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Retrospective validation of a new diagnostic criterion for hepatocellular carcinoma on gadoxetic acid-enhanced MRI: can hypointensity on the hepatobiliary phase be used as an alternative to washout with the aid of ancillary features?

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Abstract

Objectives To validate new diagnostic criteria for hepatocellular carcinoma (HCC) on gadoxetic acid-enhanced MR imaging (Gd-EOB-MRI) using hypointensity on the hepatobiliary phase (HBP) as an alternative to washout in combination with ancillary features.

Methods This retrospective study included 288 patients at high risk for HCC with 387 nodules (HCCs, n=292; non-HCCs, n=95) showing arterial phase hyper-enhancement (APHE) ≥1 cm on Gd-EOB-MRI. Imaging diagnoses of HCCs were made using different criteria: APHE plus hypointensity on the portal venous phase (PVP) (criterion 1), APHE plus hypointensity on the PVP and/or transitional phase (TP) (criterion 2), APHE plus hypointensity on the PVP and/or TP and/or HBP (criterion 3), and criterion 3 plus non-LR-1/2/M according to the Liver Imaging Reporting and Data System (LI-RADS) v2017 considering ancillary features (criterion 4). Sensitivities and specificities of those criteria were compared using McNemar's test.

Results Among diagnostic criteria for HCCs, criteria 3 and 4 showed significantly higher sensitivities (93.8% and 92.5%, respectively) than criteria 1 and 2 (70.9% and 86.6%, respectively) (p values <0.001). The specificity of criterion 4 (87.4%) was shown to be significantly higher than that of criterion 3 (48.4%, p<0.001), albeit comparable to criterion 2 (86.3%, p>0.999) and significantly lower than criterion 1 (97.9%, p=0.002).

Conclusions In the non-invasive diagnosis of HCCs on Gd-EOB-MRI, HBP hypointensity may be used as an alternative to washout enabling a highly sensitive diagnosis with little loss in specificity if it is used after excluding nodules considered to be benignities or non-HCC malignancies based on characteristic imaging features.

Key Points

- *Gd-EOB-MRI enhancement and ancillary features can be used to diagnose HCC.*
- *Exclusion of LR-1/2/M improves specificity when HBP hypointensity is used.*

Keywords Carcinoma, hepatocellular · Magnetic resonance imaging · Liver · Practice guideline

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Abbreviations

AP	Hepatic arterial phase
Gd-EOB-MRI	Gadoxetic acid-enhanced magnetic resonance imaging
HBP	Hepatobiliary phase
HCC	Hepatocellular carcinoma
LI-RADS	Liver Imaging Reporting and Data System
PVP	Portal venous phase
TP	Transitional phase

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and the third leading cause of cancer-associated mortality worldwide [1, 2]. Unlike most other malignancies, HCC can be diagnosed non-invasively in high-risk patients based on its typical enhancement pattern on dynamic contrast-enhanced imaging, i.e. arterial phase hyperenhancement (APHE) and washout on the portal venous phase (PVP) or delayed phase [3]. This non-invasive diagnosis is possible because of the high pre-test probability of HCC in patients with chronic viral hepatitis or liver cirrhosis and the characteristic vascular changes in HCC composed of increased arterial flow and decreased portal blood flow [3, 4]. However, until now, there has been no established consensus regarding the most optimal imaging modalities for the diagnosis of HCCs, and therefore recent practice guidelines include various imaging modalities such as dynamic CT with extracellular contrast agents, dynamic MRI with extracellular gadolinium agents, dynamic MRI with hepatobiliary contrast agents such as gadoxetic disodium, and contrast-enhanced ultrasound [3–9].

Recently, several meta-analyses have reported that dynamic MRI may be more sensitive than dynamic CT in the diagnosis of HCCs [10–13]. In particular, gadoxetic acid-enhanced MRI (Gd-EOB-MRI) has been reported to show comparable performance for the assessment of the typical enhancement pattern of HCC to MRI using extracellular contrast agent [14]; however, it has demonstrated higher per-lesion sensitivity than either CT or MRI using extracellular contrast agents [12, 13, 15] owing to its capability of providing tissue-specific hepatobiliary phase (HBP) imaging [16]. Indeed, many studies included in those meta-analyses have used hypointensity on the HBP as an additional diagnostic criterion of HCC [12, 15, 17]. However, even in the guidelines accepting the use of Gd-EOB-MRI, controversy remains as to the value of HBP hypointensity on liver MRI; major guidelines of eastern societies including the Asian Pacific Association for the Study of the Liver (APASL) [5] and the Japan Society of Hepatology (JSH) [18] suggest the use of HBP hypointensity as a major feature of HCC as an alternative to the washout appearance, while guidelines of the European Association for the Study of the Liver (EASL) [4] or Liver Imaging Reporting and Data System (LI-RADS) [19] state that washout should be determined on the PVP, not on the transitional phase (TP) or HBP, so as to obtain the highest specificity.

