Development of new imaging techniques for improved detection and characterization of focal liver lesions using magnetic resonance imaging
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SUMMARY

The aim of the work summarized in this thesis was to develop and evaluate new MRI sequences for improved detection and characterization of focal liver lesions, focusing on the detection of small (<10mm) focal liver lesions. The results of our research show that the SS SE-EPI sequence can be considered the new reference standard for detection of focal liver lesions. For characterization of focal liver lesions the calculation of D, f and ADC_{low} using SS SE-EPI seems promising to decrease liver biopsy procedures in the future. The presented 4D THRIVE sequence (for perfusion MRI) and the calculated parametric maps can be used to improve characterization of focal liver lesions. Further extended animal research has to be performed before magnetoliposomes for human usage can be developed. The magnetoliposomes-enhanced T1-weighted MRI experiments presented in this thesis might have the potential to better characterize colorectal liver metastases and to perform follow-up examinations during treatment.

In chapter 2 a prospective comparison was made between a respiratory-triggered (RT) FS T2w TSE and breath-hold (BH) FS T2w TSE sequence for the evaluation of focal liver lesions. Both T2w TSE sequences were acquired in 40 patients suspected for colorectal liver metastases.

Qualitatively analysis was performed for image quality, lesion conspicuity, diagnostic confidence, artifacts using two-tailed Wilcoxon signed-ranks test. Quantitative analysis was performed for lesion-to-liver CNR using two-tailed Student’s t-test. For hemangiomas, the reference standard comprised follow-up imaging. In one case tissue diagnosis by percutaneous biopsy was performed in one hemangioma. For liver metastases surgery, biopsy and/or
follow-up imaging were used as the reference standard.

Seventy-eight liver metastases and 47 liver hemangiomas were detected on both FS T2w TSE sequences. Seven liver metastases, two liver hemangiomas <10mm and three liver metastases between 10-20mm detected on RT FS T2w TSE were only retrospectively detected on BH FS T2w TSE. Qualitatively, RT FS T2w TSE performed significantly (p < 0.05) better than BH FS T2w TSE concerning image quality, lesion conspicuity, diagnostic confidence and artifacts. Mean CNR of all focal liver lesions, mean CNR of all focal liver lesions <10mm and mean CNR between liver hemangiomas and liver metastases was significantly better using the RT sequence compared with the BH sequence.

We concluded that RT FS T2w TSE performed better than BH FS T2w TSE for focal liver lesion detection and characterization in this study.

In chapter 3 a diffusion-weighted respiratory-triggered SS SE-EPI sequence using four b-values (b=0, b=20, b=300, b=800s/mm²) and T2w SS TSE in patients with focal liver lesions was prospectively compared. Special interest was on the detection of small (<10mm) focal liver lesions.

Twenty-four patients underwent routine MRI. The five sequences (SS SE-EPI using four sets of b-values (b=0, b=20, b=300, b=800s/mm²) and T2w SS TSE) were compared qualitatively for image quality, lesion conspicuity and artifacts. Quantitative analysis was performed for lesion identification and lesion-to-liver CNR. Subgroup analyses were performed for different types of lesions with different sizes. Sequences were compared by RIDIT and Kruskal-Wallis. Reference standard comprised surgery and/or follow-up.
Summary and Conclusions

The reference standard demonstrated 36 biliary cysts, 53 hemangiomas, 40 metastases. Best image quality (p<0.05) was achieved with T2w TSE and best lesion conspicuity (p<0.05) with T2w TSE for biliary cysts and SS SE-EPI DWI (b=20s/mm²) for liver hemangiomas and liver metastases. Image artifacts were lowest (p<0.05) with T2w TSE. T2w TSE was found to be the best modality (p<0.05) for identification of biliary cysts and SS SE-EPI DWI (b=20s/mm²) for liver hemangiomas and liver metastases. The lesion-to-liver CNRs were highest on T2w TSE for biliary cysts and SS SE-EPI DWI for liver hemangiomas and liver metastases (p<0.05).

We concluded that SS SE-EPI DWI (especially b-value 20s/mm²) is a promising technique for detection of small (<10mm) focal liver lesions.

In chapter 4 the added value of D, f and ADC\textsubscript{low} for differentiation between liver metastases and liver hemangiomas was prospectively examined. These measurements were based on respiratory-triggered high-resolution BB SS SE-EPI.

