MR imaging of uveal melanoma and orbit

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Introduction, aims and outline of the thesis

1.1 HISTORY OF OCULAR IMAGING

While the eyelid and anterior part of the eye are easily accessible to physical examination, the inside and posterior part of the eye, as well as the retrobulbar structures are inaccessible to clinical observation.
In 1847, Charles Babbage, an English mathematician, developed an instrument thought to resemble an ophthalmoscope, but it was in 1851 that the ophthalmoscope was invented by Hermann von Helmholtz, a German physician and physicist. This revolutionized the field of ophthalmology, as it made feasible the examination of the inside of the eye. Intraocular masses, the retina and retinal vessels, and the optic disc could then be evaluated. The possibility of visualizing the retinal vasculature is unique in the human body, and has the advantage that it can reveal impending systemic or cerebrovascular disease [1,2]. Likewise, the retina and optic disc are the only portions of the central nervous system we can observe noninvasively.
In 1895, Wilhelm Conrad Roentgen, a German mechanical engineer and physicist, invented X-ray roentgenography, which was grasped immediately by the medical community. However, the first real uses of X-ray by the ophthalmic community were only in 1912 [3].
In 1956, Ian Donald, an English obstetrician, together with engineer Tom Brown, invented ultrasound (US), and in that same year the first application of diagnostic ultrasound in the eye was reported [4].
In 1971 magnetic resonance imaging (MRI) was invented by an American chemist, Paul Lauterbur. A year later, in 1972 computer tomography (CT) was invented by Godfrey Hounsfield, an English engineer, and by Allan Cormack, a South Africa-born physicist working in Massachusetts. Ophthalmologists soon got interested in CT and MRI, with the first articles where CT and MR images of the orbit were published in 1977 [5] and 1983 [6], respectively.
Since the development of US, CT and MRI, improvements in these techniques have led to important progress in ophthalmologic imaging [7,8].

1.2 PERSONAL BACKGROUND

Before the start of this research project, CT and MRI were already widely used to evaluate the orbit, CT being the first line in trauma and infection, MRI being preferred for orbital masses. However, the MRI protocol consisted only of anatomical T1 and T2 weighted images (WI), and often no distinction between the benign or malignant etiology of an orbital lesion was possible.
Concerning ocular masses, in a way ophthalmologists have been ahead compared with other disciplines, being able to assess them well with optical techniques and ultrasound,

and therefore for a long time they did not need more complicated, and non-optimized MRI. However, before we started our research, retinoblastomas were already being assessed with MRI, with high-resolution images obtained with a child under general anesthesia or sedated [9]. But in an awake patient, besides the magnetic susceptibility effects at the air-bone interface, eye motion is also a challenge [10], and before this current research project, due to non-optimized protocols, uveal melanoma was seldom evaluated with MRI. Similarly, no optimized protocol to evaluate the eyelid was available, and as a result MRI was rarely performed to characterize eyelid lesions.

In 2008 I was invited by Alexandra Borges to give a lecture about MRI of the orbit and eye on the Erasmus Course on Magnetic Resonance Imaging which was held in Lisbon. There began my passion for the orbit. I started collating orbital pathology. I kept participating in several Congresses and Courses giving lectures about the orbit and the eye, mainly concerning MRI. All this triggered my interest in the field of orbital research. And agreeing with Juan M. Taveras, a Dominican neuroradiologist, who could be considered the father of neuroradiology:

> *"We have a responsibility not only to get the best results in a given case but also to advance the field, and this requires continuing research".*
> *In: Taveras J. M.: International neuroradiology symposium on preoperative embolization. AJNR. 7 (1986) 926.*

1.3 AIMS AND OUTLINE OF THE THESIS

The main aims of the research described in this thesis are first, to implement MRI as a diagnostic imaging technique in uveal melanoma (UM), by developing a dedicated eye MRI protocol and extensively evaluating the MR imaging characteristics of UM. Second, to improve the diagnosis and differential diagnosis on imaging of orbital inflammation. Finally, to further develop the dedicated eye MRI protocol into a protocol dedicated for the eyelid and assess whether the different eyelid layers are possibly to identify on MRI (as well as CT), in order to improve the evaluation of the local extension of an eyelid tumor. This thesis is therefore divided in three different parts: the first part regards uveal melanoma, the second part orbital inflammation, and the third part the eyelid.

