Optimal Combination of Features on Gadoxetate Disodium-enhanced MR Imaging for Non-invasive Differential Diagnosis of Hepatocellular Carcinoma: The JAMP-HCC Study

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Purpose: To determine the optimal combination of gadoxetate disodium-enhanced magnetic resonance imaging (MRI) findings for the diagnosis of hepatocellular carcinoma (HCC) and to compare its diagnostic ability to that of dynamic computed tomography (CT) in patients with chronic liver disease.

Methods: This multi-institutional study consisted of two parts: Study 1, a retrospective study to determine the optimal combination of gadoxetate disodium-enhanced MRI findings (decision tree and logistic model) to distinguish HCC (n = 199) from benign (n = 81) or other malignant lesions (n = 95) (375 nodules in 269 patients) and Study 2, a prospective study to compare the diagnostic ability of gadoxetate disodium-enhanced MRI to distinguish HCC (n = 73) from benign (n = 15) or other malignant lesions (n = 12) with that of dynamic CT (100 nodules in 83 patients). Two radiologists independently evaluated the imaging findings (Study 1 and 2) and made a practical diagnosis (Study 2).

Results: In Study 1, rim or whole enhancement on arterial phase images, signal intensities on T2-weighted/diffusion-weighted/portal venous/transitional/hepatobiliary phase images, and signal drop on opposed-phase images were independently useful for differential diagnosis. In Study 2, the accuracy, sensitivity, negative predictive value, and negative likelihood ratio of the CT decision tree (reader 2) were higher than those of MRI Model 2 (P = 0.015–0.033). There were no other significant differences in diagnostic ability (P = 0.059–1.000) and radiologist-made practical diagnosis (P = 0.059–1.000) between gadoxetate disodium-enhanced MRI and CT.

Conclusion: We identified the optimal combination of gadoxetate disodium-enhanced MRI findings for HCC diagnosis. However, its diagnostic ability was not superior to that of dynamic CT.

Keywords: hepatocellular carcinoma, magnetic resonance imaging, decision trees, logistic models, gadoxetate disodium

Introduction

Liver cancer is the third leading cause of cancer-related deaths, contributing to 781,000 deaths yearly worldwide.1 Hepatocellular carcinoma (HCC) is the predominant primary liver cancer in many countries, and HCC-related mortality continues to increase.2–4 The computed tomography (CT) and magnetic resonance imaging (MRI) characteristics of HCC are well described, and the diagnostic algorithm for HCC [Liver reporting and data system (LI-RADS)], which is based on CT, MRI with extracellular contrast material, or MRI with hepatobiliary contrast material (namely, gadoxetate disodium, also known by the trade name Primovist or Eovist), has been established.5,6
Gadoxetate disodium is a liver-specific contrast material that allows both dynamic study and hepatocyte imaging at the hepatobiliary phase (HBP). Currently, gadoxetate disodium is widely used for liver MRI in daily clinical practice because of its high performance for lesion detection and characterization.\(^7\)\(^-\)\(^9\) Gadoxetate disodium-enhanced MRI has a better diagnostic ability than that of CT for HCC in patients with cirrhosis, particularly those with small lesions.\(^10\)\(^-\)\(^12\) However, gadoxetate disodium-enhanced MRI also has some pitfalls. The image quality at the arterial phase (AP) may be insufficient due to transient dyspnea,\(^13\)\(^,\)\(^14\) inappropriate scanning time, or truncation artifact caused by low injection volume of gadoxetate disodium.\(^15\) It is often difficult to detect an enhancing capsule at the portal venous phase (PVP) or transitional phase (TP) of gadoxetate disodium-enhanced MRI\(^16\) because of high enhancement of the adjacent parenchyma on PVP or TP. HBP hypointensity is an ancillary feature that may indicate the presence of malignancy according to the LI-RADS. Although this finding is characteristic of HCC, it is not specific for HCC. Moreover, approximately 10–20% of progressed HCCs show hyperintensity on HBP.\(^17\)\(^,\)\(^18\) Therefore, we hypothesized that it is necessary to combine several imaging findings on gadoxetate disodium-enhanced MRI to correctly diagnose HCC.

The purpose of this study was to determine the optimal combination of gadoxetate disodium-enhanced MRI findings for the diagnosis of HCC and to compare the diagnostic ability of gadoxetate disodium-enhanced MRI to that of dynamic CT in patients with chronic liver disease.

**Materials and Methods**

**Study design**
This multi-institutional study consisted of two parts: Study 1, a retrospective study to determine the optimal combination of gadoxetate disodium-enhanced MRI findings to distinguish HCC from benign or other malignant lesions and construct a decision tree and logistic model for the diagnosis of HCC; and Study 2, a prospective study to compare the diagnostic ability of gadoxetate disodium-enhanced MRI to distinguish HCC from other lesions with that of dynamic CT (Fig. 1). The trial protocol was approved by a Central Ethics Committee and local Institutional Review Boards of 12 participating institutions. For Study 1, the requirement for written informed consent was waived because of the retrospective nature of the study. For Study 2, all patients gave their informed written consent before enrollment.

**Patient enrollment**

**Study 1**
Patients were consecutively enrolled from 12 hospitals between July 2008 and October 2014. The inclusion criteria were as follows: (i) available gadoxetate disodium-enhanced MRI data, (ii) pathologically confirmed HCC or other malignant lesions, and (iii) presence of chronic liver disease. Clinically diagnosed benign lesions and an HBP hypointense nodule without arterial phase hyperenhancement (APHE),\(^19\) whose size did not increase during an observation period of >1 year, were also included.

