Added Value of a Gadoxetic Acid-enhanced Hepatocyte-phase Image to the LI-RADS System for Diagnosing Hepatocellular Carcinoma

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Purpose: We investigated the added value of the hypointensity on hepatocyte-phase (HP) imaging of gadoxetic acid-enhanced MRI (EOB-MRI) in the 2014 version of the Liver Imaging Reporting and Data System (LI-RADS) for distinguishing hepatocellular carcinoma (HCC) from benign hepatic lesions in patients with chronic liver disease.

Methods: We retrospectively evaluated targeted lesions (111 HCCs, 28 benign hepatic lesions) of 139 patients (101 men, 38 women; aged 18 to 89 years, mean age, 68 ± 11 years) with chronic liver disease. EOB-MRI and dynamic contrast-enhanced computed tomography (CECT) were performed within 3 months. Two abdominal radiologists independently reviewed 3 imaging datasets: (1) EOB-MRI without an HP image using the LI-RADS system (MR imaging without HP); (2) EOB-MRI with an HP image using a modified version of the LI-RADS system in which hypointensity on the HP image was used as an additional major criterion of malignancy (MR imaging with HP); and (3) dynamic contrast-enhanced computed tomography (CECT) images using the LI-RADS system. We evaluated intra- and inter-reader agreement with kappa statistics along with 95% confidence intervals and compared diagnostic sensitivity and specificity of the 3 imaging datasets with McNemar’s test.

Results: The sensitivities of MR imaging were statistically higher with HP (Reader 1, 95% [107/111]; Reader 2, 95% [106/111]) than without HP (Reader 1, 84% [93/111], P = 0.002; Reader 2, 86% [96/111], P = 0.002). Specificity was comparably high between MR imaging with HP (Reader 1, 96% [27/28]; Reader 2, 96% [27/28]) and dynamic CECT (Reader 1, 100% [28/28], P = 0.317; Reader 2, 100% [28/28], P = 0.317) and MR imaging without HP (Reader 1, 96% [27/28], P = 1.00; Reader 2, 100% [28/28], P = 0.317).

Conclusion: The use of an HP image from EOB-MRI as an additional major criterion improved the sensitivity of LI-RADS to distinguish HCCs from benign hepatic lesions while retaining high specificity.

Keywords: gadoxetic acid-enhanced hepatocyte phase, hepatocellular carcinoma, LI-RADS system

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer-related deaths.1 Clinical practice guidelines2,3 suggest hypervascularity in the hepatic arterial phase and subsequent washout on either the portal venous phase or delayed phase as hallmark imaging-based features in the diagnosis of HCC. The presence of these findings provides extremely high specificity and positive predictive value for the di-
agnosis of HCC. However, hypervascularity is not always observed in HCCs. A recent multi-institutional study revealed that about 18% of histologically confirmed HCCs were nonhypervascular. Several recent publications suggest that the use of gadoxetic acid, a contrast agent for hepatobiliary MR imaging, can at least partially address this issue.

Recent reports indicate that gadoxetic acid-enhanced hepatocyte-phase (HP) images demonstrate hypovascular HCCs as hypointense nodules. Adding hepatobiliary-phase imaging to conventional dynamic MR imaging (precontrast, arterial, and portal venous phases) increases the sensitivity of HCC diagnosis by 11% and the negative predictive value (NPV) for the diagnosis of HCC. The 2014 version of LI-RADS allows use of gadoxetic acid for the diagnosis of HCC, especially for early diagnosis.

Ngative clinical practice guidelines do not include hepatobiliary MR contrast agents, there is an emerging demand to use gadoxetic acid for the diagnosis of HCC, especially for early diagnosis. Neither do current guidelines address the full spectrum of hepatic lesions, including pseudolesions, encountered in patients with cirrhosis. Therefore, descriptions in radiological reports of hepatic lesions in patients with cirrhosis can be somewhat subjective and not uniform among radiologists.