1.4 UVEAL MELANOMA

The first part of this thesis concerns uveal melanoma, the most common primary malignant ocular tumor in adults [11-14]. In the past, enucleation was the main treatment, but over the last decades various eye- and vision-saving treatments have become available, including

episcleral brachytherapy, proton beam radiotherapy and stereotactic radiotherapy [12,13]. Despite the significant progress in the management of uveal melanoma its prognosis has only slightly improved, 20% of patients dying of metastatic disease within 10 years [15].
The ideal imaging technique for the evaluation of UM needs firstly to aid to differentiate UM from other intra-ocular lesions. Secondly, it needs to be capable to accurately delineate the limits of the tumor and to measure them, since these are the main determinants for the choice of the type of treatment, and in case of radiotherapy for the radiotherapy planning. Thirdly, noninvasive markers that can predict treatment response and prognosis are needed [13,16] in order to adjust the frequency and type of screening according to whether the patient is at high or low risk of developing disseminated disease, and because even if a biopsy is performed, it may be not representative, due to UM being heterogeneous in terms of chromosomal aberrations [17,18]. Finally, it should be able to early assess tumor response to radiotherapy.
Ultrasound, ultrasound biomicroscopy, fundoscopy, fluorescein angiography, indocyanine green angiography and optical coherence tomography are the most frequently used techniques to evaluate UM for the diagnosis, pre-treatment planning, and follow-up after radiotherapy [13,14]. Based on these techniques, an ophthalmologist specialized in ocular oncology can make the diagnosis of UM in 95% of cases, and therefore the diagnosis of UM is generally not verified by cytological or histopathological examination, which is unique among cancers. However, diagnosis with these conventional ophthalmic imaging modalities is difficult in smaller uveal melanomas/melanocytic lesions, in atypical tumors, in lesions behind the iris and in case of opacification of the ocular media. Furthermore, US has limitations in pre-treatment planning of UM and during follow-up, only being able to evaluate dimensional changes of the lesion.

Another option for imaging the globe is magnetic resonance imaging, which has been challenging because of eye motion and/or magnetic susceptibility effects at the air-bone interface [10,19]. However, recent developments on MRI, have made it a promising diagnostic imaging modality in ophthalmology, due to its excellent soft tissue contrast and spatial resolution, as well as the possibility to generate 3D volumetric and functional images such as diffusion weighted-imaging (DWI) and perfusion weighted-imaging (PWI), and MR was increasingly being used to evaluate uveal melanoma. Clinical MR protocols were, however, not optimized for ocular masses and therefore lacked the quality for accurate assessments.

Jan-Willem Beenakker is a physicist specialized in ophthalmic MRI, who works both for the Ophthalmology and Radiology Departments in LUMC. He developed a new MRI-based method at the 7T MRI to quantitatively characterize the full three-dimensional retinal shape, which is useful for refractive surgery and will ultimately lead to the development of a new type of intra-ocular lens for cataract treatment [20]. This offered new ophthalmologic possibilities, such as for the characterization of UM with MRI [21]. As the LUMC is the National Reference

Center for UM in The Netherlands, it was logical to start evaluating UM with MRI. At this point, as a neuro and head and neck radiologist with a special interest in orbit and eye, I got involved, as suggested by Mark van Buchem, and started, together with Jan-Willem Beenakker and the ophthalmologists, to develop a dedicated eye MRI protocol to evaluate UM.

Technical/clinical developments in radiology are not easy. Back in 1975, the remarkable and inspiring Italian American neuroradiologist, Giovanni di Chiro stated:

> *"Only "innocent" practitioners, however, may delude themselves that the age of easy radiographic diagnosis has arrived".*
> *In: DI CHIRO G.: Of CAT and other beasts (editorial). AJR. 122 (1975) 659-61.*

And indeed, the creation of this dedicated UM MRI protocol would not be easy.

Our first developments of high-resolution ocular MRI were performed at 7 Tesla (7T) because its high-field strength enabled an increased signal-to-noise ratio (SNR) and spatial resolution without an increase in acquisition time. Furthermore, this research-orientated 7T MRI provided the platform needed to develop new acquisition strategies to resolve eye-specific challenges, such as eye-motion and an inhomogeneous magnetic field present in the orbit [21]. In a group of UM patients where there were doubts about the conventional US measurements, the 3D evaluation of the tumor with 7T MRI had a direct implication on the chosen therapy, enabling eye-preserving therapy in 2 of the 10 included patients [12]. This supported our idea that MRI would have an important role in the evaluation of UM. Also, from a diagnostic point of view, the additional information available via MRI, in terms of location, dimensions and local extension, was proving to be very useful for the ophthalmologists. As a result, an increasing number of UM patients started receiving an MR, either as part of their clinical care or in the context of scientific studies.

Despite our progressions at ocular MRI at 7T, with often beautiful high-resolution T1 and T2-WI achieved and being able to perform dynamic contrast-enhanced perfusion (DCE), severe artefacts were sometimes hindering the evaluation of tumor and sclera limits and we were not successful to perform clinically valuable DWI of the globe. Moreover, as a clinical neuro and head and neck radiologist, I thought we should translate these ocular techniques to 3 Tesla (3T) MRI, as it would make ocular MRI more accessible to regular clinical care. This was the beginning of my research in uveal melanoma resulting in this thesis. In **chapter 2.1**, using our experience on 7T, I developed a dedicated eye 3T MRI protocol for uveal melanoma, including both anatomical and functional scans. This protocol would be suitable to evaluate not only UM but also other ocular lesions.

