Dynamic Contrast Enhanced Magnetic Resonance Imaging Applications in High Intensity Focused Ultrasound Treatment for Uterine Fibroids

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Uterine fibroids are the most common neoplasm of the female reproductive tract occurring in 70% of women by the age of 50. Current treatments are either curative through surgery or provide symptomatic relief using medical therapies. High intensity focused ultrasound (HIFU) is a viable non-invasive option to treat the fibroids through thermal ablation. The downside to HIFU is that it is not suitable for every fibroid, depending on multiple factors, e.g. fibroid characteristics. MRI scans can provide some information on said characteristics, but do lead to ambiguity. This paper explores the potential of using DCE-MRI in the treatment of uterine fibroids using HIFU. To select patients for the suitability of HIFU treatment, it was found that hyperintense T2 weighted fibroids (Funaki type 3) do not respond well to thermal ablation. This indicates either fluid-rich tissue or high vascularization. Quantitative analysis of DCE-MRI solves this conundrum, since K_{trans} was found to be significantly correlated to ablation efficiency. A high K_{trans} translates into a large blood flow, which dissipates the heat away from the tissue. Thus Funaki type 3 fibroids can successfully be treated if the K_{trans} is low. Other significantly correlated parameters with HIFU efficiency are: enhancement of fibroids, relative peak enhancement and wash-out rate. Additionally a K_{trans} map can possibly be used to adapt the acoustic power of HIFU to the local K_{trans} value to increase ablation efficiency. Using DCE-MRI to evaluate the HIFU treatment efficacy has not been researched specifically for fibroids.

1 Introduction

1.1 Clinical background

Uterine fibroids, also known as uterine (leio)myomas, are benign tumors caused by the abnormal multiplication of tissue in the uterus. They vary in size, shape and location in the womb. The growths consist out of smooth muscle cells and fibroblast in an extracellular matrix (Stewart et al., 2016). It is the most common neoplasm of the female reproductive tract occurring in about 70% of women by the age of 50 (Stewart et al., 2003; Baird et al., 2017). Of these women 15 to 30% develop severe symptoms (Longo and Bulun, 2013), leading to heavy or prolonged menstrual bleeding, urinary symptoms, gastrointestinal symptoms, abdominal distention, fertility issues and/or pain (Stewart et al., 2003). Despite this morbidity being benign, it has a negative effect on life (Zimmermann et al., 2012).

Uterine fibroids can either be treated through drug therapy, surgery or minimally invasive therapy. Medical therapy options are non-invasive, alleviate symptoms and preserve fertility. Yet most of these treatments do not decrease the size of the fibroids and thus do not treat the underlying causes of the symptoms (Cruz and Buchanan, 2017). With the exception of gonadotrophin-releasing hormone agonists and selective progesterone receptor modulators, which do decrease fibroid volume (Sohn et al., 2018). Surgical procedures (e.g. hysterectomy and myomectomy) result in the resolution of symptoms, however these are connected to long term morbidity (Olejek, Olszak-Wąsik, and Czerwinska-Bednarska, 2016), long recovery periods and a hospital stay of 4 to 5 days (Al-Fozan et al., 2002). Making it an economic and social strain on the healthcare system (Vilos et al., 2015; Verpalen et al., 2020a).

Minimally-invasive treatments include uterine artery embolization, hysteroscopic resection and magnetic resonance-high intensity focused ultrasound (MR-HIFU). MR-HIFU is the most cost effective per quality-adjusted life-year gained (Zowall et al., 2008; Babashov et al., 2015; Kong et al., 2014). Furthermore the treatment results in shorter recovery times and less prescription medications used due to differences in reported pain (Barnard et al., 2017).

1.2 Technical background

1.2.1 HIFU

HIFU is a method to focus beams of ultrasound into one spot by setting the transducers in a concave shape. The focused ultrasound beams reach an intensity of greater than 5 $\mathrm{W/cm^2}$ (Copelan et al., 2015). The tissue in the focal area consequently increases in temperature, which induces coagulative necrosis (Siedek et al., 2019). The surrounding tissue outside of the focal point remains unaffected, making this a very precise way to ablate tissue. Monitoring is needed to target the specific tissue within the body. Therefore is HIFU often used simultaneously with MRI to provide guidance. MRI constructs 3D anatomical images and allows tissue temperature to be mapped (Haar, 2016).

