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DIAGNOSTIC ACCURACY OF MRI IN DIFFERENTIATING HEPATOCELLULAR ADENOMA FROM FOCAL NODULAR HYPERPLASIA:

PROSPECTIVE STUDY
OF THE ADDITIONAL VALUE OF GADOXETATE DISODIUM

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The purpose of this article is to prospectively determine the sensitivity of hepatobiliary phase gadoxetate disodium enhanced MRI combined with standard MRI in differentiating focal nodular hyperplasia (FNH) from hepatocellular adenoma (HCA).

SUBJECTS AND METHODS

Patients suspected of having FNH or HCA larger than 2 cm underwent gadoxetate disodium-enhanced MRI. Standard MRI was evaluated separately from the additional hepatobiliary phase by two blinded radiologists. For the largest lesion in each patient, findings were compared with histologic diagnosis. Sensitivity, positive predictive value (PPV), and distinctive features were analyzed using McNemar and analysis of variance tests.

Fifty-two patients completed the study. Histologic diagnosis revealed 24 HCAs and 28 FNHs. Characterization on standard MRI was inconclusive in 40% (21/52) and conclusive in 60% (31/52) of lesions. The sensitivity of standard MRI for HCA was 50% (12/24) with a PPV of 100% (12/12). The sensitivity for FNH was 68% (19/28) with a PPV of 95% (18/19). After review of hepatobiliary phase, the sensitivity for HCA improved to 96% (23/24) with a PPV of 96% (23/24). The sensitivity for FNH improved to 96% (27/28) with a PPV of 96% (27/28). Features with significant predictive value for diagnosis in HCA included bleeding (p < 0.001), fat (p = 0.010), and glycogen (p = 0.024). The presence of a central scar was predictive for FNH (p < 0.001).

CONCLUSION

This study shows high sensitivity of gadoxetate disodium–enhanced MRI when standard series are combined with the hepatobiliary phase for differentiation of FNH and HCA in lesions larger than 2 cm.

OBJECTIVE

The purpose of this article is to prospectively determine the sensitivity of hepatobiliary phase gadoxetate disodium enhanced MRI combined with standard MRI in differentiating focal nodular hyperplasia (FNH) from hepatocellular adenoma (HCA).

INTRODUCTION

Because of the widespread use of imaging modalities, hepatocellular adenoma (HCA) and focal nodular hyperplasia (FNH) are increasingly found incidentally [1]. It is generally accepted that FNH can be treated conservatively because of its benign nature and minimal risks of complications [2, 3]. HCA, unlike FNH, carries the risk of malignant transformation in 4.3% of lesions larger than 5 cm [4, 5], and spontaneous rupture with bleeding has been reported in 30% of lesions larger than 5 cm [4, 6]. The growth and risk of bleeding in HCA are influenced by the use of oral contraceptives. For these reasons, resection of HCAs larger than 5 cm is advised, and differentiation between HCA and FNH thus becomes important [7]. MRI and CT are mostly used for characterizing focal hepatic lesions. Diagnosis is based on lesion characteristics and enhancement patterns.

On MRI, typical findings of FNH include a central scar, lobulated shape, central feeding vessels, and arterial enhancement [8, 9]. Typical findings of HCA include hemorrhage [10], intratumoral fat, and glycogen [11], which present as high-signal foci on T1-weighted images. The fat-suppression setting will distinguish intratumoral fat. Other typical findings include peripheral feeding vessels and arterial enhancement [12]. However, these typical findings are not always present. For example, a macroscopic central scar occurs in 50% of FNHs and is often absent in FNHs smaller than 3 cm [8, 13]. In HCA, glycogen and fat are not always present, and bleeding occurs more frequently in lesions larger than 5 cm [4]. If imaging results are inconclusive, a liver biopsy may be mandatory [14]. Liver-specific hepatobiliary contrast agents for MRI are now available. Gadoxetate disodium (Eovist, Bayer HealthCare) is a gadolinium-based paramagnetic contrast agent taken up via an organic anion transport system by functioning hepatocytes [15, 16]. Approximately 50% of the contrast agent is excreted into the biliary system, and 50% is excreted by the kidneys. Hepatocyte-selective imaging allows assessment of hepatocyte function and biliary excretion. In FNH, a ductular reaction occurs along the septa, resulting in bile calculi with abnormal drainage [14]. This may result in accumulation of contrast agent in the lesion. In contrast, HCA has no or few bile ducts, and the lesional hepatocytes are thought to have diminished function [4, 14]. This may result in reduced accumulation of contrast agent in the hepatobiliary phase. This difference in accumulation of contrast agent in the hepatobiliary phase of imaging between FNH and HCA may therefore be useful for differentiation when typical features are absent. Previous studies with liverspecific contrast agents have shown promising results in differentiating FNH from HCA [7, 17]. However, those studies were limited, because the reference standard con-
sisted only of imaging or follow-up in a substantial number of included cases [18]. Therefore, the pur-
pose of this study was to prospectively determine the diagnostic accuracy of the hepatobiliary phase of
gadoxetate disodium–enhanced MRI combined with standard MRI in differentiating FNH from HCA, with histopathology as the standard of reference.

