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Gadolinium-EOB-DTPA enhanced MR
combined with standard MR imaging;
A study of diagnostic accuracy in
differentiating focal nodular hyperplasia
from hepatocellular adenoma in lesions
larger than 2 cm

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Abstract

**Background:** To prospectively determine the accuracy of Gadolinium (Gd)-EOB-DTPA combined with standard magnetic resonance (MR) imaging in differentiating focal nodular hyperplasia (FNH) from hepatocellular adenoma (HCA) with histopathology as standard of reference.

**Materials and Methods:** The study was approved by the institutional Medical Ethics Committee and written informed consent was obtained from all patients. Sixty-seven consecutive patients suspected of having one or multiple FNH or HCA lesions larger than 2cm underwent a Gd-EOB-DTPA MR of the liver (3 male, 64 female). Standard MR was separately evaluated from the hepatobiliary phase by two blinded abdominal radiologists with over 10 years experience. Findings were compared with histological diagnosis. Detection rates, PPV, and distinctive features were analyzed using McNemar and ANOVA tests.

**Results:** Sixty-seven patients were included and 52 patients completed the study. Histological diagnosis revealed 24 HCA and 28 FNH. Standard MR showed 21 inconclusive cases, 11 HCA, and 10 FNH. Detection rate for HCA was 50% (12/24), and positive predictive value (PPV) 100%. Detection rate and PPV for FNH were 64% (18/28) and 94%, respectively. The hepatobiliary phase revealed 24 HCA, and 28 FNH. Detection rate for HCA was 96% (23/24) and PPV 100%. Detection rate for FNH was 96% (27/28) and PPV 96%. Features with significant predictive value for diagnosis in HCA included bleeding, fat, and glycogen content (p<0.001; p=0.010, and p=0.024). The presence of a central scar was predictive for FNH (p<.001).

**Conclusion:** This study shows high accuracy of Gd-EOB-DTPA MR imaging when the standard series are combined with the hepatobiliary phase for differentiation of FNH and HCA in lesions larger than 2 cm.
Introduction

Due to widespread use of imaging modalities hepatocellular adenoma (HCA) and focal nodular hyperplasia (FNH) are increasingly found incidentally. It is generally accepted that FNH can be treated conservatively, because of its benign nature and minimal risks of complications.\textsuperscript{2,3} HCA unlike FNH, carries the risk of malignant transformation in 4.3% of lesions >5cm.\textsuperscript{4} and spontaneous rupture with bleeding has been reported in 30% of cases >5cm.\textsuperscript{4} The growth and risk of bleeding in HCA is influenced by the use of oral contraceptives. For these reasons, resection of HCA >5cm is advised and differentiation between HCA and FNH becomes important.\textsuperscript{5}

Magnetic Resonance (MR) and CT imaging are mostly used for the differentiation of focal hepatic lesions. Diagnosis is based on lesion characteristics and enhancement pattern. On MR imaging typical findings of FNH include a central scar, lobulated shape, central feeding vessels, and arterial enhancement.\textsuperscript{6,7} Typical findings of HCA include hemorrhage,\textsuperscript{8} intra-tumoral fat and glycogen,\textsuperscript{9} which present as high signal foci on T1 weighted images. Fat suppression setting will distinguish intratumoral fat. Other typical findings include peripheral feeding vessels, and arterial enhancement.\textsuperscript{10} However, these typical findings are not always present. For example, a macroscopic central scar occurs in 50% of FNH and is often absent in FNH <3cm.\textsuperscript{11} In HCA glycogen and fat are not always present, and bleeding occurs more frequently in lesions >5cm.\textsuperscript{12} If imaging modalities are inconclusive a liver biopsy may be mandatory.\textsuperscript{13}