In the treatment of uterine fibroids using MR-HIFU, first a pre-scan is made using MRI for screening purposes. Secondly, HIFU is used to ablate the fibroids. Lastly, a contrast-enhanced MR post-treatment scan is used to evaluate the treatment. The non-perfused volume (NPV) is measured from an MR image after intravenous administration of a contrast agent and used to determine the effectively ablated fibroid tissue (Elhelf et al., 2018). A higher NPV to fibroid volume ratio (NPV%) indicates greater tumor shrinkage, lower retreatment rates and an increase of symptom relief (Leblang, Hoctor, and Steinberg, 2010; Verpalen et al., 2019; Mindjuk et al., 2015). Reintervention is also negatively correlated to NPV% as the regrowth of fibroids is less likely when a bigger portion of the tissue is ablated (Stewart et al., 2007).

The effectiveness of MR-HIFU depends on multiple factors. The MRI pre-scan is therefore needed to deduce the suitability for the treatment. The location of the uterus and fibroids, as well as the type of the fibroids have an effect on the delivery of thermal energy (Peng et al., 2015). Characteristics of the fibroid, like vascularization, fluid-richness or degeneration, lowers the efficacy of ablation using HIFU (Funaki et al., 2007). Thus showing the importance of providing a personalized treatment plan for patients with uterine fibroids to increase clinical success with low complication rate (Mindjuk et al., 2015).

HIFU can transport energy in the form of waves through materials easily, except for bone and air. When it reaches the desired focal point, it heats up the area because of friction and cavitation. Temperatures higher than 56°C for at least one second induce coagulative necrosis (Guzman et al., 2005). A combination of acute and delayed treatment effects reduce the size of the fibroid. Acute treatment effects include protein denaturation, cell membrane collapse, a stop in DNA polymerase and enzyme activity and mitochondrial dysfunction (Chu and Dupuy, 2014). Delayed treatment effects, such as induction of apoptosis, ischaemia caused by vascular damage and inflammatory response, occur after the ablation. The amount of energy absorbed, which is converted to heat, is tissue dependent. The ability of the fibroids to heat up is essential to induce the necrosis during the HIFU treatment.

1.2.2 DCE-MRI

Contrast enhanced magnetic resonance imaging is currently used as an evaluation method for the treatment of uterine fibroids using HIFU by injecting an approved low-molecular-weight gadolinium-based contrast agent. The method visualizes the NPV, which is depicted as non-enhanced tissue (Funaki et al., 2007). Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) is used to get more information on the microcirculation of a tissue. More information on blood flow in the capillaries and the exchange between blood and extravascular space can be obtained using this method compared to contrast enhanced magnetic resonance imaging.

The blood flows from the arteries to the organs, where the arteries branch into capillaries. The speed and pressure of the blood flow is greatly reduced in the capillaries. This is where an exchange between blood and tissue happens, including hormones, nutrients and heat. Capillary permeability is the exchange between blood and interstitial space (Cuenod and Balvay, 2013). Neoplasms like uterine fibroids undergo a genesis of new and immature capillary networks (Walocha, Litwin, and Miodoński, 2003). These are different morphologically and functionally compared to normal tissue. Depending on the technique used, information on both blood flow and permeability can be extracted using DCE-MRI in a region of interest. Through (semi-)quantitative analysis, properties like vessel permeability, tissue volume fractions and vessel surface area can be derived (Gordon et al., 2014).

The principle is that the injected contrast agent is paramagnetic and thus increases the signal intensity by decreasing the longitudinal and transverse relaxation time as it disperses through the tissue (Ibrahim, Hazhirkarzar, and Dublin, 2021). A scan is made without the contrast agent to generate a baseline. During and after the injection of contrast agent a signal is measured over time, acquiring a time intensity curve in a particular region of interest. By directly analyzing the curve, semi-quantitative metrics can be derived. These metrics do mirror physiological effects, however due to subjective factors it is difficult to compare the results (Gordon et al., 2014). Parameters such as peak enhancement, relative peak enhancement, time to peak, wash-in rate, and washout rate can be used to analyze the perfusion of tissue as depicted in figure 1 (Kim et al., 2014b). (Relative) peak enhancement is the difference between the maximum signal intensity after administration of the contrast agent and the signal intensity of the baseline image. Time to peak is the time from contrast agent administration to peak enhancement. Wash-in rate is the maximum slope of the signal intensity curve while reaching peak enhancement and wash-out rate is the maximum absolute slope between the peak and end of the dynamic (Kim et al., 2014b).

