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

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Chapter 5

Improved focal liver lesion detection: Comparison of single-shot spin-echo echo-planar and superparamagnetic iron oxide (SPIO)-enhanced MRI.

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ABSTRACT

Objective: To prospectively compare Single-Shot Spin-Echo Echo Planar Imaging (SS SE-EPI) using b=0, 10, 150, 400 s/mm² with standard MRI techniques after intravenous Super Paramagnetic Iron Oxide (SPIO) in the detection and characterization of focal liver lesions with focus on small (<10mm) focal liver lesions.

Methods: A total of 25 patients suspected for colorectal liver metastases were included. Number of detected lesions was evaluated. Image quality was compared between SS SE-EPI sequence and post-SPIO (fat-suppressed T1-weighted (T1w) Gradient Echo (GE), T2-weighted (T2w) Turbo Spin Echo (TSE) and T2* GE) sequences using rank order statistic (RIDIT). Lesion characterization was performed for SS SE-EPI and for all remaining sequences pre- and post-SPIO. Reference standard comprised surgery, biopsy and/or follow-up.

Results: Reference standard demonstrated 25 hemangiomas and 70 metastases. Best lesion detection respectively best image quality (p<0.05) was achieved with SS SE-EPI (b=10s/mm²) respectively post-SPIO T1w GE and T2w TSE. Lesion characterization using all sequences pre- and post-SPIO performed best for lesion characterization compared with SS SE-EPI.

Conclusion: This preliminary study shows the potential of SS SE-EPI as a stand-alone sequence for the detection of liver hemangiomas and metastases when compared with SPIO-enhanced imaging. Sequences pre- and post-SPIO are needed for qualitative lesion characterization.
INTRODUCTION

In patients with (suspicion of) colorectal liver metastases, accurate diagnostic work up is mandatory with respect to number and characterization of lesions. Present imaging techniques have a high accuracy for detection of metastases larger than 10mm, but provide poor results for smaller liver lesions [1]. Morana G et al. [2] have shown in cadaver studies of primary colorectal carcinoma that, on average, at least one liver metastasis less than 10mm in diameter is missed for each detected liver metastasis larger than 10mm. Optimization of imaging techniques for the detection of all (benign and malignant) focal liver lesions less than 10mm is needed, especially in the detection and staging of malignant disease. Super Paramagnetic Iron Oxide (SPIO)-enhanced MR imaging nowadays is regarded as the best available non-invasive examination technique in the evaluation of hepatic metastases [3].

Characterization of the detected liver lesions is a second important step in liver imaging. Characterization of liver lesions can be very difficult especially when dealing with small liver lesions. Hemangiomas are frequently detected benign liver lesions. A good differentiation between liver hemangiomas and metastases determines the actual treatment planning in patients treated for colorectal carcinoma. SPIO-enhanced MR imaging has high sensitivity that matches that of Computed Tomography (CT) during arterioportography and higher specificity than that of CT during arterioportography [4-7]. SPIO-enhanced MRI for the moment is regarded as the best available non-invasive imaging technique in the evaluation of hepatic metastases.

Diffusion-weighted imaging in the liver is useful for the detection of focal liver lesions because of the black-blood effect when using low b-values. This black blood effect has been proven to be
SS SE-EPI sequence and post-SPIO sequences

useful in detecting focal liver lesions near the intrahepatic vessels [8]. Moreover, diffusion-weighted imaging of the liver has been shown to be promising in the detection of small (<10mm) focal liver lesions, especially -but not only- when lying in the vicinity of the intrahepatic vasculature [9].

A previous study [9] examining the potential of the presented Single-Shot Spin Echo Echo Planar Imaging (SS SE-EPI) sequence compared with a respiratory-triggered T2-weighted (T2w) Turbo Spin Echo (TSE) has demonstrated the potential of low b-values in the detection of small (< 10mm) focal liver lesions. To further evaluate the performance of SS SE-EPI in the detection of focal liver lesions, a dedicated MRI sequence in combination with the use of SPIO seems useful.

The purpose of this study is to prospectively compare SS SE-EPI as a stand-alone sequence with “state-of-the-art” MRI techniques before and after the intravenous injection of SPIO in the detection and characterization of focal liver lesions with focus on small (<10mm) focal liver lesions.

