Liver Cancer

Research Article

Liver Cancer 2025;14:638–650
DOI: 10.1159/000545965

Received: January 14, 2025
Accepted: April 4, 2025
Published online: April 22, 2025

Comparison of Gadoxetic Acid-Enhanced Liver Magnetic Resonance Imaging and Contrast-Enhanced Computed Tomography for the Noninvasive Diagnosis of Hepatocellular Carcinoma

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Keywords
Hepatocellular carcinoma · Computed tomography · Gadoxetic acid · Magnetic resonance imaging · Liver

Abstract

Introduction: Magnetic resonance imaging (MRI) has been shown to outperform computed tomography (CT) in diagnosing hepatocellular carcinoma (HCC), although inconsistencies exist across studies. We compared the performance of CT and gadoxetic acid-enhanced MRI in diagnosing HCC according to various guidelines, and to assess the incremental value of a second-line examination. ***Methods:*** This retrospective multicenter study included patients at risk of developing HCC with focal liver lesions (FLLs) ≥10 mm.

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These patients underwent both contrast-enhanced CT and gadoxetic acid-enhanced MRI between January 2015 and June 2018. Four radiologists independently assessed the images using criteria from the Liver Imaging Reporting and Data System (LI-RADS), the Asian Pacific Association for the Study of the Liver (APASL), and the Korean Liver Cancer Association-National Cancer Center (KLCA-NCC) guidelines. The diagnostic performance of CT and MRI was compared across guidelines. ***Results:*** In total, 1,590 FLLs (median size, 22.6 mm) were analyzed in 1,455 patients (median age, 59 years; male, 1,101). Sensitivity was higher with MRI than with CT for APASL (89.3% [95% CI: 87.7%, 90.8%] vs. 78.9% [95% CI: 77.0%, 80.8%], respectively) and KLCA-NCC (78.7% [95% CI: 76.7%, 85.0%] vs. 73.7% [95% CI: 71.6%, 75.7%], respectively) ($p = 0.002$ for both). However, LI-RADS showed lower sensitivity with MRI than with CT (70.6% [95% CI: 68.4%, 72.6%] vs. 74.7% [95% CI: 72.6%, 76.7%], $p = 0.002$), due to fewer nonperipheral washout. MRI re-categorized 22.4%, 32.2%, and 53.5% of non-HCC observations on CT as HCC with LI-RADS, KLCA-NCC, and APASL, respectively. CT re-classified 30.2%, 29.0%, and 25.8% of non-HCC observations on MRI as HCC with LI-RADS, KLCA-NCC, and APASL, respectively. ***Conclusion:*** The added value of gadoxetic acid-enhanced MRI after CT depends on the diagnostic criteria used. Restricting washout timing to the portal venous phase in LI-RADS reduces the sensitivity of gadoxetic acid-enhanced MRI relative to CT.

Plain Language Summary

Diagnostic guidelines vary for diagnosing hepatocellular carcinoma (HCC) noninvasively on CT and MRI. Although MRI using gadoxetic acid is known to be more sensitive than CT, the results are inconsistent between the studies. As a result, the added value of second-line examination for inconclusive lesion on the first-line examination is not investigated. The study found that the diagnostic accuracy of these two imaging methods varied depending on which diagnostic criteria used. When following the guidelines from the Asian Pacific Association for the Study of the Liver (APASL) and the Korean Liver Cancer Association (KLCA-NCC), MRI had better sensitivity than CT at diagnosing HCC. However, when using the Liver Imaging Reporting and Data System (LI-RADS) criteria, CT actually had higher sensitivity than MRI at diagnosing HCC. These differences occurred because each guideline has different specific requirements for diagnosing HCC. The study also looked at how useful it was to perform a second-line examination when the first-line examination did not definitively diagnose HCC. The added value of this second-line examination varied by guidelines. When MRI was performed after CT for non-HCC lesions, between 22% and 54% of the non-HCC lesions were newly diagnosed as HCC, depending on which guidelines were used. When CT was performed after MRI, about 25–30% of non-HCC observations were newly categorized as HCC across all guidelines. These findings offer evidence for current guidelines and help us to estimate the anticipated added value of the second-line examination for diagnosing HCC in different clinical scenarios using different imaging modalities and diagnostic criteria.