Liver-specific hepatobiliary contrast agents for MR imaging are nowadays available. Gadolinium (Gd)-EOB-DTPA (Primovist\textsuperscript{®}) is a gadolinium-based paramagnetic contrast agent taken up via an organic anion transport system by functioning hepatocytes.\textsuperscript{14,15} Approximately 50% of the contrast is excreted into the biliary system and 50% is excreted by the kidneys.\textsuperscript{16} The hepatocyte selective imaging allows assessment of hepatocyte function and biliary excretion. In FNH a ductular reaction along the septae is present.\textsuperscript{14} This may result in accumulation of contrast in the lesion. As opposed, HCA has no or few bile ducts and the lesional hepatocytes are thought to have diminished function.\textsuperscript{14} This may result in reduced accumulation of contrast in the hepatobiliary phase. This difference in accumulation of contrast in the hepatobiliary phase of imaging between FNH and HCA may therefore be useful for differentiation when typical features are absent. Previous studies with hepatospecific contrast have shown promising results in differentiating FNH from HCA.\textsuperscript{17} However, these studies were limited as the reference standard consisted only of imaging or follow-up in a substantial number of included cases.\textsuperscript{18}

Therefore, the purpose of this study was to prospectively determine the diagnostic accuracy of Gadolinium (Gd)-EOB-DTPA combined with standard MR imaging in differentiating FNH from HCA\textsuperscript{19} with histopathology as standard of reference.
Materials and methods

Design
This study was a prospective, single center, diagnostic accuracy study with paired design for differentiating FNH from HCA between January 2008 and June 2010. Standard MR was compared with the hepatobiliary phase of Gd-EOB-DTPA enhanced MR at blinded reading. The institutional Medical Ethics Committee approved the study and a written informed consent was obtained from all patients.

Study population
A total of 67 consecutive patients, above 18 years, were included (3 male, 64 female; mean age 39 years, range 18-60). Patients were primarily presented or were secondarily referred from other centers to our surgical outpatient clinic with suspicion of FNH or HCA based on CT or MR imaging without hepatocyte selective contrast. The lesions had to be 2 cm or larger, because smaller lesions could be difficult to assess with ultrasound guided liver biopsy, with a relatively higher chance of non-representative sampling. Exclusion criteria were suspicion on (metastatic) malignant disease: previous malignancy, risk factors including chronic hepatitis, cirrhosis, haemochromatosis, and elevated α-fetoprotein (AFP) or carcinoembryonic antigen (CEA) in blood serum. Further exclusion criteria were pregnancy, and contraindications for MR imaging, i.e. severe claustrophobia, metal objects or particles within the eyes or the abdomen, and impaired renal function (serum creatine > 200 µmol/L).

MR imaging protocol
The MR was performed with a 1.5 Tesla MRI scanner (Avanto, Siemens Medical System, Erlangen) using a phased array torso coil. MR series consisted of 2D Gradient (GRE) in- and opposed-phase imaging (FLASH) (repetition time (TR)/echo time (TE) in ms: 125/2.3 and 125/4.6, flip angle (fa) in degrees 70, 256x134 matrix); coronal 12w TruFISP fatsat (TR/TE 5400/76, fa70, matrix 384x230); axial diffusion weighted echo planar imaging, with b values of 50, 400, and 800 (TR/TE 5400/76, fa90, matrix 192x156; and axial breath hold T2w HASTE (TR/TE 1700/72 and 1700/399, fa150, matrix 256x156). Pre- and post-contrast axial T1w fatsat 3D FLASH (VIBE) (TR/TE 5.77/2.54, fa10, matrix 256x156). The dynamic post-contrast series were made at 30 (arterial), 60 (venous), 90, and 180 (late) seconds after intravenous bolus injection of 0.25 mmol/10kg Gd-EOB-DTPA (Primovist™, Bayer, Germany). The bolus was injected with a rate of 1 mL per second and flushed with saline. Axial and coronal hepatobiliary phase images were made at 20 minutes post injection using VIBE single breath hold sequences. Slice thickness was 4.6 mm for T2w images and in/out of phase images and 2mm for VIBE pre- and post-contrast series. All pre-contrast series and the dynamic post-contrast series after Gd-EOB-DTPA were regarded as standard MR imaging. The delayed phase images at 20 minutes were considered as hepatobiliary Gd-EOB-DTPA MR imaging.
MR imaging interpretation

The MR series were evaluated in consensus by two radiologists with over 10 years of experience in abdominal radiology. The readers were informed of the differential diagnosis of either FNH or HCA but were blinded for patient history and previous imaging. First the standard images were evaluated after which the hepatobiliary phase was evaluated in the same session.

