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MRI for planning and characterization of uveal melanoma patients treated with proton beam therapy

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7

General discussion

This thesis is part of the Protons4Vision project which aims to improve the accuracy of proton beam therapy and ultimately save the patients vision without the need for surgical marker placement. At the start of this thesis, ocular MRI was not yet performed regularly in a clinically setting. In the LUMC ocular MRI was mostly performed in a research setting on the ultra-high field MRI scanner. This work contributed to transitioning ocular MRI from the research setting towards the clinic without loss of image quality¹. Through our collaboration with Philips, this protocol^{2,3} is now available worldwide for all their clinical 3T scanners⁴. At the LUMC, ocular MRI is currently contributing to the diagnosis, more accurate ocular PT planning (**chapter 4**) and/or follow-up in over three patients every week.

As part of the protons4vision project, MRI scans have been used by Kilany Hassan to develop an semi-automatic segmentation pipeline to create an MRI based tumour and eye model that can be used for treatment planning⁵. The sclera, cornea, lens, vitreous body, retinal detachment and tumour can be segmented on co-registered T1- and T2-weighted images and subsequently be used to create a eye and tumour model. I used an adapted version of this segmentation technique in (**chapter 2**) to show that the eye and tumour shape does not change between scanning and treatment position.

In **chapter 3** I showed that MRI based GTV delineation has a low observer variation of 0.4mm. This uncertainty in the GTV definition is needed to determine the margin needed for MRI based ocular PT planning systems such as the dose engine developed as part of the protons4vision project⁶ by Emmanuelle Fleury. This dose engine calculates the optimal gaze-angle by finding the optimal trade-off between maximizing the tumour dose and limitation of the dose to the organs at risk. Unfortunately, the normal tissue complication probability of organs-at-risk such as the retina are not yet known. This should be known before this dose engine can create clinical relevant optimal gaze-angle estimations.

7

7.1 Ocular MRI from a ophthalmology perspective

My work and work from and with colleges has contributed to the acceptance of MRI in ocular oncology⁷. In the second part of this discussion I would like to reflect on this work and the work of others, to highlight possible applications for ocular MRI in clinical practise.

7.1.1 Differential diagnosis

Conventional ophthalmic imaging such as ultrasound and fundoscopy is generally sufficient to differentiate UM from other intraocular masses^{8,9}, although in some cases not all criteria can be evaluated due to the size and/or location of the tumour or presence of opaque media such as cataract, vitreous haemorrhage or massive choroidal effusion. In these cases MRI can be used to assess different aspect of the tumour such as its origin, signal intensity and functional imaging. Although, prospective studies regarding the accuracy of MR-based differential diagnosis of intraocular masses are lacking, several studies and case reports already provide clear indications of its value for current patients^{2,3,10-13}.

Based on only anatomical information, such as location, origin and signal intensity from MRI, RPE adenoma's¹⁴, neurofibroma¹⁵ and other types of intraocular lesions¹⁶⁻³¹ can be differentiated. However, the appearance on MRI can also be inconclusive for example in the diagnosis of leiomyoma^{32,33}, lymphoma³⁴ and differentiation between UM and intraocular metastasis^{13,35}. It is therefore recommended to include functional imaging such as DWI^{2,3,11,36-40} and PWI^{3,41,42} to assess whether the biological characteristics match those of UM⁴³.

Schwannomas for example, can have similar signal intensities as (amelanotic) UM²⁶. In contrast to UM, lesions can be inhomogeneous on T2 and/or show heterogeneous enhancement^{17,27,35}. Moreover, in schwannomas progressive time intensity curve have been found²⁷ in contrast to UMs. Similarly, lymphomas can be difficult to differentiate from UM based on signal intensity alone³⁴, however, a lower apparent diffusion coefficient (ADC) might help to differentiate a lymphoma from UM⁴⁰.