The appeal of DCE-MRI lies in the ability to do quantitative analyses, which inform on physiological effects in absolute numbers. Making it possible to define an objective threshold. This analysis relies on mathematical model fitting. Pharmacokinetic features are extracted by the many parameters from the model. The most common model used to analyze DCE-MRI data is the Kety/Tofts model (Tofts, 1997). Quantitative physiological properties are estimated using said model, such as K_{trans}, K_{ep}, V_e, V_p. The mentioned parameters are depicted in figure 2 (Yan, Sun, and Shen, 2017). V_p is the fractional plasma volume. V_e is the fractional volume of the extravascular extracellular space (EES). K_{ep} is the movement between EES and plasma. K_{trans} is the transfer constant and it has multiple physiological interpretations depending on the permeability and blood flow. If permeability is high, the K_{trans} will reflect blood flow. This situation is reflected in the Kety model. If permeability is low, it is the permeability-surface area product (PS), which defines the movement between plasma and EES (Tofts et al., 1999). Tissue blood flow is defined as the blood flow from the capillaries entering and exiting a volume of tissue. Tissue blood volume is the volume of capillary blood contained in the region of interest. The PS is the flow of molecules to a volume of tissue.

1.3 Purpose

During the management of uterine fibroids using MR-HIFU, assessing if the fibroids are suitable for the treatment increases the clinical success (Mindjuk et al., 2015). The state of the art is to use MRI to perform a pre-selection before the treatment and evaluate the efficiency after the treatment. DCE-MRI potentially provides more information on the vascular network supplying the fibroid. The purpose of this paper is to determine how the use of DCE-MRI potentially adds value to the prediction of HIFU ablation efficiency and to the evaluation of HIFU treatment of uterine fibroids.

2 Clinical application

2.1 Prediction

Tumor tissue with a high blood perfusion show to have a higher heat tolerance (Chen et al., 1993; Yoon et al., 2010). The correlation between heat absorbance and perfusion has been observed specifically with HIFU as well (Wiart et al., 2007). The Funaki classification divides fibroids into three different categories, which are correlated with clinical success rate. Funaki type 1 fibroids have a low intensity on T2 weighted MR images and are easily treated with HIFU. Funaki type 3 have a high intensity on said images and are often rather unresponsive to HIFU treatment (Funaki et al., 2007). Funaki type 2 falls in between, where successful HIFU treatment is attainable. A high signal intensity on T2 weighted MRI is seen in tissues with a long T2 relaxation time. This is the case in tissues with a high water content. This can be translated into a large amount of interstitial fluid, blood volume or blood flow (Verpalen et al., 2020b). The heat capacity of water is high. Meaning that when tissue has a high concentration of fluids, it results in a slower rate of temperature increase in the focal point. When the blood flow is high, the temperature disperses from the focus, since blood has a lower temperature (Yoon et al., 2010). These two mechanism both result in more difficulty heating the tissue, but the underlying reason for this phenomena differs.

2.1.1 Semi-quantitative analysis

In order to make a distinction between a high water content and a high blood flow, Yoon et al., 2010 used a dynamic contrast enhanced MRI scan on a Funaki type 3 fibroid. If the contrast agent shows a delayed enhancement in the fibroid tissue in the T1 weighted scan, the conclusion is made that the high T2 weighted signal intensity is due to high water content and not high vascularity. Enhancement is defined as the signal intensity compared to the myometrium after the administration of a contrast agent. Hence a lower signal intensity found in the fibroid compared to the myometrium is defined as low enhancement and the same or higher signal intensity as high enhancement. Delayed enhancement is attributed to a fibroid if the enhancement is low 120 seconds after injection and high after 240 seconds. The time to peak enhancement is therefore longer compared to other fibroids. One case has shown that this particular characterization can be treated successfully using HIFU, as this fibroid type still is able to absorb enough energy to heat up sufficiently (Yoon et al., 2010). Another study has observed the contrast agent in the fibroid based on a dynamic contrast enhanced imaging within 60 seconds after contrast agent administration. Three classifications have been made: slight enhancement, regular enhancement and irregular enhancement. The signals of the con-