**Study 2**
Patients were consecutively enrolled from 12 hospitals between August 2013 and February 2016. The inclusion criteria were as follows: (i) planned gadoxetate disodium-enhanced MRI and CT within 2 months due to suspicion of liver lesions and (ii) presence of chronic liver disease. Clinically diagnosed benign lesions and an HBP hypointense nodule without APHE, whose size did not increase on MRI/CT during an observation period >2 years, were included.

**Study 1: Retrospective, multicenter**
- Patients who performed gadoxetate disodium-enhanced MRI and had liver lesion: **Training set**
- Evaluating typical findings of HCC on gadoxetate disodium-enhanced MRI
  - Logistic model (Models 1\(^*\) and 2\(^{**}\))
  - Decision tree\(^3\)

\[^*\]Model 1: a model to distinguish HCC from other disease including benign and non-HCC malignant lesions

\[^{**}\]Model 2: a model to distinguish HCC from other disease via 2 steps strategy (step 1, distinguishing benign from malignant lesions; and step 2, distinguishing HCC from non-HCC malignant lesions)

\[^3\]Decision tree: step-by-step diagnosis of HCC using MR findings selected by Study 1

**Study 2: Prospective, multicenter**
- Patients who were planned both gadoxetate disodium-enhanced-MRI and dynamic CT: **Validation set**
  - Informed consent and enrollment
  - Gadoxetate disodium-enhanced MRI and dynamic CT
  - Blind reading (2 radiologists)
    - Describe the MR/CT findings for Models 1, 2, and decision tree
    - Radiologist-made practical diagnosis of HCC using 5-point scale
  - Pathological diagnosis or observation (>2 years)

*Fig. 1 Flowchart of the study design. HCC, hepatocellular carcinoma; CT, computed tomography; MRI, magnetic resonance imaging.*
A pathological diagnosis was required for HCC and other malignant lesions.

**MRI and CT protocols**

Gadoxetate disodium-enhanced MRI was performed using a superconducting magnet scanner operated at 1.5T or 3T. Gadoxetate disodium (0.025 mmol/kg body weight) was administered by using a power injector. Required sequences were as follows: $T_2$-weighted image ($T_2$WI), gradient-echo dual-phase $T_1$-weighted image ($T_1$WI), diffusion-weighted image (DWI), and dynamic study (AP, PVP, TP, and HBP). CT was performed using 64–320-detector-row CT units. Iodine contrast materials (300–370 mg/mL) were administered using a power injector. Four phases (pre-contrast, AP, PVP, and delayed phase) of dynamic study was required. The MRI and CT parameters varied depending on the clinical protocol of each hospital (Table 1) because the imaging studies were performed as part of each hospital’s daily practice.

**Image analysis**

In Study 1, gadoxetate disodium-enhanced MRI was assessed independently by two board-certificated radiologists (T.I. and H.M.) with 30 and 10 years of experience in liver imaging, respectively. They evaluated the imaging findings of target lesions in order to choose one characteristic in each sequence as follows: $T_2$WI: marked hyperintensity, hyperintensity, isointensity, or hypointensity; gradient-echo $T_1$WI: presence or absence of signal drop on opposed phase; DWI: hyperintensity, isointensity, or hypointensity; AP: no, dot-like, rim, part, or whole APHE; PVP: marked hypointensity, hypointensity, isointensity or hyperintensity; TP: marked hypointensity, hypointensity, isointensity or hyperintensity; and HBP: no uptake, part and moderate uptake, part and marked uptake, whole and moderate uptake, or wole and marked uptake of gadoxetate disodium (Fig. 2). Any discrepancy between the two readers were resolved by a third board-certificated radiologist (S.I.) with 10 years of experience in liver imaging. In Study 2, gadoxetate disodium-enhanced MRI and CT were assessed independently by two board-certificated radiologists (S.G. and K.K.), both with 17 years of experience in liver imaging. They evaluated MRI findings as in Study 1. For CT, they evaluated whether non-rim APHE and non-peripheral washout were present or not. Radiologist-made practical diagnosis of HCC was also performed for both gadoxetate disodium-enhanced MRI and CT using a 5-point scale of the confidence for the diagnosis of malignancy as well as of HCC (1, definitely benign or non-HCC; 2, probably benign or non-HCC; 3, intermediate probability of malignancy or HCC; 4, probably malignant or HCC; and 5, definitely malignant or HCC). All radiologists were aware that the patients had chronic liver diseases but were unaware of the imaging findings and the final diagnosis.