A recent study [20] reiterated this concern over the lowering of specificity as a trade-off for increased sensitivity when using HBP hypointensity as an alternative to washout on the PVP. In that study, however, only dynamic enhancement patterns were assessed [20], and the prevalent causes of false-positive diagnoses on imaging criteria including HBP hypointensity were haemangioma, intrahepatic cholangiocarcinoma (ICC) and combined hepatocellular-cholangiocarcinoma (cHCC-CCA), some of which may have been avoided if we had detected typical features of a benignity or a non-HCC malignancy on T2-weighted imaging, diffusion-weighted imaging (DWI) or dynamic contrast-enhanced imaging as suggested in LI-RADS [19, 21]. We thus surmised that both a sensitive and a specific diagnosis of HCC could be achieved by including HBP hypointensity while excluding common causes of false positives based on multiparametric assessment.

Therefore, in this study, we investigated whether hypointensity on the HBP can be used as an alternative to washout for a sufficiently sensitive and specific diagnosis of HCC with the aid of ancillary features.

Materials and methods

Patients

This single-centre retrospective cohort study was approved by our Institutional Review Board with a waiver of the requirement for informed consent. Between September 2012 and May 2013, 2,874 Gd-EOB-MRI scans were taken and made available on our picture archiving and communication system (PACS). After two radiologists (I.J. and J.M.L.) reviewed the electronic medical records and MR images, a total of 288 patients who met the following criteria were finally included: (i) patients with chronic liver disease proven by positive serum hepatitis B or C viral markers, histopathology or clinical diagnosis of liver cirrhosis [22] and (ii) patients with at least one hepatic nodular observation showing APHE ≥1 cm in diameter that was confirmed as either HCC or non-HCC. APHE refers to AP enhancement that is unequivocally greater than the surrounding liver [23]. In this study, APHE indicates homogeneous or variegated enhancement while ring enhancement or peripheral globular enhancement were excluded [24]. Unenhanced images and subtraction images, if available, were also reviewed to confirm the presence of enhancement in T1 hyperintense nodules. Nodular observation indicates that wedge-shaped perfusion alterations or tumours in vein without definite parenchymal masses were excluded. In patients with multiple hepatic nodules that satisfied the inclusion criteria, the radiologists (I.J. and J.M.L.) who finalised the

study population selected and annotated the target lesions on AP images up to a number of three for each patient in a consensus manner. As a result, a total of 387 nodules (HCCs, n=292; and non-HCCs, n=95) in 288 patients with chronic hepatitis (n=122) or liver cirrhosis (n=166) were selected for image analysis. Non-HCCs included 15 malignant lesions and 80 benign lesions. The reference standards for HCCs and non-HCCs included in this study are described in the Appendix in the Electronic Supplementary Material.

We would like to point out that the same study population had been used in a previous study [20], in which we reported the performance of different Gd-EOB-MR imaging criteria for HCCs. However, as opposed to our previous study in which we assessed the imaging criteria only based on enhancement patterns, this study proposed a new imaging criterion based not only on enhancement patterns but also on ancillary features for benignity or non-HCC malignancy, and aimed to validate that criterion in comparison with the previously reported criteria.