The following scoring points were used for evaluation of the liver: the number of lesions and the presence of steatosis (loss of signal intensity of the liver between in- and out of phase T1w series). The following scoring points were used for evaluation of the lesions: size, segmental localization, shape (round or lobulated), and demarcation (sharp or faint). Signs of bleeding were assessed (high signal foci on T1w FS series). Furthermore, a central scar (a high signal intensity ‘spokes wheel’ on TruFISP T2w series, and low-intensity on T1w series, with or without enhancement during portal or late series). Lesion-to-liver intensity was noted on pre-contrast T1w and TruFISP T2w series, and post-contrast arterial, portal and late phases.

Lesion enhancement pattern was expressed as ‘peak-pattern’ if arterial enhancement with clear loss of signal intensity during portal and/or late phases was seen, and as ‘plateau-pattern’ if signal intensity was sustained during portal and late phase of imaging. The two readers made a visual score of signal intensity and enhancement pattern. When in disagreement or doubt, a ROI was placed in the lesion to measure signal intensity of the lesion.

Diagnosis of typical FNH was based on the presence of a central scar, arterial enhancement, and absence of signs of ‘wash-out’ during portal phase. Diagnosis of typical HCA was based on arterial enhancement, the presence of hyperintense foci on T1w series suggestive for bleeding, fat or glycogen, and absence of a central scar. Lesions without these characteristics were marked as atypical lesions.

Finally, the lesions were evaluated for signal intensity compared to surrounding liver tissue on the T1w hepatobiliary series at 20 minutes post-injection. iso- or hyper signal intensity of the lesion was regarded as diagnostic for FNH and hypointensity for HCA. The pattern of contrast uptake was scored as either homogenous or inhomogeneous.

Standard of reference

The standard of reference (SOR) was defined as histopathological diagnosis. The histological specimens were obtained with resection and/or liver biopsy from tumoral and normal liver tissue. The lesion was selected on suitability for biopsy and in case of multiple lesions, the largest suitable lesion was selected. The evaluating pathologist was blinded for patient history.

in addition to standard liver stainings, including HE, collagen and CK7, a glutamine synthetase (GS) staining was performed for confirmation of histomorphological diagnosis. The diagnosis FNH was based on morphological characteristics, including the presence of stellate fibrous scarring, dystrophic arteries, ductular reaction, variable
infiltrate, and absence of cytological abnormalities. Morphological characteristics of HCA included: a proliferation of non-atypical hepatocytes with a well-developed reticulin framework, without central scar.

**Statistical analyses**
Statistical analyses were performed using SPSS 18 (IBM Corporation, Chicago, IL). Descriptive statistics were used for the study population. Continuous data were tested for normal distribution and equal variances using the Levene’s test. Features on imaging were tested for significance using the ANOVA and multivariate tests. We used the McNemar test statistic for comparing sensitivity and specificity of the standard and hepatobiliary phase of Gd-EOB-DTPA MR imaging. The confidence interval of the proportions was derived using the Wilson score method without continuity correction.20 Statistical tests were evaluated at the 5% level of significance.