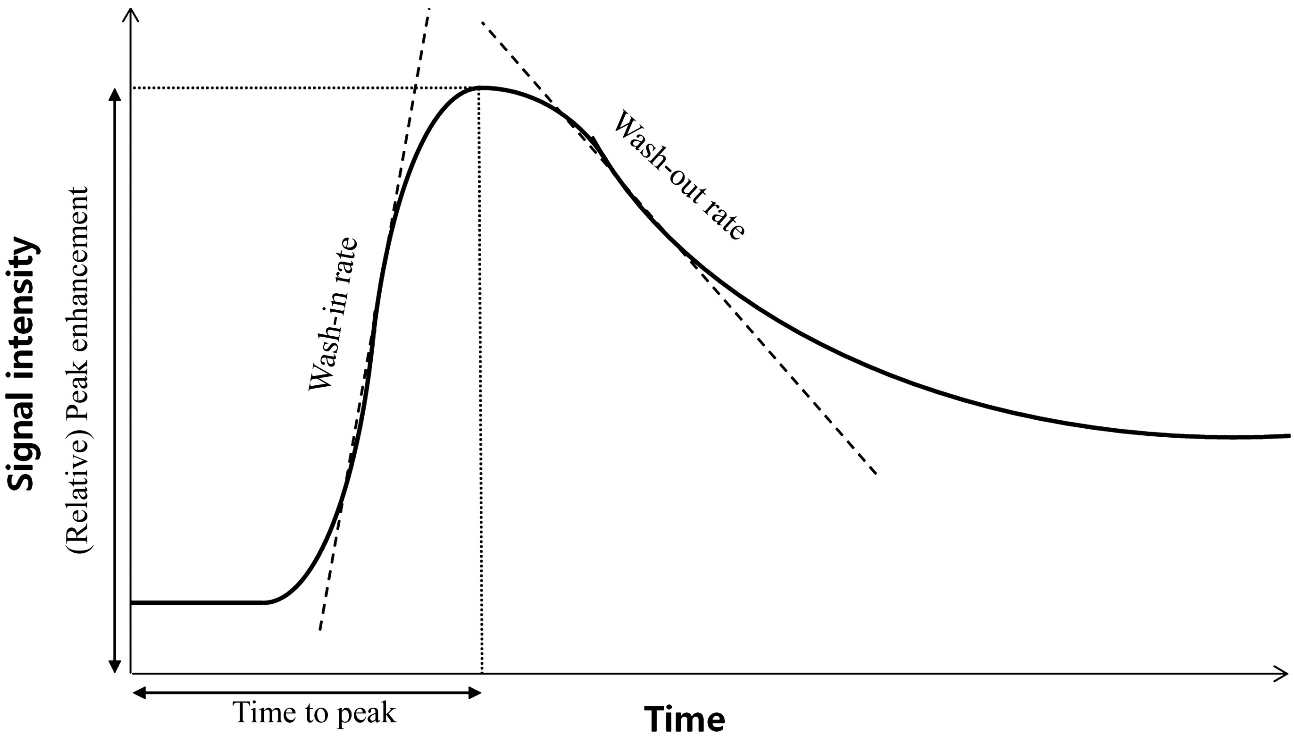

Figure 1: *Example of a time intensity curve which is used to deduce semi-quantitative parameters with DCE-MRI. The signal intensity of a pixel is shown over time. The semi-quantitative parameters are depicted. The relative peak enhancement is the difference in signal intensity from the start to the peak. The time to peak is the difference in time from the administration of contrast agent to the peak. The wash-in and wash-out rate are the slope curve to the peak and from the peak, respectively (Kim et al., 2014b).*

trast agent are yet again compared between the fibroid and the myometrium. If the signal was lower in the fibroid, it is classified as slight enhancement. If it is equal to or greater than the signal of the myometrium, it is classified as regular enhancement. Irregular enhancement means that the distribution of the signal is irregular as regions of both regular and slight enhancement are observed within the fibroid. In this study it was found that the fibroids with regular enhancement reacted poorly to HIFU treatment (Zhao, Chen, and Chen, 2016). This is another case for vascularity affecting the energy deposition of HIFU observed using DCE-MRI with a semi-quantitative approach.