MATERIALS AND METHODS

Patients

From October 2005 to November 2006, twenty-five consecutive patients (13 female; 12 male, mean age 62.8 ± 9.7 years) suspected for metachronous liver metastases from colorectal carcinoma at a tertiary referral centre were included in this study. Patients were included in the present study when at follow-up for a primary tumour, a new non-cystic focal liver lesion was detected at ultrasound (US) 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 (alanine
aminotransferase (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 intravenous injection of SPIO (Resovist®, Schering, Berlin, Germany) or for MRI. This prospective study was approved by the hospital ethics committee and written informed consent was obtained from all patients.

**MRI technique**

A 1.5T MRI whole-body scanner (Intera (release 11), Philips Medical Systems, Best, The Netherlands) with a 4-elements SENSitivity Encoding (SENSE) body phased-array coil was used. Gradients were used with a maximum gradient of 66mT/m along x-, y-, and z-axis.

An overview of the applied MRI sequences (see also Table 1) in all patients is displayed below. Sequence 1 was compared with the set of post-SPIO sequences (sequence 6 to 8) concerning lesion detection. Sequence 1 was compared with the remaining set of sequences (sequence 2 to 8) concerning lesion characterization.

**Sequence 1:** respiratory-triggered SS SE-EPI

**Sequence 2:** fat-suppressed T2w TSE (short TE)

**Sequence 3:** T2w TSE with long TE without fat suppression

**Sequence 4:** fat-suppressed T2* gradient echo (GE)

**Sequence 5:** T1-weighted (T1w) GE in and out phase imaging

**Sequence 6:** fat-suppressed T1w 3D GE imaging before the intravenous (IV) injection of SPIO, during the arterial, portal-venous, late venous phase (80 seconds after intravenous injection) and 15 minutes post-SPIO (delayed phase)

**Sequence 7:** post-SPIO fat-suppressed T2w TSE: T2w TSE (short TE with fat suppression) > 15 minutes post-SPIO (delayed phase); parameters identical to those of sequence 2
SS SE-EPI sequence and post-SPIO sequences

**Sequence 8:** post-SPIO fat-suppressed T2* GE > 15 minutes post-SPIO (delayed phase); parameters identical to those of sequence 4

Details of the respiratory-triggered SS SE-EPI (sequence 1) are as follows: axial fat-suppressed single-shot spin-echo (SE) type of EPI sequence with b-values of 0, 10, 150, and 400 s/mm². The motion-probing gradient pulses of the SS SE-EPI sequence were placed along the S, P and M (Slice, Phase and Measurement) direction. During image interpretation, we used only the isotropic images synthesized from the three images in which the motion-probing gradient pulses were placed in each direction. The measured voxel size was 1.91mm x 2.42mm x 7mm and the reconstructed voxel size was 1.19mm x 1.19mm x 7mm. Depending on the respiratory efficiency of each patient, the acquisition time for this sequence ranged from 3 to 5 minutes. Further details of the above mentioned sequences are given in table 1.

In all patients 1.4ml of SPIO was administered intravenously as a bolus immediately followed by a bolus of 20ml of physiologic saline (NaCl 0,9%). Injection of SPIO and saline was performed at an infusion rate of 3ml/s using a Spectris MR injector (Medrad, Maastricht, The Netherlands).

**MRI image analysis: lesion detection and characterization**

After the initial US examination, anonymous patient labels were assigned to each patient for blinded image interpretation. Then the images were sent to the Picture Archiving and Communication System (PACS; Agfa, Mortsel, Belgium) viewing stations for further evaluation. Liver cysts were not evaluated as they (almost) never pose any differential diagnostic problem using MRI.
### Table 1. Parameters of the studied sequences