METHODS

This study was a prospective single-center diagnostic accuracy study with paired design for differentiating FNH from HCA conducted between January 2008 and June 2010. Standard MRI was compared with the hepatobiliary phase of gadoxetate disodium–en-
hanced MRI at a blinded reading. The institutional medical ethics committee approved the study, and written informed consent was ob-
tained from all patients. A total of 67 consecutive patients were included (mean age, 39 years; range, 18–60 years). Patients either primarily pre-
sented to our surgical outpatient clinic or were secondarily referred from other centers with suspicion of FNH or HCA on the basis of CT or MRI without hepatobiliary-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 nonrepresentative sampling. The pa-
tients were 18 years old or older. Exclusion criteria were suspicion of metastatic malignant disease, previous malignancy, and other risk factors, including chronic hepatitis, cirrhosis, hemochromatosis, and elevated alpha-fetoprotein or carcinoem-
byronic antigen levels in blood serum. Further exclusion criteria were pregnancy and
contraindications for MRI (i.e., severe claustrophobia, metal objects or particles within
the eyes or the abdomen, and impaired renal function, which was defined as serum crea-
tine level > 200 μmol/L). One patient discontinued the study because of claustrophobia.
Six patients were excluded because our MRI revealed typical hemangiomia or hamartoma.
Eight patients were excluded because histologic confirmation was not obtained, either
because of sampling errors or because consent was withdrawn. 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 were excluded from
the subanalyses of enhancement. This was because of possible alteration in enhancement and sig-
nal intensity of the lesion after embolization of feeding vessels. Hence, data of 52 patients (2 men
and 50 women; mean age, 39 years; range, 18–56 years) were available for evaluation.

MRI Protocol

The MRI series were reviewed in consensus by two radiologists with more than 10 years of experi-
ence in abdominal radiology. The readers were informed of the differential diagnosis of either FNH
or HCA but were blinded to patient history and previous imaging findings. First, the standard images
were evaluated, after which the hepatobiliary phase was evaluated in the same session. The following
characteristics were used for evaluation of the liver: the number of lesions and the presence of steato-
sis (i.e., visual loss of signal intensity of the liver between in- and out of phase Ti-weighted series).
The following items were noted regarding the lesions: size, segmental localization, shape (round or
lobulated), and demarcation (sharp or faint). High-signal foci on Ti-weighted series were assessed;
foci with loss of signal intensity on the Ti-weighted out-of-phase series were regarded as fat, and small
foci without loss of signal intensity were regarded as glycogen. Larger irregular high-signal areas on
Ti-weighted series were regarded as recent bleeding, whereas low-signal areas were regarded as older
bleeding. Diffuse loss of signal intensity regarded as diffusion fat content within the lesion. Furthermore, a central scar (a high-signal-intensity “spokes wheel” on true
FISP T2-weighted series and low signal intensity on Ti-weighted series, with or without enhance-
ment during portal or late series). Lesion-to-liver intensity was noted on unenhanced Ti-weighted
and true FISP T2-weighted series, and contrast-enhanced arterial, portal, and late phases. The lesion
enhancement pattern was expressed as a “peak pattern,” if arterial enhancement with clear loss of
signal intensity during portal or late phases was seen, and as a “plateau pattern,” if signal intensity was
sustained during portal and late phases of imaging. The two readers made a visual score of signal intensity and enhancement pattern. When in doubt, a region of interest was placed in the lesion to
measure signal intensity of the lesion. The diagnosis of FNH was based on the presence of a central
scar, arterial enhancement, and absence of signs of washout during portal phase. A diagnosis of HCA
was based on arterial enhancement, with possible washout during portal phase; the presence of bleed-
ing, fat, or glycogen; and the absence of a central scar. MRI of lesions without these characteristics was
regarded as inconclusive. Finally, the lesions were evaluated for signal intensity compared with sur-
rounding liver tissue on the Ti-weighted hepatobiliary series at 20 minutes after injection. Isointense
or hyperintense signal intensity of the lesion was regarded as diagnostic for FNH, and hypointensity
was considered diagnostic for HCA. The pattern of contrast agent uptake was scored as either homo-
geneous or inhomogeneous.