The American College of Radiology (ACR) recently released the Liver Imaging Reporting and Data System (LI-RADS), a standardized system, to address the limitations of the current clinical practice guidelines. Using LI-RADS, radiologists can make a standardized report for liver imaging in patients at risk of developing HCC. The 2014 version of LI-RADS allows use of a hepatobiliary contrast agent for MR imaging but does not include the features on gadoxetic acid-enhanced hepatocyte-phase images as a major criterion. Rather, those findings are ancillary features that may lead to down- or upgrading according to the subjective decision of the radiologists. Considering the above-mentioned abundant evidence, we hypothesized that imaging features in the gadoxetic acid-enhanced hepatocyte phase could help increase the diagnostic ability of HCC.

Thus, we conducted this study to evaluate the diagnostic performance of LI-RADS for dynamic computed tomography (CT) and MR imaging with gadoxetic acid. Specifically, we aimed to reveal if an additional major criterion of hypointensity on gadoxetic acid-enhanced HP images improves the diagnostic performance of LI-RADS for HCC in patients with chronic liver disease.

Materials and Methods

Patients

The institutional review board of our hospital approved this retrospective study, and the requirement for written informed consent was waived. We reviewed the radiological archives from January 1st 2008 to October 31st 2013 for patients who underwent both gadoxetic acid-enhanced MR imaging (EOB-MRI) and dynamic contrast-enhanced computed tomography (CECT) within 3 months for the evaluation of focal liver lesions, patients with chronic liver disease, and patients with at least one hepatic lesion larger than 5 mm in size; a hepatic cyst was not counted as a hepatic lesion. Among 4135 patients who underwent dynamic MR imaging of the liver during the target time, 267 patients met the inclusion criteria. Of these, we excluded 90 subjects with an uncertain diagnosis based on the reference standard of this study and 38 with malignant liver lesions other than HCCs, which included 19 intrahepatic cholangiocarcinomas, 17 liver metastases, one malignant lymphoma, and one undifferentiated carcinoma.

Finally, we included 139 patients (101 men, 38 women; aged 18 to 89 years, mean age, 68 ± 11 years). The mean duration between CECT and EOB-MRI examinations was 18 ± 21 days (range, 0 to 91 days).

Reference standards for the lesions

We chose the largest of multiple lesions to avoid a cluster effect in the analysis and the malignant lesion when benign and malignant lesions were found in the same slice of one patient. Eight of the 139 patients had multiple lesions (average, 3.25; range, 2 to 5).

All 111 HCCs were pathologically confirmed by either partial hepatectomy (n = 70) or percutaneous needle biopsy (n = 41). The histopathological grades of HCCs were well differentiated in 18, moderately differentiated in 71, and poorly differentiated in 21; one case was fibrolamellar HCC. Benign lesions were confirmed by either pathological diagnosis (hemangioma, n = 2; nonspecific hypervascular lesion without specific histopathological alteration [presumed arterioportal shunt], n = 2) or combined imaging criteria with more than 12 months’ follow-up (n = 24).

Using the combined imaging criteria, a lesion was diagnosed as hemangioma (n = 9) if it showed: (i) peripheral or rapid early contrast enhancement on the arterial phase of CT images and residual...
Patients who fulfilled the following criteria (n = 267)
1. Dynamic contrast-enhanced CT within 3 months
2. with chronic liver disease
3. with at least one hepatic lesion (>5mm) except hepatic cyst

Excluded (n = 128)
- Uncertain diagnosis of focal liver lesion (n = 90)
- Malignant liver lesion other than HCC (n = 38)
  - intrahepatic cholangiocarcinomas (n=19)
  - liver metastases (n=17)
  - malignant lymphoma (n=1)
  - undifferentiated carcinoma (n=1)