| Parameter                        | Setting                              |
|----------------------------------|--------------------------------------|
| **MRI**                          |                                      |
| $T_2$-weighted image with or without fat-saturated | Repetition time/echo time (ms) 2000–20000/66.56–99.94 |
| Matrix                           | 144–384 × 160–356                    |
| Field of view (cm)               | 30–40 × 22–47                        |
| Section thickness/intersection gap (mm) | 4–8/1–10                            |
| Flip angle (°)                   | 90–170                               |
| $T_1$-weighted gradient-echo image |                                       |
| Repetition time/echo time (ms)    | 4.28–280/1.12–5.80                   |
| Matrix                           | 173–384 × 136–256                    |
| Field of view (cm)               | 32–42 × 27–45                        |
| Section thickness/intersection gap (mm) | 3–8/0–10                            |
| Flip angle (°)                   | 12–80                                |
| Diffusion-weighted image         |                                      |
| Repetition time/echo time (ms)    | 1200–12000/49.9–82                   |
| Matrix                           | 72–160 × 72–192                      |
| Field of view (cm)               | 35–45 × 22–47                        |
| Section thickness/intersection gap (mm) | 5–8/0–10                            |
| Flip angle (°)                   | 90                                   |
| b-Value (s/mm$^2$)               | 800–1000                             |
| Dynamic study                    |                                      |
| Repetition time/echo time (ms)    | 2.52–5.90/1.08–2.10                  |
| Matrix                           | 154–320 × 160–288                    |
| Field of view (cm)               | 30–40 × 27–47                        |
| Section thickness/intersection gap (mm) | 2.5–8/0–3                           |
| Flip angle (°)                   | 10–15                                |
| Hepatobiliary phase              |                                      |
| Repetition time/echo time (ms)    | 2.92–7.89/1.23–2.12                  |
| Matrix                           | 154–384 × 160–288                    |
| Field of view (cm)               | 30–42 × 27–47                        |
| Section thickness/intersection gap (mm) | 2.5–8/0–3                           |
| Flip angle (°)                   | 10–20                                |
| Scan delay after injection (min)  | 15–20                                |
| CT                               |                                       |
| Detector row number              | 64–320                               |
| Section thickness (mm)           | 1–5                                  |
| Helical pitch                    | 0.5–1.375                            |
| Field of view                    | 28–35                                |
| Iodine dose (mgI/kg)             | 500–600                              |
| Injection rate (mL/s)            | 2–4                                  |

MRI, magnetic resonance imaging; CT, computed tomography.
Typical findings of HCC on gadoxetate disodium-enhanced MRI were evaluated by logistic regression analysis to generate a logistic model in Study 1 (secondary endpoint). Two types of models were generated: Model 1 was intended to directly distinguish HCCs from other disease including benign and non-HCC malignant lesions; Model 2 was intended to make a diagnosis in line with the LI-RADS guidelines, that is, using a two-step strategy [step 1, distinguishing benign (LR1 and LR2) from malignant lesions; and step 2, distinguishing HCC from non-HCC malignant lesions]. In Study 2, the diagnostic ability of the two logistic models was determined, and the decision tree based on gadoxetate disodium-enhanced MRI to distinguish HCC from other lesions was validated and compared with a CT decision tree (Fig. 3a) (primary endpoint). The CT decision tree was defined on the basis of the classical diagnostic method consisting of non-rim APHE and non-peripheral washout. The ability of a radiologist-made practical diagnosis was compared between CT and MRI.

**Fig. 2** Examples of magnetic resonance images with visual assessment (only item-specific annotation was needed). (a) Signal intensity of $T_2$-weighted images ($T_2$WI), (b) signal drop of opposed phase, (c) signal intensity of the portal venous phase (PVP) or transitional phase (TP), (d) pattern of arterial phase hyperenhancement (APHE), and (e) uptake of gadoxetate disodium at the hepatobiliary phase (HBP). All images were obtained in the axial plane. (a) On $T_2$WI, hyperintensity was higher than that of the surrounding liver but lower than that of water (arrow), while marked hyperintensity was similar to that of water (arrow). (b) Signal drop of opposed phase was defined as a signal of opposed phase lower than in phase signal (arrow). (c) On PVP or TP, hypointensity was lower than that of the surrounding liver but higher than that of water (arrow), while marked hypointensity was similar to that of water (arrow). (d) Pattern of APHE was divided into five categories: no APHE, whole hypointensity on the arterial phase (arrow); dot-like APHE, peripheral slightly marked nodular enhancement (arrows); rim APHE, peripheral layer enhancement (arrow); part APHE, partially higher intensity than in the surrounding liver (arrow); whole APHE, overall higher intensity than in the surrounding liver (arrow). (e) On HBP, pattern of gadoxetate disodium uptake was divided into five categories: no uptake, overall hypointensity (arrow); part and moderate uptake, partially moderate hyperintensity (similar intensity compared with that of the surrounding liver) (arrow); part and marked uptake, partially marked hyperintensity (higher intensity compared with surrounding liver) (arrows); whole and moderate uptake, overall moderate hyperintensity (arrow); whole and marked uptake, overall marked hyperintensity (arrow).
The weighted kappa coefficient was calculated to assess interobserver agreement. Agreement was considered excellent for kappa values ($\kappa$) > 0.8, good for $0.6 < \kappa \leq 0.8$, moderate for $0.4 < \kappa \leq 0.6$, fair for $0.2 < \kappa \leq 0.4$, and poor for $\kappa \leq 0.2$. All statistical analyses were performed by professional statisticians outside of this study committee using R (version 3.4.3; The R Foundation for Statistical Computing, Vienna, Austria) and IBM SPSS (version 23.0.0.0; IBM Corporation, Armonk, NY, USA). $P$-values <0.05 were considered statistically significant.

Results

Study 1
Of the 273 patients (382 lesions) initially enrolled in Study 1, four patients (7 lesions) were excluded (Fig. 4). Therefore, the final cohort consisted of 269 patients (198 men and 71 women; mean age, 67.4 ± 10.0 [range, 32–89] years) with 375 liver lesions. The underlying liver diseases of the 269 patients and final diagnoses of the 375 lesions were shown in Fig. 4. The mean size of liver lesions was as follows: HCC, 30.2 ± 24.3 [range, 3–167] mm; benign lesions, 13.2 ± 8.9 [3–56] mm; non-HCC malignant lesions including premalignant lesions, 22.5 ± 17.0 [4–80] mm. The mean time interval between gadoxetate disodium-enhanced MRI and pathological diagnosis was 56.5 ± 81.5 days in HCC and 48.3 ± 40.8 days in other lesions. All the images were evaluable for the blind reading.