The MRI series were performed with a 1.5-T MRI scanner (Avanto, Siemens Healthcare) using a phased-
array torso coil. MRI series consisted of 2D gradient-echo in- and opposed-phase imaging FLASH
(TR/TE, 125/2.3 and 125/4.6; flip angle, 70°; matrix, 256 × 134); coronal T2-weighted true fast imaging
arrays (TR/TE, 125/2.3 and 125/4.6; flip angle, 70°; matrix, 256 × 134); axial diffusion weighted echo-planar imaging with b values of 50, 400, and 800 s/mm2 (TR/
TE, 5400/76; flip angle, 90°; matrix, 192 × 156); axial and coronal hepatobiliary phase images were made at 20 minutes after injection using VIBE single breath-hold sequences. Slice thickness was 4–6 mm for Ti-weighted images and in-
and out-of-phase images and 2 mm for VIBE unenhanced and contrast-enhanced series. All unenhanced
series and the dynamic contrast-enhanced series after gadoxetate disodium were regarded as standard
MRI. The delayed phase images at 20 minutes were considered as hepatobiliary gadoxetate disodium-
enhanced MRI.

The MRI series were reviewed in consensus by two radiologists with more than 10 years of experi-
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or hyperintense signal intensity of the lesion was regarded as diagnostic for FNH, and hypointensity
was considered diagnostic for HCA. The pattern of contrast agent uptake was scored as either homo-
geneous or inhomogeneous.
The standard of reference was defined as histopathologic diagnosis. The histologic specimens were obtained by resection or liver biopsy from tumoral and normal liver tissue. The evaluating pathologist was blinded to patient history. In addition to standard liver stainings, including H and E, collagen, and CK7, glutamine synthetase staining was performed for confirmation of histomorphologic diagnosis [19]. The diagnosis of FNH as based on morphologic characteristics, including the presence of stellate fibrous scarring, dystrophic arteries, ductular reaction, variable infiltrate, and absence of cytologic abnormalities. Morphologic characteristics of HCA included a proliferation of nonatypical hepatocytes, with a well-developed reticulin framework, without a central scar.

In cases of multiple lesions, the largest lesion or the lesion most suitable for biopsy was selected on imaging. The location of this lesion was recorded by the investigator, who also instructed the interventional radiologist as to which lesion to biopsy. The investigator also monitored the preoperative selection of the lesions and the postoperative examination by the pathologist to guarantee proper matching between imaging and histopathology.

Histologic diagnoses were 24 HCAs and 28 FNHs, diagnosed in 25 patients on resection and in 27 patients on biopsy specimens. Biopsy material (six HCAs and 21 FNHs) and resection specimens (18 HCAs and seven FNHs) were used. All FNHs but one showed a typical maplike pattern staining of glutamine synthetase, which was absent in HCAs. This one lesion was composed of nonatypical hepatocytes together with scarring, ductular reaction, thick-walled vessels, and inflammatory infiltrates but lacked the typical maplike glutamine synthetase staining. On the basis of morphologic features, lack of serum amyloid A, and C-reactive protein overexpression, the lesion was diagnosed as FNH.

