Development of new imaging techniques for improved detection and characterization of focal liver lesions using magnetic resonance imaging
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Citation for published version (APA):

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Chapter 4

Evaluation of true diffusion, perfusion factor, and apparent diffusion coefficient in non-necrotic liver metastases and uncomplicated liver hemangiomas using black-blood echo planar imaging.

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Eur J Radiol 2007, Oct 18, Epub ahead of print
ABSTRACT

Objective: To assess the added value of true diffusion (D), perfusion factor (f) and Apparent Diffusion Coefficient at low b-values (ADC_{low}) for differentiation between liver metastases and hemangiomas based on respiratory-triggered high-resolution Black-Blood Single-Shot Spin-Echo Echo Planar Imaging (BB SS SE-EPI).

Methods: Twenty-five patients suspected for malignant colorectal liver lesions were included in this study. A total of 106 lesions were examined. Different b-value images were compared for lesion conspicuity, image quality and artifacts using rank order statistic (RIDIT) and Student’s t-test. D, f, and ADC_{low} values were calculated. Pearson correlation coefficient is used for comparison of interobserver variability.

Results: 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, D in metastases (D_{met}) was significantly (p<0.05) lower than D in hemangiomas (D_{hem}); f and ADC_{low} of metastases (f_{met} respectively ADC_{low met}) was significantly (p<0.05) higher than f and ADC_{low} of hemangiomas (f_{hem} respectively ADC_{low hem}). All Pearson correlations were statistically significant at a 0.01 level.

Conclusion: This preliminary study shows the potential of BB SS SE-EPI as a useful technique to aid in differentiating between liver metastasis and hemangioma. The calculation of D, f and ADC_{low} provides useful additional information for differentiating metastases from hemangiomas.
INTRODUCTION

Recently, diffusion-weighted imaging techniques for the identification of focal liver lesions have been studied [1, 2]. Using Black-Blood Single-Shot Spin-Echo Echo Planar Imaging (BB SS SE-EPI), black-blood images of the liver are obtained by applying low b-values, facilitating differentiation between a lesion and vessel [1, 3].

In a previously published paper [4, 5], BB SS SE-EPI showed promising results in the detection of small (<10mm) focal liver lesions. Although detection of small focal liver lesions is an important issue in the follow-up of oncologic patients, the main goal remains the characterization of all detected focal liver lesions.

Diffusion-weighted MRI is sensitive to molecular diffusion due to random and microscopic translational motion of molecules, known as Brownian motion, because random motion in the field gradient produces incoherent phase shifts that result in signal attenuation. Flowing spins induce the same attenuation effect; the pseudorandom organization of the moving spins at the voxel level, such as perfusion, can also be considered to be an incoherent motion, and this effect can induce much larger signal attenuation than the diffusion effect on an image with very low motion-probing gradients (MPGs) [6]. On the basis of this theory, the apparent diffusion coefficient (ADC) value calculated from the images with no and low MPGs is considered to be more strongly influenced by the flowing spins (microcirculation) than molecular diffusion. The true diffusion coefficient (D) can be obtained from the calculation from images with the higher MPGs [7]. D as measured at IntraVoxel Incoherent Motion (IVIM) MR imaging is a true parameter of molecular diffusion [7]. It therefore permits characterization of tissues and pathologic conditions. Furthermore, the perfusion fraction f as measured at
IVIM MR imaging provides another useful measure enabling characterization of abdominal organs and hepatic lesions [8].

The primary purpose was to study the differential diagnostics between liver metastases and hemangiomas by quantitative evaluation of D, f and ADC\textsubscript{low} using a respiratory-triggered BB SS SE-EPI sequence with four b-values (b=0, b=10, b=150, b=400s/mm\textsuperscript{2}). Evaluation of lesion conspicuity, image quality and artifacts were the secondary purpose of this study.