Fig. 1. Inclusion criteria

CT imaging parameters

Dynamic CECT was performed on a 64- or 320-detector row scanner (Aquilion™ and Aquilion ONE™; Toshiba Medical Systems, Otawara, Japan). A helical CT acquisition with a 64-detector row configuration was used for both 64- and 320-detector row scanners with parameters: tube voltage, 120 kVp; variable tube current, 280 to 450 mA (automatically adjusted to the patient’s body build) to maintain an established index of image noise (10 Hounsfield units as the standard deviation of the image noise); detector configuration, 64 × 0.5 mm; field of view (FOV), 300 × 350 mm; and 5-mm slice thickness with 5-mm section interval. An anionic contrast medium dose of 600 mgI/kg (either Omnipaque 300, Daiichi-Sankyo, Tokyo, Japan; Iomeron 350, Eisai Global, Tokyo, Japan; or Iopamiron 370, Bayer Healthcare) was administered intravenously over 30 s (at 2.6 to 5.0 mL/s depending on the patient’s body weight) using a power injector (Auto Enhance A-50; Nemoto Kyorindo, Tokyo, Japan). A 4-phase scan was obtained with precontrast, arterial (40 s after the start of the injection), portal venous (70 s), and delayed (180 s) phases.

MR imaging parameters

MR imaging was performed using a 1.5-tesla system (Signa EXCITE HD, GE Medical Systems, Waukesha, WI, USA) and an 8-channel phased-array coil or a 3T MR system (Discovery 750, GE Medical Systems) with a 32-channel phased-array coil. After acquisition of a precontrast dual-echo gradient spoiled echo (GRE) T1-weighted image in an axial plane, dynamic MR imaging with a fat-saturated 3-dimensional (3D) GRE sequence was performed. Fat-saturated fast spin echo (FSE) T2WI and diffusion-weighted echo planar images (DWI) were acquired after contrast injection. Dynamic MR imaging was performed using a fat-saturated 3D-GRE sequence. The scan delay for the arterial phase was adjusted with a fluoro-triggering technique that monitored the intensity of the thoracic aorta. Subsequently, images of the portal venous phase were obtained one minute after contrast injection; of the late phase, 3 min after contrast injection; and of the hepatobiliary phase, 20 min after contrast injection. For the dynamic scan, gadoxetic acid (Primovist; Bayer HealthCare, Berlin, Germany) was administered as an intravenous bolus (0.025 mmol/kg) at a rate of one mL/s with a power injector (Sonic Shot 50; Nemoto Kyorindo, Tokyo, Japan) and followed by a 20-mL saline flush.

Detailed MR parameters for each sequence follow. Precontrast dual-echo GRE T1-weighted axial images were acquired with a 2-dimensional (2D) (1.5T) or 3D (3T) sequence with echo time (TE), 2.1 ms and 4.2 ms for 3T scans and 2.2 ms and 4.5 ms for 1.5T scans; repetition time (TR), 6.2 ms (3T) and 150 to 170 ms (1.5T); flip angles, 15° (3T) and 12° (1.5T); FOV, 38 cm; matrix size, 350 × 160; section thickness, 6 mm; intersection overlap, 0 mm; and parallel imaging (ASSET) factor, 2 (3T) and 2.
(1.5T). Parameters for respiratory-triggered fat-saturated axial T2-weighted FSE images were: TR, 2500 to 8000 ms; TE, 64 ms; flip angle, 90°; FOV, 32 to 40 cm; and matrix size, 256 × 192. Parameters for axial diffusion-weighted single-shot echo planar images were: TR, 150 to 170 ms; TE, 4.5 ms; b value, 0.75 ms (3T) and 73 ms (1.5T); flip angle, 90°; FOV, 40 cm; matrix size, 256 × 160; section thickness, 5 mm; and intersection overlap, 0 mm. Parameters for axial fat-suppressed gradient-echo T1-weighted images (T1WI) with a 3-dimensional (3D) acquisition were: TR, 150 to 170 ms; TE, 4.5 ms; flip angle, 15°; matrix size, 256 × 160; section thickness, 5 mm; and intersection overlap, 2.5 mm), and these were obtained before contrast administration.