Twenty-five patients suspected for colorectal liver metastases were included in this study. Different b-value images were compared for lesion conspicuity, image quality and artifacts using RIDIT and Student’s t-test. D, f, and ADC\textsubscript{low} values were calculated. Pearson correlation coefficient was used for comparison of interobserver variability. Reference standard comprised surgery, biopsy and/or follow-up.

The reference standard demonstrated a total of 106 focal liver lesions (67 metastases and 39 hemangiomas). Best lesion conspicuity (p<0.05) was achieved with BB SS SE-EPI (b=0s/mm² and b=10s/mm²); best image quality (p<0.05) with b=10s/mm².
Image artifacts were lowest (p<0.05) with b=0s/mm². Over the whole sample, true diffusion coefficient D in liver metastases ($D_{\text{met}}$) was significantly (p<0.05) lower than true diffusion coefficient D in liver hemangiomas ($D_{\text{hem}}$); perfusion fraction f in liver metastases ($f_{\text{met}}$) and ADC value calculated from the images with no and low MPGs (ADC$_{\text{low}}$) in liver metastases (ADC$_{\text{low met}}$) was significantly (p<0.05) higher than perfusion fraction f in liver hemangiomas ($f_{\text{hem}}$) and ADC value calculated from the images with no and low MPGs (ADC$_{\text{low hem}}$) in liver hemangiomas. All Pearson correlations were statistically significant at a 0.01 level.

We concluded that BB SS SE-EPI is a useful technique to aid in differentiating between liver metastases and liver hemangiomas. The calculation of D, f and ADC$_{\text{low}}$ provides useful additional information for differentiating liver metastases from liver hemangiomas.

In chapter 5 a SS SE-EPI using b=0, 10, 150, 400 s/mm² was prospectively compared with standard MRI sequences pre- and post-SPIO in the detection and characterization of focal liver lesions. Patients suspected for metachronous liver metastases from colorectal carcinoma were evaluated with special focus on small (<10mm) focal liver lesions.

A total of 25 patients suspected for colorectal liver metastases were included. The number of detected focal liver lesions was evaluated. Image quality was compared between SS SE-EPI sequence and post-SPIO (T1w FS GE, T2w TSE and T2* GE) sequences using RIDIT. Focal liver lesion characterization was performed for SS SE-EPI and for all standard sequences pre- and post-SPIO. Reference standard comprised surgery, biopsy and/or follow-up.
Summary and Conclusions

The reference standard demonstrated 25 liver hemangiomas and 70 liver metastases. Best lesion detection ($p<0.05$) was achieved with SS SE-EPI ($b=10s/mm^2$). Best image quality ($p<0.05$) was achieved with post-SPIO T1w GE and T2w TSE. Lesion characterization using all standard MRI sequences pre- and post-SPIO performed best for lesion characterization compared with SS SE-EPI.

This preliminary study showed the potential of SS SE-EPI as a stand-alone sequence for the detection of liver hemangiomas and liver metastases when compared with SPIO-enhanced imaging. Standard sequences pre- and post-SPIO were needed for qualitative lesion characterization.

In chapter 6 a prospective comparison was made between FDG-PET/CT and MRI (including unenhanced SS SE-EPI and SPIO-enhanced MRI) for the detection of colorectal liver metastases.

Twenty-four consecutive patients with known or suspected liver metastases were investigated by both MRI and FDG-PET/CT. Histopathology or cross-sectional imaging follow-up were used as a reference standard.

Seventy-seven metastases were detected. In 9 patients, MRI and PET/CT gave concordant results. Sensitivities for unenhanced SS SE-EPI, MRI without SS SE-EPI and FDG-PET/CT respectively were 100% ($p = 9.10^{-10}$ vs PET, $p = 8.10^{-3}$ vs MRI without SS SE-EPI), 90% ($p = 2.10^{-7}$ vs PET) and 60%. PET/CT sensitivity dropped significantly with decreasing size, from 100% in lesions larger than 20 mm (identical to MRI), over 54% in lesions between 10 and 20 mm ($p = 3.10^5$ versus SS SE-EPI), to 32% in lesions under 10 mm ($p = 6.10^{-5}$ versus SS SE-EPI). Positive predictive value of PET and MRI was 100%.
We concluded that MRI, particularly unenhanced SS SE-EPI, has good sensitivity as well as positive predictive value for the detection of colorectal liver metastases. Its sensitivity is better than that of FDG-PET/CT, especially for small lesions.

