MR imaging of uveal melanoma and orbit

Guerreiro Gonçalves Ferreira, T.A.

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Summary, discussion, future perspectives and conclusion

This thesis describes the development of dedicated high-resolution MRI protocols for evaluation of the eye and of the eyelid and their application in the characterization of uveal melanoma and of the eyelid anatomy. Furthermore, it focuses on the characterization of orbital inflammation on MRI and CT, its differentiation from orbital tumors and infection, and how to distinguish the most common orbital inflammatory diseases.

It is the result of almost a decade of close work between myself, as a radiologist, a physicist, radiology technicians, ophthalmologists, pathologists, other radiologists, radiation oncologists, clinical scientists from Philips and other PhD students from different disciplines.

Solving clinical problems lies at the heart of the research described in this thesis, therefore this research improved the diagnosis and treatment of specific disease entities, with a clear benefit for the patient. This can only be done properly within a multidisciplinary team, as we have. Hippocrates:

"The health and well-being of my patient will be my first consideration".
In: last revision of the Declaration of Geneva (2017) (World Medical Association).

Radiology is continuously evolving and improving. It involves image interpretation, but also the improvement of image quality and the development of new techniques and for the latter, radiologists need the help of physicists and of radiology technicians. In our research group, a physicist together with a radiology technician developed the high-resolution MR images, in collaboration with the radiologist, but tailored to the clinical needs understood during the close work between the different medical specialties. The different input from the different medical specialties, complementing each other, is of utmost importance.

5.1 UVEAL MELANOMA

Eye MRI protocol

Despite the challenges of susceptibility artefacts and eye motion when imaging the eye with MR, good quality multiparametric MR images of the eye and UM can be obtained.

In **chapter 2.1** an *eye 3T MRI protocol* was developed. First, several different sequences were performed in 9 uveal melanoma patients, at 3T using an eye-coil. These sequences included multi-slice (MS) sequences with 1 and 2 mm, 3D turbo spin-echo (TSE) sequences with 0.8 and 1 mm, 3D turbo field-echo (TFE) sequences with 0.8 mm, non-EPI TSE DWI with 2.4 mm and b values of 0, 400 and 800 s/mm^2 and apparent diffusion coefficient (ADC), and a dynamic contrast enhanced (DCE) sequence with 1.5 mm and a temporal resolution of 2 sec. In-plane images were evaluated for general image quality, contrast, identification of the sclera and tumor limits and differentiating the tumor from retinal detachment. The isotropic sequences were evaluated regarding geometrical accuracy and identification of the sclera. The DWI sequences were evaluated in terms of signal-to-noise ratio (SNR), distortion and contrast resolution. The quality of the DCE curves was assessed, in particular with respect to eye motion and consequent misregistration artefacts. After evaluation of all these sequences a dedicated eye MRI protocol was designed. This clinical protocol consisted of MS 2 mm 2D sequences (T1, T1 with fat signal saturation after contrast and T2) and a non-EPI TSE DWI (b values of 0 and 800 s/mm^2) and ADC, acquired perpendicular to the main axis of the tumor. It also included isotropic 3D TSE sequences (T1, T1 with fat signal saturation before and after contrast and T2) and a DCE sequence, acquired on the axial plane non-angulated. The MS 2 mm 2D sequences have the highest in-plane resolution and are therefore the best for lesion characterization and local extension evaluation. The isotropic 3D TSE sequences allow retrospective reformatting in all directions and 3D reconstructions, and are essential to assess tumor geometry and accurate size measurements. The DWI and PWI sequences aid in the differential diagnosis, and potentially, provide prognostic information, predict treatment response and permit earlier assessment of tumor response to radiotherapy than US. Overall, this dedicated eye 3T MRI protocol provides high resolution MR-images of UM, crucial to improve its diagnosis, treatment planning and follow-up, and moreover it can also be used for other ocular lesions.

Before starting evaluating UM at 3T, we assessed them at 7T MRI because of its high-field strength, for which we had also developed an *eye 7T MRI protocol*. Our research group prospectively compared the diagnostic performance of 7T and 3T to evaluate the eye and UM. On one hand, with 7T the highest quality images could be obtained under optimal conditions. On the other hand, severe artefacts making an exam undiagnostic are more common (2D sequences of diagnostic quality on 69% on 7T, compared to 99% on 3T). On average, 2D MS

sequences image quality was better on 3T compared to 7T, and 3D SE sequences image quality and measuring tumor dimensions, were comparable between 3T and 7T [1].