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Seq 1</th>
<th>Seq 2</th>
<th>Seq 3</th>
<th>Seq 4</th>
<th>Seq 5</th>
<th>Seq 6</th>
</tr>
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<tbody>
<tr>
<td>TR (ms)</td>
<td>1122</td>
<td>777</td>
<td>1343</td>
<td>10</td>
<td>177</td>
<td>4.2</td>
</tr>
<tr>
<td>TE (ms)</td>
<td>55.83</td>
<td>60</td>
<td>350</td>
<td>4.2</td>
<td>2.3/4.6</td>
<td>2</td>
</tr>
<tr>
<td>Flip (°)</td>
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<td>90</td>
<td>90</td>
<td>30</td>
<td>80</td>
<td>20</td>
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<td>axial</td>
<td>axial</td>
<td>axial</td>
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<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
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<td>FOV (mm)</td>
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<td>375</td>
<td>375</td>
<td>375</td>
<td>375</td>
<td>400</td>
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<td>RecFOV (%)</td>
<td>95</td>
<td>70</td>
<td>70</td>
<td>70</td>
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<td>256</td>
<td>256</td>
<td>256</td>
<td>256</td>
<td>192</td>
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<tr>
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<td>80</td>
<td>70</td>
<td>60</td>
<td>80</td>
</tr>
<tr>
<td>Half scan factor</td>
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<td>0.6</td>
<td>0.6</td>
<td>none</td>
<td>none</td>
<td>none</td>
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<tr>
<td>Act.BW (Hz/pixel)</td>
<td>15.3</td>
<td>415.6</td>
<td>394.6</td>
<td>148.2</td>
<td>571.4</td>
<td>399.1</td>
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<tr>
<td>ST (mm)</td>
<td>7</td>
<td>6</td>
<td>6</td>
<td>7</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Slice gap (mm)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SENSE-factor</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Fat-suppression mode</td>
<td>SPAIR</td>
<td>SPIR</td>
<td>none</td>
<td>SPIR</td>
<td>none</td>
<td>SPIR</td>
</tr>
<tr>
<td>delay:</td>
<td>52.2 ms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scan mode</td>
<td>Resp.tr.</td>
<td>Resp.tr</td>
<td>Resp.tr</td>
<td>BH</td>
<td>BH</td>
<td>BH</td>
</tr>
</tbody>
</table>

Seq.: sequence, TR: repetition time, TE: time to echo, NSA: Number of Signal Averages indicates the number of times each (acquired) line in k-space is sampled, FOV: Field-of-View, RecFOV: rectangular FOV (reduction of the number of phase-encodings to x%), scan percentage: is a percentage of phase-encoding values (profiles) of k-space around k=0 profile, half scan factor: is a method in which approximately only one half of k-space in the phase-encoding direction is acquired, Act.BW: actual band width, ST: slice thickness, SPAIR: SPectral Attenuated Inversion Recovery inversion delay, SPIR: SPectral Inversion Recovery, Resp.Tr.: respiratory-triggering, BH: breath-hold. PS: Sequence 2 identical parameters compared with sequence 7; sequence 4 identical parameters compared with sequence 8.
Lesion detection

Lesion detection was independently performed by reader 1 and 2 (both radiologist with respectively 6 years and 14 years of experience in abdominal MRI). The two radiologists did not have any other information about patient history, laboratory results, findings of other imaging techniques, or final diagnosis during this evaluation session, except for the US findings necessitating additional imaging techniques.

Sequence 1 was evaluated separately for all b-values (b=0, 10, 150, 400 s/mm²) and in random patient order and independently by reader 1 and 2. These two readers evaluated the images for lesion detection, number of hepatic lesions, size of the lesions (<10mm, 10-20mm, >20mm). Measurement of lesion size was performed on that b-value image that most sharply depicted a lesion. Measurement of the lesion size was performed in one consensus reading by reader 1 and 2. Post-SPIO sequences (sequence 6 to 8) were evaluated for lesion detection, presence of hepatic lesions, number of hepatic lesions, size of the lesions (<10mm, 10-20mm, >20mm). For each detected lesion the location was recorded by writing down the number of the sequence slice. After blinded evaluation, matching was possible by comparing the slice numbers of each sequence of reader 1 and 2. Consensus reading was not required for detection due to absence of inconsistent results.

Lesion characterization

Lesion characterization was also independently performed by reader 1 and 2. Lesion characterization was performed using SS SE-EPI and using all other MRI sequences. On sequence 1, all detected lesions were only visually/qualitatively evaluated (hyperintense or
hypointense lesion) for lesion characterization. All other MRI sequences (2 to 8) were evaluated for characterization (for a maximum of ten lesions per patient) independently and in one session by reader 1 and 2 with an interval of two weeks after the evaluation of SS SE-EPI. Characterization of the focal liver lesions was performed on the basis of lesion characteristics described in the literature using SPIO [10, 11]. During the perfusion phase (and persisting during delayed imaging) using SPIO-enhanced T1w GE imaging, a significant increase of signal intensity is seen in hemangiomas [11-13]. Hemangiomas often lose signal on delayed T2w imaging [12]. During the perfusion phase using SPIO-enhanced T1w GE imaging, ring enhancement is highly suggestive of malignant liver lesions [11]. Metastases show increased lesion conspicuity post-SPIO on T2w imaging compared with unenhanced T2w imaging [14-16]. Consensus reading was not required for characterization due to absence of inconsistent results.