In chapter 7 a prospective comparison for lesion conspicuity and image quality between SS SE-EPI DWI before, immediately after and 5 minutes after IV injection of SPIO in the detection and characterization of focal liver lesions was made. For comparison with SS SE-EPI concerning lesion detection and characterization, non-CE and post-SPIO T2w TSE sequences were additionally performed.

Twenty-five patients with known focal liver lesions with difficulty in characterization using US and/or CT or patients who were suspected for colorectal liver metastases were included. Lesion detection and characterization using 2-sided Fisher’s Exact Test was compared between SS SE-EPI DWI and T2w TSE (for both protocols non-CE and post-SPIO). Image quality and lesion conspicuity was compared for SS SE-EPI DWI (non-CE and post-SPIO) sequences using RIDIT. Reference standard comprised surgery, biopsy and/or follow-up.

Reference standard demonstrated different types of benign and malignant focal liver lesions (7 hemangiomas, 6 adenomas and 5 focal nodular hyperplasias, 40 colorectal metastases and 3 hepatocellular carcinomas). Best lesion detection (p<0.05) was achieved with non-CE SS SE-EPI DWI. Lesion characterization was best using T2w TSE. Best image quality and lesion conspicuity (p<0.05) was achieved with non-CE SS SE-EPI DWI.

We concluded that non-CE SS SE-EPI DWI is the most accurate sequence for focal liver lesion detection. SS SE-EPI DWI
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(non-CE and post-SPIO) in this study was not useful for focal liver lesion characterization.

In chapter 8 a prospective evaluation of a newly developed perfusion imaging sequence (4D THRIVE) using 3T was performed. Perfusion imaging of the whole liver in high temporal and spatial resolution using 4D THRIVE was evaluated. The characterization of focal liver lesions using parametric maps was also evaluated.

Fifteen patients suspected for colorectal liver metastases were included. Qualitative and quantitative evaluation (ROI placement including entire focal liver lesions) of the parametric maps was performed for all detected focal liver lesions. Reference standard comprised surgery with histopathology or follow-up imaging. RIDIT analysis was used for the evaluation of qualitative results and two-tailed student’s t-test for evaluation of quantitative results.

In total 29 liver metastases, 17 liver hemangiomas and four focal nodular hyperplasias were evaluated using 4D THRIVE. Qualitative analysis of the parametric maps resulted in significant differences in ring enhancement and lesion heterogeneity comparing liver metastases with benign focal liver lesions (liver hemangiomas and focal nodular hyperplasias). Quantitative analysis of the parametric maps comparing liver metastases, liver hemangiomas and focal nodular hyperplasias resulted in non-significant differences for perfusion parameters $K_{ep}$ and $K_{el}$.

We concluded that 4D THRIVE has the potential for perfusion imaging of the whole liver in high temporal and spatial resolution enabling the calculation of parametric maps. Qualitative evaluation was accurate for differentiating malignant and benign focal liver lesions. ROI placement including entire focal liver lesions...
was not useful for quantitative differentiation of malignant and benign focal liver lesions.

In chapter 9 the feasibility to incorporate phospholipids, derivatized with a metal complexing moiety, into an ML coat and to load the resulting nanocolloids with gadolinium ions was evaluated. The main goal of this study was to deliver a proof that it is feasible to construct a corona of lanthanide ions on top of nanosized MLs.

Small unilamellar phospholipid vesicles containing the PE-DTPA conjugate as one of the building stones were constructed. The ability of these colloids to complex gadolinium-III-ions at the surface of both the inner and outer bilayer shell was verified using a colorimetric method with Arsenazo III as a dye indicator.

Upon incubation of these functionalized vesicles with MLs, i.e. nanometer-sized magnetite cores encapsulated in a phospholipid bilayer, PE-DTPA percolates into the ML coat. The PE-DTPA content could be fine-tuned by varying the conjugate concentration in the donor vesicles. In the experimental conditions applied, up to 500 Gd$^{3+}$ ions were immobilized per ML colloid.

We concluded that it is feasible to construct a corona of lanthanide ions on top of nanosized MLs. The resulting ML-Gd$^{3+}$ complexes might have great potential, e.g. as a novel MRI contrast agent.

Magnetoliposomes have pronounced signal-enhancing effect on T1-weighted (T1w) images of the liver which may be beneficial for demonstrating peri-tumoural vasculature. In chapter 10 we correlated peri-tumoural vasculature (ring-enhancement) surrounding colorectal liver metastases after injection of
magnetoliposomes in a rat model using T1w imaging with histopathology.