**MATERIALS AND METHODS**

**Patients**

Twenty-five consecutive patients (11 female; 14 male, mean age 62.3 ± 13.1 years) suspected for metastatic focal liver lesions from colorectal carcinoma were included in this study. Patients were included in the present study when at screening a new non-cystic focal lesion was detected at ultrasound and/or laboratory results showed elevated Carcino Embryonic Antigen > 3.4 ng/ml for non-smokers, >4.3 ng/ml for smokers in combination with elevated transaminase levels (ALT >41 U/l for male, >31 U/l female patients), elevated alkaline phosphatase >129 U/l, and elevated bilirubin (total bilirubin > 1.2 mg/dl). Patients were excluded when there were contraindications for IV injection of Small Particles of Iron Oxide (SPIO) or MRI.

In total 106 liver lesions were present. Twelve liver metastases were diagnosed at surgery, and 7 were diagnosed on the basis of the pathologic study of the biopsy specimen. The remaining 48 liver metastases showed lesion regression or progression on serial CT (LightSpeed 16, General Electric Medical Systems, Milwaukee, USA) and/or MRI examinations during treatment, respectively corresponding with response respectively
absent/insufficient response to treatment. Progressive disease in this study is defined as at least 20% increase of the maximum initial diameter or at least 5mm increase of the maximum initial diameter of a focal liver lesion. Partial response in this study is defined as at least 20% decrease of the maximum initial diameter or at least 5mm decrease of the maximum initial diameter of a focal liver lesion.

The site of primary disease included the colon and rectum in all cases. The diameter of the liver metastases ranged from 3 to 39mm (mean 13.9mm). There were no necrotic liver metastases present in this study.

The diagnosis of 39 hepatic lesions was hemangioma on the basis of typical findings on contrast-enhanced CT scans and stability in size and morphology on serial US (Aplio, Toshiba Medical Systems Corporation, Tochigi, Japan) scans after a minimum of 6 months. The diameter of the hemangiomas measured on MR images ranged from 3 to 28mm (mean 12.1mm). None of the hemangiomas showed signs of complications.

Liver cysts were not evaluated as they (almost) never pose any differential diagnostic problem using MRI.

This prospective study was approved by the hospital ethics committee and written informed consent was obtained from all patients.

**Technique**

A 1.5T MRI whole-body scanner (Intera (release 11.1.3), Philips Medical Systems, Best, The Netherlands) with a 4-elements SENSE (SENSitivity Encoding) body phased-array coil was used. Gradients were used with a maximum gradient of 66mT/m along x-, y-, and z-axis. A routine MRI examination was performed using T2w TSE Half-Fourier (short TE with fat suppression and long TE without
Respiratory-triggered BB SS SE-EPI sequence

fat suppression), T2* GE, in and out phase imaging, and fat saturated T1w 3D gradient echo imaging before the IV injection of SPIO (Resovist®, Schering, Berlin, Germany), during the arterial, portal-venous, late venous phase (80 seconds after IV injection) and 15 minutes after IV injection of SPIO, followed by T2w TSE Half-Fourier (short TE with fat suppression) and T2* GE in the delayed phase (>15 minutes after IV injection of SPIO) in all patients.

All these MRI examinations were combined with a respiratory-triggered BB SS SE-EPI. The respiratory-triggered BB SS SE-EPI images were acquired at the start of each MRI examination using the following parameters:

Axial fat-suppressed BB SS SE-EPI sequence with b-values of 0, 10, 150, and 400 s/mm²: TR: single shot technique, TE: 55.83 ms (gradient over-plus), flip angle: 90°, NSA: 4, FOV: 300 mm x 315 mm, matrix 160x256 with 80% scan percentage, half scan factor 0.6, slice thickness 7 mm, slice gap 0 mm, foldover direction RL, EPI-factor 51, SENSE-factor 2 along the in-plane phase-encoded direction, Spectral Attenuated Inversion Recovery (SPAIR) pulse inversion delay: 52.2 ms, water fat shift: maximal. The measured voxel size was 1.91 mm x 2.42 mm x 7 mm and the reconstructed voxel size was 1.19 mm x 1.19 mm x 7 mm. Respiratory-triggering using a belt system was performed with scanning performed during the expiration phase. Depending on the breathing frequency of each patient, the acquisition time for this sequence ranged from 3 to 5 minutes.