Statistical analysis was per patient for the largest suitable lesion using SPSS (version 18, IBM). Descriptive statistics were used for the study population. Continuous data were tested for normal distribution and equal variances using the Levene test. Features on imaging were tested for significance between FNH and HCA using the analysis of variance and multivariate tests. The sensitivity, specificity, and positive predictive value (PPV) of the standard and hepatobiliary phases of gadoxetate disodium–enhanced MRI were calculated with the McNemar test and the 95% CI of the proportions on the Wilson procedure without correction for continuity [20]. Statistical tests were evaluated at the 5% level of significance.

Figure 1

- A: Transverse T2-weighted MRI (Fat saturated; TR/TE, 5400/76; Flip Angle, 70°; Matrix, 384 × 230) shows hyperintense lesion (arrow) in right liver.
- B: In subsequent arterial transverse T1-weighted image (TR/TE, 5.77/2.54; Flip Angle, 10°; Matrix, 256 × 156), lesion (arrow) shows strong signal intensity to surrounding liver parenchyma, without typical features of FNH or HCA. C: Portal phase image shows slight hyperintense lesion (arrow) without typical features to differentiate between FNH and HCA. D: Differentiation could, however, be made on transverse hepatobiliary phase T1-weighted fat-saturated image 20 minutes after contrast agent injection. Lesion (arrow) was interpreted to have less signal intensity compared with surrounding liver tissue, which is consistent with HCA.

28-YEAR-OLD WOMAN WITH ATYPICAL HCA, DULL PAIN IN UPPER ABDOMEN, AND HISTORY OF LONG-TERM ORAL CONTRACEPTIVE USE. A: Transverse T2-weighted MRI (Fat saturated; TR/TE, 5400/76; Flip Angle, 70°; Matrix, 384 × 230) shows hyperintense lesion (arrow) in right liver. B: In subsequent arterial transverse T1-weighted image (TR/TE, 5.77/2.54; Flip Angle, 10°; Matrix, 256 × 156), lesion (arrow) shows strong signal intensity to surrounding liver parenchyma, without typical features of FNH or HCA. C: Portal phase image shows slight hyperintense lesion (arrow) without typical features to differentiate between FNH and HCA. D: Differentiation could, however, be made on transverse hepatobiliary phase T1-weighted fat-saturated image 20 minutes after contrast agent injection. Lesion (arrow) was interpreted to have less signal intensity compared with surrounding liver tissue, which is consistent with HCA.
A total of 52 patients completed the study. The two men both presented with FNH. Forty-seven of the 50 women reported long-term use of oral contraceptives. Thirty-one patients presented with abdominal pain or discomfort, three of whom presented with acute bleeding requiring arterial embolization (16 with HCA and 15 with FNH). Eighteen of the 24 patients with HCA (75%) underwent resection of the lesion (mean [± SD] diameter, 8.5 ± 4.9 cm; range, 4.4–25 cm). Seven of 28 patients with FNH (25%) underwent resection of the lesion because of discomfort (mean diameter, 6.8 ± 3.0 cm; range, 3.7–12.0 cm). Patients who presented with discomfort often had bleeding (nine with HCA) or a large lesion with mass impact on the surrounding liver parenchyma and organs. However, one patient with extreme discomfort only had a 2.5-cm FNH. Thirty-five lesions were 5 cm or larger (20 HCAs and 15 FNHs), and resection was advised if the diagnosis was HCA. The group of patients with a lesion smaller than 5 cm (n = 17) consisted of four with HCA (24%) and 13 with FNH (76%). In the overall group, 15 patients had a solitary lesion at imaging (four with HCA and 11 with FNH), eight had two or three lesions (five with HCA and 11 with FNH), six had four to 10 lesions (five with HCA and one with FNH), and 12 patients had more than 10 lesions characterized on MRI (nine with HCA and three with FNH). Of the 19 patients with HCA and multiple lesions, three also presented with a lesion compatible with FNH on imaging, with high or isointense signal on the hepatobiliary phase. One lesion was also confirmed to be FNH at histopathologic analysis.