Three rats were injected with CC531 colon carcinoma cells in the portal vein and were imaged at 3T. The presence of liver metastases, signal intensity changes within intrahepatic vessels, peri-tumoural vasculature (ring-enhancement) surrounding liver metastases on T1w imaging and histopathology, and the histopathological distribution of iron particles were evaluated. MRI findings were correlated with histopathology.

The diameter of the detected liver metastases using MRI ranged from 1.5mm to 4.7mm (mean: 2.4mm ; SD: 0.8mm). Ring-enhancement surrounding liver metastases was present in all detected liver metastases using contrast-enhanced T1w GE sequences. Ring-enhancement on T1w imaging corresponded with the presence of iron particles (blood-pooling of intact magnetoliposomes) within the dilated sinusoids surrounding the liver metastases on histopathology. SS SE-EPI detected five additional liver metastases compared with the T1w sequences. All liver metastases detected on MRI were confirmed by histopathology.

The blood-pooling of the iron oxide particles within the magnetoliposomes was demonstrated with increased hyperintensity of vessels after injection of magnetoliposomes on T1w sequences. Ring-enhancement on T1w sequences was useful for the detection and characterization of liver metastases in this study. Unenhanced SS SE-EPI was the most accurate MRI sequence for the detection of liver metastases.
CONCLUSIONS AND FUTURE RESEARCH

Conclusions

With the SS SE-EPI sequence described in this thesis for examining patients suspected for colorectal liver metastases, an improved detection of focal liver lesions is obtained with MRI as compared to standard work up. This SS SE-EPI sequence allows for detection of focal liver lesions as small as 2-3 mm. The SS SE-EPI sequence provides images depicting focal liver lesions as hyperintense foci that stand out like beacons against dark-gray liver parenchyma. The ability to detect (small) focal liver lesions easily – at the start of a liver protocol – makes SS SE-EPI a useful roadmap sequence. SS SE-EPI is particularly valuable for staging metastatic disease in patients suspected for colorectal liver metastases. Initially, SPIO-enhanced sequences (pre- and post-contrast) were included as a quality control measure when SS SE-EPI was used. However, the BB SS SE-EPI sequence has proved to be so robust that SPIO-enhanced sequences are no longer considered necessary for focal liver lesion detection. SS SE-EPI can therefore be considered as the new MRI reference standard for detection of focal liver lesions.

A relatively higher b-value between 400 and 800s/mm² provides more diffusion sensitivity and can therefore aid in lesion characterization. With a higher b-value, liver cysts will appear more hypointense when compared with liver hemangiomas and solid focal liver lesions. For further characterization of small (<10mm) non-cystic focal liver lesions calculation of $D$, $f$ and $ADC_{low}$ can be performed. Calculating $D$, $f$ and $ADC_{low}$ for liver metastases and liver hemangiomas, true diffusion in liver metastases ($D_{met}$) was lower than true diffusion in liver hemangiomas ($D_{hem}$); the perfusion factor of liver metastases ($f_{met}$) was higher than the perfusion factor of liver hemangiomas ($f_{hem}$) and the apparent diffusion coefficient at low b-
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values of liver metastases ($\text{ADC}_{\text{low met}}$) was higher than the apparent
diffusion coefficient at low $b$-values of liver hemangiomas ($\text{ADC}_{\text{low hem}}$). For characterization of focal liver lesions the calculation of $D$, $f$
and $\text{ADC}_{\text{low}}$ seems promising to decrease liver biopsy procedures in
the future.

With the 4D THRIVE sequence described in this thesis
examining patients suspected for colorectal liver metastases, T1-
weighted perfusion imaging of the whole liver with high temporal
and spatial resolution was performed. The characterization of focal
liver lesions using qualitative analysis of parametric maps seems
promising for differentiating malignant and benign focal liver lesions.
The calculation of perfusion parameters using ROI placement was
not useful for quantitative differentiation of malignant and benign
focal liver lesions in the studies performed in this thesis.

In the rat pilot study described in this thesis examining 3 rats
injected with human CC531 coloncarcinoma cells, unenhanced SS
SE-EPI and unenhanced and magnetoliposomes-enhanced T1-
weighted MRI at 3T was performed and correlated with
histopathology. The blood-pooling of the iron oxide particles within
the magnetoliposomes was demonstrated. Ring-enhancement
surrounding the liver metastases was seen on T1w imaging and
corresponded histopathologically with the presence of iron particles
(magnetoliposomes) within the dilated sinusoids surrounding the
liver metastases. Unenhanced SS SE-EPI was the most accurate MRI
sequence for the detection of liver metastases.