**Results**
One patient discontinued the study due to claustrophobia. Six patients were excluded as our MR imaging revealed typical hemangioma or hamartoma. Eight patients were excluded because histological confirmation was not obtained, either because of sampling errors, or withdrawn consent. Three patients presented with major bleeding from the lesion for which arterial embolization was indicated. These patients were included in the overall analyses of differentiating HCA from FNH, but excluded from the sub-analyses of enhancement. This was due to possible alteration in enhancement and signal intensity of the lesion after embolization of feeding vessel(s). Hence, data of 52 patients were available for evaluation (2 male, 50 female; mean age 39 years, range 18-56)

**Standard of reference**
Histological diagnoses were 24 HCA and 28 FNH, diagnosed in 25 patients on resection and in 27 on biopsy specimens. Biopsy material (6 HCA; 21 FNH) and resection specimens (18 HCA; 7 FNH) were used. All cases of FNH but one, showed a typical map-like pattern GS staining which was absent in HCA. This one lesion was composed of non-atypical hepatocytes together with scarring, ductular reaction, thick-walled vessels and inflammatory infiltrates, but lacked the typical (map-like) GS staining. Based on morphological features, lack of SAA and CRP over expression and homogeneous GS staining, this lesion was diagnosed as FNH.

**Study population**
A total of 52 patients completed the study. The two male patients both presented with FNH. In 47 of 50 women reported chronic use of oral contraceptives. Thirty-one patients presented with abdominal pain or discomfort, of whom three presented with
Table 1  Diagnosis on standard MR series and on hepatobiliary MR series

<table>
<thead>
<tr>
<th></th>
<th>Histology</th>
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<tbody>
<tr>
<td></td>
<td>HCA</td>
</tr>
<tr>
<td>Standard MR</td>
<td></td>
</tr>
<tr>
<td>Inconclusive</td>
<td>11</td>
</tr>
<tr>
<td>HCA</td>
<td>12</td>
</tr>
<tr>
<td>FNH</td>
<td>1</td>
</tr>
<tr>
<td>Hepatobiliary Phase</td>
<td></td>
</tr>
<tr>
<td>Inconclusive</td>
<td>0</td>
</tr>
<tr>
<td>HCA</td>
<td>24</td>
</tr>
<tr>
<td>FNH</td>
<td>1</td>
</tr>
</tbody>
</table>

acute bleeding requiring arterial embolization (16 HCA; 15 FNH). Eighteen of the 24 patients with HCA underwent resection of the lesion (75%; mean diameter 8.5cm; SD 4.9; 4.4-25cm). Seven of 29 patients with FNH underwent resection of the lesion, because of discomfort (24%; mean diameter 6.8cm; SD 3.0; 3.7-12.0cm). Thirty-five lesions were ≥5cm (20 HCA; 15 FNH) and resection was advised if diagnosis was HCA. The group of patients with a lesion <5cm (n=17) consisted of 4 HCA (23%) and 13 FNH (76%). In the overall group 15 patients had a solitary lesion at imaging (4 HCA; 11 FNH), 18 had 2-3 (5 HCA; 13 FNH), 6 had 4-10 (5 HCA; 1 FNH) and 12 patients had more than ten lesions (9 HCA; 3 FNH). Of the patients with multiple HCA at imaging, 3/19 also presented with a lesion characteristic for FNH.

**Standard MR imaging**

Imaging results are summarized in Table 1. With standard MR imaging a confirmative diagnosis could not be made in 21/52 patients (11 HCA and 10 FNH with median size 5.0 cm)(Figure1, 2). Of the remaining 31 patients, 12 were diagnosed as HCA and 19 as FNH. Compared to histological diagnosis this resulted in a detection rate for HCA of 50% (12/24, Confidence interval of the proportion (CI) 31%-69%), with a positive predictive value (PPV) of 100% (CI 76%-100%). The detection rate for FNH was 64% (18/28, CI 46%-79%), with a PPV of 94% (CI 75%-99%).