Gadoxetic acid-enhanced liver MRI

Liver MRI studies were performed using either a 3.0T or 1.5T MR system: Signa HDxt 1.5T (GE Medical Systems) (n=127), Magnetom Verio or Magnetom Trio or Biograph mMR (Siemens Healthineers) (n=53), or Ingenia 3.0T (Philips Medical System) (n=53) at our institution, and various 3.0T or 1.5T scanners at an outside hospital (n=55). Our routine MRI protocol consisted of a respiratory-triggered T2-weighted fast spin-echo sequence, a half-Fourier acquisition single-shot turbo spin-echo sequence (HASTE), free-breathing diffusion-weighted imaging (DWI) using b values of 0 and 800 mm^2/s, a breath-hold three-dimensional (3D) in- and opposed-phase T1-weighted gradient-echo (GRE) sequence, and dynamic phase imaging with a fat-suppressed 3D T1-weighted GRE sequence. For dynamic phase imaging, after obtaining unenhanced T1-weighted images, a standard dose (0.025 mmol/kg) of gadoxetic acid (Primovist; Bayer Healthcare) was administered intravenously via an antecubital venous catheter at a rate of 1.0 ml/s using a power injector (Spectris Solaris EP; Medrad), followed by a 20-ml saline flush. AP images were acquired 7–8 s after the contrast material arrived at the distal thoracic aorta as observed using real-time MRI fluoroscopic monitoring. Thereafter, PVP, TP and HBP images were obtained approximately 50–60 s, 3 min and 20 min, respectively, after beginning contrast medium injection. Acquisition of 3D GRE data for each dynamic phase was finished during a single breath-hold (15–20 s) at the end of expiration.

Image analysis

For the image analysis, another two board-certified abdominal radiologists (D.H.L. and J.H.J.) reviewed the MR images in consensus. They were aware that the study population consisted of high-risk patients for HCCs and were given captured AP images of each annotated target observation; however, they were blinded to the final diagnosis of each observation. The reviewers then determined whether or not any part of each observation showed hypointensity relative to the surrounding hepatic parenchyma on PVP, TP and HBP images. In addition, they assigned an LI-RADS category for each observation as follows: LR-M (definitely or probably malignant but not specific for HCC), LR-TIV (tumour in vein), LR-1~5 (1: definitely benign, 2: probably benign, 3: indeterminate probability of HCC, 4: probably HCC, 5: definitely HCC) [19, 21]. LI-RADS categorisation was determined after a comprehensive review of all image sequences, and category adjustments and tie-breaking rules were optionally applied [19].

Based on the results of image review regarding the relative signal intensity of hepatic observations on the PVP, TP or HBP without or with a combination of LI-RADS categorisation, the same radiologists who assessed MR imaging features and LI-RADS categories finally determined whether each observation can be non-invasively diagnosed as HCC according to the pre-defined imaging criteria for HCCs in a consensus method. Four different imaging criteria were applied as follows: APHE plus hypointensity relative to the surrounding hepatic parenchyma on the PVP (criterion 1), on the PVP and/or TP (criterion 2), on the PVP and/or TP and/or HBP (criterion 3); and a new criterion: criterion 3 plus non-LR-1/2/M (criterion 4). The new criterion includes hypointensity on the HBP as an alternative to washout but excludes observations suggestive of benignity or non-HCC malignancy based on characteristic imaging features of not only enhancement patterns but also ancillary features.

Statistical analysis

Per-lesion sensitivity, specificity, positive-predictive values (PPV), negative-predictive values (NPV) and accuracy were calculated for each imaging diagnostic criteria of HCC. Thereafter, per-lesion sensitivities and specificities of imaging criteria were compared using McNemar's test. All statistical analyses were performed using MedCalc software version 17.9.2 (MedCalc Software). A p-value of less than 0.05 was considered to indicate statistical significance.

Results

Hypointensity on PVP, TP and HBP

Among HCCs (n=292), hypointensity relative to the surrounding hepatic parenchyma was seen in 70.9% (207/292) on PVP, 86.6% (253/292) on PVP and/or TP, and 93.8% (274/292) on PVP and/or TP and/or HBP (p<0.001) (Fig. 1) (Table 1). As for non-HCCs (n=95), hypointensity was seen