Imaging results are summarized in Table 1. For 31 of 52 patients, MRI was conclusive and diagnosed 12 lesions as HCA and 19 as FNH. Compared with histologic diagnosis, this resulted in a sensitivity for HCA of 50% (12/24; 95% CI, 31–69%), and a PPV of 100% (95% CI, 76–100%). The sensitivity for FNH was 64% (18/28; 95% CI 46–79%) with a PPV of 95% (18/19; 95% CI 75–99%). With standard MRI, characterization was inconclusive in 21 of 52 patients, including 11 with HCA (Fig. 1) and 10 with FNH (Fig. 2). Two of 10 FNHs showed a small central scar. In comparison, 16 of 18 FNHs contained a scar when diagnosis was conclusive on standard MRI. In 11 HCAs, the MRI was regarded inconclusive, although in five lesions, high-signal foci were dubiously present. The mean diameter of lesions was 7.1 cm on conclusive standard MRI and 6.4 cm on inconclusive MRI (p = 0.420).

On the hepatobiliary series, no cases were regarded as inconclusive (Table 1). Twenty-four lesions were hypointense compared with surrounding liver tissue and were characterized as HCA (Fig. 3). Twenty-eight lesions were isointense or hyperintense and therefore characterized as FNH (p < 0.01) (Fig. 4). Compared with the histologic diagnosis, this resulted in a sensitivity of 96% for HCA (23/24; 95% CI, 80–99%), with a PPV of 96% (95% CI, 80–99%). The sensitivity for FNH was 96% (27/28; 95% CI, 82–99%), with a PPV of 96% (95% CI, 82–99%). High signal intensity of FNH (n = 27) during the hepatobiliary phase was homogeneous in 14 cases (52%) and inhomogeneous in 13 cases (48%). One case

**Results**

**Standard MRI**

**Imaging**

**Hepatobiliary Phase**
of FNH showed low homogeneous signal intensity compared with surrounding parenchyma during the hepatobiliary phase and was incorrectly characterized as HCA. One case of HCA was isointense and therefore falsely characterized as FNH.

### TABLE 1: Diagnosis of Hepatocellular Adenoma (HCA) and Focal Nodular Hyperplasia (FNH) on Standard and Hepatobiliary MRI Series

<table>
<thead>
<tr>
<th>Type of MRI, Diagnosis</th>
<th>Histologic Diagnosis</th>
<th>FNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>HCA</td>
<td>FNH</td>
</tr>
<tr>
<td>Inconclusive</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>HCA</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>FNH</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>Hepatobiliary phase</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Inconclusive</td>
<td>23</td>
<td>1</td>
</tr>
<tr>
<td>FNH</td>
<td>1</td>
<td>27</td>
</tr>
</tbody>
</table>

Note—Data are no. of lesions.

### FIGURE 3

**22-year-old woman with focal nodular hyperplasia (FNH) and chronic dull pain in upper abdomen.**

A: **Transverse arterial phase T1-weighted image** (fat saturated; TR/TE, 5.77/2.54; flip angle, 10°; matrix, 256 × 156) shows arterial enhancement of lesion in segment IV of liver (arrow), with hypointense area in center of lesion; central scar (arrowhead) is also seen.

B: **Corresponding hepatobiliary phase T1-weighted image** obtained 20 minutes after contrast agent injection shows isointense-to-hyperintense signal of lesion (arrow) compared with surrounding liver, consistent with FNH.

### TABLE 2: Characteristics of Focal Nodular Hyperplasia (FNH) and Hepatocellular Adenoma (HCA) Lesions

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total</th>
<th>HCA</th>
<th>FNH</th>
<th>HCA</th>
<th>FNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histologic outcome</td>
<td>12</td>
<td>24</td>
<td>26</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Size of lesion (cm), mean (range)</td>
<td>6.0 (2–12)</td>
<td>7.7 (2.3–25)</td>
<td>6.0 (2–12)</td>
<td>7.6 (2.3–25)</td>
<td>5.1 (2–9)</td>
</tr>
<tr>
<td>No. of lesions per patient</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Note—Data are no. of lesions except where indicated otherwise.
Features and Characteristics