Furthermore, our research group developed, both for 3 and 7 T, an *eye silicon oil MRI protocol* as an extension of the eye MRI protocol. This protocol corrects for the strong off-resonance effects caused by the silicon oil (SiOil) tamponade in patients after vitrectomy. Since the presence of intraocular SiOil prevents US imaging, these patients would generally be enucleated, as diagnosis, treatment planning and subsequent follow-up would be impossible. This dedicated protocol made possible for some patients with UM in eyes with silicon oil to save their eye and vision [2].

Finally, our research group developed, together with the HollandPTC, an *eye pre-proton beam therapy 3T MRI protocol*, for accurate measurement of the clip-tumor distances. In ocular proton beam therapy, 2.5 mm tantalum clips are surgically sutured near the UM border for clinical target volume marking. Conventionally, the clip-tumor distances are assessed peroperatively using transillumination, indentation and/or fundoscopy. The protocol developed permits the assessment of the clip-tumor distances with MRI and our research group retrospectively evaluated it on 23 UM patients. Moreover, the eye biometry was evaluated with MRI and compared with conventional ophthalmic measurements. MRI turned out to be less accurate on the evaluation of the clip-tumor distances in case of flat UM, because the limits of these tumors are more difficult to determine on MRI. However, MRI was more reliable on the evaluation of the eye length, and on measuring the clip-tumor distances of anterior located and mushroom shaped tumors. MR imaging of these patients will result in more accurate target definition, thereby possibly reducing toxicity and improving probability to retain vision [3]. Although we were the first center to include an MRI for all ocular proton therapy patients, more centers are now including MRI in their workflow and using protocols which are based on ours [4].

MR imaging characteristics of uveal melanoma

In **chapter 2.2** the MR imaging anatomical and functional characteristics of 42 uveal melanomas were assessed, MR features were compared with fundoscopy and ultrasound, and on 14 enucleated cases with histopathology.

UM with complex tumor-shapes, such as a mushroom configuration, should be recognized because they would benefit from special attention at the radiotherapy planning. This study showed the importance of the multiplanar reconstructions for its recognition and was consistent with the known fact that the mushroom configuration of a UM is associated with breaks in Bruch's membrane. Tumor pigmentation is important in the differential diagnosis with other intraocular masses and it may have prognostic significance [5], although the latter warrants further analysis [6]. A significant relationship between the signal intensity on T1

and pigmentation on histopathology was found (p=0.024). T1-hyperintense UM were always moderately or strongly pigmented on histopathology, while T1-hypointense UM were either pigmented or non-pigmented. This is valuable because the assessment of tumor pigmentation with fundoscopy is not representative in the case of heterogeneous UM and it may be difficult in case of retinal detachment. The ADC of the UM was $1.16 \pm 0.26 \times 10^{-3}$ mm^2/s. Two-thirds of the UM had a wash-out and the remaining a plateau perfusion time-intensity curve (TIC) and the mean peak intensity of UM was 1.62. An increase of tumor ADC correlated with a plateau TIC (p=0.011). Both the presence of monosomy 3 and of extracellular matrix patterns "loops" are important determinants of poor prognosis and they frequently coexist. The study from Kamrava et al. found a significant correlation between monosomy 3 and perfusion values such as higher k^{trans} and v_e [7]. Interestingly, in our study, it seems that UM with loops also tend to have different perfusion values than UM without loops, such as a shorter time to peak and a bigger peak intensity, consistent with the fact that extracellular matrix patterns are pseudovascular channels. Knowing the ADC and perfusion characteristics is valuable for the differential diagnosis with other intraocular masses. Furthermore, PWI looks promising on the identification of UM at higher risk of metastasis, which could serve as a substitute for histopathology in patients that undergo an eye-sparing treatment, but needs further investigation.

Assessment of tumor size is essential for the choice of treatment modality and planning of radiotherapy. MRI was limited in evaluating the basal diameter of flat tumors with a tendency to underestimate the size due to unclear tumor margins. In comparison to MR, US tends to overestimate tumor size, showing larger tumor prominence (0.5mm larger, p=0.008) and largest basal diameter (1.4mm larger, p<0.001). An increase of tumor prominence was associated with lower ADC values (p=0.030) and favored a wash-out TIC (p=0.028).