Useful findings for distinguishing HCC from benign or non-HCC malignant lesions (Model 1) included signal intensities on $T_2$WI and PVP/TP images as well as pattern of APHE (all $P < 0.001$). Signal intensity on $T_2$WI showed the highest partial regression coefficient (2.0302–2.2667) (Table 2). In step 1 of Model 2, useful findings for distinguishing benign lesions from malignant lesions (HCC and non-HCC malignant lesions) included size, signal intensities of $T_2$WI, DWI and HBP images as well as pattern of APHE (all $P \leq 0.001$). Signal intensities of $T_2$WI, DWI and HBP images and pattern of APHE showed high partial regression coefficient (3.4136–5.2645) (Table 3). In step 2 of Model 2, useful findings for distinguishing HCC from non-HCC malignant lesions included signal intensity on $T_2$WI, PVP, and TP images as well as pattern of APHE and signal drop on opposed-phase gradient-echo $T_1$WI ($P < 0.001–0.046$). Signal intensity on $T_2$WI and pattern of APHE showed high partial regression coefficient (2.1234–3.9804) (Table 3). The probability of the lesion being HCC or benign was calculated by substituting $\alpha$ into the equation shown in Appendix. If the probability was greater or than equal to the cut-off value calculated from receiver operating characteristic analysis, the lesion was considered HCC or benign. Model 1 had a tendency of higher sensitivity compared with Model 2 (0.879 vs. 0.804), while Model 2 tended to have higher specificity compared with Model 1 (0.881 vs. 0.784) (Table 4). However, Models 1 and 2 showed similar accuracy for distinguishing HCC from other lesions (0.835 vs. 0.840) (Table 4). The diagnostic ability for distinguishing benign lesions from malignant lesions tended to be better than that for distinguishing HCC from non-HCC malignant lesions (Table 5). An MRI decision tree for distinguishing HCC from other lesions was generated through classification and the regression tree algorithm (Fig. 3b).

Study 2
Of the 144 patients (203 lesions) enrolled in Study 2, 61 patients (103 lesions) were excluded (Fig. 4). Therefore, the final cohort consisted of 83 patients (60 men and 23 women; mean age, 70.0 ± 8.6 [range, 33–85] years) with 100 liver lesions. The underlying liver diseases of the 83 patients and final diagnoses of the 100 lesions were shown in Fig. 4. The mean size of liver lesions was as follows: HCC, 36.4 ± 34.9 mm.
Table 2 Multivariate logistic model of Model 1 in Study 1

| Variable                                      | Partial regression coefficient | Odds ratio (95% confidence interval) | P-value |
|-----------------------------------------------|---------------------------------|--------------------------------------|---------|
| HCC (1) vs. others (0) [benign and non-HCC malignant lesions] |                                 |                                      |         |
| (Constant)                                    | −3.9855                         | 1.02 (1.00–1.04)                     | 0.056   |
| Size                                          | 0.0197                          | 1.02 (1.00–1.04)                     |         |
| T2WI Marked hyperintensity                    |                                 |                                      |         |
| Hyperintensity                                | 2.2667                          | 9.65 (3.42–27.22)                    | <0.001* |
| Isointensity                                  | 2.0302                          | 7.62 (2.56–22.67)                    | <0.001* |
| Hypointensity                                 | −13.4752                        | 0.00 (0.00–Inf)                      | 0.984   |
| APHE Dot-like                                  |                                 |                                      |         |
| No                                            | −1.8239                         | 0.16 (0.02–1.48)                     | 0.106   |
| Rim                                           | −1.9214                         | 0.15 (0.05–0.42)                     | <0.001* |
| Part                                          | 0.8467                          | 2.33 (0.84–6.50)                     | 0.105   |
| Whole                                         | 1.7276                          | 5.63 (2.61–12.15)                    | <0.001* |
| PVP or TP Hypointensity                       | 1.8279                          | 6.22 (2.98–12.98)                    | <0.001* |
| Others                                        |                                 |                                      |         |

*P < 0.05. HCC, hepatocellular carcinoma; T2WI, T2-weighted image; APHE, arterial phase hyperenhancement; PVP, portal venous phase; TP, transitional phase.
Table 3  Multivariate logistic models of Model 2 in Study 1

| Step 1: Benign (1) vs. malignant lesions (0) | Partial regression coefficient | Odds ratio (95% confidence interval) | P-value |
|-------------------------------------------|-------------------------------|--------------------------------------|---------|
| (Constant)                                | −3.3126                       | 0.87 (0.82–0.93)                     | <0.001* |
| Size                                      | −0.1375                       | 1.87 (1.82–1.93)                     | <0.001* |
| T₂WI                                      |                               |                                       |         |
| Marked hyperintensity                     | 5.2645                        | 193.34 (47.51–786.86)                |         |
| Others                                    | Reference category            |                                      |         |
| T₁WI                                      |                               |                                       |         |
| Without signal drop on OP                 |                               |                                       |         |
| With signal drop on OP                    | 1.5623                        | 4.77 (0.82–27.79)                    | 0.082   |
| DWI                                       |                               |                                       |         |
| Isointensity                              | Reference category            |                                      |         |
| Hyperintensity                            | 1.2802                        | 3.60 (0.92–14.14)                    | 0.067   |
| Hypointensity                             | 4.8834                        | 132.07 (12.01–1451.88)               | <0.001* |
| APHE                                      |                               |                                       |         |
| Dot-like                                  | 3.4136                        | 30.37 (4.02–229.22)                  | 0.001*  |
| Others                                    | Reference category            |                                      |         |
| HBP                                       |                               |                                       |         |
| No uptake of gadoxetate disodium          | Reference category            |                                      |         |
| Marked uptake of gadoxetate disodium      | 3.8693                        | 47.91 (8.17–280.97)                  | <0.001* |
| Moderate uptake of gadoxetate disodium    | 1.7115                        | 5.54 (0.80–38.09)                    | 0.082   |
| PVP or TP                                 |                               |                                       |         |
| Hypointensity                             | Reference category            |                                      |         |
| Others                                    | 0.8611                        | 2.37 (0.72–7.82)                     | 0.158   |