Kim et al., 2014a also focused on the semi-quantitative parameters as a predictor of the efficiency of HIFU treatment. Univariate analysis showed that relative peak enhancement is significantly correlated to heating efficiency and ablation efficiencies. Heating efficiency is the estimated ablation volume compared to the intended volume defined by the measured temperature change during treatment. Ablation efficiency is measured by looking at the NPV% after the procedure. Relative peak enhancement signifies the peak enhancement value relative to the baseline enhancement before the administration of contrast agent. Values of relative peak enhancement under 220% are suggested as a screening guideline to increase HIFU efficiency. This cutoff value made the biggest difference in maximizing heating and ablation efficiency. Additionally, the wash-out rate was significant for ablation efficiency, which can complement the other parameters during screening. The other semi-quantitative parameters used in this research (peak enhancement, time to peak and wash-in rate) did not significantly correlate with the treatment outcome. In addition multivariate analysis showed that only T2 signal intensity ratio between the uterine fibroid and skeletal muscles is significantly correlated with both heating and ablation efficiency. Relative peak enhancement was just significantly correlated to heating efficiency using multivariate analysis. Concluding that T2 signal intensity ratio seemed to have had a stronger effect on predicting treatment efficiency compared to the perfusion parameters.

2.1.2 Quantitative analysis

Kim et al., 2011 looked at the correlation between tissue perfusion and HIFU efficiency for uterine fibroids using DCE-MRI using quantitative analysis. To quantify the data, the extended Kety two-compartment model was used. The efficiency of the HIFU treatment was measured with NPV% and 240 EM. The latter indicates the theoretical area of tissue necrosis, since it is the biological equivalent of heating tissue at 43°C for 240 minutes (Sapareto and Dewey, 1984). Using univariate and multivariate analysis, it was found that K_{trans} is a statistically significant predictor for NPV%. In the same study the T2 signal intensity ratio between uterine

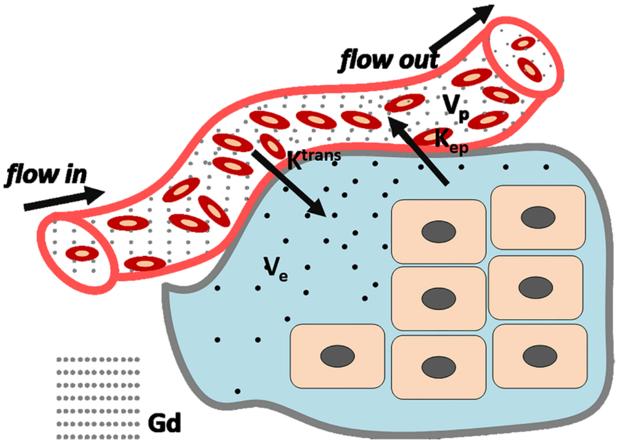

Figure 2: *Physiological depiction of quantitative parameters of DCE-MRI from the Kety/Tofts model. The grey dots represent gadolinium. This is present in the blood vessels next to the red blood cells. The blood and contrast agent flow in and out of the vessel. While the blood flows from one side to the other, the contrast agent can diffuse into the extravascular extracellular space (EES). This is quantified with K_{trans}. V_e signified the portion of contrast agent in the EES and V_p in the blood vessel. K_{ep} indicates the movement of gadolinium from the EES back to the blood vessel (Yan, Sun, and Shen, 2017).*

fibroids and skeletal muscles did not show a significant correlation with NPV% nor 240 EM, concluding that K_{trans} provides better insights on the effectiveness of HIFU.

Liu et al., 2014 builds further on this notion by exploring the idea of using this information during treatment by using two cases. The fibroids often do not show homogeneity when it comes to perfusion (Li et al., 2020). It is theorized that K_{trans} maps can provide information on vascularity within a fibroid. The HIFU beam can be altered in power when encountering different vascularity. Hypo-vascular regions need less energy to be ablated while the hyper-vascular regions need more. Consequently, K_{trans} maps can be used to plan the sonification of a fibroid (Liu et al., 2014).