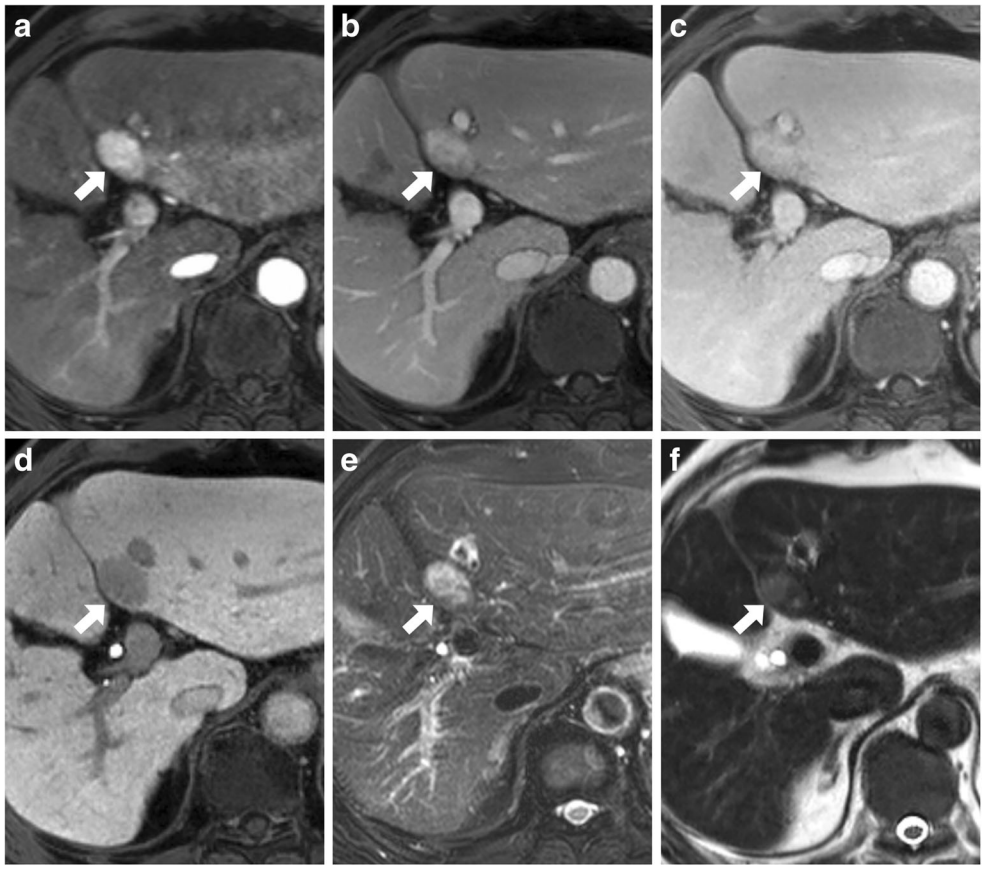

Fig. 1 A surgically-proven hepatocellular carcinoma (HCC) in a 62-year-old male patient with liver cirrhosis. On gadoxetic acid-enhanced MRI, a nodular lesion (arrow) with arterial phase hyper-enhancement (APHE) (not rim) is seen in segment III of the liver (**a**) and does not show the washout appearance on the portal venous phase (PVP) (**b**) or transitional phase (TP) (**c**); rather, it shows hypointensity on the hepatobiliary phase (HBP) (**d**), moderate hyperintensity on moderately T2-weighted imaging (**e**) and mild hyperintensity on heavily T2-weighted imaging (**f**). As none of the imaging features suggest benignity or non-HCC malignancy for this lesion, it would not be categorised as LR-1 or LR-2 or LR-M according to the Liver Imaging Reporting and Data System (LI-RADS) v2017. While the imaging criteria of 'APHE plus hypointensity on PVP' or 'APHE plus hypointensity on PVP and/or TP' could not make a non-invasive diagnosis of HCC for this lesion, 'APHE plus hypointensity on PVP and/or TP and/or HBP' and our new criterion of 'APHE plus hypointensity on PVP and/or TP and/or HBP plus non-LR-1/2/M' help achieve the correct diagnosis of HCC

in 2.1% (2/95: cHCC-CCA) on PVP, 13.7% (13/95: cHCC-CCA, n=3; CC, n=6; metastasis, n=1; haemangioma, n=3) on PVP and/or TP, and 51.6% (49/95; cHCC-CCA, n=3; CC, n=10; metastasis, n=2; haemangioma, n=32; inflammatory lesion, n=2) (Figs. 2 and 3), which can result in false-positive diagnosis of HCC according to the imaging criteria used in this study.

Table 1 Diagnostic performances of different imaging criteria on gadoxetic acid-enhanced MRI for hepatocellular carcinoma

Imaging criteria	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Arterial phase hyper-enhancement					
1) + Hypointensity on PVP	70.9 (207/292)	97.9 (93/95)	99.0 (207/209)	52.2 (93/178)	77.5 (300/387)
2) + Hypointensity on PVP and/or TP	86.6 (253/292)	86.3 (82/95)	95.1 (253/266)	67.8 (82/121)	86.6 (335/387)
3) + Hypointensity on PVP and/or TP, and/or HBP	93.8 (274/292)	48.4 (46/95)	84.8 (274/323)	71.9 (46/64)	82.7 (320/387)
4) + Hypointensity on PVP and/or TP, and/or HBP + Non-LR-1/2/M	92.5 (270/292)	87.4 (83/95)	95.7 (270/282)	79.0 (83/105)	91.2 (353/387)

