion MRI – still under development as an application for retinoblastoma – have shown promising initial results in terms of follow-up for the differentiation between viable and necrotic tumor tissue.

**DISCUSSION**

There are different approaches to generate high-quality MR images of eyes: with a 1.5T system and a surface coil or, as in this study, with a 3T system and a 32-channel head coil. The advantage of 1.5T imaging is that these systems are more readily available. On the other hand, positioning of a head coil is less cumbersome than positioning a surface coil. Head coils also generate better images of deeper structures, including the entire brain. At the time of retinoblastoma diagnosis, MRI of the brain is recommended to exclude trilateral retinoblastoma (ocular retinoblastoma combined with an intracranial midline primitive neuroectodermal tumor).

The cases included in this article were specifically selected to show certain aspects of retinoblastoma. This approach carries the risk of introducing selection bias and potentially overestimating the diagnostic value of MRI (e.g., imaging of vitreal and subretinal seeds remains difficult, even though we were able to show successful examples). Also, the included patients are from a highly specialized center; therefore, most of these patients have more advanced retinoblastoma.

Before the introduction of intra-arterial chemotherapy, patients with retinoblastoma and the presence of metastatic risk factors such as massive choroidal invasion or postlaminar optic nerve invasion would have underwent enucleation with systemic chemotherapy after after histopathologic proof of the Figure 4. This axial VIBE (volumetric interpolated brain examination) image (A) shows a broad area of reduced enhancement of the choroid (arrows) corresponding with temporal choroidal ischemia clearly visible on fundoscopy (B) and fluorescent angiography (C).
risk factor or have received systemic chemotherapy in the form of chemoreduction followed by local treatment. Systemic chemotherapy, then, might have successfully prevented systemic metastasis. Nowadays systemic chemotherapy, and its potential negative long-term effects, can be avoided in certain cases by using intra-arterial or intravitreal chemotherapy; however, this does require a reasonable certainty that there are no metastatic risk factors, adding to the importance of reliable non-invasive imaging like MRI.\textsuperscript{41}

To give an idea and provide a reference of the diagnostic accuracy of conventional MRI, we have reported diagnostic accuracy estimates when available. Nevertheless, with these limitations in mind, MRI becomes increasingly important with increasing eye-saving treatment, and we believe that high-resolution MRI can contribute to better clinical decision making.

CT may also be used for the diagnosis, staging, and follow-up of retinoblastoma, but even though evidence for the use CT is scarce, available evidence does suggest that MRI is superior to CT for almost all previously described applications, most importantly the metastatic risk factors.\textsuperscript{26} Even for the calcifications, CT has no added value as ultrasound in combination with MRI accurately detects calcifications.\textsuperscript{13} Most important though, CT should be avoided because of the potential harmful effect of radiation in small children, especially those with hereditary retinoblastoma.\textsuperscript{32,42,43} A disadvantage of MRI is that it might not be accessible in developing countries; therefore, we believe that only when MRI is not available, CT should be considered as an alternative method for imaging.

**CONCLUSION**

We have provided an overview of the clinical application of retinoblastoma imaging with MRI. Magnetic resonance imaging at its current technological state can be of great help in retinoblastoma patient care. Since more and more eye-saving treatment options have entered clinical practice, other indications for MRI in retinoblastoma patients have emerged, such as imaging during conservative treatment: e.g., for the detection of tumor response, tumor recurrence, and adverse effects of treatment. Unfortunately MRI does not have perfect diagnostic accuracy for the detection of metastatic risk factors like massive choroidal and postlaminar optic nerve invasion, but it currently is the best available tool, and its performance is constantly improving.

**METHOD OF LITERATURE SEARCH**

We searched the literature in PubMed (Medline) for English, Dutch or German full-text articles published through 2014. Alternatively found articles (e.g., through checking reference lists of retrieved articles, including from De Jong et al.\textsuperscript{26}) were also considered. No articles were translated and we discarded articles in any other language even if they were accompanied by an English abstract. The search strategy included MeSH terms and Text Words to retrieve articles on retinoblastoma, optic nerve invasion, choroidal invasion, scleral invasion, metastasis, magnetic resonance imaging, computed tomography, diagnosis, staging, and follow-up.
REFERENCES


3T high-resolution MRI for retinoblastoma