Step 2: HCC (1) vs. non-HCC malignant lesions (0)

| (Constant)                                | −4.7852                       |                                       |         |
| T₂WI                                      |                               |                                       |         |
| Iso- or hypointensity                     | Reference category            |                                       |         |
| Marked hyperintensity                     | 2.7356                        | 15.42 (1.30–182.20)                   | 0.030*  |
| Hyperintensity                            | 0.9572                        | 2.60 (1.11–6.09)                      | 0.027*  |
| T₁WI                                      |                               |                                       |         |
| Without signal drop on OP                | Reference category            |                                       |         |
| With signal drop on OP                   | 1.3777                        | 3.97 (1.03–15.33)                     | 0.046*  |
| APHE                                      |                               |                                       |         |
| Dot-like or rim                           | Reference category            |                                       |         |
| No                                        | 2.1234                        | 8.36 (2.89–24.22)                     | <0.001* |
| Part                                      | 2.9058                        | 18.28 (5.25–63.59)                    | <0.001* |
| Whole                                     | 3.9804                        | 53.54 (19.13–149.82)                  | <0.001* |
| HBP                                       |                               |                                       |         |
| Part uptake of gadoxetate disodium       | Reference category            |                                       |         |
| Whole uptake of gadoxetate disodium      | 2.3740                        | 10.74 (0.96–119.61)                   | 0.054   |
| No uptake of gadoxetate disodium         | 0.6253                        | 1.87 (0.63–5.58)                      | 0.262   |
| PVP or TP                                 |                               |                                       |         |
| Hypointensity                             | 1.9608                        | 7.11 (2.84–17.78)                     | <0.001* |
| Others                                    | Reference category            |                                       |         |

*P < 0.05. T₂WI, T₂-weighted image; T₁WI, T₁-weighted image; OP, opposed phase; DWI, diffusion-weighted image; APHE, arterial phase hyperenhancement; HBP, hepatobiliary phase; PVP, portal venous phase; TP, transitional phase; HCC, hepatocellular carcinoma.
Table 4 Diagnostic performance of Study 1 [HCC vs. others (benign and non-HCC malignant lesions)]

|                | Model 1                          | Model 2                          |
|----------------|----------------------------------|----------------------------------|
| Accuracy       | 0.835 (313/375)                  | 0.840 (315/375)                  |
| Sensitivity    | 0.879 (175/199)                  | 0.804 (160/199)                  |
| Specificity    | 0.784 (138/176)                  | 0.881 (155/176)                  |
| PPV            | 0.822 (175/213)                  | 0.884 (160/181)                  |
| NPV            | 0.852 (138/162)                  | 0.799 (153/194)                  |
| LR+ (95% CI)   | 4.073 (3.059–5.423)              | 6.739 (4.485–10.125)             |
| LR− (95% CI)   | 0.154 (0.105–0.226)              | 0.223 (0.167–0.296)              |
| AUC (95% CI)   | 0.903 (0.872–0.933)              | N/A                              |

HCC, hepatocellular carcinoma; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR−, negative likelihood ratio; CI, confidence interval; AUC, area under the curve, N/A, not applicable.

Table 5 Diagnostic performance of Model 2 in Study 1

|                              | Benign lesions (n = 81) vs. malignant lesions (n = 294) | HCC (n = 199) vs. non-HCC malignant lesions (n = 95) |
|------------------------------|----------------------------------------------------------|--------------------------------------------------|
| Accuracy                     | 0.955 (358/375)                                          | 0.840 (247/294)                                  |
| Sensitivity                  | 0.963 (78/81)                                             | 0.854 (170/199)                                  |
| Specificity                  | 0.952 (280/294)                                           | 0.811 (77/95)                                    |
| PPV                          | 0.848 (78/92)                                             | 0.904 (170/188)                                  |
| NPV                          | 0.989 (280/283)                                           | 0.726 (77/106)                                   |
| LR+ (95% CI)                 | 20.231 (12.107–33.776)                                    | 4.508 (2.963–6.861)                              |
| LR− (95% CI)                 | 0.039 (0.013–0.118)                                       | 0.180 (0.127–0.255)                              |
| AUC (95% CI)                 | 0.982 (0.970–0.994)                                       | 0.880 (0.835–0.926)                              |

HCC, hepatocellular carcinoma; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR−, negative likelihood ratio; CI, confidence interval.