**Reference standard: lesion detection and characterization**

**Lesion detection**

The sum of focal liver lesions detected on SS SE-EPI and on the post-SPIO sequences (sequences 6 to 8) was used to determine the total number of lesions.

For comparison of lesion detection between SS SE-EPI and the post-SPIO sequences, only the maximum number of discrete lesions detected on a complete set of diffusion-weighted images (b=0, 10, 150, 400 s/mm²) or on the post-SPIO sequences (sequences 6 to 8) as a whole was used to determine the total number of discrete lesions.
Lesion characterization

Surgical findings

For those lesions that were operated on, intra-operative US (IOUS) with histopathology was used as the reference standard in this study. Patients operated on for hepatic malignant disease all routinely had an IOUS examination. Individual lesions detected with SS SE-EPI or SPIO-enhanced imaging were matched by a hepatic surgeon having 11 years of experience in hepatic surgery using IOUS examination before hepatic resection was performed. During the IOUS examination the findings on all MRI sequences were available.

Follow-up

Suspected lesions that were not operated on underwent a US-guided biopsy of one of the lesions suspected for a metastatic lesion and/or were included in the following imaging study protocol: an MRI examination of the liver (all sequences including sequence 1) was performed as a reference examination just before the start of the therapy and as a follow-up examination with an interval of 12 weeks during therapy. Follow-up of the liver with MRI using this protocol was performed (at least) twice during therapy. A time interval of 12 weeks comprised the time of six cycles of chemotherapy. In case of progressive disease (as defined below) a follow-up was performed until the moment where the therapeutic effect was at least stable disease (stable disease in this study defined as a less than 20% change of the maximum initial diameter and less than 5mm change of the maximum initial diameter of a focal liver lesion) or (partial) response (as defined below) or until the moment when therapy was of a merely palliative use. In case of response (partial or complete) or in case of progressive disease
(according to the below stated definition) the focal liver lesions were considered as metastatic lesions.

Lesion characterization was compared as well on SS SE-EPI, as on the reference and follow-up MRI sequences 2 to 8. Individual detected lesions were matched with follow-up imaging assigning a specific liver segment for each detected lesion using Couinaud’s segmental anatomy.

**MRI image quality analysis**

Image quality analysis was independently performed by reader 3 and 4 (reader 3 and 4, both have 16 years of experience in abdominal MRI) to evaluate overall image quality independent of lesion conspicuity. Reader 3 and 4 were aware of the location and number of the lesions detected by reader 1 and 2. Reader 3 and 4 rated each set of b-values and the post-SPIO sequences for overall image quality (in total seven sets of images) in order to evaluate a possible correlation of overall image quality on lesion detection. Overall image quality was based on the following five grading scales: unacceptable = 1; poor = 2; fair = 3; good = 4; and excellent = 5.

**Statistical analysis**

McNemar test was used to compare the best set of SS SE-EPI images with the post-SPIO set for the detection of all liver metastases.

The above mentioned seven sets of images were compared for image quality by RIDIT analysis. RIDIT analysis was originally developed by Bross [17] for the analysis of ordinal data. The null hypothesis is an a priori RIDIT of 0.5, which implies a fifty-fifty distribution. The RIDITs were all subtracted by 0.5 to have the mean at zero and multiplied by (-1) to have positive values for the
SS SE-EPI sequence and post-SPIO sequences

promising results. The more positive the RIDIT the better the result, the more negative the worse the result is for the considered imaging protocol. A RIDIT of zero means that the distribution of values of the criterion under consideration in the subgroup, is not different from the distribution of values in the reference population. A difference was considered statistically significant with $p<0.05$.

RESULTS

Lesion Detection

In total 95 hepatic lesions were detected on SS SE-EPI and post-SPIO sequences (sequences 6 to 8); 25 of them were found to be hemangiomas and 70 were metastases using surgical and follow-up findings (tables 2 and 3).