It is important to acknowledge that not all radiological characteristics of the lesions in the differential diagnosis of UM are known, nor have a 100% specificity (figure 7.1), therefore definite diagnoses based on MRI alone can be challenging. If one or more atypical features are present in a tumour an MRI could be requested. MRI can provide detailed information on tumour localization, the layer of origin, tumour extension and perfusion^{2,3} (**chapter 3,4,5,6**). In our experience this information can provide important information for the diagnosis or substantiates a (risky) biopsy especially when combined with ophthalmic imaging. However, we also found that there is a learning curve. The radiologist needs to get experience with MRI of intraocular masses and ophthalmologists need to grow in confidence in the radiologist. Having a multidisciplinary meeting discussing the MRI's can help grow understanding and confidence from both sides. Moreover, we found that providing the radiologists with a clear question on the MRI request and adding relevant clinical information is very important to help focus the assessment of the images and formulate a relevant conclusion.

For example, if there is doubt between specific diagnoses it would be helpful to provide these diagnoses options as MRI might be able to rule out one of the two.

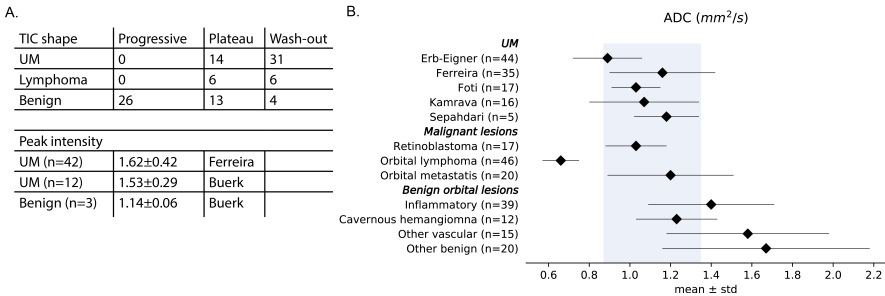


Figure 7.1: (A) UM's generally show a wash-out curve whereas most benign lesions have a progressive curve. Lesions with a plateau curve can be either benign or malignant. [3, 41, 42] According to Ferreira and Buerk the peak intensity of a UM is around 1.6 [3, 44]. (B) The ADC value of UM is $1.11 \pm 0.24 \times 10^{-3} \text{ mm}^2/\text{s}$ (grey area) which is lower than most benign orbital lesions and higher than orbital lymphoma. [3, 11, 37–40]

7.1.2 Therapy planning

Size is important for determination of the optimal treatment and therapy planning. For conventional radiotherapy planning of these tumours, 2D tumour dimensions are used⁴⁵. MRI, however, provides volumetric imaging allowing tumour measurements in all possible angles, which can help to provide a better determination of the tumour prominence². In general, there is an agreement between ultrasound and MRI³. However, for large and anterior located tumours MRI was considered more reliable (**chapter 4**). An analysis of 72 patients, from different studies I participated in, confirmed these findings. Ultrasound measurements were slightly larger than MRI ($p < 0.01$, Prominence; median 6.3mm vs 6.1mm and largest basal diameter (LBD); 14.7mm vs 14.0mm). The unreliable ultrasound measurements occurred more often in anterior tumours compared to posterior tumours (73% vs 27%, $p < 0.001$), figure 7.2C. Therefore when there is doubt about tumour dimensions and small change in size could change optimal treatment or treatment is planned based on the tumour dimensions, an MRI is recommended.

The second advantage of MRI over ultrasound is that entire orbit is imaged, allowing for assessment of the relation between tumour and different organs at risk. For patients undergoing brachytherapy, MRI might be used for verification of plaque position^{46,47}. MRI might also add information to the conventional model based treatment planning especially for measurements of the axial length and distance between tantalum markers and tumour in certain types of tumours

