Differentiation of hepatic hyperintense lesions seen on gadoxetic acid-enhanced hepatobiliary phase MR imaging

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Purpose

1. Gadoxetic acid disodium
   - The newest biphasic hepatobiliary contrast agent
   - Can be taken up by normal hepatocytes at approximately 50% of the injected dose
   - Allow hepatobiliary phase imaging within 10 to 20 minutes after contrast injection [1,2]
   - Most malignant lesions show hypointensity on gadoxetic acid-enhanced hepatobiliary phase images
     - Poor uptake of the contrast agent [3,4]

2. Increased uptake of contrast agent on gadoxetic acid-enhanced hepatobiliary phase images
   - Focal nodular hyperplasia (FNH), hepatic adenoma, and biliary cystadenoma [5-8]
   - Some hepatocellular carcinomas (HCCs) as well as dysplastic nodules may show hyperintensity [9,10]
   - Imaging features that could help to distinguish hyperintense HCCs from other benign lesions: not well established

3. The purpose of our study
   - To define imaging features that may help characterize hyperintense lesions seen on hepatobiliary phase images of gadoxetic acid-enhanced hepatic MR examinations

Methods and Materials

1. Institutional review board approval was obtained for this retrospective study, and informed consent was waived

2. Patient population
   1) Review of our radiology information database from May 2007 to Apr 2009
2) 52 patients who presented with a hyperintense nodule on hepatobiliary phase images among 1891 patients who underwent gadoxetic acid-enhanced MR imaging

3) Exclusion: Four patients with a diagnosis of hyperintense lesions that was not confirmed

4) Study population: 48 hyperintense lesions in 48 patients (mean age, 59.5 years; range, 20-85 years), and 18 women (mean age, 51.2 years; range, 29-77 years)

5) 16 HCCs, 14 FNHs, 18 benign nodules associated with cirrhosis (benign nodules): confirmed by histopathologically diagnosis in 15 lesions or typical MR imaging finding and follow-up MR exam in 33 lesions

3. MR Imaging

1) All patients were examined with a 3.0-T MR system (MAGNETOM Trio a Tim;Syngo MR B15; Siemens Medical Solutions, Erlangen, Germany) except for four patients examined with a 1.5-T MR system

2) Dynamic MR imaging: gadoxetic acid disodium (Primovist, Bayer Schering Pharma, Germany; 0.025 mmol/kg) injected as a rapid bolus, immediately followed by a 30-ml saline flush with a power injector at 1 or 2 ml/s

3) Hepatobiliary phase images: 15-20 min after contrast injection

4) The MR parameters: TR/TE 3.3/1.16, a flip angle of 13°, a 256×192 matrix, one signal acquired, and 2-mm slice thickness using an interpolation technique

4. Image analysis

1) Qualitative

- Only the hepatobiliary phase images were independently analyzed by two gastrointestinal radiologists

- Interobserver agreement of the independent analysis using kappa statistics

- Resolved interpretation discrepancies by consensus at a second session

- Shape, texture, margin, border, expansile nature, focal defects in contrast agent uptake, nodule-in-nodule pattern, central scar, internal septation, and the presence of a hypointense or dark rim around the lesion

  - Lesion shape: round-ovoid or lobulated
  - Texture: the overall lesion signal intensity; homogenous or heterogeneous
• Margin: well-defined, or ill-defined
• Borders: smooth or undulated
• Expansile nature: a mass effect such as a vascular or bile duct displacement, or bulging of the hepatic capsule
• Focal defect in contrast agent uptake: an area of geographic hypointensity that was less than 1/3 of the lesion
• Nodule-in-nodule pattern: an area within the lesion of visually different uptake
• Internal central scar: linear, strand-like hypointense structure mainly in the central area of the lesion that suggested FNH
• Internal septation: hypointense structure that completely divided the lesion into more than two compartments
• Hypointense or dark rim: a thickness of 2 mm or more, and encircled at least two-thirds of the circumference of a lesion at the periphery

2) Quantitative

- Regions of interest (ROIs) were drawn in the focal lesion and hepatic parenchyma at a workstation (Centricity 2.0, GE Healthcare, U.S.A.)
- Measuring the postcontrast lesion-to-liver contrast ratio (CR)