Table 2. Overview of the reference standard used for the characterization of liver hemangiomas

<table>
<thead>
<tr>
<th>Size (mm)</th>
<th>IOUS with resection</th>
<th>IOUS w/o resection</th>
<th>Follow-up typical app.</th>
<th>Follow-up no typ.app.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>1</td>
<td>2</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>10-20</td>
<td>0</td>
<td>3</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>&gt;20</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>5</td>
<td>18</td>
<td>1</td>
</tr>
</tbody>
</table>

IOUS with resection: including histopathology for final diagnosis; IOUS w/o resection: final diagnosis on the basis of IOUS findings without resection/histopathology; follow-up typical app: final diagnosis using only follow-up imaging and having typical imaging appearance (typ.) on sequences 2 to 8; follow-up no typ. app: final diagnosis using only follow-up imaging and having no typical (typ.) imaging appearance on sequences 2 to 8.

The 95 hepatic lesions (25 hemangiomas and 70 metastases) detected in total on SS SE-EPI and post-SPIO images, classified by size and type are displayed in table 4.
Table 3. Overview of the reference standard used for the characterization of liver metastases

<table>
<thead>
<tr>
<th>Size (mm)</th>
<th>IOUS with resection</th>
<th>biopsy w/o resection</th>
<th>Follow-up typical app.</th>
<th>Follow-up no typical app.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>15</td>
<td>0</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>10-20</td>
<td>12</td>
<td>0</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>&gt;20</td>
<td>9</td>
<td>1</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>1</td>
<td>27</td>
<td>6</td>
</tr>
</tbody>
</table>

IOUS with resection: including histopathology for final diagnosis; biopsy w/o resection: final diagnosis on the basis of biopsy/histopathology without resection; follow-up typical app: final diagnosis using only follow-up imaging and having typical imaging appearance (app.) on sequences 2 to 8; follow-up no typical app: final diagnosis using only follow-up imaging and having no typical imaging appearance on sequences 2 to 8.

Table 4. The sum of focal liver lesions detected on SS SE-EPI and on the post-SPIO sequences (total number of lesion detection)

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Hemangioma</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (mean diameter±SD)</td>
<td>N (mean diameter±SD)</td>
</tr>
<tr>
<td>&lt;10mm</td>
<td>15 (6.9 ± 1.4)</td>
<td>25 (6.1 ± 2.0)</td>
</tr>
<tr>
<td>10-20mm</td>
<td>9 (12.3 ± 1.8)</td>
<td>22 (13.8 ± 3.1)</td>
</tr>
<tr>
<td>&gt;20mm</td>
<td>1 (22)</td>
<td>23 (40.6 ± 25.4)</td>
</tr>
<tr>
<td>Total</td>
<td>25 (9.4 ± 4.0)</td>
<td>70 (20 ± 20.8)</td>
</tr>
</tbody>
</table>

N: Number of lesions. SD: Standard Deviation. Numbers in brackets are given in mm.

In table 5 the data on the separate sequences (4 sets of b-values of SS SE-EPI and the post-SPIO sequences) by type are displayed. The best set of SS SE-EPI images (b=10s/mm²) was significantly (z= -2.12; p=0.034) better for the detection of liver metastases compared with the post-SPIO set of images. All lesions
SS SE-EPI sequence and post-SPIO sequences

missed on the different sequences comprised only small (<10mm) liver lesions (table 5).

**Table 5.** Number of detected lesions on the 4 sets of b-values of SS SE-EPI and the post-SPIO sequences

<table>
<thead>
<tr>
<th>Lesion</th>
<th>b=0</th>
<th>b=10</th>
<th>b=150</th>
<th>b=400</th>
<th>post-SPIO sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemangioma</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Metastasis</td>
<td>50</td>
<td>69</td>
<td>65</td>
<td>63</td>
<td>63</td>
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<tr>
<td>Total</td>
<td>75</td>
<td>94</td>
<td>90</td>
<td>88</td>
<td>88</td>
</tr>
</tbody>
</table>

Using b=0s/mm² images for lesion detection, 20 lesions <10mm were missed; these lesions were all hard to differentiate from nearby intrahepatic vessels. Using b=10s/mm² images, one lesion <10mm in subphrenic location was missed; this lesion could only be visualized on post-SPIO fat-suppressed T2w TSE. Using b=150s/mm² respectively b=400s/mm² images, five respectively seven lesions <10mm in subphrenic locations were missed. Using post-SPIO sequences for lesion detection, seven lesions <10mm were missed; these lesions were all hard to differentiate from nearby intrahepatic vessels (fig.1).