Table 4 and 5 show the diagnostic performance of gadoxetate disodium-enhanced MRI compared to CT for distinguishing HCC from other lesions, including benign and non-HCC malignant lesions. The results indicate that gadoxetate disodium-enhanced MRI has a good diagnostic accuracy (AUC = 0.903–0.933) and predictive values (PPV = 0.840–0.904, NPV = 0.811–0.904), suggesting its potential for improving the diagnostic process for non-invasive diagnosis of HCC. However, the reproducibility of signal intensity on T2WI and pattern of APHE findings can be helpful. Although gadoxetate disodium is widely used for liver MRI, further studies are needed to evaluate its clinical impact in the differential diagnosis of HCC from benign and non-HCC malignant lesions.
### Table 6 Results of Study 2 by decision tree and logistic model [HCC vs. others (benign and non-HCC malignant lesions)]

|                | CT decision tree | MRI decision tree | P-value (vs. CT) | MRI Model 1 | P-value (vs. CT) | MRI Model 2 | P-value (vs. CT) |
|----------------|------------------|-------------------|------------------|-------------|------------------|-------------|------------------|
| Accuracy (n/n) | Reader 1         | 0.850 (85/100)    | 1.000            | 0.860 (86/100) | 1.000            | 0.820 (82/100) | 0.663           |
|                | Reader 2         | 0.860 (86/100)    | 0.383            | 0.780 (78/100) | 0.153            | 0.740 (74/100) | 0.031           |
| Sensitivity (n/n) | Reader 1     | 0.877 (64/73)     | 0.366            | 0.959 (70/73)  | 0.083            | 0.904 (66/73)  | 0.593           |
|                | Reader 2         | 0.945 (69/73)     | 0.248            | 0.904 (66/73)  | 0.366            | 0.836 (61/73)  | 0.033           |
| Specificity (n/n) | Reader 1      | 0.778 (21/27)     | 0.257            | 0.593 (16/27)  | 0.059            | 0.593 (16/27)  | 0.059           |
|                | Reader 2         | 0.630 (17/27)     | 0.739            | 0.444 (12/27)  | 0.166            | 0.481 (13/27)  | 0.248           |
| PPV (n/n)      | Reader 1         | 0.914 (64/70)     | 0.320            | 0.864 (70/81)  | 0.113            | 0.857 (66/77)  | 0.078           |
|                | Reader 2         | 0.873 (69/79)     | 0.594            | 0.815 (66/81)  | 0.129            | 0.813 (61/75)  | 0.121           |
| NPV (n/n)      | Reader 1         | 0.700 (21/30)     | 0.592            | 0.842 (16/19)  | 0.208            | 0.696 (16/23)  | 0.967           |
|                | Reader 2         | 0.810 (17/21)     | 0.229            | 0.632 (12/19)  | 0.172            | 0.520 (13/25)  | 0.015           |
| LR+ (95% CI)   | Reader 1         | 3.945 (1.938–8.032) | 0.323            | 2.354 (1.490–3.719) | 0.117 | 2.219 (1.400–3.519) | 0.082 |
|                | Reader 2         | 2.552 (1.557–4.186) | 0.594            | 1.627 (1.152–2.299) | 0.132 | 1.612 (1.105–2.351) | 0.123 |
| LR− (95% CI)   | Reader 1         | 0.159 (0.083–0.302) | 0.594            | 0.069 (0.022–0.219) | 0.226 | 0.162 (0.075–0.350) | 0.967 |
|                | Reader 2         | 0.087 (0.032–0.236) | 0.238            | 0.216 (0.095–0.490) | 0.179 | 0.341 (0.178–0.653) | 0.020 |
| Kappa value    | Reader 1         | 0.714 (0.557–0.870) | 0.616            | 0.415 (0.432–0.801) | 0.452 | –                | –               |
|                | Reader 2         | 0.741 (0.557–0.870) | 0.616            | 0.415 (0.432–0.801) | 0.452 | –                | –               |

*P < 0.05. HCC, hepatocellular carcinoma; CT, computed tomography; MRI, magnetic resonance imaging; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR−, negative likelihood ratio; CI, confidence interval.

### Table 7 Diagnostic performance of Study 2 by radiologist-made practical diagnosis [HCC vs. others (benign and non-HCC malignant lesions)]

|                | CT | MRI | P-value |
|----------------|----|-----|---------|
| AUC (95% CI)   | Reader 1 | 0.865 (0.775–0.955) | 0.799 (0.694–0.904) | 0.169 |
|                | Reader 2 | 0.867 (0.777–0.958) | 0.866 (0.779–0.952) | 0.976 |
| Accuracy (n/n) | Reader 1 | 0.869 (86/99) | 0.818 (81/99) | 0.267 |
|                | Reader 2 | 0.890 (89/100) | 0.890 (89/100) | 1.000 |
| Sensitivity (n/n) | Reader 1 | 0.917 (66/72) | 0.918 (67/73) | 1.000 |
|                | Reader 2 | 0.932 (68/73) | 0.959 (70/73) | 0.414 |
| Specificity (n/n) | Reader 1 | 0.741 (20/27) | 0.538 (14/26) | 0.059 |
|                | Reader 2 | 0.778 (21/27) | 0.704 (19/27) | 0.414 |
| PPV (n/n)      | Reader 1 | 0.904 (66/73) | 0.848 (67/79) | 0.061 |
|                | Reader 2 | 0.919 (68/74) | 0.897 (70/78) | 0.465 |
| NPV (n/n)      | Reader 1 | 0.769 (20/26) | 0.700 (14/20) | 0.487 |
|                | Reader 2 | 0.808 (21/26) | 0.864 (19/22) | 0.520 |
| LR+ (95% CI)   | Reader 1 | 3.536 (1.862–6.715) | 1.989 (1.306–3.029) | 0.064 |
|                | Reader 2 | 4.192 (2.064–8.512) | 3.236 (1.806–5.799) | 0.467 |
| LR− (95% CI)   | Reader 1 | 0.113 (0.051–0.250) | 0.153 (0.066–0.355) | 0.487 |
|                | Reader 2 | 0.088 (0.037–0.210) | 0.058 (0.019–0.182) | 0.524 |
| Kappa value    | Reader 1 | 0.687 (0.521–0.853) | 0.662 (0.475–0.848) | – |