Another study used the extended Tofts-Kety model to evaluate the correlation between DCE-MRI metrics and NPV%. The metrics that were taken into account are K_{trans}, K_{ep}, V_e, V_p. The following T1 perfusion parameters were also examined: blood flow and blood volume. Only K_{trans}, blood flow and blood volume showed a statistically significant correlation with the NPV% when dividing the patients in two groups. One group has an NPV% of equal or bigger than 70% after treatment and the other smaller than 70%. A high K_{trans} was again concluded to predict poor HIFU results. Combining K_{trans} with blood flow provided the best predictions. Indicating that blood flow has a larger influence on HIFU compared to blood volume (Wei et al., 2018).

2.2 Evaluation

Evaluating the efficiency of HIFU treatment of uterine fibroids using DCE-MRI has not been investigated yet, so the technique is going to be explored with other neoplasms. Hijnen et al., 2012 used DCE-MRI to look at tumors in rats after treating them with HIFU. A 2-parameter Tofts and Kermode model was used to extract the parameters. K_{trans} was the only constant which showed a significant decrease after treatment. Outside of the treated volume, the K_{trans} did not change significantly. Subsequently K_{trans} was used to calculate the NPV by thresholding said constant(Hijnen et al., 2012).

In one study prostate cancer DCE-MRI is used to detect local recurrences after HIFU ablation (Rouvière et al., 2010). Residual tumors are hypervascular while the necrotic tissue is homogenous and hypovascular. The patients were screened using a T2 weighted MR image and a DCE image. Suspicious areas were compared and targeted biopsies were taken based on information of the images next to routine biopsies. Tissues were considered suspicious when the time-to-peak was low and it showed a high relative peak enhancement on DCE-MRI. It was found that using DCE imaging was useful for locating residual tumors compared to the T2 weighted MR images .

HIFU induces more vascular alterations than the commonly analyzed NPV. Using DCE-MRI has the potential of providing more detailed information on the pathophysiological changes post-HIFU treatment. Jacobs et al., 2015 studied this in a tumor model in the hind limbs of mice. Directly after HIFU treatment it was observed that the NPV overestimates the volume compared to histology derived non-viable tissue. After 3 days the two evaluation methods were in better agreement. The NPV directly after HIFU treatment significantly increases and after 3 days decreases slightly again. Additionally it is probable that the histology derived non-viable volume increases, due to the delayed cell death responses of HIFU. The tumor vasculature surrounding the ablated region gets damaged, which induces necrosis at a later stage. However this is difficult to prove since the animals were sacrificed to gather the histology derived information. With DCE-MRI it was found that the central ablation zone had a low K_{trans} and V_e. The zone next to it has low K_{trans} and high V_e. This region has signs of structural disruption, hemorrhage, vacuolation and vascular congestion. The region further away from the central zone has high K_{trans} and high V_e. This is associated with edema, inflammation, increased vascular permeability and hyperemia. This method can provide more information on the consequences of vascular alterations in tumor tissue (Jacobs et al., 2015).

3 Discussion

The potential added value of using DCE-MRI in the HIFU treatment of uterine fibroids can be divided in two parts. It can be used as a predictor of treatment efficiency or to evaluate the treatment. The Funaki classification shows that T2 weighted hyperintense fibroids do not respond well to HIFU. This could either indicate a large blood flow or blood volume. This can be narrowed down using DCE-MRI through (semi-)quantitative analysis. The semi-quantitative observations which are significantly correlated with NPV% are regular enhancement of fibroids (Zhao, Chen, and Chen, 2016; Yoon et al., 2010), relative peak enhancement and wash-out rate (Kim et al., 2014a). K_{trans} was the only quantitative parameter which was significantly correlated with treatment efficiency (Kim et al., 2011; Wei et al., 2018).

However, it is observed that relative peak enhancement is significant for ablation efficiency when doing univariate analysis but does not produce the same result with multivariate analysis (Kim et al., 2014a). This can mean that relative peak enhancement is only predictive because it is associated with other predictors.