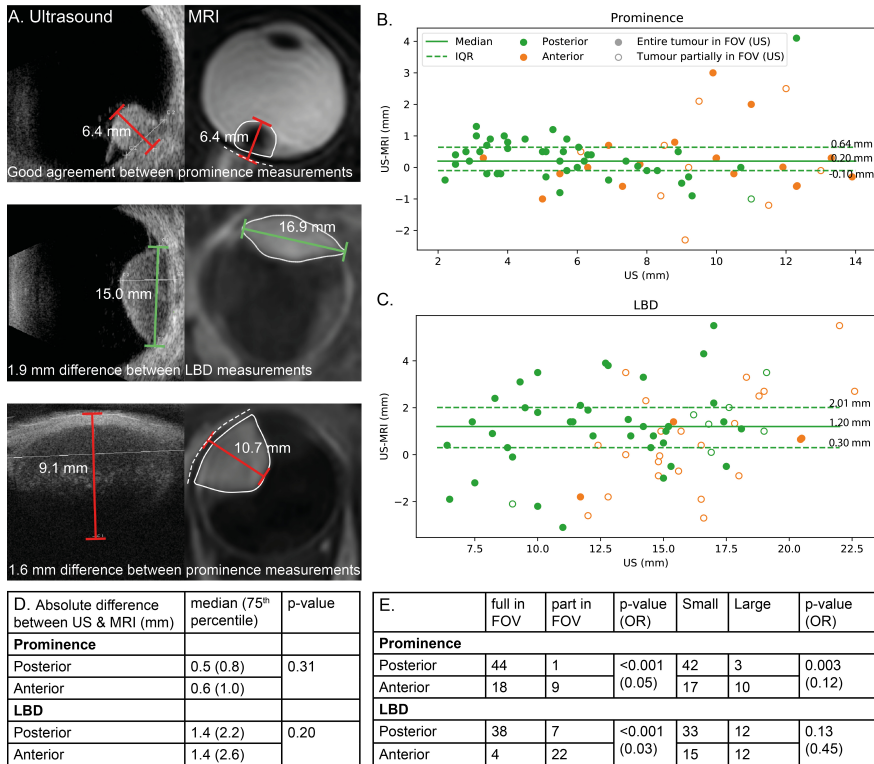


Figure 7.2: Difference between tumour dimensions measured on US and MRI. (A) Typical examples of US and MRI measurements adopted with permission from Klaassen et al. (B,C) Difference between US and MRI with posterior tumours in green and anterior tumours in orange. The median and the inter quartile range (IQR) for the difference between MRI and US measurements is visualized for patients with a posterior tumour. (D) The prominence and LBD measurements were larger on US (Wilcoxon signed-rank test, $p < 0.01$). Anterior tumours had a higher absolute difference between US and MRI for the prominence measurement. The difference in LBD is less clear. (E) Anterior tumours were more often only partially imaged. Small tumours were defined as prominence < 10 mm or LBD < 16 mm. FOV: Field of view

(**chapter 4**). Moreover, it has been shown in that the inter-observer variation in the delineation of uveal melanoma is low with respect to other tumours and ultrasound (**chapter 3**). Even though MRI based treatment planning has been investigated, it is not yet readily available in clinical practice⁴⁸⁻⁵⁴. On the other hand, planning systems such as OCTOPUS and RayOcular have become available and enable incorporation of MRI based information into the traditional model based treatment planning⁵⁵⁻⁵⁸. Importantly, it has been shown that MRI can be performed safely and reliably even with surgically placed markers and regardless of tumour and head orientation⁵⁹⁻⁶¹ (**chapter 2**).

7.1.3 Follow-up

In our experience it is very important to provide patients with information about treatment response as early as possible. MRI provides the opportunity for this early treatment response monitoring especially in patients after proton beam therapy as these tumours have been shown to slowly decrease in size.

The follow-up of patients after treatment for UM is primarily focused on the reduction in tumour volume or prominence. In proton therapy however, the reduction in size, measured with ultrasound, is slow and in over 5% of the patients the tumour increases in size in the first 6-12 months⁶². Other disadvantages are the large inter-observer variation (0.3-0.6mm^{63,64}) with respect to size reduction and the challenge to find the same plane as previous measurements.