Qualitative analysis

Two abdominal radiologists, experienced in interpreting liver MRI in daily clinical practice (6 years and 14 years of experience respectively), independently evaluated all BB SS SE-EPI images and
subjectively rated each BB SS SE-EPI sequence \((b=0, 10, 150\) and 400s/mm\(^2\)) for overall lesion conspicuity, image quality and artifacts. Overall lesion conspicuity and image quality were based on the following five grading scales: excellent = 5; good = 4; fair = 3; poor = 2; and unacceptable = 1. The presence of artifacts was rated using the following four grading scales: absent = 4; mild = 3; moderate = 2; and severe = 1.

**Lesions characterization**

**ROI placement**

Both readers placed the regions of interest (ROIs) independently on all the focal liver lesions. The ROIs were drawn manually to encompass the whole lesion at maximum diameter. ROIs were drawn starting on the images where lesions could be best detected \((b=10s/mm^2)\). Then, each ROI was copied to the corresponding other \(b\)-value images to most accurately encompass each lesion with a ROI. One value of signal intensity was measured by each reader and the average was computed.

Signal intensities were measured independently by the same two abdominal radiologists experienced in interpreting liver MRI in daily clinical practice. They were unaware of the measurements and evaluations performed by each other. They did not have any other information about patient history, clinical examination, laboratory results, findings of other imaging techniques, or final diagnosis.

After at least a four weeks interval after ROI placement consensus reading for identification of the earlier detected focal liver lesions on the BB SS SE-EPI images was performed based on the routinely obtained MRI sequences.
Quantitative analysis

The contribution of flowing spins/microperfusion to the signal intensity is almost negligible [9] when performing diffusion imaging of the liver with a b-factor of 150 and 400 s/mm². In this study the true diffusion value, \( D \), was calculated as:

\[
D = \frac{\ln \left( \frac{SI(b=150)}{SI(b=400)} \right)}{250}
\]

\( SI(b=150) \): the average signal intensity of a focal liver lesion measured in a ROI on a b=150 image

The perfusion factor \( f \) was calculated as:

\[
f = \frac{SI(b=0) - SI_a}{SI(b=0)}
\]

\( f \) is the (microperfusion) deviation factor representing the fractional volume (of spins) occupied in the voxel by flowing spins (= sum of the spins in the microcirculation and spins in turbulent flow)

\( SI_a \) is the expected signal intensity based on diffusion effects only at \( b = 0 \).

\( SI_a \) can be obtained from the following equation:

\[
\ln (SI_a) = \ln (SI(b=150)) + 150 \times D
\]

Apparent diffusion coefficient at low b-values (\( ADC_{low} \)), which integrates the effects of both diffusion and perfusion is defined and calculated as:

\[
ADC_{low} = \frac{\ln \left( \frac{SI(b=0)}{SI(b=10)} \right)}{10}
\]

The \( ADC_{low} \) value is expected to be relatively more affected by flowing spins than true diffusion [9].
Statistical Analysis

The different b-value images were compared qualitatively for lesion conspicuity, image quality and artifacts using rank order statistic (RIDIT) and Student’s t-test for independent groups.

The mean $D$, $f$ and $ADC_{\text{low}}$ of liver metastases and liver hemangiomas were compared using the two-tailed Student’s t-test. Besides overall comparison in the sample, analysis was repeated for three subgroups categorized by lesion size: group 1 with size < 10mm; group 2 with size ranging between 10mm and 20mm; and group 3 with size >20mm.

Lesion resection and histopathologic verification could not be performed in many cases. As a consequence sensitivity, specificity and accuracy cannot be calculated because of lack of best reference standard. Therefore Pearson correlation coefficient is used for comparison of interobserver variability.

Numeric $D$, $f$ and $ADC_{\text{low}}$ measurements of two readers are compared for six sets of lesion-size combinations. Lesions are metastases and hemangiomas, sizes are <10mm, 10-20mm and >20mm in diameter.