**Lesion Characterization**

Concerning lesion characterization, all 95 hepatic lesions were displayed as hyperintense focal liver lesions on all b-value images of SS SE-EPI making qualitative lesion characterization impossible using only SS SE-EPI.

Using sequences 2 to 8 for lesion characterization, 2 hemangiomas (resp. 4mm and 6mm) could not be characterized using typical imaging characteristics. The hemangioma of 6mm was
resected during partial hepatectomy for liver metastases. A follow-up period of 8 months did not show any change in the hemangioma of 4mm. The remaining 23 hemangiomas showed typical imaging appearances diagnostic for hemangioma using sequences 2 to 8. The diameter of all detected hemangiomas measured on the MR images ranged from 4 to 22 mm (mean diameter: 9.4 mm ± SD: 4.0 mm). Table 2 gives an overview of the reference standard used for the final characterization of hemangiomas.

Using sequences 2 to 8 for lesion characterization, 17 metastases (all <10mm) could not be characterized using typical imaging characteristics. For 6 liver metastases follow-up was needed for characterization. Four of these 6 metastases showed complete response and two showed partial response. In total 36 metastases were resected (including 15 metastases <10mm among which 11 metastases that could not be characterized using typical imaging characteristics on sequences 2 to 8). One metastasis (>20mm) was biopsied but not operated on. The diameter of all detected liver metastases ranged from 2 to 123 mm (mean diameter: 19.8 mm ± SD: 20.8 mm). Table 3 gives an overview of the reference standard used for the final characterization of metastases.

**Image Quality**

Image quality (fig.2) for seven sets of images (4 sets of b-values and the post-SPIO sequences) was compared using RIDIT analysis. Post-SPIO fat-suppressed T1w GE and T2w TSE both had significantly (p<0.05) better image quality when compared with SS SE-EPI.
Figure 1. A 54-year-old female patient with a medical history of colorectal carcinoma for which she had been operated on. On the b-value image (b=0s/mm²; fig.1a) an intrahepatic vessel can be depicted in the vicinity of the surgically proven small (<10mm) liver metastasis (long arrow). Due to the black blood effect when applying SS SE-EPI the detection of the metastasis is clearly facilitated. Using SS SE-EPI, b-value image (b=10s/mm²; fig.1b) clearly shows only one lesion (long arrow). The relatively bright extended area in the liver to the right of the indicated liver metastasis (in this case) is caused by chemical shift of subcutaneous fat. Post-SPIO fat-suppressed T2w TSE (falsely) shows two hyperintensities suggestive of metastatic lesions (fig.1c). Post-SPIO fat-suppressed T2* GE (falsely) shows two hyperintensities suggestive of metastatic lesions (fig.1d).
DISCUSSION

The studied SS SE-EPI sequence using $b=10\text{s/mm}^2$ showed the best ($p<0.05$) results for detection of focal liver lesions, especially for small ($<10\text{mm}$) focal liver lesions in the vicinity of intrahepatic vessels. This sequence did not allow for characterization of liver hemangiomas and metastases. Combining sequences before and post-SPIO allowed the characterization of many but not all lesions. Best image quality was achieved with post-SPIO fat-suppressed T1w GE and T2W TSE when comparing SS SE-EPI and all post-SPIO sequences.