The local extension of a UM should be assessed so that it can be taken into account in the treatment plan. Moreover, the presence of extraocular growth and of optic nerve invasion is associated with an increased rate of orbital recurrence and poorer prognosis. MRI was good in diagnosing ciliary body involvement, extrascleral extension and optic nerve invasion, but contrarily to what has been previously reported, limited on identifying scleral invasion.

MR imaging follow-up of UM after brachytherapy and proton beam therapy

Foti et al showed that in UM treated with proton-beam therapy, ADC variations precede volume changes, and early change in ADC value 1 month after therapy significantly correlated with tumor regression [8]. The value of DWI and PWI in the follow-up of UM after both brachytherapy and proton-beam therapy needs to be further evaluated, which our research group is currently doing. As preliminary results, PWI especially showed favorable changes before volume changes, enabling an earlier assessment of UM response to radiotherapy than US. This is reassuring both for the clinicians and for the patients.

Clinical value and impact of MR imaging of UM

MRI enabled high quality images of the globe and UM. It is however more expensive than US and it seemed relevant to assess whether MRI would have an added economic value for UM treatment. Our research group therefore retrospectively evaluated on 60 patients whether the extra cost of an MRI generated economic benefit or change in optimal treatment. Tumor measurements are more accurate with MRI than with US and they are critical for the choice of treatment modality. Smaller tumors can be eligible for brachytherapy, while larger tumors will undergo more expensive treatments such as enucleation or proton beam therapy. Our study showed that, if only the costs of treatment are considered, an additional MRI is cost-effective for patients where there is doubt on the accuracy of US measurements, if the tumor appears to be slightly too large for brachytherapy, and in UM patients who cannot be evaluated with US and would otherwise undergo enucleation. In 10% of patients with intermediate tumor size MRI indicated a smaller tumor prominence than US, resulting in a change from PBT or enucleation to brachytherapy. This decreases the costs by €24,000, while the costs of MRI are €200-1000. Moreover, MRI adds value in terms of quality of care, as it enables for some patients to be afforded a treatment modality that spares more of their vision, the annual total economic burden of severe vision impairment associated with eye removal being €10.000 [9,3].

The LUMC is the National Reference Center for UM in The Netherlands, receiving approximately 220 UM per year [10]. The evaluation of UM with MRI brought several advantages and has changed clinical practice in our hospital. Before our research rarely a UM patient would receive an MRI before treatment. Nowadays we perform MRI in several circumstances. Firstly, whenever the ophthalmologist cannot evaluate an ocular mass, because something is obscuring the view on fundoscopy or US, either blood opacifying the ocular media or the presence of silicon oil. Secondly, whenever there is doubt about the diagnosis of UM. Thirdly, when there is doubt about measurements or local extension, as MRI is more accurate than US, in order to choose the best treatment. Fourthly, before PBT, pre-clips positioning mainly for accurate tumor and eye dimensions, post-clips placement for determination of the clip-tumor distances. Fifthly, in the early follow-up after brachytherapy and PBT in order to assess response to treatment, and we are currently evaluating the best time-point/indications. Sixthly, in the follow-up after enucleation, in particular when extra-scleral extension was known to be present. Finally, in the follow-up of UM after treatment whenever eye or orbital recurrence is suspected. On average we scan 3 to 4 UM per week. Overall MRI increased the precision of UM treatment.
Our eye 3T MRI protocol has also caught the interest of several other foreign centers, in Europe but also in the United States, and in collaboration with Philips, is now available online. Furthermore, our UM results will be part of the new edition of the WHO Classification of Tumours of the Eye Book.