RESULTS

From all patients diffusion-weighted images (figure 1, 2 and 3) could be obtained and consequently signal intensity measurements were calculated in all detected focal liver lesions excluding all biliary cysts.

In total 67 liver metastases (30, 23, and 14 metastases with a diameter of respectively <10mm, 10-20mm, and >20mm) and 39 liver hemangiomas were identified (20, 13, and 6 hemangiomas with a diameter of respectively <10mm, 10-20mm, and >20mm). Nineteen liver metastases were histologically proven.
Figure 1. Two small liver metastases (<10mm) (white arrows). The detection of one of these metastases abutting the intrahepatic vasculature is clearly hampered using BB SS SE-EPI (b=0s/mm², fig.1a).

The usefulness of the coinciding black-blood effect using BB SS SE-EPI (b=10s/mm², fig.1b; b=150s/mm², fig.1c; b=400s/mm², fig.1d) for the detection of one of these metastases abutting the intrahepatic vasculature is illustrated. Fig.1e shows the corresponding T2w TSE Half-Fourier (short TE with fat suppression) in the delayed phase (>15minutes) after IV injection of SPIO. The metastasis abutting the intrahepatic vasculature is harder to detect.
Figure 2. A medium size subphrenic liver metastasis (white arrow) using BB SS SE-EPI (b=0s/mm², fig.2a; b=10s/mm², fig.2b; b=150s/mm², fig.2c; b=400s/mm², fig.2d). Susceptibility artifacts of the lungs sometimes hamper the evaluation in lesions which are located at the periphery of the liver in the subphrenic hepatic areas especially in the higher b-value BB SS SE-EPI images.

Fig.2e shows the corresponding T2w TSE Half-Fourier (short TE with fat suppression) in the delayed phase (>15 minutes) after IV injection of SPIO of the subphrenic metastasis (white arrow).
Respiratory-triggered BB SS SE-EPI sequence

Figure 3. A typical behaviour of a liver metastasis (white arrow; b=10s/mm², fig.3a; b=400s/mm², fig.3b) and a liver hemangioma (white arrow; b=10s/mm², fig.3c; b=400s/mm², fig.3d) using BB SS SE-EPI with low (b=10s/mm²) and high (b=400s/mm²) b-value. A decrease of signal intensity at higher b-values is more in keeping with a hemangioma than a metastasis.

Qualitative analysis

Lesion conspicuity

For all liver metastases, a significantly (p<0.05) better lesion conspicuity was obtained with BB SS SE-EPI with b=10s/mm² (Figure 4a) when compared with the remaining BB SS SE-EPI b-value images. Lesion conspicuity of liver hemangiomas was also significantly (p<0.05) better with BB SS SE-EPI with b=10s/mm²
when compared with the remaining BB SS SE-EPI b-value images (Figure 4b).

**Figure 4a.** Comparison of the lesion conspicuity for all liver metastases.

**Figure 4b.** Comparison of the lesion conspicuity for all liver hemangiomas.
Image quality

There was significantly (p<0.05) better overall image quality for BB SS SE-EPI (b=0s/mm² and b=10s/mm²) when compared with the remaining BB SS SE-EPI b-value images (Figure 4c). BB SS SE-EPI with b=150s/mm² and b=400s/mm² had significantly (p<0.05) inferior overall image quality which in part could be explained by a loss of signal.

Artifacts

Image artifacts were significantly (p<0.05) less in BB SS SE-EPI with b=0s/mm² when compared with the remaining BB SS SE-EPI b-value images (Figure 4d).

Lesions identification

A substantial part of the focal liver lesions included were <10mm in diameter. This is important for an accurate comparison of the studied sequences for the purpose of lesion detection.
Quantitative analysis

The mean D (D mean), mean f (f mean) and mean ADC_{low} (ADC_{low} mean) for metastases and hemangiomas in the liver are summarized in table 1.