**Hepatobiliary phase**

On the hepatobiliary series no cases were inconclusive (Table 1). Twenty-four of 52
patients were diagnosed as HCA and 28 patients as FNH (Figure 3). Compared with the histological diagnosis this resulted in a detection rate for HCA of 96% (23/24, CI 80%-99%), with a PPV of 95% (CI 80%-99%). The detection rate for FNH was 96% (27/28, CI 82%-99%) with a PPV of 96% (CI 82%-99%). High signal intensity of FNH (n=27) during the hepatobiliary phase was homogeneous in 14 cases (51%) and inhomogeneous in 13 cases (48%). One case of FNH showed low homogeneous signal intensity compared to surrounding parenchyma during the hepatobiliary phase.

Figure 1. MR images of a 28 year old woman with atypical HCA, dull pain in the upper abdomen and a history of chronic oral contraceptive use. Transverse T2w (FS, TR/TE 5400/76, flip angle 70°, matrix 384x230) image shows a hyperintense lesion in the right liver (arrow)[A]. The subsequent arterial transverse T1w image shows strong signal intensity to surrounding liver parenchyma, without typical features of FNH or HCA (arrow)[B]. Portal phase image shows a slight hyperintense lesion without typical features to differentiate between FNH and HCA (arrow)[C]. Differentiation could however be made on the transverse hepatobiliary phase T1w FSE images 20 minutes after contrast injection. The lesion was interpreted to have less signal intensity compared to surrounding liver tissue, which is consistent with HCA (arrow)[D].
Figure 2. MR images of a 29 year old woman with atypical FNH, pain in the upper abdomen and a history of 20 years of oral contraceptive use. Transverse T2w (F5, TR/TE 5400/76, flip angle 70°, matrix 384x230) image shows a hyperintense lesion protruding from the caudate lobe of the liver compressing the left liver (arrow) (A). The arterial transverse T1w image the lesion shows high signal intensity compared to surrounding liver parenchyma, without typical features of FNH or HCA (white arrow) (5.77/2.54, flip angle 10°, matrix 256x156) (B). The portal phase image shows a slight hyperintense lesion without typical features to differentiate between FNH and HCA (arrow)(C). On the transverse hepatobiliary phase T1w F5 images 20 minutes after contrast injection the lesion shows equal to more signal intensity compared to surrounding liver tissue (arrow). Thus, the lesion was interpreted as FNH. Although no intervention is necessary for this benign lesion, the patient underwent resection of the caudate lobe. The mass effect of the tumor on the stomach and left liver caused severe discomfort, which completely subsided after resection(B).

**Features and characteristics**

The lesion characteristics are summarized in Table 2. Diffuse parenchymal steatosis of the liver was found in 9/24 patients with HCA (38%) and in 3/28 patients with FNH (11%, p=.022), features with significant predictive value for HCA included fat content in 5 cases (p=.010). High signal foci on T1w series consistent with bleeding were found in 11 HCA and 0 FNH (Fig. 4, p<.001). This was histomorphologically confirmed in 5 of 6 surgical specimens. Finally, glycogen was detected in 4 HCA and 0 FNH (p=.024). Features with significant predictive value for FNH included a central scar in 18/28 FNH and 0/24 HCA (Figure 4, p<.001). In FNH <5cm, 6/14 showed no central scar. FNH was often lobulated (21/28) compared to HCA (12/24, p=.064). Peripheral vessels were found in 2 FNH and 3 HCA (p=.523) and none of the lesions showed central feeding vessels.
Table 2. Lesion characteristics of FNH and HCA on MR imaging

<table>
<thead>
<tr>
<th>Lesion characteristics</th>
<th>Overall patient group n = 52</th>
<th>Inconclusive standard MR n = 21</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>HCA</td>
</tr>
<tr>
<td>Histological outcome</td>
<td>52</td>
<td>24</td>
</tr>
<tr>
<td>Steatosis of the liver</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Shape</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Round / oval</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>Lobular</td>
<td>33</td>
<td>12</td>
</tr>
<tr>
<td>Circumscription</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well defined</td>
<td>43</td>
<td>19</td>
</tr>
<tr>
<td>Unclear</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Size of the lesion mean (cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.8 (2-25)</td>
<td>7.7 (2.3-25)</td>
</tr>
<tr>
<td>Number of lesions:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>2 – 3</td>
<td>28</td>
<td>5</td>
</tr>
<tr>
<td>4 – 10</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>10 &lt;</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Central scar</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>High signal foci on T1w:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Fat</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Glycogen</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Peripheral Vessels</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