Imaging analysis

Two abdominal radiologists blinded to the final diagnoses reviewed the 3 imaging datasets using a commercially available picture archiving and communication system (SYNAPSE, Fujifilm Medical, Tokyo, Japan). Imaging Dataset A consisted of routine MR images (axial fat-saturated T2WI, axial precontrast dual-echo T1WI, and axial DWI) and EOB-MRI without an HP image (MR imaging without HP); Imaging Dataset B included all of Dataset A images plus an HP image (MR imaging with HP); and Imaging Dataset C was images obtained by dynamic CECT (4 phases, including precontrast).

The 2 readers were asked to apply one of the LI-RADS grades (LR1, LR2, LR3, LR4, LR5, or LR5V) to the target lesions (American College of Radiology, Liver Imaging Reporting and Data System version 2014. www.acr.org/Quality-Safety/Resources/LIRADS). Because this was a cross-sectional study at a specific time point, we did not apply a criterion of “threshold growth,” which requires acquisition of longitudinal data. In the evaluation of Dataset B (MR imaging with HP), we used modified LI-RADS criteria, in which hypointensity on the HP image was a major criterion of HCC and isointensity on the HP image was a major criterion of benignity. Figure 2 shows the modified LI-RADS criteria. We evaluated the 3 datasets more than one month apart to diminish the memory bias of the readers. Half of the cases were provided in the order of the Image Datasets, A, B, and C, and the rest were provided in the order of C, A, and B. One of the 2 readers was asked to re-evaluate the imaging datasets in the same manner 4 months after the first reading to evaluate intra-reader grading agreement.

Statistical analysis

We evaluated intra- and inter-reader agreement in the grading of the 3 imaging datasets by kappa values with 95% confidence intervals (95% CI). Kappa values of 0.81 to 1.00 represented excellent agreement; 0.61 to 0.80, good agreement; 0.41 to 0.60, moderate agreement; 0.21 to 0.40, fair agreement; and 0.00 to 0.20, poor agreement.9

We used McNemar’s test to assess statistically different sensitivities and specificities between different imaging datasets for each reader and chi-squared test to determine positive and negative predictive values. During the evaluation of these diagnostic abilities, grades of LR1, 2, and 3 by the readers were regarded as a radiological decision of benignity and LR4, 5, and 5V as that of malignancy. An area under the receiver operating characteristic (ROC) curve (AUC) analysis was performed with the LI-RADS 5-grade scale to compare the overall diagnostic ability of each imaging dataset; grades of LR5 and LR5V were combined into the LR5 categories. Subanalysis was also performed with lesions measuring less than 2 cm.

All data were analyzed with JMP ver.10.0 software (SAS Institute Japan, Tokyo, Japan). Because a one-by-one comparison was repeated among the 3 imaging datasets, we employed a Bonferroni correction for multiple comparisons in which a 2-sided P value less than 0.016 was considered statistically significant.

Results

Intra- and inter-reader agreement

The intra-reader agreements were excellent for Imaging Datasets A (0.838, [95%CI, 0.769 to 0.907]) and B (0.838 [0.770 to 0.906]) and good for set C (0.724 [0.641–0.807]), and inter-reader agreements were all good: kappa value, 0.733 (0.652 to 0.815) for Set A; 0.795 (0.721 to 0.868) for Set B; and 0.678 (0.590 to 0.765) for Set C (Table 1).

Diagnostic ability of the 3 imaging datasets

For Reader 1, sensitivity of Imaging Dataset A was 84% (93/111); of Imaging Set B, 95% (107/111); and of Imaging Set C, 84% (95/111). For Reader 2, sensitivity of Imaging Dataset A was 86% (96/111); of Imaging Set B, 95% (106/111); and of Imaging Set C, 89% (99/111). For both readers, the sensitivity of Set B was significantly higher than that of Set A (P = 0.002). For Reader 1, a statistically significant difference in sensitivity was also observed between Sets B and C (P = 0.005). However, for Reader 2, no evidence of stat-
Hepatocyte-phase Imaging for HCC Diagnosis