Results for the whole sample show true diffusion in metastases (D_{met}) was significantly (p<0.05) lower than true diffusion in hemangiomas (D_{hem}); the perfusion factor of metastases (f_{met}) was significantly (p<0.05) higher than the perfusion factor of hemangiomas (f_{hem}); and the apparent diffusion coefficient at low b-values of metastases (ADC_{low met}) was significantly (p<0.05) higher than the apparent diffusion coefficient at low b-values of hemangiomas (ADC_{low hem}).

The same pattern applied for small lesions <10mm.

For medium size lesions, only D showed statistical significant difference (p<0.05) between metastases and hemangiomas.

For lesions >20mm, D and f showed statistical significant difference (p<0.05) between metastases and hemangiomas.
Respiratory-triggered BB SS SE-EPI sequence

Table 1. Comparison of D, f and ADC\textsubscript{low} between liver metastases and hemangiomas

<table>
<thead>
<tr>
<th></th>
<th>Metastasis</th>
<th>Hemangioma</th>
<th>t-value</th>
<th>two-tailed p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>D mean</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>all</td>
<td>0.001097</td>
<td>0.002118</td>
<td>7.266</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;10mm</td>
<td>0.001284</td>
<td>0.001491</td>
<td>2.6079</td>
<td>0.014</td>
</tr>
<tr>
<td>10-20mm</td>
<td>0.001093</td>
<td>0.003213</td>
<td>8.5208</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;20mm</td>
<td>0.0007</td>
<td>0.001833</td>
<td>5.8175</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>f mean</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>0.20594</td>
<td>0.05474</td>
<td>-6.6166</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;10mm</td>
<td>0.159047</td>
<td>0.002909</td>
<td>-5.963</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>10-20mm</td>
<td>0.197692</td>
<td>0.119932</td>
<td>-1.9092</td>
<td>0.066</td>
</tr>
<tr>
<td>&gt;20mm</td>
<td>0.319976</td>
<td>0.086261</td>
<td>-7.2943</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>ADC\textsubscript{low} mean</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>0.013413</td>
<td>0.007037</td>
<td>-3.5612</td>
<td>0.001</td>
</tr>
<tr>
<td>&lt;10mm</td>
<td>0.018743</td>
<td>0.005023</td>
<td>-4.9542</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>10-20mm</td>
<td>0.007827</td>
<td>0.008919</td>
<td>0.3829</td>
<td>0.706</td>
</tr>
<tr>
<td>&gt;20mm</td>
<td>0.011171</td>
<td>0.009672</td>
<td>-0.8672</td>
<td>0.397</td>
</tr>
</tbody>
</table>

Results of Pearson correlation coefficient are given in table 2. All Pearson correlations are statistically significant at a 0.01 level.
Table 2. Calculation of interobserver agreement using Pearson correlation coefficient for D, f and ADC_{low}

<table>
<thead>
<tr>
<th>Lesion type</th>
<th>Lesion size (in mm)</th>
<th>Pearson Correlation Coefficient (D)</th>
<th>Pearson Correlation Coefficient (f)</th>
<th>Pearson Correlation Coefficient (ADC_{low})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastasis</td>
<td>&lt;10</td>
<td>0.969</td>
<td>0.993</td>
<td>0.994</td>
</tr>
<tr>
<td>Metastasis</td>
<td>10-20</td>
<td>0.991</td>
<td>0.998</td>
<td>0.963</td>
</tr>
<tr>
<td>Metastasis</td>
<td>&gt;20</td>
<td>0.999</td>
<td>0.999</td>
<td>0.997</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>&lt;10</td>
<td>0.993</td>
<td>0.999</td>
<td>0.981</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>10-20</td>
<td>0.999</td>
<td>0.999</td>
<td>0.999</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>&gt;20</td>
<td>0.983</td>
<td>0.999</td>
<td>0.978</td>
</tr>
</tbody>
</table>