Introduction

Hepatocellular carcinoma (HCC) is the most prevalent form of primary liver cancer. It can be diagnosed by its distinctive imaging characteristics, which include nonrim arterial phase hyperenhancement (APHE) and nonperipheral portal or delayed washout in hepatic observations ≥ 10 mm, as seen on contrast-enhanced CT or MRI according to established guidelines [1]. In terms of diagnostic performance, studies have shown that gadoxetic acid-enhanced MRI is the most sensitive method compared to other tools [2]. However, other research indicates that dynamic MRI using extracellular contrast agents exhibits higher sensitivity than gadoxetic acid-enhanced MRI [3, 4]. While the guidelines agree on these noninvasive diagnostic criteria, they differ in certain specifics, particularly concerning gadoxetic acid-enhanced MRI. A notable discrepancy is the timing of washout definition in gadoxetic acid-enhanced MRI: the Liver Imaging Reporting and Data System (LI-RADS) [5], endorsed by the American Association for the Study of Liver Diseases (AASLD) [1], defines washout during the portal venous phase. In contrast, the Asian Pacific Association for the Study of the Liver (APASL) [6] and the Korean Liver Cancer Association-National Cancer Center (KLCA-NCC) guidelines consider washout timing to extend to the hepatobiliary phase (HBP) [7]. The phase used to define "washout" can influence the comparative value of gadoxetic acid-enhanced MRI versus CT.

All three guidelines recommend second-line imaging for focal liver lesions (FLLs) that do not meet the diagnostic criteria for HCC on initial examination. However, no study has evaluated the actual gains of the second-line examinations and how variations in diagnostic criteria across these guidelines affect the incremental value of second-line imaging, particularly with gadoxetic acid-enhanced MRI. Therefore, this study aimed to

compare the effectiveness of CT and gadoxetic acid-enhanced MRI in diagnosing HCC using different diagnostic criteria in patients at risk for HCC, and to determine the incremental value of MRI as a secondary test based on these guidelines.

Materials and Methods

Eleven academic institutions in South Korea participated in this retrospective multicenter study. The Institutional Review Boards of each hospital waived the requirement for informed consent. This work received financial support from Bayer; however, the authors maintained complete control over the data and information submitted for publication at all times.

Patients

The MRI data for this study have previously been published for comparing four HCC diagnostic criteria and readers' judgment on MRI [8]. To summarize, we searched our radiology database from January 2015 to June 2018 to identify consecutive patients who met the following eligibility criteria: (a) patients at risk for HCC according to KLCA-NCC criteria; (b) no history of HCC; (c) non-cystic FLL ≥10 mm; (d) histologic diagnosis available, or clinically stable benign FLLs; and (e) dynamic liver CT scan available. Patients were excluded for any of the following reasons: (a) missing critical sequences of MRI or CT; (b) presence of multiple FLLs (≥6); (c) lack of appropriate reference standards (pathology for malignant FLLs within 3 months, and pathology or clinical follow-up for benign FLLs); (d) FLLs with inconclusive pathology; (e) an interval exceeding 8 weeks between CT and MRI in cases of malignant FLLs; (f) unequivocal changes in the size of FLLs between CT and MRI; or (g) treatment received between the CT and MRI scans.

MRI Acquisition

MRI scans were performed using either 1.5 T (n = 149) or 3 T (n = 1,306) scanners. The imaging protocols included heavily T2-weighted images, T2-weighted images, and diffusion-weighted images with at least two b-values ranging from 0 to 1,000 s/mm^2. The sequences also covered in-phase and opposed-phase imaging, along with precontrast, arterial, portal, transitional phases, and HBP. A standard dose of gadoxetic acid (0.025 mmol/kg, Eovist or Primovist by Bayer) was administered. Detailed information regarding scan parameters is presented in the online supplement (for all online suppl. material, see https://doi.org/10.1159/000545965).

CT Acquisition

CT scans were performed using multi-detector scanners equipped with 4–256 channels, operating at 80–140 kVp in accordance with the protocols of each institution. The exams encompassed precontrast, arterial, portal venous, and delayed phases. Iodine contrast media, at a dosage of 1.5–1.6 mL/kg, was administered. Detailed information about the scan parameters and scanners can be found in the Supplement.