K_{trans} quantifies the transport of the contrast agent from the intravascular space to the extravascular extracellular space. This is dependent on either blood flow or permeability surface area product. Meaning that a high K_{trans} might signify that there is a high blood flow or a large vessel surface area, depending on the permeability of the blood vessels. Kim et al., 2011 stated that the permeability of the microvessels is homogenous and low in uterine fibroids. This assumption is taken, yet no research is to be found on the permeability of uterine fibroid blood vessels. Additionally the Kety model was opted for during these experiments, which makes the assumption that the fibroids reside in a highly permeable vascular network (Tofts et al., 1999). There is a discrepancy on the assumptions made about permeability of fibroid vasculature.

The vasculature of fibroids first of all depend on size. Fibroids with a diameter between 1 and 3 mm are almost avascular. Fibroids up to 1 cm have more surrounding vessels and a few small blood vessels that penetrate the fibroid. Fibroids which are larger than 1 cm have a hypovascularized core surrounded with a dense vascular capsule (Walocha, Litwin, and Miodoński, 2003; Ciarmela et al., 2021). There is no direct research to be found on the vascular permeability of fibroids, however it can be assumed that their physiological behavior would be similar to other neoplasms. It has been found that benign breast tumors are more homogeneous and less permeable than malignant breast tumors (Makkat et al., 2007). Malignant tumors tend to be hyperpermeable (Nagy et al., 2006). Uterine fibroids are benign neoplasms and probably share more commonalities with other benign tumors. However this needs to be researched to have concrete data about this to further understand the factors that influence the efficiency of HIFU treatment using DCE-MRI.

In addition there is also a lack of knowledge on the way gadolinium functions in the microvessels supplying the uterine fibroids. The repercussion is that the results are not easily explained when discussing the DCE-MRI parameters (Kim et al., 2011). A high K_{trans} may rule out that the fibroid has a large blood volume. Blood flow probably affects the thermal efficiency of HIFU more compared to both blood volume and vessel surface area based on Pennes' bioheat equation (Giordano, Gutierrez, and Rinaldi, 2010). Blood flow dissipates the temperature from the focal point. A larger blood volume can make it that more energy is needed to have the desired increase in temperature. A larger vessel surface area can result in more water moving into the surrounding tissue, however the dominant movement in the EES is through hindered diffusion (Nugent and Jain, 1984). Concluding that the water molecules will not move far enough during HIFU treatment to affect the heating of the focal point.

A considerable limitation is that multiple studies used an insubstantial amount of cases (Li et al., 2020; Kim et al., 2011; Yoon et al., 2010). For Kim et al., 2011 this probably led to inconsistencies regarding T2 signal intensity ratio as a predictor for HIFU efficiency. Both significant correlations and insignificant correlations are reported (Kim et al., 2014a; Kim et al., 2011). The significant correlation is found using 77 women and 119 fibroids, while the insignificant correlation is found only using the largest fibroid of 10 patients. As previously noted T2 signal intensity is not the most accurate predictor for HIFU success, since it can be attributed to the fluid-richness of a fibroid. This might be another explanation for the inconsistency.

HIFU is an elegant way to treat fibroids, because of its noninvasive nature. The culprit is that it is a relatively selective treatment. Success rate depends on age, fibroid location and type (Younas et al., 2016). The last reported satisfaction rate after HIFU treatment is 72.4% (Verpalen et al., 2020b). This can be increased if patient selection improves before undergoing treatment. Knowing the underlying reason why a HIFU treatment might fail, helps in this regard. Funaki type 3 fibroids respond poorly to HIFU ablation, and with the addition of DCE-MRI further characterization can be done. Blood flow is a larger hinderance of reaching the desired temperature compared to blood volume. This has been concluded using DCE-MRI parameters. By adding a DCE-MRI scan to the protocol a better estimation of clinical success can be achieved. Since the treatment efficacy depends on so many factors it is highly important to personalize this process to provide better care for women with uterine fibroids.