Future perspectives

An important goal in ocular MR imaging in the near future is to further improve the differential diagnosis of ocular masses, where we expect MRI to have a pivotal role. We have evaluated the MR imaging characteristics of UM, the ones of retinoblastoma had already been assessed [11-16], but the MR imaging features of other common benign and malignant intraocular masses still need to be known and published, which we are currently investigating. Benign ocular lesions are expected to have higher ADCs [17] and mostly a progressive or plateau TIC at DCE, although functional evaluation of choroidal nevi can still be hampered by their very small size. In other intraocular malignant lesions, such as metastases and lymphomas, the main clues for the differential diagnosis are the lesion number, configuration and signal intensity. For example, in the study from Lemke et al. with 200 UM, no tumor had a flat-placoid shape [18], which is the predominant shape of ocular metastases.
Additionally, 3D MRI-based ocular proton therapy treatment planning, without the need for tantalum clips placement, is desirable, and our research group is currently working on this [19].
Finally, the promising value of PWI on the identification of UM at higher risk of metastasis, as noticed both in our study and in the study from Kamrava et al [7]., needs further investigation, as it could serve as a substitute for histopathology in patients that undergo an eye-sparing treatment. To this end, we have recently further improved quantification of PWI, by correcting for eye-motion and the confounding effect of tumor pigmentation [20].

5.2 ORBITAL INFLAMMATION

In **chapter 3.1** the CT and MR imaging characteristics of scleritis were retrospectively evaluated in 11 cases in which CT and/or MR imaging were performed during the active phase of the disease. The imaging findings of scleritis were scleral enhancement (100%) (may involve the whole sclera or be preferentially peripheral), scleral thickening (83%), and focal periscleral cellulitis (42%). MR imaging is the most useful examination in the diagnosis of scleritis, differentiating the sclera from the other ocular layers, but scleritis could also be accurately diagnosed on CT. Scleritis is almost invariably of inflammatory etiology – idiopathic, in the spectrum of idiopathic orbital inflammation (IOI), or in the context of a systemic disease. Infectious scleritis is rare. Scleritis can occur isolated or in association with other orbital abnormalities. It is important not to misdiagnose it for a tumor. Clues to the inflammatory (versus neoplastic) nature of the process include the presence of pain, cellulitis and the specific sclera location.

In **chapter 3.2** a literature review was carried out regarding the imaging protocols and characteristics of orbital inflammation. MR imaging is the modality of choice for the

evaluation of orbital inflammation because of its superior soft tissue contrast and spatial resolution, as well as its ability to generate functional images such as diffusion and perfusion weighted imaging, crucial for distinguishing benign from malignant lesions. The specific radiological characteristics of inflammation affecting the various orbital structures, such as of scleritis, uveitis, dacryoadenitis, optic perineuritis and optic neuritis, myositis and orbital cellulitis, were described. Furthermore, the imaging characteristics of specific inflammatory diseases, such as of IOI, sarcoidosis, thyroid-associated orbitopathy (*Graves* Disease), Immunoglobulin G4-related Disease (IgG4 RD), granulomatosis with polyangiitis (*Wegener* granulomatosis), idiopathic sclerosing orbital inflammation (ISOI) and *Erdheim-Chester* disease were presented. Finally, different imaging and clinical clues were combined in a decision tree, that will allow one to recognize an orbital solid enhancing lesion as inflammatory, and not as infection or tumor. Subsequently, we have shown that the orbital radiological pattern found can point to an underlying inflammatory disease or at least shorten its differential diagnosis. Overall, these considerations enable the treating physician to establish an adequate treatment and at times a biopsy can be avoided.

Clinical value and impact of MR imaging of orbital inflammation

Before this research into orbital inflammation, MRI was already the exam of choice both for orbital inflammation and for an orbital tumor, and the MRI protocol in LUMC already included DWI. But it did not include PWI, and at that time, we decided to add PWI to our orbit protocol. These studies, together with the experience gained with the use of PWI, gave us much more confidence to make the differentiation between the infectious, inflammatory and malignant nature of an orbital lesion. That changed clinical practice in our hospital. Since then, whenever the MRI characteristics of an orbital lesion are suggestive of inflammation, the clinical symptoms and laboratory results are consistent and if the lesion is not of easy access with biopsy, the ophthalmologists in LUMC will consider to start medical treatment without histopathological confirmation. This is less invasive for the patient and less costly.

Future perspectives

In differentiating a benign from a malignant orbital mass, the contribution of the DWI (ADC and IVIM) has been recently further investigated in a quantitative way [21,22], and so has the value of DCE [23-25]. However, the specific diffusion and perfusion characteristics of the different orbital tumors and orbital inflammation should still be a focus of attention, which will further help in the differential diagnosis of orbital masses.