**DISCUSSION**

In this study, the potential of BB SS SE-EPI [4, 5] for identification and characterization of focal liver lesions was examined. Overall lesion conspicuity, image quality and artifacts are better using BB SS SE-EPI at low b-values. The RIDIT plots 4a and 4b suggest that a solid lesion that becomes less conspicuous at higher b-values is more in keeping with hemangioma rather than metastases (fig.3). The calculation of D seems promising in differentiating between liver metastases and liver hemangiomas when considering all subgroups of focal liver lesions. The calculation of f performs second best as an indicator of differentiation since it shows only a non-significant difference in the medium size lesion subgroup. The calculation of ADC_{low} seems less promising as an indicator for differentiation between metastases and hemangiomas since it only shows statistical significant differences in the whole sample and for small sized lesions. These study results have to be
confirmed in future studies. For all six sets of lesion-size combinations, a very good interobserver agreement was obtained. All Pearson correlations are statistically significant at a 0.01 level. This means that the studied technique for calculation of $D$, $f$ and $\text{ADC}_{\text{low}}$ is invariant from the reader and thus stable.

The overall better lesion conspicuity for BB SS SE-EPI with $b=10\text{s/mm}^2$ can be explained by the black blood effect in these images, which is especially helpful for detection of small ($<10\text{mm}$) lesions in the vicinity of intrahepatic vessels. The overall better image quality for BB SS SE-EPI at low $b$-values ($b=0$ and $10\text{s/mm}^2$) when compared with the BB SS SE-EPI at higher $b$-values ($b=150$ and $400\text{s/mm}^2$) can be explained by a loss of signal at higher $b$-values. The overall less present artifacts for BB SS SE-EPI at low $b$-values ($b=0$ and $10\text{s/mm}^2$) when compared with the BB SS SE-EPI at higher $b$-values ($b=150$ and $400\text{s/mm}^2$) can be explained by less pronounced susceptibility artifacts.

Comparison with previous studies is difficult as for the moment there is few literature available. If available the size of the focal liver lesions is not mentioned or the study is performed with large liver lesions. Yamada I et al. [10] do not report on the dimensions of the examined liver lesions. Accurate comparison with our study is not possible as Yamada et al. used a combination of low and high $b$-values for their calculations. Moteki T et al. [7] report on the $D$, $f$ and $\text{ADC}_{\text{low}}$ of focal liver lesions with a diameter of more than $20\text{mm}$. True diffusion in their study was lower when considering all metastases and was comparable with our results when considering all hemangiomas. However, they did not find any significant differences regarding $f$ when comparing liver metastases and liver hemangiomas. Taouli B et al. [11] report on the ADC (calculated with low and high $b$-values) of focal liver lesions with a diameter of
more than 20mm (when focusing on the liver metastases and the liver hemangiomas). The ADC values for liver metastases and liver hemangiomas cannot be compared with the \( \text{ADC}_{\text{low}} \) values in our study. Koh D-M et al. [12] report on the \( D, f \) and ADC of liver metastases from colorectal malignancies with a mean diameter of 21mm. They report a mean \( D \) and \( f \) value in the range of values which were obtained in our study. The ADC value in their report was clearly lower than the ADC value in our study. The ADC calculation was performed with signal intensities of lesions on the \( b=0 \) and \( b=10 \) images (Koh D-M et al. used the combination of \( b=0, b=150 \) and \( b=500 \text{s/mm}^2 \)); the perfusion effect being more pronounced (compared with the diffusion effect) in our study could explain the higher ADC values in our study.