Further using DCE-MRI to guide the ablation therapy is also a good suggestion by Liu et al., 2014. Overlaying a K_{trans} map over the fibroid will provide more localized information, which has the potential to make HIFU more effective. A high acoustic power can be used for the highly perfused areas. However there is no research done on the feasibility of this method. There is a probability that the blood flow still dissipates the heat in a large rate or that the higher acoustic power is too damaging for surrounding tissues or near-field. The HIFU waves travel through the cutaneous, subcutaneous, and intermediary tissue layers before reaching the fibroid. This leads to undesirable heating, which may cause discomfort or irreversible damage of adipose tissue (Baron et al., 2014). The research just showed the K_{trans} map on two cases to show the potential of the idea. It has not been tried and evaluated. So there is no information available on the success and reintervention rate after such a procedure.

Not a substantial amount of research has been done on the use of DCE-MRI for HIFU treatment of uterine fibroids, however the same results have been reproduced across multiple research groups. Making it more probable that the correlation between K_{trans} and NPV% and thus clinical success is a causal dependency. However, the small amounts of patients used in combination with the lack of research, does lead to a larger uncertainty regarding this correlation. Quantitative analysis, which is performed using mathematical models, and semi-quantitative analysis, which extracts information out of the time intensity curve, differ in reproducibility. Quantitative DCE parameters are known to be absolute (Gordon et al., 2014). Yet this does not guarantee reproducibility. V_e and enhancement are reproducible within patients and thus suitable to use to track changes as treatment progresses. K_{trans} and K_{ep} have a larger variance, but if corrected for measurement errors still usable. Reductions of more than 14% and increases larger than 16% can still be detected in a group of 16 patients, and nevertheless be clinically significant (Galbraith et al., 2002). The disadvantage of semi-quantitative analysis is that subjective factors, such as injection protocol, contrast agent properties, sequence parameters, scan duration, amount of contrast agent and hardware setting, influence the results (Gordon et al., 2014). Meaning that it is difficult to compare the parameters to each other, since these subjective factors induce a larger variance.

Using DCE-MRI to evaluate the treated uterine fibroids can provide more information on the physiology after treatment. This research has not been performed on uterine fibroids. The mouse tumor model has been characterized after ablation with K_{trans} and V_e, which explains the mechanisms happening the following days after ablation (Hijnen et al., 2012; Jacobs et al., 2015). This information is useful to gain understanding of the DCE-MRI parameters within the fibroids, however it cannot be used in the clinic to help the evaluation of the procedure. Using a K_{trans} map to find residual perfused tumor cells after treatment of prostate cancer seems like an interesting approach that could possibly be adopted for uterine fibroids. The K_{trans} map were compared to T2 weighted MR images. The K_{trans} map depicted more accurately where the residual tumor cells were residing. A better comparison would be with T1 weighted MR images, since those are used to evaluate the NPV%. T1 and T2 weighted MR scans are compared and a low signal intensity on T1 scans provided more histologically accurate NPV, since the signal intensity on T2 weighted scan cannot differentiate between edema, vascularity and degeneration (Mindjuk et al., 2015). Uterine fibroids do differ from tumors, since the former are benign neoplasms and the latter malignant. The physiological differences between the two are yet to be researched.

3.1 Future perspective

There are multiple gaps of knowledge regarding using DCE-MRI during the HIFU treatment of uterine fibroids, which lead to inconsistencies. Research on the vascular characteristics, e.g. permeability, of uterine fibroids can get rid of some of the taken assumptions. The notion that heterogeneous Funaki type 3 fibroids can be treated by adapting acoustic power to a K_{trans} map has potential to improve this treatment. The higher end of the acoustic power needs to be tested, to ensure that it will affect the fibroids without causing safety concerns in adjacent tissues.

The ablation evaluation needs to be studied on fibroids using DCE-MRI. There is no knowledge on the DCE parameters after treatment. Perhaps there is are more correlations to be found compared to NPV%. For example DCE parameters could give a more accurate prediction on regrowth or reintervention rates.

4 Conclusion

DCE-MRI may help in the selection process to classify uterine fibroid suitability for HIFU. The quantitative parameters derived from DCE-MRI using Tofts/Kety modelling provide more insights on the vascularity. A large blood flow hinders the tissue to reach the necessary temperature to induce coagulative necrosis. DCE-MRI can provide added value by further classifying the T2 hyperintense fibroids, which can either be the result of a high blood volume or flow, which eventually may result in a better patient selection prior to treatment. Further options like using a K_{trans} map to adapt acoustic power and finding residual tumor cells need to be further researched in order to conclude that it is a viable option.

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