Numbers in parentheses were used to calculate percentages

PVP portal-venous phase, *TP* transitional phase, *HBP* hepatobiliary phase, *Non-LR-1/2/M* exclusion of LR-1, 2 and M observations, *PPV* positive-predictive value, *NPV* negative predictive value

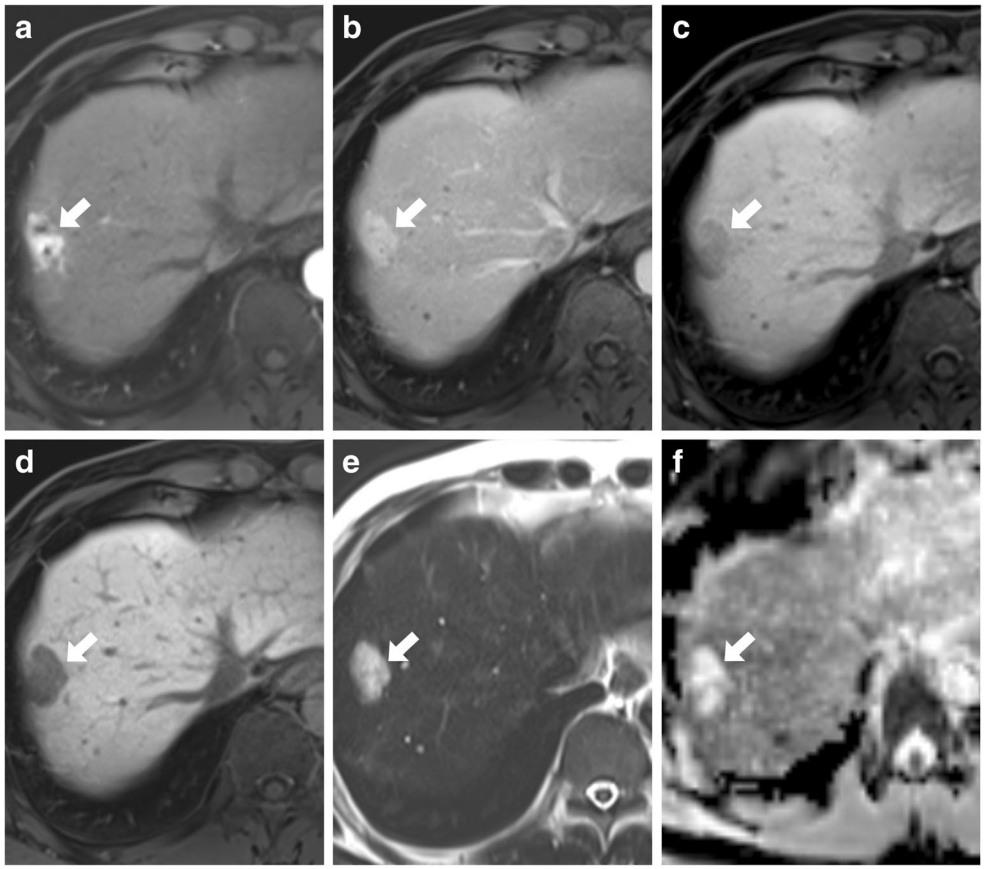

Fig. 2 A case of haemangioma diagnosed by imaging in a 66-year-old male patient with chronic hepatitis B. There is an arterially-enhancing nodule (arrow) in the right lobe of the liver (**a**) that shows hyperintensity on the portal venous phase (PVP) (**b**) and hypointensity on the transitional phase (TP) (**c**) and hepatobiliary phase (HBP) (**d**). Only based on the dynamic enhancement pattern, this lesion would be false-positively diagnosed as a hepatocellular carcinoma (HCC) using the criteria of 'arterial phase hyper-enhancement (APHE) plus hypointensity on PVP and/or TP' or 'APHE plus hypointensity on PVP and/or TP and/or HBP' whereas the criteria of 'APHE plus hypointensity on PVP' can help avoid a false-positive diagnosis. However, with combined interpretation of imaging features on the dynamic phases and HBP (**a**–**d**) and on the other sequences (bright hyperintensity on heavily T2-weighted imaging (**e**) and high ADC value (**f**)), this lesion would be considered a haemangioma and will be assigned as LR-1. Therefore, our new criterion of 'APHE plus hypointensity on PVP and/or TP and/or HBP plus non-LR-1/2/M' can also avoid the false-positive diagnosis of HCC for this haemangioma