**Modified LI-RADS criteria**

![Modified LI-RADS criteria diagram](image)

Fig. 2. Modified Liver Imaging Reporting and Data System (LI-RADS) criteria. Because this was a cross-sectional study at a specific time point, we did not use “threshold growth”. We used hypointensity on the hepatocyte phase (HP) of gadoxetic-enhanced magnetic resonance imaging (EOB-MRI) as the major diagnostic feature in the modified LI-RADS criteria. Because nonhypointensity (= isointensity or hyperintensity) in the HP suggests benignity, none of the major features was categorized as LR2 or 3 instead of LR3 or 4. We excluded non-hepatocellular carcinoma (HCC) malignancy in this study.

**Table 1.** Kappa values of the blinded reading results for each imaging dataset

<table>
<thead>
<tr>
<th></th>
<th>MR imaging without HP</th>
<th>MR imaging with HP</th>
<th>Computed tomography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-reader agreement</td>
<td>0.838</td>
<td>0.838</td>
<td>0.724</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>0.769–0.907</td>
<td>0.770–0.906</td>
<td>0.641–0.807</td>
</tr>
<tr>
<td>Inter-reader agreement</td>
<td>0.733</td>
<td>0.795</td>
<td>0.678</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>0.652–0.815</td>
<td>0.721–0.868</td>
<td>0.590–0.765</td>
</tr>
</tbody>
</table>

HP, hepatocyte phase; MR, magnetic resonance

Statistical significance was observed between Sets B and C (P = 0.052). Neither was there significant difference between Sets A and C for either reader. No significant difference was observed in specificity among the 3 imaging datasets.

Set B achieved the highest NPV among the 3 imaging sets (60% [27/45] for Set A; 87% [27/31] for Set B; and 64% [28/44] for Set C for Reader 1 and 65% [28/43] for Set A; 87% [27/32] for Set B; and 70% [28/40] for Set C for Reader 2). A significant difference was observed in NPV between Sets A and B (P = 0.009) for Reader 1.

Positive predictive values (PPVs) were 99 to 100% for all imaging datasets, among which no statistical difference was observed (Table 2).

For both readers, Dataset B achieved the highest AUC values among the 3 sets (Reader 1: Set A, 0.979 [0.930 to 0.994]; Set B, 0.989 [0.961 to 0.997]; and Set C, 0.979 [0.948 to 0.991]; Reader 2: Set A, 0.981 [0.959 to 0.991]; Set B, 0.989 [0.966 to 0.996], and Set C, 0.971 [0.940 to 0.986]). However, the difference was not statistically significant for either reader (Table 2).

**Subanalysis with lesions smaller than 2 cm**

The sensitivities of Sets A, B, and C in small (<2 cm) hepatic lesions for Reader 1 were 72% (31/43) for Set A; 95% (41/43) for Set B; and 70% (30/43) for Set 3, and for Reader 2, they were 77% (33/43) for Set A; 93% (40/43) for Set B; and 74% (32/43) for Set C (Table 3). Sensitivities were significantly higher of Set B (P = 0.002) than Set A (P = 0.002).
and $P = 0.008$, respectively) and Set C ($P = 0.002$ and $P = 0.011$, respectively) for both readers. No significant difference was observed in specificity and AUC values among the 3 imaging datasets (Table 3).

**False-positive and false-negative results**

MR imaging with HP yielded fewer false-negative results than MR imaging without HP and CECT. Table 4 shows the false-negative and false-positive results from all 3 image datasets.