5.3 EYELID

In **chapter 4.1** a retrospective evaluation of the normal eyelid anatomy, in terms of identification of the eyelid layers, on MRI and CT was performed, in 38 normal eyelids. Furthermore, tumor extension was assessed in three eyelid tumors and validated with histopathology. Despite the small size of the various components of eyelid anatomy and although imaging the eyelid is challenging due to susceptibility and motion artifacts, the identification of most of the eyelid structures is possible with an optimized MRI protocol, including the use of a surface coil, and to a lesser extent with CT. Axial planes should be chosen over sagittal planes to identify the tarsal plates, with the superior tarsal plate being more readily recognizable due to its larger size. The superior and inferior orbital septa were easier to identify on the sagittal plane on MRI, while on CT their identification was easier on the axial plane. Both on MRI and CT the inferior septum is more difficult to see than the superior septum. MRI is the modality of choice to evaluate the extension of an eyelid tumor due to the high resolution and with diffusion and perfusion weighted imaging helping to differentiate between the malignant tumor and potentially surrounding inflammation. A surface coil is optimal for the evaluation of tumor extension in the eyelid, but also for the invasion of adjacent structures by an eyelid tumor. CT should mainly be used as a complementary technique in the evaluation of bone invasion. The application of the image eyelid anatomy knowledge on the evaluation of eyelid tumors extension was limited, since only 3 patients were evaluated, and because an accurate correlation between imaging and pathology is not possible and therefore pathology cannot always act as the gold standard for the evaluation of the MRI findings. As the assessment of tumor invasion of the tarsal plate and orbital septum is not always possible through physical examination, imaging can contribute significantly to the T-staging of eyelid tumors, improving treatment planning and therefore will have a positive impact on both patients' short-term morbidity and longtime outcome.

Clinical value and impact of MR imaging of the eyelid

This research in the eyelid also changed clinical practice in LUMC. Previous to this research, an MRI was only made to check whether an eyelid tumor was invading the orbit. This study allowed a better understanding of the potential role of MRI in the evaluation of an eyelid lesion. In particular, we now know that most eyelid layers are visible on MRI, making the evaluation of the local extension of an eyelid tumor in the eyelid possible, which was previously impossible. It also made it possible to evaluate orbital invasion with more confidence. As a consequence, we more regularly perform MRI for evaluation of an eyelid tumor, to define its extension and sometimes for the diagnosis. Regarding the diagnosis, at the moment, the role of MRI is mainly to differentiate a benign from a malignant tumor, and only in a few cases being able to make the specific diagnosis.

Our MR images of the eyelid also caught the attention of foreign centers, with current interest in including them in the new edition of the WHO Classification of Tumours of the Eye book.

Future perspectives

The accuracy of MRI to evaluate the local extension of an eyelid tumor should be further assessed in a large group of eyelid tumors.
Finally, a good characterization with MRI of the most common benign and malignant eyelid tumors seems also important, as occasionally, mainly in children, the diagnosis of an eyelid mass is the main question for the MRI.

CONCLUSION

The work described in this thesis opened new perspectives in the diagnosis of several ophthalmologic pathologies, allowing for better treatment results and therefore contributing for the patient's well-being. Moreover, together with the previous MR works on retinoblastoma [12], it made a step in the history of ophthalmologic imaging, as it brought MR-imaging of the eye and of the eyelid to the same level as the rest of the body.
The increasing number of requests of ocular and eyelid MRI scans urge further subspecialization within neuroradiologists, as specific knowledge is required, also regarding ophthalmic imaging techniques, with close work with the ophthalmologists and related specialisms being warranted. Furthermore, it is important to further better combine the information radiologists get from MRI with the information the ophthalmologists get from the optical imaging techniques, in particular with fundoscopy and fluorescein angiography.
It is my wish to continue to deepen our knowledge of eye, eyelid and orbital imaging. The current MR images of the orbital segments of the optic nerves are suboptimal and could be focus of improvement, perhaps by extending our eyelid 3T MRI protocol. This protocol uses two surface coils which provide a better SNR posterior to the globe. However, similar to our eye 3T MRI protocol special attention will be needed for the eye movement artefacts. The eyelid 3T MRI protocol should subsequently be compared with our current orbit 3T MRI protocol, to check for added value in terms of SNR, but also to evaluate whether sufficient resolution is achieved at the level of the cavernous sinuses. An improved MRI protocol, together with further knowledge of specific diffusion and perfusion characteristics of the different orbital tumors and orbital inflammation, would further help in the differential diagnosis of orbital masses.
It is also my wish to continue to disseminate our knowledge, so that worldwide other centers can improve their clinical practice in this area. Ideally, international workgroups could be created to improve imaging protocols and develop best practices regarding the diagnosis of different ophthalmologic areas and diseases.