The use of the black-blood effect for facilitating detection of liver lesions has been described previously [18]. This coinciding black-blood effect mainly when using a low $b$-value is useful in this study for detecting small ($<10\text{mm}$) lesions especially when lying in the vicinity of intrahepatic vessels. Nasu K. et al. [3] retrospectively compared accuracy of SS SE-EPI with that of SPIO-enhanced MRI in the evaluation of hepatic metastases. They concluded that combined
image interpretation with SS SE-EPI and T2w TSE and dual-echo T1w GE imaging yielded better accuracy in the detection of hepatic metastases than did SPIO-enhanced MR imaging. Liver hemangiomas were not included in their study. In clinical practice, the differentiation of micrometastases from small hemangiomas is important in treatment planning. In the presented study, a SS SE-EPI sequence was prospectively examined as a stand-alone sequence and compared with MRI sequences before and post-SPIO for detection of liver hemangiomas and metastases. SS SE-EPI (especially b=10s/mm² images) performed best for lesion detection when compared with post-SPIO sequences. Disturbing signals from the intrahepatic vessels using b=0s/mm² images might explain the hampered detection of nearby small liver lesions whereas artifacts from air in the lungs might explain hampered detection of subphrenic lesions using higher b-value images (b=150 respectively b=400s/mm²). Disturbing signals from nearby intrahepatic vessels might explain why small lesions were missed using the post-SPIO sequences even when using post-SPIO fat-suppressed T1w GE for more accurate identification of small vessels. The hard differentiation between small intrahepatic vessels and small liver lesions has been mentioned before in the literature [19]. In the presented study a prospective evaluation of patients suffering from a colorectal primary is made comparing SS SE-EPI as a stand-alone sequence for the detection and characterization of liver hemangiomas and metastases.

Unfortunately, the characterization of liver hemangiomas and liver metastases was impossible in this study using only a visual evaluation of SS SE-EPI. The high signal intensity of liver hemangiomas on all b-value images in this study could be explained by a combination of a long T2 relaxation time and impaired diffusion
by the septa present in hemangiomas. The high signal intensity of liver metastases on all b-value images in this study could be explained by impaired diffusion due to a high concentration of (malignant) cells within the liver metastases. Characterization of the focal liver lesions on the basis of measurements of signal intensities of lesions with calculation of true diffusion, perfusion factor and apparent diffusion coefficient was not useful in this study. Characterization of focal liver lesions on the basis of measurements of signal intensities of lesions with calculation of apparent diffusion coefficient is a valuable method for larger liver lesions. However, in this study a substantial number of focal liver lesions were <10mm in diameter resulting in suboptimal Region-of-Interest (ROI) measurements (difficult delineation of small focal liver lesions with suboptimal ROI placement; partial volume effects. Therefore, only visual/qualitative evaluation for lesion characterization was feasible in this study. Combining the findings of sequences before and post-SPIO allowed the characterization of many lesions, but still some small (<10mm) lesions could not be differentiated. The apparent superiority of SPIO-enhanced MRI for lesion characterization may have been increased by the availability of the unenhanced T2-weighted images, which were not available during the reading of the diffusion-weighted images. The purpose of this study was to compare SS SE-EPI with “state-of-the-art” MRI techniques in lesion detection and characterization. During one session, SS SE-EPI was evaluated separately for all b-values and in random patient order. Still some bias might be present concerning the evaluation of the different sets of b-value images. However, it seems unlikely that the b=10s/mm² value images would have had an advantage in lesion detection compared with the remaining b-value images. The lack of histological proof in many lesions is a limitation of this study and
many other studies on this topic. As the best reference standard for lesion detection – being IOUS with resection and histopathologic correlation - could not be performed in many cases, reading of other available imaging examinations and follow-up imaging were used as a reference. Therefore sensitivity, specificity and accuracy cannot be calculated. In this study SS SE-EPI was always performed as the first sequence. One could argue that SS SE-EPI in this study performs better in lesion detection when compared with the post-SPIO sequences due to an increase of patient movement at the end of an MRI examination. However, the best image quality is seen in fat-suppressed T1w GE and T2W TSE. Therefore it seems unlikely that patient movements had an impact on the evaluation of the studied sequences.

The World Health Organization (WHO) and Response Evaluation Criteria in Solid Tumours (RECIST) criteria are widely used to judge progression or regression of tumour size, but have well known limitations with respect to monitoring treatment response, especially when concerning small lesions. When reviewing the literature, the use of RECIST criteria for small lesions is controversial. For example, Therasse et al. [20] even classify lesions <10mm as non-measurable disease. For this reason, other criteria were used in this study to judge lesion size.

In conclusion, this study shows the potential of SS SE-EPI (especially b=10s/mm²) as an accurate stand-alone sequence for the detection of liver hemangiomas and especially (small) liver metastases when compared with SPIO-enhanced imaging. Combining the findings at SS SE-EPI with sequences before and post-SPIO allowed the characterization of many lesions, but still some small lesions could not be differentiated.
REFERENCES