; The signal intensity (SI) of the lesion and adjacent liver tissue was measured --> CR =SI tumor / SI liver

5. Data analysis

- Interobserver agreement between the two observers for assessment of imaging findings before consensus was determined using a weighted #-statistic
- The Student t-test (patient age) or the Mann-Whitney U test (diameter and CR of a lesion) to compare continuous variables between the HCC and benign lesion groups
- The chi-square or Fisher’s exact test
  - To assess differences between the groups in serum viral markers, chronic liver disease, and Child-Pugh class distribution in patients with chronic liver disease
  - To determine association of qualitative variable

- Logistic regression analysis to assess individual clinical and MR findings for malignancy prediction
  - Variables with p-values less than 0.05 by univariate logistic regression analysis were selected as variables for multiple logistic regression analysis
  - Receiver operating characteristic (ROC) curves were drawn for
the criteria significant for lesion diameter by logistic regression analysis, and the most appropriate cutoff value, sensitivity and specificity were determined

- Odds ratios with 95% confidence interval (CI) for differentiating HCC from other benign focal hepatic lesions were calculated for each MR criterion

- A p-value of less than 0.05 was considered significant

## Results

### Patient and lesion characteristics

- A significant difference in sex distribution between the HCC and benign lesion groups (Table 1 on page)

- Lesion diameters were significantly larger (p=0.021) in the HCC group (mean 4.0 cm; range, 0.6-10 cm) compared to the benign lesion group (mean 2.6 cm; range, 0.6-7.2 cm)

- No significant difference in age distribution, positive results for serum viral markers, chronic liver disease, Child-Pugh class distribution, or multiplicity

### Image analysis

: Qualitative analysis after consensus reading (Table 2) on page - No significant difference was seen between the HCC and benign lesion groups for shape, texture, or border of the lesions

**a well-defined margin** (14 of 16, 87.5% in HCC vs. 19 of 32, 59.4% in benign lesions, p=0.048), **expansile nature** (50% in HCC vs. 12.5% in benign, p=0.01), **internal septation** (50% vs. 3.1%, p<0.001), and **hypointense rim** (75% vs. 15.6%, p<0.001): significantly higher in the HCC group (Figure 1 on page 6, Figure 2 on page 8 and Figure 3 on page 10)

- A **central scar**: 17 of 32 (53.1%) benign lesions, but none of the HCC cases (p <0.001) (Figure 4 on page 12 and Figure 5 on page 12)

- Lesion-to-liver CR was comparable between the two groups (mean 1.31, range 1.06-1.88 in HCCs and mean 1.28, range 1.06-1.79 in benign lesions, p = 0.63)
Diagnostic values of hepatobiliary phase image findings

1) Univariate logistic regression analysis using clinical and MR imaging variables: five MR imaging findings: expansile nature (p=0.0078), focal defect in contrast agent uptake (p=0.0002), internal septation (p=0.0024), hypointense rim (p=0.0002) and lesion diameter: significant predictors for HCC

2) Multivariate logistical regression analysis: Only focal defect in contrast agent uptake (p=0.024) and hypointense rim (p=0.019) independent predictors of HCC (Table 3) on page: an odds ratio of 38.6 (95% CI, 1.63-912.2) for focal defect, and 19.7 (95% CI, 1.62-238.6) for hypointense rim

For hyperintense lesions meeting at least one of the two findings that were identified as HCCs; sensitivity of 88% (14 of 16), specificity of 81% (26 of 32), and accuracy of 83% (40 of 48) (Table 4) on page: For lesions having both findings, a sensitivity of 56% (9 of 16), a specificity of 100% (32 of 32), and an accuracy of 85% (41 of 48)