Diagnostic performances of Gd-EOB-MR imaging criteria

Sensitivity, specificity, PPV, NPV and accuracy of each imaging criterion are listed in Table 1. Among Gd-EOB-MRI diagnostic criteria, criterion 3 (APHE plus hypointensity on PVP and/or TP, and/or HBP) and 4 (APHE plus hypointensity on PVP and/or TP, and/or HBP plus non-LR-1/2/M), which included hypointensity on the HBP as an alternative to washout, showed significantly higher sensitivities (93.8% and 92.5%, respectively) than criterion 1 (APHE plus hypointensity on PVP) and 2 (APHE plus hypointensity on PVP and/or TP) (70.9% and 86.6%) (p values <0.001) (Tables 1 and 2) (Fig. 1). As for specificity, criterion 4 (87.4%) showed significantly higher specificity than criterion 3 (48.4%, p<0.001). In comparison to criterion 3, criterion 4 was able to avoid false-positive diagnoses in one cHCC-CCA, ten CCs, two metastases, 32 haemangiomas and two inflammatory lesions (Figs. 2 and 3). In addition, the specificity of criterion 4 was comparable to criterion 2 (86.3%, p>0.999) but significantly lower than that of criterion 1 (97.9%, p=0.002) (Tables 1 and 2).

LI-RADS categories

LI-RADS categories of hepatic observations included in this study are described in Table 3. The majority of HCCs were categorised as either LR-5 (56.5%, 165/292) or LR-4 (37.3%, 109/292). Non-HCC malignancies including cHCC-CCA, CC and metastasis were assigned as LR-4 (n=5), LR-5 (n=2), LR-M (n=7) or LR-TIV (n=1) (Table 3). Therefore, the specificity of LR-5 was (97.9%, 93/95). Two false-positive cases of LR-5 were