Web Platform-Based Template Development

The development of the review system, which utilizes a commercially available web platform (Mint Lesion, Mint Medical), has been described in detail elsewhere [8]. For each FLL, 46 questionnaires were used to assess MRI features, and 31 were used for CT imaging features. These questionnaires specifically addressed major and ancillary features, LR-M features, and the presence of tumor-in-vein (TIV). The template automatically provided diagnostic classifications according to three guidelines: LI-RADS v.2018, KLCA-NCC v.2018, and APASL v.2017. For FLLs classified with LR-TIV, LR-scores were determined based on imaging features other than TIV as the TIV category is not included in the other guidelines.

Template-Based Image Analysis

A fellowship-trained body radiologist, J.M.L., with 25 years of experience, annotated index tumors on both CT and MRI using a web-based review platform. This radiologist did not participate in the subsequent review sessions. Four other fellowship-trained body radiologists (J.H.Y., J.W.K., S.K., M.W.Y., with respective experiences of 11, 5, 7, and 9 years) independently reviewed the index tumors. These reviewers were blinded to clinical information and the diagnosis. The interval between the CT and MRI review sessions exceeded 6 months. The diagnosis of assessed FLL was automatically assigned as reviewers completed a questionnaire based on APASL, KLCA-NCC, and LI-RADS criteria (online Supplement Table S1). Manual adjustments were allowed only for the LR-category under LI-RADS. Reviewers were instructed to adjust LR categories solely based on documented imaging features, and only in specific cases where tie-breaking rules applied, such as in the evaluation of certain high-flow hemangiomas or focal nodular hyperplasia [8]. Additionally, the reviewers independently assessed the presence of liver cirrhosis based on imaging features during the MRI review. Cirrhosis was defined based on the consensus of at least three reviewers when histologic results of the liver parenchyma were unavailable.

Reference Standard

All malignant FLLs were histologically confirmed within 90 days following gadoxetic acid-enhanced MRI. Benign FLLs were diagnosed either through histology or by characteristic imaging features, along with stable or decreased size on follow-up imaging over a period of 2 years. The presence of cirrhosis was determined using histology when available; otherwise, results from imaging reviews were utilized [8].

Statistical Analysis

Data were presented as mean ± standard deviation (SD) or median (interquartile range, IQR). The pooled sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of three guidelines were estimated using four readers' review data and evaluated using generalized estimating equations (GEE) with a binomial distribution and logit link function to account for correlations between multiple observations within patients. An independent working correlation matrix was utilized for the GEE. The incremental value of sequential CT and MRI examinations was assessed for each guideline when the initial diagnostic test did not yield a "HCC" or "definite HCC/LR-5" classification. Interobserver agreement for nonrim APHE, non-peripheral washout, enhancing capsule, hypointensity on transitional phase, and HBP was assessed using the Fleiss kappa scale (<0.2, slight agreement; 0.21–0.4, fair agreement; 0.41–0.6, moderate agreement; 0.61–0.8, substantial agreement; 0.81–1.0, almost perfect agreement) [9].

All statistical analyses were conducted using SPSS (ver. 27, IBM), SAS 9.4 (SAS Institute Inc.). The overall test revealed a significant difference ($p < 0.05$), and a pairwise comparison was applied. Multiple comparisons between the guidelines were corrected by the Benjamini-Hochberg method using the false discovery rate (FDR) [10]. An FDR-adjusted p value <0.05 was regarded as statistically significant.

Results

Among the 42,726 patients from 11 institutions who underwent gadoxetic acid–enhanced MRI, 1,455 patients (median age, 59 years [IQR: 53–66]; male, 1,101) with 1,590 FLLs (median size, 22.6 mm [IQR: 17.5–44.8 mm]) met the eligibility criteria and were included in the study (Fig. 1). Approximately 72.9% (1,159/1,590) of the FLLs were diagnosed as HCC. Benign FLLs (n = 237) were diagnosed either histologically (n = 131) or clinically (n = 106). Of these, 33.5% (532/1,590) were small FLLs (<20 mm) with a median size of 15.2 mm (IQR: 12.8, 17.6 mm). The median interval between MRI and pathology confirmation was 13 days (IQR: 5–27 days), and the median interval between CT and MRI was 11 days (IQR: 5–21 days). Detailed information is provided in Table 1 and online supplement.