<table>
<thead>
<tr>
<th>Table 2. Diagnostic performance of the 3 imaging datasets</th>
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<tbody>
<tr>
<td><strong>Imaging datasets</strong></td>
</tr>
<tr>
<td>---------------------------------------------------------</td>
</tr>
<tr>
<td>A, MRI w/o HP</td>
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<tr>
<td>---------------------------------------------------------</td>
</tr>
<tr>
<td>Reader 1</td>
</tr>
<tr>
<td>Sensitivity</td>
</tr>
<tr>
<td>84% (93/111)</td>
</tr>
<tr>
<td>Specificity</td>
</tr>
<tr>
<td>96% (27/28)</td>
</tr>
<tr>
<td>PPV</td>
</tr>
<tr>
<td>99% (93/94)</td>
</tr>
<tr>
<td>NPV</td>
</tr>
<tr>
<td>60% (27/45)</td>
</tr>
<tr>
<td>AUC</td>
</tr>
<tr>
<td>0.979</td>
</tr>
<tr>
<td>A vs. C</td>
</tr>
<tr>
<td>0.671</td>
</tr>
<tr>
<td>Reader 2</td>
</tr>
<tr>
<td>Sensitivity</td>
</tr>
<tr>
<td>86% (96/111)</td>
</tr>
<tr>
<td>Specificity</td>
</tr>
<tr>
<td>100% (28/28)</td>
</tr>
<tr>
<td>PPV</td>
</tr>
<tr>
<td>100% (96/96)</td>
</tr>
<tr>
<td>NPV</td>
</tr>
<tr>
<td>65% (28/43)</td>
</tr>
<tr>
<td>AUC</td>
</tr>
<tr>
<td>0.981</td>
</tr>
<tr>
<td>A vs. B</td>
</tr>
<tr>
<td>0.724</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3. Diagnostic performance of the datasets in small hepatic lesions (&lt;2 cm)</th>
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<tbody>
<tr>
<td><strong>Imaging datasets</strong></td>
</tr>
<tr>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>A, MRI</td>
</tr>
<tr>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Reader 1</td>
</tr>
<tr>
<td>Sensitivity</td>
</tr>
<tr>
<td>72% (31/43)</td>
</tr>
<tr>
<td>Specificity</td>
</tr>
<tr>
<td>96% (22/23)</td>
</tr>
<tr>
<td>PPV</td>
</tr>
<tr>
<td>0.9525</td>
</tr>
<tr>
<td>AUC</td>
</tr>
<tr>
<td>[0.851–0.986]</td>
</tr>
<tr>
<td>A vs C</td>
</tr>
<tr>
<td>0.782</td>
</tr>
<tr>
<td>Reader 2</td>
</tr>
<tr>
<td>Sensitivity</td>
</tr>
<tr>
<td>77% (33/43)</td>
</tr>
<tr>
<td>Specificity</td>
</tr>
<tr>
<td>100% (23/23)</td>
</tr>
<tr>
<td>PPV</td>
</tr>
<tr>
<td>0.959</td>
</tr>
<tr>
<td>AUC</td>
</tr>
<tr>
<td>[0.912–0.981]</td>
</tr>
<tr>
<td>A vs B</td>
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<tr>
<td>0.238</td>
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</table>

Both readers recorded one false-positive result for MR imaging datasets with/without HP—a benign lesion measuring 15 mm that showed slightly high signal intensity on T2WI, arterial enhancement, persistent enhancement on the portal venous phase, faint hypointensity on the late phase, and hypointensity on HP imaging. Delayed washout was not observed on dynamic CT. The lesion did not increase in size for 5 years and was judged to be benign.

Both readers also recorded 15 false-negative re-
sults for MR imaging without HP, including 5 small hypervascular HCCs (10 to 13 mm) with no washout on the late phase of EOB-MRI (Fig. 3), 3 hypervascular HCCs with high signal intensity on precontrast T1WI and no hypointensity on late-phase MR imaging (Fig. 4), and 7 hypovascular HCCs (Fig. 5).

The MR findings with HP results included 4 false-negative cases by both readers—3 hypervascular HCCs that demonstrated uptake of gadoxetic acid that showed isointensity on the late phase and HP of EOB-MRI but typical washout on CECT and one hypovascular HCC of 10 mm (< 2 cm) detected only on the HP of EOB-MRI, thereby fulfilling only one major criterion (LR3).