Several studies showed decrease in tumour size using MRI following treatment⁶⁵⁻⁶⁷. Together with Michael Tang and other LUMC colleagues we compared MRI and ultrasound based measurements for proton beam therapy and brachytherapy patients. This study found that the measurements between ultrasound and MRI are comparable. Although it was found that ultrasound overestimated the tumour prominence in some patient at 3 and 6 month post treatment due to treatment related effects.

Functional imaging showed changes earlier than size and therefore allows for early treatment response monitoring^{11,68}. We have shown a wash-out decrease in the majority of patients as early as 3 month after treatment (figure 1.4). It would be interesting to further quantify these changes using the method proposed in **chapter 6**. The diffusion within the tumour has shown to increase after proton beam therapy and brachytherapy^{11,68,69}. Due to the large variation however, DWI might not be a useful biomarker between patients.

Finally, retinal detachment, a common complication after proton beam therapy is often treated with a vitrectomy with silicon oil tamponade. Unfortunately ultrasound imaging is hindered in these patients. Follow-up with MRI is possible

after minor adjustments in the imaging protocols (**chapter 5**). It is important to keep in mind that for treatment response monitoring also a pre-treatment MRI is needed.

7.2 Future perspectives

With the field of ocular MRI still moving forward the possibilities and indications for ocular MRI will most likely increase. First of all, more and more patients receiving ocular PT will get an MRI. In (**chapter 4**) I showed how MRI can contribute to conventional model based ocular PT planning and we see more and more centres starting to perform MRI for this patient group. There are however prospective studies needed to evaluate the effects of MRI on the outcome in these patients. (**Chapter 3**) shows that the uncertainty in the GTV delineation is higher at the sclera edge of the tumour compared to the part of the tumour adjacent to the vitreous. In combination with known differences in uncertainties in the treatment delivery system this could be a starting point to investigate different treatment planning strategies with a margin that varies in different directions. In combination with MRI based treatment planning and the two-beam strategy proposed by Fleury et al⁷⁰ this might contribute to reduction in visual impairment after ocular PT.

In this thesis, I have addressed some challenges in the quantification of PWI. We are working together with Philips to implement B_1^+ mapping and masked registration into the DCE-MRI analysis software as recommended in **chapter 6**. Implementation of the analysis into clinical software will make quantitative functional MRI more easily available in clinical practice as it currently is a complicated and time consuming process using mostly in-house developed software. Besides implementation in the clinic, additional research in larger cohorts is needed to determine the perfusion characteristics of UM and other intraocular masses. Analysis of a large uveal melanoma cohort is needed in order to determine the expected values in uveal melanoma. It would be valuable to have similar studies to determine the anatomical and functional features of other intraocular masses to further improve the value of MRI in the differential diagnosis of intraocular masses. Moreover, a study is needed on patients with histology and a long follow-up period in order to investigate the possible prognostic value of PWI-MRI as there are already some indications that tumour perfusion can be related to monosomy 3, an important genetic marker for metastatic risk^{3,39}. Finally, the first effective treatments for metastatic uveal melanoma are now becoming available⁷¹. These and other therapies could also be used as (neo)adjuvant treatments for high risk patients. Quantitative PWI analysis could play a role as a non invasive alternative to a biopsy in order to identify high-risk patients that

might benefit from these (neo)adjuvant treatments.

With the growing patient population and increasing cost from expensive medicines and high-tech solutions it is important to provide evidence on the cost effectiveness of ocular MRI. There are already clear indications that ocular MRI in the clinical care of uveal melanoma patients can be cost effective⁷². This should be investigated more thoroughly for different indications and health care systems.

Finally, during my thesis I experienced that the field of UM research is sometimes fragmented. One of the reasons is that treatment of UM also is fragmented. For example, it can occur that the centre for the diagnosis and the centre for treatment are over 200 km apart. I was very fortunate to be able to work in such a multidisciplinary team with people who are open for ideas and imaging techniques from other disciplines. This helped bridging the gap between disciplines and has led to new MRI sequences and protocols that improved the care for ocular oncology patients.

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