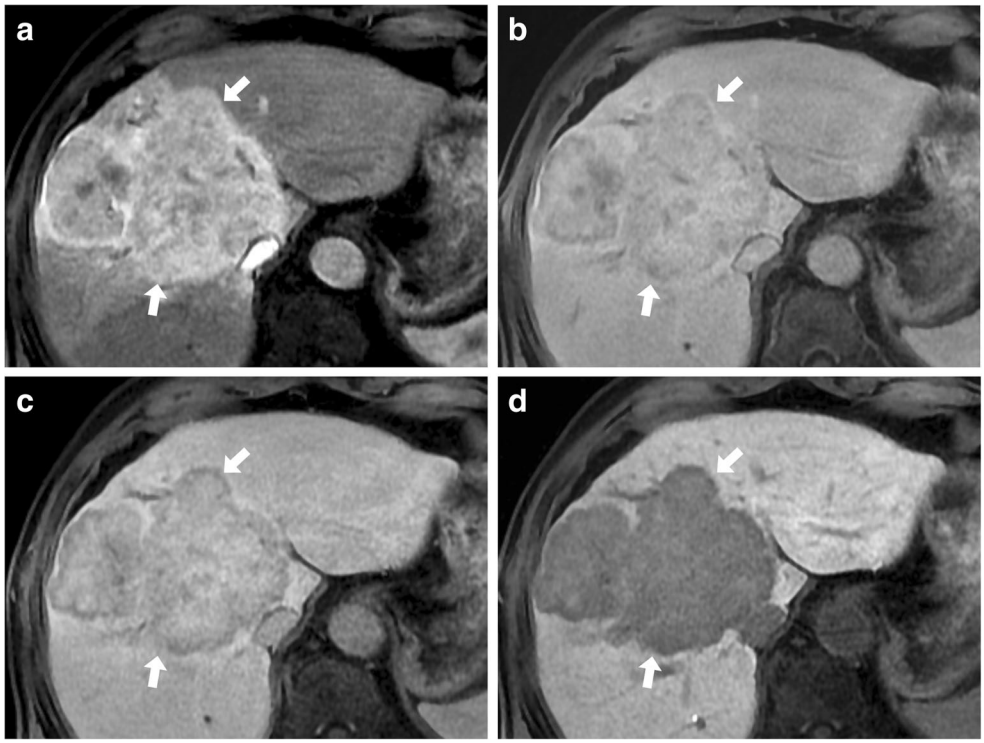

Fig. 3 A biopsy-proven intrahepatic cholangiocarcinoma in a 71-year-old male patient with alcoholic liver cirrhosis. A 12-cm lobulated mass (arrows) is observed in the liver showing arterial phase hyper-enhancement, but not rim enhancement (**a**). On portal venous phase (PVP) (**b**) and transitional phase (TP) (**c**), the mass demonstrates a targetoid appearance (i.e. peripheral hypointensity and central hyperintensity), which is a suggestive feature for LR-M (definitely or probably malignant, not specific for hepatocellular carcinoma [HCC]) according to the Liver Imaging Reporting and Data System (LI-RADS) v2017. The mass shows hypointensity on the hepatobiliary phase (HBP) (**d**). Thus, the criteria of 'arterial phase hyper-enhancement (APHE) plus hypointensity on PVP and/or TP and/or HBP' may lead to a false-positive diagnosis of HCC for this lesion. However, as this mass would be assigned as LR-M, the criterion of 'APHE plus hypointensity on PVP and/or TP and/or HBP plus non-LR-1/2/M' would not result in a false-positive diagnosis of HCC

pathologically confirmed cHCC-CCAs that showed hypointensity on the PVP. In addition, although hypointensity on the TP and/or HBP was frequently seen in haemangiomas with APHE (94.1%, 32/34), most haemangiomas were able to be accurately assigned as LR-1 or 2 (91.2%, 31/34) (Fig. 2) (Table 3).

Discussion

For the non-invasive diagnosis of HCCs on Gd-EOB-MRI, our study results showed that criteria including HBP hypointensity (criteria 3 and 4) were shown to provide significantly higher sensitivities (93.8% and 92.5%, respectively)

Table 2 *P*-values in the comparison of sensitivity and specificity according to imaging criteria

	Sensitivity			Specificity		
Imaging criteria	1)	2)	3)	1)	2)	3)
Arterial phase hyper-enhancement						
1) + Hypointensity on PVP	-	-	-	-	-	-
2) + Hypointensity on PVP and/or TP	<0.001*	-	-	0.001*	-	-
3) + Hypointensity on PVP and/or TP, and/or HBP	<0.001*	<0.001*	-	<0.001*	<0.001*	-
4) + Hypointensity on PVP and/or TP, and/or HBP + Non-LR-1/2/M	<0.001*	<0.001*	0.125	0.002*	>0.999	<0.001*

Data are *p*-values

PVP portal-venous phase, *TP* transitional phase, *HBP* hepatobiliary phase, *Non-LR-1/2/M* exclusion of LR-1, 2 and M observations

* Indicates a statistically significant difference with *p*-values <0.05

Table 3 LI-RADS categories of hepatic observations on gadoxetic acid-enhanced MRI

	HCC (n=292)	Non-HCC (n=95)	Non-HCCs of each LI-RADS category
LR-1	0% (0/292)	50.5% (48/95)	APS (n=28), haemangioma (n=20)
LR-2	0% (0/292)	23.2% (22/95)	APS (n=5), haemangioma (n=11), inflammatory lesion (n=1), FNH-like nodule (n=5)
LR-3	1.7% (5/292)	7.4% (7/95)	Haemangioma (n=1), inflammatory lesion (n=1), FNH-like nodule (n=5)
LR-4	37.3% (109/292)	8.4% (8/95)	CC (n=4), metastasis (n=1), haemangioma (n=2), FNH-like nodule (n=1)
LR-5	56.5% (165/292)	2.1% (2/95)	cHCC-CCA (n=2)
LR-M	1.4% (4/292)	7.4% (7/95)	CC (n=5), cHCC-CCA (n=1), metastasis (n=1)
LR-TIV	3.1% (9/292)	1.1% (1/95)	CC (n=1)

Numbers in parentheses were used to calculate percentages

APS arterioportal shunt, *FNH* focal nodular hyperplasia, *CC* cholangiocarcinoma, *cHCC-CCA* combined hepatocellular-cholangiocarcinoma

than criteria that did not include HBP hypointensity (criteria 1 and 2) (79.9% and 86.6%, respectively). In addition, we also found that criterion 4, which excludes observations of LR-1, LR-2 and LR-M, demonstrated considerably higher specificity (87.4%) than criterion 3 (48.4%), which only assessed dynamic enhancement patterns, although it was still significantly lower than that of criterion 1 (97.9%), which only included PVP hypointensity to assess the washout appearance. From a global perspective, whether emphasis should be placed on sensitivity or specificity in the diagnosis of HCCs can be influenced by the practice patterns of different geographic areas, as manifested in the HCC diagnosis guidelines of more than 20 organisations [8]. Based on our study results, criterion 1 or LR-5, which showed the highest specificity but at a cost of low sensitivity, may be reasonable in regions such as North America or Europe where deceased donor liver transplantation constitutes a major treatment option for HCC as patients with imaging diagnosis of HCC may receive priority for liver transplantation, while criterion 4 showing high sensitivity with modest specificity could be applied to regions such as Asia in which loco-regional therapies are more commonly used.