The lesion characteristics are summarized in Table 2. Diffuse parenchymal steatosis of the liver was found in nine of 24 patients with HCA (38%) and in three of 28 patients (11%) with FNH (p = 0.022). Features with significant predictive value for HCA included fat content in five cases (p = 0.010). High-signal foci on T1-weighted series consistent with bleeding were found in 11 HCAs and zero FNHs (p < 0.001). This was histopathologically confirmed in five of six surgical specimens. Finally, glycogen was detected in four HCAs and zero FNHs as hyperintense small areas on T1-weighted imaging (p = 0.024). Features with significant predictive value for FNH include a central scar in 18 of 28 FNHs (p < 0.001). Among 14 FNHs smaller than 5 cm, six showed no central scar. FNH was often lobulated (21/28) compared with HCA (12/24; p = 0.064). Peripheral vessels were found in two FNHs and three HCAs (p = 0.523), and none of the lesions had central feeding vessels. Lesion-to-liver intensity is summarized in Table 3. Three HCAs were not included in the analyses because of prior arterial embolization of a feeding vessel after bleeding. During unenhanced T1-weighted series, FNHs overall showed significantly lower signal intensity than did HCAs, even if bleeding was excluded from analyses (p < 0.001). During the T1-weighted arterial phase, all 28 FNHs and 20 of 21 HCAs showed arterial enhancement. During the T1-weighted portal phase, hyperintense signal compared with surrounding liver parenchyma was seen in 22 of 28 FNHs and 14 of 21 HCAs (p = 0.026). On the portal phase, hypointensity (washout) was seen in three HCAs and in none of the FNHs. During the late phase, hyperintense signal was seen in 18 FNHs and 13 HCAs, isointense signal was seen in eight FNHs and six HCAs, and hypointense signal was seen in two FNHs and two HCAs, with no significant difference between the two groups (p = 0.802). The enhancement pattern showed a plateau pattern in FNHs and a peak pattern in HCAs (p = 0.009) (Table 4). In the hepatobiliary phase in 24 of 52 patients, the lesions were hypointense compared with surrounding liver tissue characterized as HCA and in 28 of 52 patients, the lesion was isointense or hypointense and was characterized as FNH (p < 0.01) (Fig. 4).

Discussion

In previous studies, enhancement with gadoxetate disodium has shown promising results in differentiating FNH from HCA [7]. The limitation of those studies was the use of only CT or follow-up as the standard of reference in most of the included cases. Therefore, we evaluated our imaging results with histologic analysis as the standard of reference in all cases. The present study shows the high accuracy of gadoxetate disodium–enhanced MRI 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 MRI was inconclusive because of the lack of typical features. In the literature, this occurs in 30–42% of cases, especially when lesions are smaller than 3 cm [8, 10–12]. Difficulties may arise in detecting a small scar in FNH. For example, in one FNH, we detected the small scar on the hepatobiliary phase only. Bleeding was mostly detected as hyperintense signal on T1-weighted images, and may therefore be confused with a scar. This was the case in one HCA thought to be an FNH on standard MRI. The lesion was correctly characterized on the hepatobiliary phase. In two other lesions, the readers were uncertain about differentiating bleeding from a scar and therefore characterized the standard MRI as inconclusive.