On CECT, both readers recorded 8 HCCs with false-negative results—4 hypovascular HCCs and 4 hypervascular HCCs without subsequent washout. All eight were graded LR3 on CECT, and seven were graded LR4 and one as LR5 on MR imaging with HP.

Table 4. Lists of false-negative and false-positive results

<table>
<thead>
<tr>
<th></th>
<th>Reader 1</th>
<th>Reader 2</th>
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<tbody>
<tr>
<td></td>
<td>A  B  C</td>
<td>A  B  C</td>
</tr>
<tr>
<td>false-negative cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC graded as LR1</td>
<td>1  1  2</td>
<td>0  0  1</td>
</tr>
<tr>
<td>HCC graded as LR2</td>
<td>1  1  2</td>
<td>0  0  1</td>
</tr>
<tr>
<td>HCC graded as LR3</td>
<td>16  2  12</td>
<td>15  5  10</td>
</tr>
<tr>
<td>false-positive cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign lesion graded as LR4</td>
<td>1  1  0  0  1  0</td>
<td></td>
</tr>
<tr>
<td>Benign lesion graded as LR5</td>
<td>0  0  0  0  0  0</td>
<td></td>
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</tbody>
</table>

This table does not include cases that were correctly diagnosed by all 3 image datasets. The numbers in the columns are scores according to the Liver Imaging Reporting and Data System (LI-RADS). A, Image Dataset A, dynamic magnetic resonance imaging (MRI) without hepatocyte-phase (HP) image; B, Image Dataset B, dynamic MRI with HP image; C, dynamic CT

Discussion

We found that adding the HP of EOB-MRI as an additional major criterion increased the diagnostic sensitivity of LI-RADS for HCCs while retaining high specificity, specifically enabling the diagnosis of a hypovascular HCC, a lesion that cannot be diagnosed by CECT or dynamic MR imaging alone.

It has been well studied that the HP of EOB-MRI is the most useful imaging method to detect a hypovascular HCC.1,11,20 The uptake of gadoxetic acid is supposed to be determined by expression of organic anion transporting polypeptide 8 (OATP8), which is usually decreased or absent in HCCs.21 During hepatocarcinogenesis, OATP8 expression may be reduced even before hemodynamic changes in the HCCs, which are visible on dynamic contrast-enhanced CT/MR imaging.20,22 Previous studies showed improved diagnostic sensitivity/PPV by adding HP images to dynamic MR imaging or by comparing them with CECT.7,8,20,23–25 Our results agreed with those of the previous studies.

Fig. 3. A 75-year-old man with a small hypervascular hepatocellular carcinoma (HCC). This lesion showed enhancement on the arterial phase of contrast-enhanced computed tomography (CECT) but no washout on the delayed phase. Hypointensity is seen on the hepatocyte phase (HP) of gadoxetic-enhanced magnetic resonance imaging (EOB-MRI). The Liver Imaging Reporting and Data System (LI-RADS) scores of this lesion were LR3 on CECT and MR imaging without HP and LR4 on MR imaging with HP.
Using hypointensity as a major feature, we can more effectively categorize a hypovascular HCC of at least grade LR3.

Hypervascularity on an image of the arterial phase is a hallmark finding for imaging-based diagnosis of HCCs. In our series, 12 of 111 HCCs (11%) showed hypovascularity, which does not allow diagnosis of HCC by the conventional approach using dynamic CT/MR imaging. These hypovascular HCCs tend to be small, so the added value of HP was most obvious for lesions smaller than 2 cm.
One recent study pointed out that for LI-RADS, a washout appearance had only moderate inter-reader agreement with the use of extracellular contrast agents.\textsuperscript{26} This is probably due to low contrast between the lesion and liver on the delayed phase. We observed slightly better inter-reader agreement for MR imaging with HP than MR imaging without HP or CECT, which might be explained by the excellent contrast between the lesion and liver on a gadoxetic acid-enhanced HP.\textsuperscript{26}

An AP shunt as the main hypervascular pseudo-lesion is typically easy to categorize as LR1 or LR2 when it has a wedge-like, irregular, or linear in shape. However, a nodular-shaped AP shunt sometimes mimics a hypervascular HCC and can be categorized as LR3. Adding an HP might help to downgrade such an AP shunt to LR2 or LR1.\textsuperscript{17,27} In our series, 15 benign lesions showed hypervascularity without washout on CECT or the late phase of dynamic MR imaging. Among them, 2 lesions were categorized as LR3. These 3 lesions were downgraded to LR2 when HP was added as a major criterion.