REFERENCES

1. Tang MCY, Jaarsma-Coes MG, Ferreira TA, Fonk LZ-G, Marinkovic M, Luyten GPM, Beenakker J-WM. A comparison of 3T and 7T MRI for the clinical evaluation of uveal melanoma. J Magn Reson Imaging. 2022 May;55(5):1504-1515.
2. Jaarsma-Coes MG, Ferreira TAG, van Haren GR, Marinkovic M, Beenakker J-WM. MRI enables accurate diagnosis and follow-up in uveal melanoma patients after vitrectomy. Melanoma Res. 2019 Dec;29(6):655-659.
3. Jaarsma-Coes MG, Ferreira TA, Marinkovic M, Vu THK, van Vucht L, van Haren GR, Rodrigues MF, Klaver YLB, Verbist BM, Luyten GPM, Rasch CRN, Beenakker J-WM. Comparison of magnetic resonance imaging-based and conventional measurements for proton beam therapy of uveal melanoma. Ophthalmol Retina. 2022 Jul 13;S2468-6530(22)00339-6.
4. OPTIC workgroup meeting, PTCOG, Miami, 2022.
5. Lemke AJ, Hosten N, Bornfeld N, Bechrakis NE, Schüler A, Richter M, Stroszczynski C, Felix R. Uveal melanoma: correlation of histopathologic and radiologic findings by using thin-section MR imaging with a surface coil. Radiology 1999 Mar;210(3):775-783.
6. Berus T, Halon A, Markiewicz A, Orlowska-Heitzman J, Romanowska-Dixon B, Donizy P. Clinical, histopathological and cytogenetic prognosticators in uveal melanoma – a comprehensive review. Anticancer Res. 2017 Dec;37(12):6541-6549.
7. Kamrava M, Sepahdari AR, Leu K, Wang P-C, Roberts K, Demanes DJ, McCannel T, Elligson BM. Quantitative multiparametric MRI in uveal melanoma: increased tumor permeability may predict monosomy 3. Neuroradiology. 2015 Aug;57(8):833–840.
8. Foti PV, Longo A, Reibaldi M, Russo A, Privitera G, Spatola C, Raffaele L, Salamone V, Farina R, Palmucci S, Musumeci A, Caltabiano R, Ragusa M, Mariotti C, Avitabile T, Milone P, Ettorre GC. Uveal melanoma: quantitative evaluation of diffusion-weighted MR imaging in the response assessment after proton-beam therapy, long-term follow-up. Radiol Med. 2017 Feb;122(2):131–139.
9. Fonk LG, Ferreira TA, Webb AG, Luyten GPM, Beenakker J-WM. The economic value of MR-imaging for uveal melanoma. Clin Ophthalmol. 2020 Apr 28;14:1135–1143.
10. Integraal Kankercentrum Nederland (IKNL).
11. de Graaf P, Barkhof F, Moll AC, Imhof SM, Knol DL, van der Valk P, Castelijns JA. Retinoblastoma: MR imaging parameters in detection of tumor extent. Radiology. 2005 Apr;235(1):197-207.
12. de Graaf P, Göricke S, Rodjan F, Galluzzi P, Maeder P, Castelijns JA, Brisse HJ, European Retinoblastoma Imaging Collaboration (ERIC). Guidelines for imaging retinoblastoma: imaging principles and MRI standardization. Pediatr Radiol. 2012 Jan;42(1):2-14.
13. de Graaf P, Pouwels PJW, Rodjan F, Moll AC, Imhof SM, Knol DL, Sanchez E, van der Valk P, Castelijns JA. Single-shot turbo spin-echo diffusion-weighted imaging for retinoblastoma: initial experience. Am J Neuroradiol. 2012 Jan;33(1):110-118.
14. Rodjan F, de Graaf P, van der Valk P, Moll AC, Kuijer JPA, Knol DL, Castelijns JA, Pouwels PJW. Retinoblastoma: value of dynamic contrast-enhanced MR imaging and correlation with tumor angiogenesis. AJNR Am J Neuroradiol. 2012 Dec;33(11):2129-2135.