Figure 3. MR images of a 45-year-old asymptomatic woman with a 15-year history of oral contraceptive use. She presented with typical HCA on standard MR, but on the hepatobiliary phase the lesion was interpreted as iso to hypointense compared to the surrounding liver parenchyma, consistent with FNH. Due to motion artefacts the transverse images were difficult to evaluate. The transverse arterial T1w (5.77/2.54, flip angle 10°, matrix 256x156) image was interpreted as an inhomogeneous isointense lesion protruding caudally from segment 3 (white arrow). The hypointense areas within the lesions were scored as bleeding(A). The subsequent portal phase image shows an inhomogeneous lesion (white arrow) with a slight loss of signal intensity compared to the liver (black arrow head) (B). The lesion signal intensity (white arrow) on transverse hepatobiliary phase T1w image was interpreted as equal compared to the liver (black arrow head), consistent with FNH. However, histomorphologically and immunohistochemically the lesion was consistent with HCA (inflammatory subtype)(C).
Table 3. Lesion-to-liver signal intensity of FNH and HCA

<table>
<thead>
<tr>
<th>Signal Intensity</th>
<th>Pre-contrast phase</th>
<th>Post-contrast phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T2-weighted</td>
<td>T1-weighted</td>
</tr>
<tr>
<td>Focal Nodular Hyperplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperintense</td>
<td>16 (57)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Isointense</td>
<td>8 (29)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypointense</td>
<td>12 (43)</td>
<td>17 (61)</td>
</tr>
<tr>
<td>Hepatocellular Adenoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperintense</td>
<td>14 (67)</td>
<td>12 (57)</td>
</tr>
<tr>
<td>Isointense</td>
<td>7 (33)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Hypointense</td>
<td>7 (33)</td>
<td>2 (10)</td>
</tr>
</tbody>
</table>

Number of lesions followed by percentages in parentheses

Enhancement
Lesion-to-liver intensity is summarized in Table 3. Three HCA were not included in the analyses, due to prior arterial embolization of a feeding vessel after bleeding. During pre-contrast T1w series FNH showed significantly lower signal intensity than HCA (p<0.001). During the T1w arterial phase all 28 FNH and 19/21 HCA showed arterial enhancement. During the T1w portal phase, hyper signal intensity compared to surrounding liver parenchyma was seen in 22/28 FNH and 14/21 HCA (p=0.126). On portal phase, hypointensity (wash-out) was seen in 3 HCA and in none of FNH. During the late phase hyper signal intensity was seen in 18/28 FNH and 13/21 HCA, iso signal intensity in 8/28 FNH and 8/21 HCA, and hypo signal intensity in 2/28 FNH and 2/21 HCA, with no significant difference between the two groups (p=0.802). The enhancement pattern showed a ‘plateau-pattern’ in FNH, and a peak-pattern in HCA (p=0.009) (Table 4).

Inconclusive cases on standard MR imaging
On standard MR 21 cases remained inconclusive (Figure 1 and Figure 2). FNH in this group showed a small central scar in 2/10 cases (20%). In comparison, 16/18 FNH (89%) contained a scar when diagnoses could be made on standard MR imaging. In the 11 HCA in the inconclusive group 2 showed signs of bleeding, 1 of fat content on the MR, and 2 showed glycogen content. The mean lesion diameter was 6.4 cm in the inconclusive group, and 7.1 cm in the diagnostic group (p=0.420).
Figure 4. Typical MR images of FNH (A,B) and HCA (C,D). The corresponding transverse arterial phase T1w image shows arterial enhancement of a lesion in segment 4 of the liver (white arrow), with a hypointense area in the center of the lesion; a central scar (black arrow head) [FS, TR/TE 5.77/2.54, flip angle 10°, matrix 256x156](A). The hepatobiliary phase T1w image 20 minutes after contrast injection shows iso-to hyper- signal intensity of the lesion compared the surrounding liver, consistent with FNH(B). The transverse arterial phase T1w image shows arterial enhancement of a lesion in segment 2/3 of the liver (white arrow). The hypointense area within the lesion was interpreted as bleeding which is typical for HCA (black arrow head) [FS, TR/TE 5.77/2.54, flip angle 10°, matrix 256x156](C). The transverse image of the hepatobiliary T1w phase 20 minutes after contrast injection shows less signal intensity of the lesion compared to surrounding liver tissue consistent with HCA(D).