Previous reports indicate that approximately 9 to 20% of HCCs, typically the moderately differentiated type, show increased expression of OATP8 that results in high signal intensity on HP imaging.\textsuperscript{13,21} Although rare, early HCCs can also show gadoxetic acid uptake.\textsuperscript{28} In our study, this nontypical finding led to a false-negative assessment of 3 of 11 HCCs that showed iso- or slight hyperintensity on HP images. Unlike benign dysplastic nodules, an HCC taking up gadoxetic acid is reported to demonstrate heterogeneous signal intensity and often displays a hypointense rim in the hepatobiliary phase.\textsuperscript{29} Two of the 3 HCCs showing hyperintensity in HP images in our study were heterogeneous, and all three had a hypointense rim that was ambiguous on the HP. Apart from inter-reader variability, we may have further improved the sensitivity for MR imaging with HP by taking into account these features in the modified LI-RADS guidelines.\textsuperscript{27} High signal intensity even in precontrast T\textsubscript{1}WI can be another confounder. Even if the uptake of gadoxetic acid is reduced in the nodule, the high signal of the nodule on precontrast T\textsubscript{1}WI could mask the feature of hypointensity in HP images. Subtraction between the images can solve this issue. However, we could not address the issue because our sequences of precontrast and HP images at 20 min after contrast administration were separated by several sequences, including dynamic MR imaging, T\textsubscript{2}WI, and DWI. Thus, tuning or gain settings were different, and 2 separated sequences could not be compared.

In our series, there was one false-positive result on MR imaging with/without HP. Although the pathological results in that case are unknown, the imaging features without interval changes for 5 years strongly suggest benignity of the lesion. We suppose the nodule is a hemangioma, the most common benign hepatic tumor, which presents bright hyperintensity on T\textsubscript{2}WI and a gradual filling-in enhancement pattern after contrast administration. Sclerosing hemangioma, however, is a rare type of hepatic hemangioma composed of abundant cellular hyalinized tissue that usually presents an atypical pattern. Hyalinized hemangiomas show only slightly high signal intensity on T\textsubscript{2}WI.\textsuperscript{30} It should be noted that an atypical hemangioma can be misdiagnosed as an HCC on EOB-MRI.

Our study has several limitations. Its major limitation was the inclusion of only a small number of benign lesions. Moreover, because the study was retrospective, it did not include some other types of benign hepatic lesions, such as adenoma and focal nodular hyperplasia. Second, we did not include benign cirrhotic nodules or dysplastic nodules because our focus was lesions larger than 5 mm. Also because the study was retrospective, EOB-MRI was performed on different MR imaging systems (1.5 and 3.0 T). A prospective study with a large cohort would be expected to confirm our results here. Finally, we did not directly compare the diagnostic ability of LI-RADS version 2014 and our modified LI-RADS. We believe that ancillary features are not concrete criteria and might yield varying results depending on the personal experience of radiologists. Assessment of differences between LI-RADS version 2014 and our modified LI-RADS would require multi-institutional study that included many radiologists as blind readers whose radiological decisions regarding ancillary features could represent the potential variation.

Conclusion

In conclusion, the modified LI-RADS criteria with the HP as a major criterion can improve sensitivity while retaining high specificity for the diagnosis of HCC.

Conflict of interest: The authors declare that they have no conflict of interest.

References


Hepatocyte-phase Imaging for HCC Diagnosis