15. Brisse HJ, de Graaf P, Galluzzi P, Cosker K, Maeder P, Göricke S, Rodjan F, de Jong MC, Savignoni A, Aerts I, Desjardins L, Moll AC, Hadjistilianou T, Toti P, van der Valk P, Castelijns JA, Sastre-Garau X, European Retinoblastoma Imaging Collaboration (ERIC). Assessment of early-stage optic nerve invasion in retinoblastoma using high-resolution 1.5 Tesla MRI with surface coils: a multicentre, prospective accuracy study with histopathological correlation. Eur Radiol. 2015 May;25(5):1443-1452.

16. de Jong MC, de Graaf P, Brisse HJ, Galluzzi P, Göricke SL, Moll AC, Munier FL, Popovic MB, Moulin AP, Binaghi S, Castelijns JA, Maeder P, European Retinoblastoma Imaging Collaboration (ERIC). The potential of 3T high-resolution magnetic resonance imaging for diagnosis, staging, and follow-up of retinoblastoma. Surv Ophthalmol. 2015 Jul-Aug;60(4):346-355.

17. Sepahdari AR, Politi LS, Aakalu VK, Kim HJ, Razek AAKA. Diffusion-weighted imaging of orbital masses: multi-institutional data support a 2-ADC threshold model to categorize lesions as benign, malignant, or indeterminate. Am J Neuroradiol. 2014 Jan;35(1):170-175.

18. Lemke AJ, Hosten N, Wiegel T, Prinz RD, Richter M, Bechrakis NE, Foerster PI, Felix R. Intraocular metastases: differential diagnosis from uveal melanomas with high-resolution MRI using a surface coil. Eur Radiol. 2001;11(12):2593–2601.

19. Fleury E, Trnková P, Erdal E, Hassan M, Stoel B, Jaarsma-Coes M, Luyten G, Herault J, Webb A, Beenakker J-W, Pignol J-P, Hoogeman M. Three-dimensional MRI-based treatment planning approach for non-invasive ocular proton therapy. Med Phys. 2021 Mar;48(3):1315-1326.

20. Jaarsma-Coes MG, Ferreira TA, van Houdt PJ, van der Heide UA, Luyten GPM, Beenakker J-WM. Eye-specific quantitative dynamic contrast-enhanced MRI analysis for patients with intraocular masses. MAGMA. 2022 Apr;35(2):311-323.

21. Hiwatashi A, Togao O, Yamashita K, Kikuchi K, Kamei R, Yoshikawa H, Takemura A, Honda H. Diffusivity of intraorbital lymphoma vs inflammation: comparison of single shot turbo spin echo and multishot echo planar imaging techniques. Eur Radiol. 2018 Jan;28(1):325-330.

22. Lecler A, Duron L, Zmuda M, Zuber K, Bergès O, Putterman M, Savatovsky J, Fournier L. Intravoxel incoherent motion (IVIM) 3T MRI for orbital lesion characterization. Eur Radiol. 2021 Jan;31(1):14-23.

23. Sun B, Song L, Wang X, Li J, Xian J, Wang F, Tan P. Lymphoma and inflammation in the orbit: diagnostic performance with diffusion-weighted imaging and dynamic contrast-enhanced MRI. J Magn Reson Imaging. 2017 May;45(5):1438-1445.

24. Xu X-Q, Hu H, Liu H, Wu J-F, Cao P, Shi H-B, Wu F-Y. Benign and malignant orbital lymphoproliferative disorders: differentiating using multiparametric MRI at 3.0T. J Magn Reson Imaging. 2017 Jan;45(1):167-176.

25. Hu H, Xu X-Q, Liu H, Hong X-N, Shi H-B, Wu F-Y. Orbital benign and malignant lymphoproliferative disorders: differentiation using semi-quantitative and quantitative analysis of dynamic contrast-enhanced magnetic resonance imaging. Eur J Radiol. 2017 Mar;88:88-94.