HCC, hepatocellular carcinoma; CT, computed tomography; MRI, magnetic resonance imaging; AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR−, negative likelihood ratio.
Table 8 Reproducibility of MRI and CT findings between the two readers in Study 2

| MRI findings                                           | Reader 1 | Reader 2 | \( \kappa \)-value (95% confidence interval) |
|--------------------------------------------------------|----------|----------|---------------------------------------------|
| SI of \( T_2 \)WI (hypo/iso/hyper/marked hyper)        | 0/16/74/10 | 0/5/92/3 | 0.348 (0.147–0.550)                         |
| Signal drop on OP (yes/no)                            | 23/77    | 25/75    | 0.562 (0.369–0.755)                         |
| SI of DWI (hypo/iso/hyper)                            | 0/28/72  | 3/12/85  | 0.523 (0.325–0.721)                         |
| Pattern of APHE (no/dot-like/rim/part/whole)           | 18/3/2/20/57 | 16/2/10/22/50 | 0.664 (0.491–0.838)                        |
| SI of PVP (marked hypo/hypo/iso/hyper)                | 77/1/14/8 | 74/5/10/11 | 0.645 (0.461–0.829)                        |
| SI of TP (marked hypo/hypo/iso/hyper)                 | 82/1/12/5 | 80/5/9/6 | 0.584 (0.365–0.803)                         |
| Uptake of gadoxetate disodium on HBP (no/part and moderate/part and marked/whole and marked) | 86/6/3/3/2 | 73/20/0/4/3 | 0.659 (0.393–0.926)                        |
| CT findings                                           |          |          |                                             |
| Non-rim APHE (yes/no)                                 | 84/16    | 92/8     | 0.534 (0.284–0.784)                         |
| Non-peripheral washout (yes/no)                       | 73/27    | 80/20    | 0.751 (0.598–0.905)                         |

MRI, magnetic resonance imaging; CT, computed tomography; SI, signal intensity; \( T_2 \)WI, \( T_2 \)-weighted image; OP, opposed phase; DWI, diffusion-weighted image; APHE, arterial phase hyperenhancement; PVP, portal venous phase; TP, transitional phase; HBP, hepatobiliary phase; AP, arterial phase.

Fig. 5 A case of cholangiolocellular carcinoma (CoCC) misdiagnosed as hepatocellular carcinoma (HCC) on magnetic resonance imaging (MRI). The top and middle rows show MR images and the bottom row shows computed tomography (CT) images. A 78-year-old woman had CoCC (24 mm) at S2 (arrows). This lesion did not show marked hyperintensity on \( T_2 \)-weighted images (\( T_2 \)WI). Non-rim arterial phase hyperenhancement (APHE) was shown on both CT and MRI. Signal drop of opposed phase (OP) and gadoxetic acid uptake at the hepatobiliary phase (HBP) were not observed. Portal venous phase (PVP) and transitional phase (TP) images on MRI showed hyperintensity. This lesion was misdiagnosed as HCC by the logistic model, decision tree of MRI, and radiologist-made practical diagnosis of MRI (both readers scored 5 for both malignancy and HCC). On CT, this lesion was correctly diagnosed as “other lesion” (a category that includes benign and non-HCC malignant lesions) by the decision tree and radiologist-made practical diagnosis (reader 1 scored 2 for malignancy while reader 2 scored 5 for malignancy and 2 for HCC) because non-peripheral washout was not observed. \( T_1 \)WI, \( T_1 \)-weighted image; IP, in phase; Fat-sat., fat-saturated; DWI, diffusion-weighted image.
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Fig. 6 A case of hepatocellular carcinoma (HCC) misdiagnosed as “other lesion” (a category that includes benign and non-HCC malignant lesions) on computed tomography (CT) while correctly diagnosed on magnetic resonance imaging (MRI). The top row shows CT images and the middle and bottom rows show MR images. A 73-year-old man had HCC (22 mm) at S5 (arrows). This lesion showed rim arterial phase hyperenhancement (APHE) on CT. Therefore, it was misdiagnosed as “other lesion” (benign and non-HCC malignant lesions) by the decision tree and radiologist-made practical diagnosis (reader 1 scored 2 and reader 2 scored 3 for malignancy). On MRI, this lesion did not show marked hyperintensity on T₂-weighted images (T₂WI). Non-rim APHE and signal drop of opposed phase (OP) were observed. Gadoxetic acid uptake on hepatobiliary phase (HBP) was not observed. Portal venous phase (PVP) and transitional phase (TP) images on MRI showed hypointensity. This lesion was correctly diagnosed as HCC by the logistic model, decision tree of MRI, and radiologist-made practical diagnosis of MRI (both readers scored 5 for both malignancy and HCC). T₁WI, T₁-weighted image; IP, in phase; Fat-sat., fat-saturated; DWI, diffusion-weighted image.