Comparison between Guidelines on Contrast-Enhanced CT

On CT, APASL had the highest sensitivity (78.9%) followed by LI-RADS and KLCA (74.7% and 73.7%, respectively, p = 0.002 for all) (Table 2 and S2, Fig. 2). APASL had the lowest specificity (71.1%, p = 0.002) while LI-RADS and KLCA-NCC did not show a difference in specificity (84.6% and 84.9%, respectively, p = 0.495). In small (<20 mm) FLLs, APASL also showed higher sensitivity than the other two guidelines (66.2% [95% CI: 61.9%, 72.0%], p = 0.002 for both), while its specificity was lowest (82.6% [95% CI: 77.9%, 86.4%], p = 0.002 for both) (online suppl. Tables S3 and S4).

Comparison of Diagnostic Performance between CT and Gadoxetic Acid-Enhanced MRI according to Guidelines

In LI-RADS, sensitivity was lower with MRI than with CT: 70.6% for MRI and 74.7% for CT (p = 0.002), while specificity was higher with MRI than with CT (90.4% vs. 84.6% for LI-RADS, p = 0.002) (Table 3, Fig. 3). Accuracy was not different between CT and MRI for LI-RADS (p = 0.13). Using the APASL criteria, sensitivity increased from 78.9% with CT to 89.3% with MRI (p = 0.002), while specificity decreased from 71.1% with CT to 54.3% with MRI (p = 0.002). The diagnostic accuracy was higher with MRI: 76.8% with CT versus 79.8% with MRI (Table 3). KLCA-NCC also showed higher sensitivity with MRI (73.7% with CT vs. 78.7% with MRI, p = 0.002), without a difference in specificity (84.9% on both CT and MRI, p > 0.99) (Fig. 4). Higher accuracy was observed with MRI than with CT with the KLCA-NCC criteria (76.7% with CT vs. 80.4% with MRI, p = 0.002).

In small (<20 mm) FLLs, LI-RADS showed similar sensitivity with CT and MRI (64.2% with CT and 62.2% with MRI, p = 0.63), while specificity was higher with MRI than with CT (91.7% vs. 86.0, p = 0.002, Table S5). There was no significant difference between the accuracy of CT and MRI (72.3% for CT vs. 73.2% for MRI, p = 0.75) in LI-RADS. APASL had a higher sensitivity with MRI than with CT (86.8% vs. 66.2%, respectively, p = 0.003), while lower specificity was observed with