In our study, the liver metastases had lower \( D \) values when compared with liver hemangiomas. This can be explained by their high tumoural content, which restricts the water diffusion. All the metastatic lesions included in our study were solid and did not manifest necrotic components that can increase the \( D \) value. In this study, an overall higher \( f \) (representing the density of the capillaries containing flowing blood) and \( \text{ADC}_{\text{low}} \) value in the liver metastases when compared with hemangiomas is seen. Hemangiomas are composed of vascular lakes containing lakes of blood pooling. Therefore, it is expected that their blood fraction should be lower than that of colorectal liver metastases recruiting arterial neoangiogenetic vessels. The blood pooling in the hemangiomas in this study is probably too slow to be influenced by the diffusion-weighted sequence. Another explanation can be that results in this study are biased by partial volume effects as many lesions in this study were <10mm.
To our knowledge this is the first study reporting on $D$, $f$ and $\text{ADC}_{\text{low}}$ values comparing liver metastases and liver hemangiomas of different size ranges. When dealing with small liver lesions, the differentiation between liver metastases and liver hemangiomas can be difficult. Since a previously described BB SS SE-EPI sequence [4, 5] allows for the detection of small (<10 mm) liver lesions, the characterization of these small lesions is of clinical importance, especially in the staging of an oncologic disease. This study is a first step in offering additional tools for the characterization of focal liver lesions by calculating $D$, $f$, and $\text{ADC}_{\text{low}}$. In case of difficult characterization of focal liver lesions, the calculation of $D$, $f$, and $\text{ADC}_{\text{low}}$ might be useful when comparing the quantitative values $D$, $f$, and $\text{ADC}_{\text{low}}$.

Our study has several limitations. Biliary cysts were excluded as these are highly affected by the flowing spins, even in the absence of perfusion [7]. Therefore, this study was focused on the calculation of $D$ and $f$ in non-necrotic liver metastases and in non-complicated liver hemangiomas. Considering that breath movement may rock both the liver and the cysts within it, it is very likely that turbulent flow causes marked signal attenuation in the images with MPGs when dealing with cystic/necrotic liver lesions. When dealing with cystic or necrotic lesions/components in a lesion, movements of any kind will affect the different diffusion values in an unpredictable manner [7]. This is a limitation in our study.

When measuring the different diffusion values in focal liver lesions, some authors stress the importance of performing the scanning within each patient with an identical time delay after the QRS-complex/systolic contraction of the heart. This allows obtaining images with comparable perfusion between different heart beats. Also, pulse triggering to the diastolic heart phase is important to
some authors as it leads to reduced motion artifacts on the diffusion-weighted images and to a significantly improved accuracy and reproducibility of measurements of the ADCs of the abdominal organs [13]. As described above, this study was performed only using respiratory-triggering. In a pilot study (unpublished data), we experienced that the addition of ECG- or pulse-triggering to this sequence on average caused a near three-fold increase in scan time of the above described BB SS SE-EPI sequence. Moreover, movements of some patients during this long-lasting sequence caused considerable artifacts.

An additional limitation of this study is the lack of atypical hemangiomas which can be particularly difficult to differentiate from liver metastases. A future study focusing on the differentiation between these two types of liver lesions seems useful.

The results in this study could be biased by partial volume effects as many lesions in this study were <10mm. The lack of histological proof in many lesions is a limitation of this study.

In conclusion, this study provides evidence that diffusion-weighted MR imaging can give additional physiologic information of focal liver lesions. Diffusion-weighted MR imaging allows the calculation of $D$, $f$ and $\text{ADC}_{\text{low}}$ values which can potentially be useful for the differentiation between liver metastases and liver hemangiomas. The most appropriate and time-effective b-value combination for the daily practice as a consequence of this study are as follows: overall lesion conspicuity/detection for liver metastases and hemangiomas is optimized using BB SS SE-EPI with $b=10\text{s/mm}^2$. Using two different b-values (150 s/mm$^2$ or higher (e.g. 400 s/mm$^2$)) allows the calculation of true diffusion. Combining these two different b-values (150 s/mm$^2$ or higher) with $b=0$ and
Respiratory-triggered BB SS SE-EPI sequence

10s/mm² allows the calculation of D, f and \(\text{ADC}_{\text{low}}\). Considering these results, diffusion-weighted imaging and the calculation of D, f, and \(\text{ADC}_{\text{low}}\) could have a useful clinical impact to the more standard used sequences for the characterization of focal liver lesions and seems a promising sequence to decrease biopsy procedures in the future. Further studies are required to confirm the presented results.
REFERENCES