Images for this section:
**Fig. 1:** Figure 1. HCC at segment 5 of the liver in a 52-year-old man with cirrhosis associated with chronic hepatitis B. (a, b) Transverse hepatobiliary phase MR images (a, upper; b, lower) demonstrate a well-defined 5.5-cm, round, hyperintense mass showing a smooth border, expansile nature (bulging of hepatic capsule), a focal defect in contrast agent uptake (black arrow), hypointense septation (arrowhead), and a dark-intensity rim (white arrows). Background liver shows coarse architecture suggesting cirrhotic change. (c) The patient underwent right lobectomy and the lesion was confirmed pathologically as a moderately-differentiated HCC (Edmondson grade II) with complete fibrous capsule formation. The yellowish inner portion (arrow) of the mass seen in the surgical specimen corresponds to the focal defect in contrast uptake (black arrow in b) by MR imaging, and
indicates an area of tumor necrosis. (d) Photomicrograph shows that the fibrous capsule (arrows) delimits the tumor from the surrounding tissue. Histologically, the tumor showed a trabecular and pseudoglandular pattern composed of hepatic type cells. (Hematoxylin-eosin stain; original magnification, 40X).
**Fig. 2:** Figure 2. HCC in a 54-year-old man with cirrhosis associated with chronic hepatitis B. (a) A transverse hepatobiliary phase MR image with a 2.2-cm, lobulated, well-defined hyperintense mass, showing a nodule-inodule pattern, internal septation (arrow) and hypointense rim (arrowheads). A central scar was not present. (b) Photograph of right lobectomy specimen. The lesion was confirmed by pathology as a moderately-differentiated HCC (Edmondson grade I and II) with partial fibrous capsule formation. (c) Photomicrograph of surgical specimen shows the well-differentiated area (left upper) is separated from the moderately differentiated area by an internal septation (arrows). Microscopically, the tumor was trabecular, partly pseudoglandular and partly compact, and composed of hepatic-type cells. (Hematoxylin-eosin stain; original magnification, 40X).
Fig. 3: HCC in a 57-year-old man with chronic alcoholic hepatitis. (a) Transverse hepatobiliary phase MR image shows a 1.7-cm, oval-shaped, well-defined nodule at the left lateral segment, showing a focal defect in contrast agent uptake (arrow) and nodule-in-nodule pattern (hypointense foci in hyperintense nodule), but no expansile nature or hypointense rim. (b) The patient underwent left lobectomy and the lesion was confirmed as a moderately differentiated HCC (Edmondson grade I and II) with partial fibrous capsule formation. The area of dark color (arrow in b) seen in the surgical specimen is consistent with the focal defect in contrast uptake on MR imaging (arrow in a). (c) Photomicrograph shows areas with different degrees of differentiation, with moderately
differentiated on the left side and well-differentiated at right. Histologically, the tumor showed a trabecular and pseudoglandular pattern of hepatic-type cells. (Hematoxylin-eosin stain; original magnification, 40X). The focal defect in contrast uptake can indicate the correct diagnosis and reflect the different histologic components.

![Image](image-url)

**Fig. 4:** Figure 4. A benign nodule in a 56-year-old man with alcoholic liver cirrhosis. (a) A transverse hepatobiliary phase MR image shows a 1.5-cm, round, well-defined, homogenous mass with a smooth border at segment 4 of the liver. The mass shows a hypointense rim but no other findings suggesting HCC. (b) Photograph of surgical specimen. The lesion was confirmed as a high-grade dysplastic nodule (arrow).
**Fig. 5:** Figure 5. An atypical FNH in 38-year-old man without chronic liver disease. (a) A transverse hepatobiliary phase MR image shows a 3.5-cm, oval mass at the right posterior inferior of the non-cirrhotic liver. The lesion has no finding suggestive of HCC, but shows a strand-like hypointense structure in the central area, which was not typical of the central stellate scar of an FNH. The possibility of hepatic adenoma or atypical HCC was suspected by preoperative interpretation, and a biopsy was recommended. (b) The patient requested surgical resection, and the lesion was revealed as a FNH by pathological examination.
Conclusion

1. Hyperintense HCCs on gadoxetic acid-enhanced hepatobiliary phase MR images
   - Can be distinguished from hyperintense benign lesions by several characteristic MR findings

2. A focal defect in contrast agent uptake, and the presence of a hypointense rim
   - Two most important independent MR findings that are useful for distinguishing hyperintense HCCs from benign focal lesions on gadoxetic acid-enhanced hepatobiliary phase images

References


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