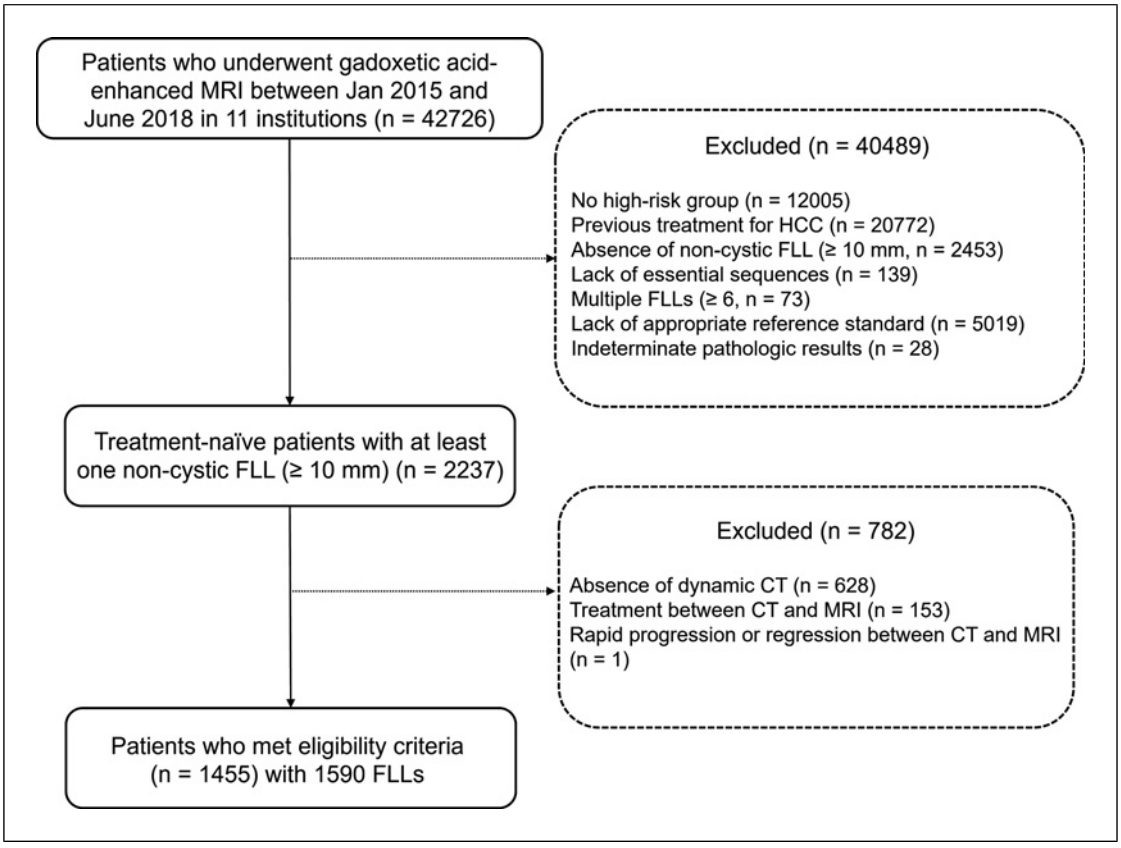

Fig. 1. Study flow. FLL, focal liver lesion, HCC, hepatocellular carcinoma.

MRI (76.0% vs. 82.6%, p = 0.02). KLCA-NCC showed higher sensitivity with MRI (80.4% with MRI vs. 63.9% with CT, p = 0.003), while similar specificity was observed between CT and MRI (86.1% with CT vs. 84.6% with MRI, p = 0.64). Accuracy increased with MRI versus CT (82.8% vs. 72.3%, p = 0.003) using the APASL criteria. Using the KLCA-NCC criteria, MRI also showed higher accuracy than CT (82.0% vs. 72.2%, p = 0.003).

Comparison of the Presence of Major Diagnostic Criteria between CT and MRI

The presence of nonrim APHE was observed in 72.5% of MRI (95% CI: 70.6%, 74.3%) and 72.4% of CT (95% CI: 70.4%, 74.2%) (p = 0.92) (Table 4). The presence of nonperipheral portal washout was observed in 63.3% of MRI (95% CI: 61.3%, 65.2%), while nonperipheral portal or delayed washout was observed in 70.3% of CT (95% CI: 68.5%, 72.0%) (p < 0.001). In FLLs ≥20 mm, an enhancing capsule was more frequently observed on CT than on MRI (47.5% [95% CI: 45.3%, 49.6%] vs. 44.6% [95% CI: 42.5%, 46.8%], p = 0.004) (Fig. 5).

Added Value of the Second-Line Examination for Non-HCC Observations

In the scenario of MRI following CT: Of non-LR-5 FLLs on CT (n = 2,631), 22.4% (590/2,631) were classified as LR-5 on MRI (Table 5). Of these, 89.5% (528/590) were HCCs, while 10.5% (62/590) non-HCCs were falsely diagnosed as LR-5. In APASL, 53.8% (1,185/2,201) of FLLs deemed "not HCC" on CT were re-categorized as "HCC" on MRI: 65.5% (776/1,185) of these re-categorized FLLs were HCCs while 34.5% (409/1,185) were falsely diagnosed as HCCs. Regarding KLCA-NCC, 32.2% (863/2,684) of FLLs that did not meet the criteria of "definite HCC" on CT were diagnosed as "definite HCC" on MRI; furthermore, 83.0% (716/863) of re-categorized FLLs were HCC, while 17.0% (147/863) were falsely diagnosed as "definite HCC" on MRI.

In cases where CT followed MRI: Among the non-LR-5 FLLs on MRI, 30.2% (882/2,923) were re-categorized as LR-5 on CT, consisting of 81.6% (720/882) HCCs and 18.4% (162/882) non-HCCs. In APASL, 29.0% (414/1,430) FLLs deemed "not HCC" on MRI were diagnosed

Table 1. Demographic characteristics of the patients

Variables	Values
Sex (male:female)	1,101:354
Age, years	59 (53, 66)
Male	58 (53, 66)[a]
Female	60 (53, 68)[a]
Underlying liver disease	
Chronic hepatitis B	1,136 (78.1)
Non-viral cirrhosis[b]	222 (15.3)
Chronic hepatitis C	79 (5.4)
Co-infection of hepatitis B and C viruses	11 (0.8)
Alcoholic and chronic hepatitis B	7 (0.5)
Child-Pugh classification	
Chronic liver disease	620 (42.6)
Class A	746 (51.3)
Class B	73 (5.0)
Class C	16 (1.1)
Diagnostic confirmation	
Hepatic resection	1,120 (77.0)
Biopsy	240 (16.5)
Clinical follow-up	95 (6.5)
FLLs per patient, *n*	
1	1,332 (91.5)
2	111 (7.6)
3	12 (0.8)
Size of FLLs, mm	
HCC (*n* = 1,159)	27.5 (18.7, 44.4)
Non-HCC malignancy (*n* = 194)	42.9 (23.1, 68.9)
Benign (*n* = 237)	16.1 (12.7, 23.8)