dobenate dimeglumine (MultiHance, Bracco) [21] also differentiates FNH from HCA [21, 23]. The first major difference between gadobenate disodium and gadobenate dimeglumine is the total injected dose excreted into the biliary system (50% and 2–4%, respectively). Second, the accumulation of contrast agent into hepatocytes takes place within 20 minutes after dose injection with gadobenate disodium, compared with 20 minutes with gadobenate dimeglumine. This makes gadobenate disodium more practical for clinical use. A central scar in FNH and a steatotic surrounding liver, bleeding, fat, and glycogen in HCA were significantly predictive for diagnosis, which is comparable with earlier reports [8, 10–12]. The accumulation of contrast agent into hepatocytes takes place within 20 minutes after dose injection with gadobenate disodium, compared with 20 minutes with gadobenate dimeglumine. This makes gadobenate disodium more practical for clinical use. A central scar in FNH and a steatotic surrounding liver, bleeding, fat, and glycogen in HCA were significantly predictive for diagnosis, which is comparable with earlier reports [8, 10–12]. Difficulties may arise in detecting a small scar in FNH. For example, in one FNH, we detected the small scar on the hepatobiliary phase only. Bleeding was mostly detected as hyperintense signal on T1-weighted images, and may therefore be confused with a scar. This was the case in one HCA thought to be an FNH on standard MRI. The lesion was correctly characterized on the hepatobiliary phase. In two other lesions, the readers were uncertain about differentiating bleeding from a scar and therefore characterized the standard MRI as inconclusive.
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 [12]. 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 MRI 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 before MRI. 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 unenhanced T1-weighted series compared with FNH. High-signal foci on T1-weighted images may be due to bleeding or glycogen content in lesions [24], but we did not include these foci in the evaluation of lesion signal intensity. Steatosis of the liver may also explain a relatively high signal intensity of the lesions on the T1-weighted fat-suppressed series. Steatosis was more often present in HCA compared with FNH, but this did not explain the high signal intensity in all lesions. Furthermore, the uptake of contrast agent was significant for HCA because none of the FNHs showed hypointense signal on this phase. This might be the result of the disappearance of portal tracts and the increase of arterial feeding vessels, causing rapid loss of contrast agent after the arterial phase. However, this washout sign is highly suggestive for hepatocellular carcinoma (HCC) [25] and, therefore, cannot be used as a diagnostic criterion if any suspicion for malignancy exists. Overall, when intensity of the lesion to liver is evaluated, the unenhanced T1-weighted phase and signs of washout 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, in which lesions enhance faster, creating a peak pattern. These different lesion enhancement patterns may help differentiate FNH from HCA.

We found isointense-to-hyperintense signal intensity of the lesion in the hepatobiliary phase in all but one FNH and in one HCA, compared with surrounding liver parenchyma. In FNH, isointense-to-hyperintense signal intensity of the lesion in the hepatobiliary phase is seen in 83–90% of cases [17]. Other studies suggested this to be rare in HCA [8, 26]. In our single case of HCA, the signal intensity of the lesion was regarded as slightly hyperintense along the border of the HCA lesion. The lesion was difficult to compare with normal liver on axial scans because of motion artifacts. 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 stain for C-reactive protein and serum amyloid A. 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 [27]. The lesion shrank from more than 7 cm to 3 cm in less than a year after discontinuation of oral contraceptive use. The ringlike high signal intensity possibly could be explained by regeneration. On standard MRI, this lesion showed signs of bleeding and was scored as HCA. Furthermore, one FNH showed hypointense signal on the hepatobiliary series compared with the surrounding liver. No typical characteristics of FNH or HCA were present at MRI. Histomorphology was consistent with FNH with the presence of a ductular reaction, inflammatory infiltrates, thick-walled vessels, and fibrotic bands. Immunohistochemistry showed no overexpression of serum amyloid A and C-reactive protein. However, the glutamine synthetase stain was negative. Glutamine synthetase staining has been reported to be negative in FNH-like nodules in a cirrhotic liver [28]. This does not apply to the patient discussed in here but should be considered when morphology and immunohistochemical staining results do not concur.

Uptake of hepatobiliary contrast agent has also been described in HCC [26, 29]. In welldifferentiated HCCs, the function of hepatocytes is preserved, and, thus, uptake of contrast agent is possible [29]. This implies that no diagnosis can be made solely on the basis of the hepatobiliary phase of the MRI in patients with a liver tumor in general. If a patient presents with a positive history of malignancy or with a lesion with washout on the portal phase, the diagnosis should be malignancy until proven otherwise [25].

The histologic 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 standardize 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 15–10 times higher than that of HCA [30, 31]. Referral of patients with HCA may have been more likely 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, because 64% of all lesions in this study and 83% of HCAs were larger than 5 cm. Patients with typical FNH may have been less likely to be referred, because there are no surgical consequences to this diagnosis. The current bias is therefore toward cases with a more problematic diagnosis. In conclusion, this study shows high accuracy of gadoxetate disodium–enhanced MRI 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 gadoxetate disodium–enhanced MRI for accurate differentiation of FNH and HCA.

References