At present, LI-RADS v2017 recommends that washout should be determined on the PVP of Gd-EOB-MRI and states several HBP findings as only ancillary features [19, 25, 26]. Accordingly, recent studies for the application of LI-RADS on Gd-EOB-MRI were able to demonstrate a high specificity of more than 95%, although they showed a relatively lower sensitivity in the range of 57.3–64% for the diagnosis of HCCs [27–30] compared to the reported sensitivities of recent meta-analytic studies [12, 13, 15]. Indeed, criterion 1 in our study suggests that the specificity of 'APHE and PVP washout', corresponding to current LI-RADS criteria, may be at least equivalent or even higher than the specificities of ECCM-enhanced MRI [21, 31]. Using ECCM-enhanced MRI, Renot et al [31] reported that LR-5 criteria provided 89% specificity in patients with HCCs of <3 cm, and a systematic review by Tang et al [21] described that the specificity was in the range of 85–100%. Therefore, we believe that among our imaging criteria of Gd-EOB-MRI, criterion 1 should be preferred in situations where a high specificity for HCCs is desirable. However, an approach involving a more sensitive diagnosis of HCC may be essential for the early diagnosis of HCCs [32], which can lead to improved survival with timely treatment [33]. Thus, to achieve higher sensitivity, our study results would suggest that the use of HBP hypointensity should be included for the diagnosis of HCCs. Our study results demonstrating increased sensitivity using criteria 3 and 4 are quite similar to a recent study by Chen et al [34], which also demonstrated improvement in the sensitivity for an HCC diagnosis using HBP hypointensity as an additional major criterion to the LI-RADS criteria.

In addition to the higher sensitivity, maintaining a high specific diagnosis of HCC is also essential in order to avoid inappropriate or unnecessary treatment [21, 35]. In our study, we found that by excluding LR-1, LR-2 and LR-M categories prior to determining the dynamic enhancement pattern, we were able to prevent a large loss in specificity using HBP hypointensity as a major feature of HCC. This improvement in the specificity of criterion 4 in comparison to criterion 3 mainly stems from the decreased false-positive diagnosis of haemangiomas and ICCs, based on the bright hyperintensity on T2WI of haemangiomas and LR-M features of ICCs by using the multiparametric capability of Gd-EOB-MRI. However, the differential diagnosis of cHCC-CCA from HCCs was still difficult using any of the four criteria, and two out of three cHCC-CCAs were not assigned as LR-M and showed PVP washout. Our study results are in good agreement with the results of a previous study by Fraum et al [36],

which demonstrated that there were considerable overlaps in the imaging appearances of cHCC-CCA and HCC.

In this study, the LR-5 category provided a sensitivity of 56.5% and a specificity of 97.9% which was similar to previous studies regarding the performance of LI-RADS [29, 37]. In our study, in comparison to criterion 4, LR-5 resulted in lower sensitivity but higher specificity, and none of the ICCs were categorised as LR-5. These results are also in good agreement with those of a previous study by Choi et al [38], which demonstrated that the use of PVP washout instead of PVP and/or TP washout on Gd-EOB-MRI prevented misclassification of ICC as HCC.

This study had several limitations. First, owing to the retrospective single-centre nature of our study design, our results may have had selection bias and may be limited in generalisability. In order to increase generalisability, additional multicentre studies are warranted. Second, we used a composite reference standard for the determination of benignity. However, biopsy for highly suspected benign lesions is not usually performed, and application of a strict standard of reference (pathological proof) for benign observations may have brought additional selection bias.

In conclusion, in the non-invasive diagnosis of HCCs on Gd-EOB-MRI, HBP hypointensity may be used as an alternative to washout after excluding nodules suggestive of benignity or non-HCC malignancy based on characteristic imaging features, enabling a highly sensitive diagnosis with little loss in specificity, which would be particularly more appropriate in regions where loco-regional therapies are widely used for HCC.

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Compliance with ethical standards

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Conflict of interest The authors of this article declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Study subjects or cohorts overlap The same study cohort has been previously reported in Eur Radiol 2015; 25: 2859-68.

Methodology
• Retrospective, diagnostic study, performed at one institution

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