Values are presented as median (IQR) or number (percentage). FLL, focal liver lesion; HCC, hepatocellular carcinoma; PIVKA-II, protein induced by vitamin K absence-II. [a]No significant difference between male and female patients ($p = 0.08$). [b]Cryptogenic (*n* = 119), alcoholic (*n* = 53), metabolic dysfunction associated steatohepatitis (*n* = 35), biliary cirrhosis (*n* = 12), Wilson disease (*n* = 2), autoimmune hepatitis (*n* = 1).

Table 2. Comparison of the diagnostic performance of CT among diagnostic guidelines

Criteria	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Accuracy, %
LI-RADS	74.7 (3,463/4,636) [72.6, 76.7]	84.6 (1,458/1,724) [81.6, 87.1]	92.9 (3,463/3,729) [91.3, 94.1]	55.4 (1,458/2,631) [51.8, 58.9]	77.4 (4,921/6,360) [75.7, 79.0]
APASL	78.9 (3,660/4,636) [77.0, 80.8]	71.1 (1,225/1,724) [67.5, 74.4]	88.0 (3,660/4,159) [86.1, 89.6]	55.7 (1,225/2,201) [51.8, 59.4]	76.8 (4,885/6,360) [75.1, 78.4]
KLCA-NCC	73.7 (3,416/4,636) [71.6, 75.7]	84.9 (1,464/1,724) [82.0, 87.4]	92.9 (3,416/3,676) [91.4, 94.2]	54.5 (1,464/2,684) [51.0, 58.1]	76.7 (4,880/6,360) [75.0, 78.4]
p value	<0.001	<0.001	<0.001	<0.001	<0.001

Values in parentheses are numerators/denominators and those in brackets are 95% confidence intervals. A p value <0.05 indicates statistically significant differences among the guidelines. The false discovery rate adjusted p value of pairwise comparison is in Table S1. LI-RADS, Liver Imaging Reporting and Data System, APASL, Asian Pacific Association for the Study of the Liver, KLCA-NCC, Korean Liver Cancer Association-National Cancer Center, NPV, negative predictive value, PPV, positive predictive value.

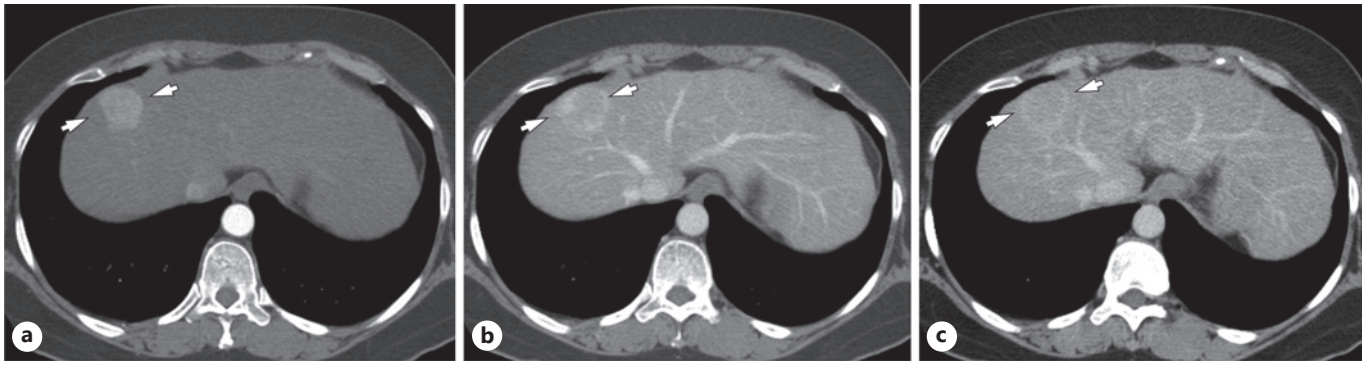

Fig. 2. A 58-year-old female patient with surgically confirmed hepatocellular carcinoma (HCC). A 36.3 mm mass in segment 4/8 shows nonrim arterial phase hyperenhancement (**a**, arrows), while no washout is observed in both the portal venous (**b**) and delayed phases (**c**). An enhancing capsule was observed on portal venous and delayed phases (arrows). The radiologic diagnosis is "definite HCC," "probable HCC," and "not HCC" according to LI-RADS, KLCA-NCC and APASL criteria, respectively. APASL, Asian Pacific Association for the Study of the Liver; KLCA-NCC, Korean Liver Cancer Association-National Cancer Center; LI-RADS, Liver Imaging Reporting and Data System.