Table 4. Enhancement Pattern of FNH and HCA

<table>
<thead>
<tr>
<th></th>
<th>HCA</th>
<th>FNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Plateau</td>
<td>12</td>
<td>25</td>
</tr>
</tbody>
</table>

Enhancement of the lesion can be expressed as a peak pattern with enhancement in the arterial phase of scanning, followed by loss of contrast during later phases. A plateau pattern is defined as arterial enhancement with lingering of contrast during later phases. This pattern was significantly different between both groups as FNH showed mostly a plateau pattern (p<0.009)
Discussion

Gd-EOB-DTPA showed promising results in differentiating FNH from HCA in previous studies. The limitation of these studies was the use of only CT imaging or follow-up as standard of reference in most of the included cases. Therefore, we evaluated our imaging results with histology as standard of reference in all cases. This study shows high accuracy of Gd-EOB-DTPA MR imaging when the standard series are combined with the hepatobiliary phase for differentiation of FNH and HCA in lesions larger than 2 cm.

In 40% of cases standard MR imaging was inconclusive, because of lack of typical features. In literature this occurs in 30-42% of cases, especially when lesions are smaller than 3cm. Diagnosis is important, because FNH and HCA have opposing therapeutic consequences. Risk of complications like bleeding or even malignant transformation are known to occur in HCA larger than 5 cm, unlike in FNH. Therefore resection is advised for these HCA, while FNH is only resected if symptoms of pain or discomfort are severe.

Gd-EOB-DTPA is an easily applicable hepatobiliary contrast agent although not the only contrast agent in use. Gadobenate dimeglumine (MultiHance®, tracco, Milano Italy) also differentiates FNH from HCA. The first major difference between Gd-EOB-DTPA and Multihance® is the total injected dose excreted into the biliary system: 50% and 2-4% respectively. Secondly, accumulation of contrast into hepatocytes takes place within 20 minutes after dose injection with Gd-EOB-DTPA compared to 120 minutes with Multihance®. This makes Gd-EOB-DTPA more practical for clinical use. In FNH a central scar, and in HCA a steatotic surrounding liver, bleeding, fat, and glycogen were significantly predictive for diagnosis, which is comparable with earlier reports. However, not all features listed as typical for FNH or HCA were significant in our series. We mostly found lobulated FNH, however, no significant difference was found compared with HCA in which 50% of the lesions also showed a lobulated shape. Peripheral vessels were found both in HCA and FNH. This feature is considered diagnostic for HCA on CT imaging. Hence, shape and peripheral vessels may not be used as sole criteria on which differentiation between HCA and FNH is based.

Lesion-to-liver intensity during dynamic phases of MR imaging could further help in differentiating FNH from HCA. Three patients were excluded from these analyses after they were treated for bleeding from the lesion with embolization of one or multiple vessels prior to MR imaging. After this procedure the normal anatomy of the lesion is structurally altered. Therefore, these cases cannot be compared with the lesions in the overall patient group. Our series showed significant hyperintensity of HCA during pre-contrast 11w series compared to FNH. This could be due to bleeding or glycogen content in lesions. Furthermore, hypointensity on portal phase was significant for HCA as none of the FNH showed hypointensity on this phase. This might be due to disappearance of portal tracts and the increase of arterial feeding
vessels, causing rapid loss of contrast after the arterial phase. However, this ‘wash-out’ sign is highly suggestive of HCC, and can therefore not be used as a diagnostic criterion if any suspicion for malignancy exists. Overall, when intensity of the lesion to liver is evaluated the pre-contrast T1w phase and signs of ‘wash-out’ might help differentiate FNH from HCA.