than that of dynamic CT. The advantages of gadoxetate disodium-enhanced MRI are linked to the HBP, which can detect small HCCs; distinguish HCCs from hypervascular pseudolesions; and discover HBP hypointense nodules without APHE and early HCC or a premalignant lesion that is expected to become a typical HCC over time. In our study, the diagnostic performance of gadoxetate disodium-enhanced MRI was not superior to that of dynamic CT, as only 11% (11/100) of the lesions in Study 2 were small (<1 cm). Additionally, only one HBP hypointense nodule without APHE was included and was not targeted as an endpoint. Nonetheless, we believe that our results do not deny the utility of gadoxetate disodium-enhanced MRI for management of patients with cirrhosis/HCC. More studies are necessary to investigate the advantages of gadoxetate disodium-enhanced MRI over dynamic CT. In general, specificity is important for diagnosis of HCC. However, the specificity of gadoxetate disodium-enhanced MRI in our study was relatively low for both readers (0.444–0.667) compared with that in previous reports (~0.9). This was because of differences in target cases: our study included many mimickers of HCC, such as intrahepatic cholangiocarcinoma, cholangiolocellular carcinoma, neuroendocrine tumor, and hypervascular pseudolesion, which can be misdiagnosed as HCC because of non-rim APHE and hypointensity on HBP. According to the Liver Cancer Study Group of Japan registry data in 2006–2007, the ratio of intrahepatic cholangiocarcinoma vs. HCC was 208:15250 (~1:73) in patients with chronic liver disease. Our study population tended toward non-HCC malignancy (intrahepatic cholangiocarcinoma and combined hepatocellular-cholangiocarcinoma) (non-HCC malignant lesions [n = 12] vs. HCC [n = 73] ~ 1:6). Therefore, the distributions of HCC and non-HCC did not represent the natural population, although the data were prospectively collected in Study 2. The positive predictive value of gadoxetate disodium-enhanced MRI could be sufficiently high within our results, if the incidence rates of HCC and non-HCC were considered.

Our study has some limitations. First, although we enrolled patients prospectively in Study 2, the ratio of HCC and non-HCC lesions was different from that of the general...
population. We were unable to calculate accurate positive/negative predictive values. Second, our study cohort of 100 lesions in Study 2 was relatively small in terms of sample size. However, we discontinued enrollment because reasonable statistical power was expected with this number of cases. Third, we evaluated the diagnostic ability of CT and gadoxetate disodium-enhanced MRI for HCC in patients with relatively good liver function who could undergo surgery or biopsy, rather than of patients with advanced or end-stage cirrhosis and HCC. This could have influenced the diagnostic ability of gadoxetate disodium-enhanced MRI. Fourth, the MRI and CT parameters were not necessarily not along with LI-RADS recommendation because the imaging studies were performed as part of each hospital’s daily practice.

**Conclusion**

In summary, we show an MRI decision tree and logistic models for HCC diagnosis. A combination of gadoxetate disodium-enhanced MRI findings was useful for HCC diagnosis. However, its diagnostic ability was not superior to that of dynamic CT. Further studies warranted to further define the role of gadoxetate disodium-enhanced MRI in patients with chronic liver disease because the ratio of HCC and non-HCC lesions was different from that of the general population in our study cohort.

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**Conflicts of Interest**

This project was supported by Bayer Yakuhin, Ltd. There are no other conflicts of interest to declare.

**Appendix: Method for Determining Lesions in Logistic Model**

**Model 1 [HCC vs. others (benign and non-HCC malignant lesions)]**

\[
\text{logit } P = -3.9855 + 1.8279 \times \text{hypointensity on } \text{T}_2\text{WI }[0, 1] - 1.8239 \times \text{dot-like APHE }[0, 1] - 1.9214 \times \text{rim APHE }[0, 1] + 0.8467 \times \text{part APHE }[0, 1] + 1.7276 \times \text{whole APHE }[0, 1] + 2.6267 \times \text{hypointensity on } \text{T}_2\text{WI }[0, 1] + 2.0302 \times \text{isointensity on } \text{T}_2\text{WI }[0, 1] - 13.4752 \times \text{hypointensity on } \text{T}_2\text{WI }[0, 1] + 0.0197 \times \text{size (mm)}
\]

If \(P \geq 0.5150\), the lesion was judged as HCC.

**Model 2 (benign vs. malignant lesions)**

\[
\text{logit } P = -3.3126 + 0.1375 \times \text{size (mm)} + 5.2645 \times \text{marked hyperintensity on } \text{T}_2\text{WI }[0, 1] + 1.5623 \times \text{signal drop on } \text{OP }[0, 1] + 1.2802 \times \text{hyperintensity on } \text{DWI }[0, 1] + 4.8834 \times \text{hypointensity on } \text{DWI }[0, 1] + 3.4136 \times \text{dot-like APHE }[0, 1] + 3.8693 \times \text{marked uptake of gadoxate disodium on } \text{HBP }[0, 1] \times \text{moderate uptake gadoxate disodium on } \text{HBP }[0, 1] + 0.8611 \times \text{except for Hypointensity on } \text{PVP} \text{and } \text{TP }[0, 1]
\]

If \(P \geq 0.1871\), the lesion was judged as benign lesions.

**Model 2 (HCC vs. non-HCC malignant lesions)**

\[
\text{logit } P = -4.7852 + 2.7356 \times \text{marked hyperintensity on } \text{T}_2\text{WI }[0, 1] + 0.9572 \times \text{hyperintensity on } \text{T}_2\text{WI }[0, 1] + 1.3777 \times \text{signal drop on } \text{OP }[0, 1] + 2.1234 \times \text{no APHE }[0, 1] + 2.9058 \times \text{part APHE }[0, 1] + 3.9804 \times \text{whole APHE }[0, 1] + 2.3740 \times \text{whole uptake of gadoxate disodium on } \text{HBP }[0, 1] + 0.6253 \times \text{no uptake of gadoxate disodium on } \text{HBP }[0, 1] + 1.9608 \times \text{hypointensity on } \text{PVP} \text{or } \text{TP }[0, 1]
\]

If \(P \geq 0.6774\), the lesion was judged as benign lesions.

In those equations, if applicable, 1 was assigned and if not applicable, 0 was assigned to the category variable.

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