Table 3. Comparison of diagnostic performance for hepatocellular carcinoma between CT and MRI with different guidelines

Criteria	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Accuracy, %
	MRI	MRI	MRI	MRI	MRI
LI-RADS	70.6 (3,271/4,636) [68.4, 72.6]	90.4 (1,558/1,724) [88.1, 92.3]	95.2 (3,271/3,437) [93.9, 96.2]	53.3 (1,558/292) [49.9, 56.7]	75.9 (4,829/6,360) [74.2, 77.6]
Difference[a]	−4.1 [−6.4, −1.9]	5.8 [3.4, 8.2]	2.3 [1.2, 3.4]	−2.1 [−4.3, 0.0]	−1.4 [−3.2, 0.3]
p value	0.002	0.002	0.002	0.07	0.13
APASL	89.3 (4,142/4,636) [87.7, 90.8]	54.3 (936/1,724) [50.0, 58.5]	84.0 (4,142/4,930) [81.9, 85.9]	65.5 (936/1,430) [60.8, 69.8]	79.8 (5,078/6,360) [78.0, 81.5]
Difference[a]	14.0 [8.3, 12.5]	−16.8 [−24.0, −13.1]	−4.0 [−5.2, −2.7]	9.8 [6.1, 13.5]	3.0 [1.1, 5.0]
p value	0.002	0.002	0.002	0.002	0.003
KLCA-NCC	78.7 (3,647/4,636) [76.7, 85.0]	84.9 (1,464/1,724) [82.1, 87.4]	93.3 (3,647/3,907) [91.9, 94.5]	59.7 (1,464/2,453) [56.1, 63.2]	80.4 (5,111/6,360) [78.8, 81.9]
Difference[a]	5.0 [2.8, 7.2]	0.0 [−2.8, 2.8]	0.4 [−0.8, 1.6]	5.1 [2.7, 7.5]	3.6 [1.9, 5.4]
p value	0.002	>0.99	0.54	0.002	0.002

Values in parentheses are numerators/denominators and those in brackets are 95% confidence intervals. [a]Difference between MRI and CT using the same diagnostic criteria. A false discovery rate adjusted *p* value <0.05 indicates statistically significant differences between MRI and CT. LI-RADS, Liver Imaging Reporting and Data System; APASL, Asian Pacific Association for the Study of the Liver; KLCA-NCC, Korean Liver Cancer Association-National Cancer Center; NPV, negative predictive value; PPV, positive predictive value.

as "HCC" on CT: 71.0% (294/414) of re-categorized FLLs were HCC. With KLCA-NCC guidelines, 25.8% (632/2,453) of FLLs that were not "definite HCC" on MRI were re-classified as "HCC" on CT. Among them, 76.7% (485/632) were HCCs.

Interobserver Agreement

The interobserver agreement for nonrim APHE was 0.653 (95% CI: 0.624, 0.683) and 0.607 (95% CI: 0.577, 0.637) for CT and MRI, respectively. Nonperipheral portal or delayed washout showed agreement of 0.524