Clinical/radiological aspects

MRI is increasingly used as the definitive imaging modality
for the detection and characterization of focal liver lesions [1, 2].
Recent developments in MRI technology and the availability of novel
Summary and Conclusions

MRI contrast agents have resulted in MRI being recognized as the pre-operative standard in patients examined for focal liver lesions. This thesis describes new MRI developments for improved detection and characterization of liver metastases, focusing on the detection of small (<10mm) focal liver lesions. According to the studies in this thesis SS SE-EPI is considered the new gold standard for detection of focal liver lesions improving pre-operative evaluation of patients – especially in an oncological setting. Preliminary studies indicate the potential using perfusion MRI (4D THRIVE) to perform MRI of the whole liver with multiple dynamic (arterial and venous) phases. Its impact on the ability to differentiate malignant from benign focal liver lesions has to be examined further. The use of 4D THRIVE with parametric maps enables spatially matching tumour vascular characteristics such as blood volume, blood flow, permeability and leakage space. Parametric maps therefore have the advantage that they can be used in clinical practice and might also be useful for follow-up purposes (e.g. during therapy in an oncological setting). The magnetoliposomes-enhanced T1-weighted MRI experiments provide the proof-of-principle that magnetoliposomes can be used as stealth-magnetoliposomes improving the blood-pooling effect of the magnetoliposomes and demonstrating ring-enhancement surrounding liver metastases using magnetoliposomes-enhanced T1-weighted imaging. In this rat pilot study, the potential of magnetoliposomes-enhanced T1-weighted MRI to better characterize colorectal liver metastases is shown. Further animal experiments are needed to evaluate the usefulness of magnetoliposomes-enhanced T1-weighted MRI for follow-up examinations during treatment of colorectal liver metastases.

Considering the economically oriented choice for a diagnostic imaging technique, it is often debated that MRI is too expensive to
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screen for liver metastases. However, in cases where no liver metastases are visualized but underlying liver metastases are likely (e.g. abnormal laboratory results) or a limited number of liver metastases are found which are potentially resectable, a staging examination using MRI and BB SS SE-EPI seems essential. The cost of this additional MRI examination is relatively low considering the more accurate pre-operative assessment and more accurate choice of expensive therapeutic modalities tailored to the patient’s pathologic assessment.

Future research

Clearly, continuing improvements in imaging are allowing liver metastases to be identified at an earlier stage but still a different approach is needed to improve the detection of liver metastases smaller than 2-3 mm. All liver metastases start out as microscopic seedlings which eventually grow to a size where they become visible on imaging. The literature on liver imaging is generally limited by inadequate methods for verifying findings, and in most studies false negative lesions are not assessed. This inevitably means that reported sensitivities are overestimated and that the true incidence of disease is underestimated. Moreover, in more recent studies investigators have attempted to judge their results against more rigorous reference standards so there has been little if any improvement in apparent sensitivities despite continuing improvements in imaging techniques. It is also likely that these results continue to underestimate the problem of liver metastases in the millimeter size range and reported sensitivities remain falsely elevated. Even when histological examination of the resected liver is used as the 'gold standard' the verification of very small
focal liver lesions is questionable since most specimens are sectioned at 1 cm intervals. Furthermore, recent follow-up studies have confirmed that a proportion of small liver metastases are undetected by preoperative imaging and surgery with IOUS [1]. Magnetic Resonance Elastography (MRE) is a non-invasive method of measuring the visco-elastic properties of the liver. MRE allows the measurement of tissue elasticity and tissue viscosity, both of which are promising for the non-invasive evaluation of human tissues. MRE has shown promise for the grading of liver fibrosis [3, 4] and improved characterization of breast tumours [5]. Applying this novel MRE technique for the characterization of focal liver lesions may be promising. Recently MRI has been used to measure Hepatic Perfusion Indices (HPI) [6, 7] but the technique remains developmental and the best measurement method is still to be determined. Once the methodology is established, rigorous multi-observer studies will be required to validate the technique and determine its impact on patient management. The use of molecular imaging techniques for the detection and characterization of liver metastases in clinical practice is even more futuristic.
REFERENCES