Regarding lesion enhancement patterns, we found FNH to have a plateau pattern. This is in contrast to the enhancement pattern seen in HCA, which loses contrast significantly faster, creating a peak-pattern. These different lesion enhancement patterns may help differentiate FNH from HCA.

We found iso-hyper signal intensity of the lesion in the hepatobiliary phase in all but 1 FNH and in 1 HCA, compared to surrounding liver parenchyma. In FNH, iso- to hyper signal intensity of the lesion on the hepatobiliary phase is seen in 83%-90% of cases. Other studies suggested this to be rare in HCA. In our single case of HCA the signal intensity of the lesion was regarded slightly hyperintense along the border of the HCA lesion. The lesion was difficult to compare with normal liver on axial scans, because of motion artefacts.

Histomorphology of the lesion was consistent with HCA and showed telangiectatic changes, ductular dilation and inflammation. Immunohistochemically this case was an inflammatory HCA with positive staining for CRP and SAA. The high signal intensity on the hepatobiliary series may be explained by sufficient functioning hepatocytes and ductular proliferation, which is seen in telangiectatic HCA formerly described as telangiectatic FNH. The lesion shrunk from over 7 cm to 3 cm in less than a year after discontinuation of oral contraceptive use. Possibly, the ring-like high signal intensity could be explained by regeneration. On standard MR this lesion showed signs of bleeding, and was scored as HCA. Furthermore, one FNH was hypointense on the hepatobiliary series compared to the surrounding liver. No typical characteristics of FNH or HCA were present at MR imaging. Histomorphology was consistent with FNH with the presence of a ductular reaction, inflammatory infiltrates, thick-walled vessels and fibrotic bands. Immunohistochemistry showed no over expression of SAA and CRP. However, the GS staining was negative. GS staining has been reported negative in FNH-like nodules in a cirrhotic liver. This does not apply to the patient discussed in this article, but should be considered when morphology and immunohistochemical staining do not concur.

Uptake of hepatobiliary contrast has also been described in HCC. In well differentiated HCC the function of hepatocytes is preserved and thus, uptake of contrast is possible. This implies that no diagnosis can be made based solely on the hepatobiliary phase of the MR in patients with a liver tumor in general. If a patient presents with a positive history of malignancy, or a lesion with ‘wash-out’ on the portal phase, diagnosis should be malignancy until proven otherwise.

The histological standard of reference was obtained in all patients. Thus, patients presenting with a possible central scar also underwent a liver biopsy. This was done
to standardise the design and to avoid misdiagnosing cases mimicking a central scar. This study has a selection bias even though patients were included consecutively. Of all the lesions of included patients, 54% were diagnosed as FNH and 46% as HCA, whereas in the general population the estimated prevalence of FNH is 5-10 times higher than HCA. Referral of patients with HCA may have been more likely for the following reasons: because patients presented with symptoms, e.g., after bleeding when intervention was needed, or because patients presented with larger lesions for which resection was indicated. The latter is reflected in our patient group as 64% of all lesions in this study, and 83% of HCA were larger than 5 cm. Patients with typical FNH may have been less likely referred, because there are no surgical consequences to this diagnosis. The current bias is therefore towards cases with a more problematic diagnosis.

In conclusion, this study shows high accuracy of Gd-EOB-DTPA MR imaging when the standard series are combined with the hepatobiliary phase for differentiation of FNH and HCA in lesions larger than 2 cm. The results of this study advocate the use of the Gd-EOB-DTPA enhanced MR imaging for accurate differentiation of FNH and HCA.
References