Once having a dedicated eye MRI protocol for uveal melanoma, the MRI characteristics of UM needed to be evaluated, due to their importance at diagnosis, but also to their

clinical implications for treatment planning, and potentially being able to provide prognostic information. However, until then, the evaluation of the MR characteristics of UM had been scarce, with few original studies addressing it and with no full evaluation of UM characteristics with MRI performed, including diffusion and quantifiable perfusion parameters. As a result, the added value of MRI was not known in many centers, UM being frequently only evaluated with ultrasound. In **chapter 2.2** the MRI characteristics of UM were comprehensively assessed. This evaluation included not only anatomical parameters, such as the origin, configuration, signal intensities on T1- and T2-weighted images (WI), dimensions, local extension and presence of retinal detachment, but also functional parameters, such as the apparent diffusion coefficient (ADC) and quantifiable perfusion characteristics. Furthermore, the clinical parameters related to treatment and/or prognostication, such as tumor dimensions, pigmentation and involvement of nearby structures, were compared between MRI and conventional ophthalmic techniques, including fundoscopy and US. These findings were validated with histopathology when available. Finally, attention was given to potential MRI prognostic markers, which would help to identify high-risk UM.

1.5 ORBITAL INFLAMMATION

The second part of this thesis regards orbital inflammation. Scleritis is an inflammation or infection of the sclera. It is a rare, often treatable vision-threatening condition. Correctly diagnosing scleritis is important given the potential for complications, the frequent association with systemic disease, of which scleritis might be the presenting manifestation [22,23], and in order not to misdiagnose it as a malignant tumor which can lead to unnecessary enucleations [24-26]. Clinical assessment and ultrasonography are the criterion standards in diagnostic imaging of this condition, but are often insufficient, with posterior scleritis being one of the most underdiagnosed diseases in ophthalmology [27]. Moreover, sonography is of limited value in evaluating other intraorbital structures, often involved in the presence of scleritis. The use of CT and MRI could potentially improve the diagnostic accuracy of scleritis, but studies on the diagnostic value of these imaging techniques on scleritis have been lacking. In **chapter 3.1,** the role of CT and MRI in the diagnosis of scleritis was evaluated, emphasizing the array of CT and MR imaging findings in scleritis.

Orbital inflammation can involve different anatomical orbital structures and it can be idiopathic or in the context of a specific disease. The diagnosis of orbital inflammation is made through combining the radiological findings, laboratory data and characteristics of other organ involvement, and if the diagnosis still remains unclear, then tissue characterization is needed. Possibly due to the fact that no systematic evaluation of orbital inflammation on CT and MRI had been published, imaging findings of orbital inflammation are often mistaken for

infection and tumor [28-32] and their underlying inflammatory disease is often overlooked. This often delays the adequate treatment and it can lead to unnecessary biopsies/enucleations. It was important to improve the diagnosis and treatment of orbital inflammation. In **chapter 3.2** the imaging protocols and characteristics of orbital inflammation were reviewed and a systematic approach for the radiological evaluation of these patients was proposed.

1.6 EYELID

The third and final part of this thesis regards the eyelid. Diseases of the eyelid are easily accessible to the ophthalmologist, making the diagnosis straightforward or easily determined with a biopsy. The treatment planning of eyelid malignancies is based on the tumor-node-metastasis (TNM) staging system, with the T-staging including determination of tumor dimensions, the invasion of eyelid structures such as the tarsal plate and orbital septum, and the invasion of nearby structures namely the orbit, globe, lacrimal sac/nasolacrimal duct, orbital walls, paranasal sinuses and brain [33-35]. The evaluation of deeper extensions in the orbit, globe, orbital walls, paranasal sinuses and brain has already been investigated and published. However, normal eyelid MRI anatomy had rarely been published, possibly because of being challenging, and therefore it was not known whether the different layers of the eyelid were possible to identify. The invasion of the tarsal plate and of the orbital septum has however direct clinical implications. On the one hand, in a tumor confined to the eyelid, which is treated with local resection and reconstructive surgery [33,36,37], knowledge about the presence of tarsal invasion preoperatively can be indispensable in planning surgical reconstruction and adequate information cannot be obtained solely by physical examination. On the other hand, when orbital invasion is present, an orbital exenteration must be considered [37-39]. The visualization of these small anatomical structures in the eyelid, both on MRI and CT, is therefore crucial in order to evaluate whether they are invaded by an eyelid tumor, not clinically accessible, and needed to be investigated. Strangely, unlike the other head and neck tumors, for eyelid malignancies T-staging according to TNM staging system is based on clinical evaluation only, which is clearly insufficient. American Joint Committee (AJCC) staging system regarding the T-staging already considers CT for evaluating extension inside the orbit, nasal cavity, paranasal sinuses and skull base, and MRI for perineural spread. Both TNM and AJCC do not consider image for evaluation of tumor extension inside the eyelid [34,35]. In **chapter 4.1** the normal eyelid anatomy on MRI and CT was evaluated, and knowledge gained subsequently applied to the evaluation of the extension of eyelid tumors and validated via histopathology.

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