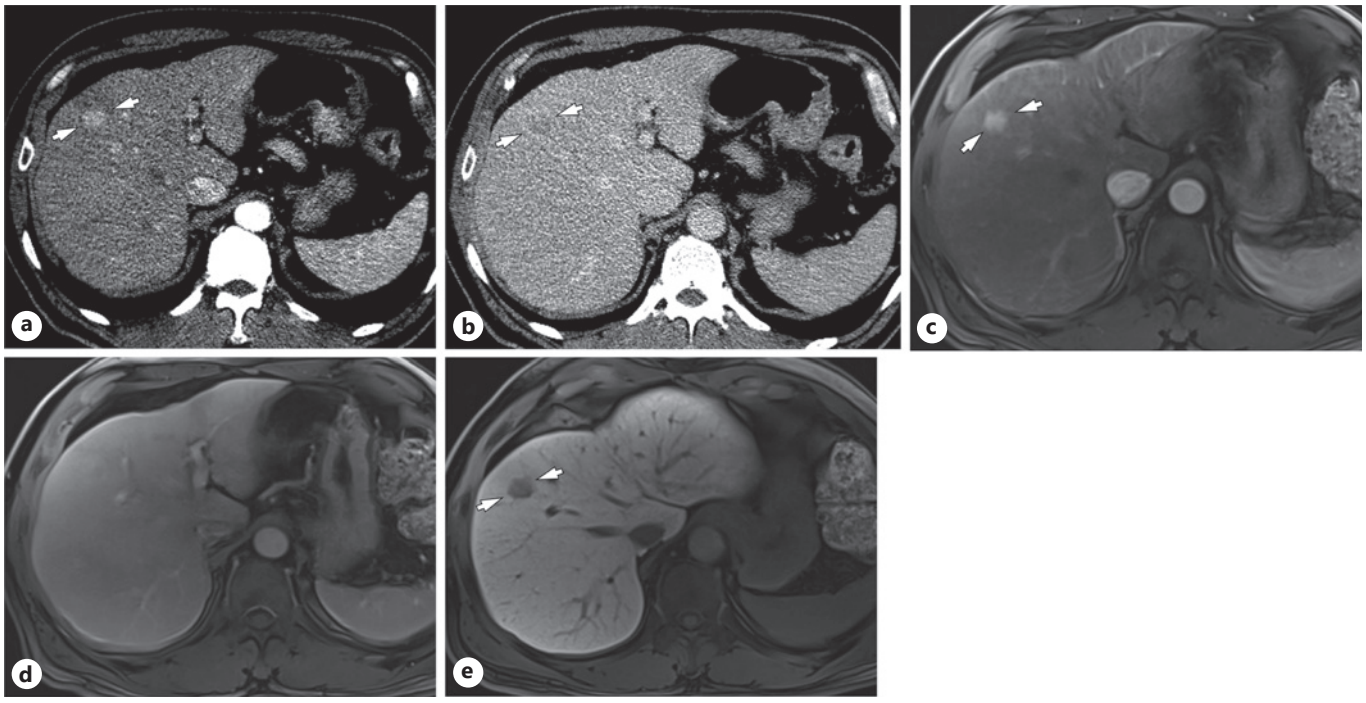

Fig. 3. A 53-year-old male patient with surgically confirmed hepatocellular carcinoma (HCC). A 14.9 mm nodule in segment 8 shows nonrim arterial phase hyperenhancement (APHE) in the arterial phase (**a**, arrows), no portal washout (not shown) and delayed nonperipheral washout (**b**, arrows) on CT. On gadoxetic acid-enhanced MRI, the nodule shows nonrim APHE (**c**, arrows), no portal washout (**d**), and nontargetoid defect on hepatobiliary phase (**e**). The radiologic diagnosis is "HCC" for APASL and "definite HCC" for KLCA-NCC and LI-RADS with CT. With MRI, the diagnosis is "HCC" for APASL, "definite HCC" for KLCA-NCC, and "probable HCC" for LI-RADS. APASL, Asian Pacific Association for the Study of the Liver; KLCA-NCC, Korean Liver Cancer Association-National Cancer Center; LI-RADS, Liver Imaging Reporting and Data System.

(95% CI: 0.495, 0.553) on CT, and nonperipheral portal washout had agreement of 0.564 (95% CI: 0.535, 0.592) on MRI. Interobserver agreement for enhancing capsule was 0.314 (95% CI: 0.284, 0.343) on CT and 0.347 (95% CI: 0.318, 0.376) on MRI. Nontargetoid transitional or hepatobiliary phase hypointensity had agreement of 0.654 (95% CI: 0.615, 0.693) and 0.735 (95%CI: 0.681, 0.790), respectively.

Discussion

Our study compared the diagnostic performance of three guidelines — LI-RADS, APASL, and KLCA-NCC — for diagnosing HCC using contrast-enhanced CT, and evaluated their performance against gadoxetic acid-enhanced MRI. Gadoxetic acid-enhanced MRI enhanced the diagnostic performance for the APASL and KLCA-NCC guidelines by increasing sensitivity. However, LI-RADS exhibited lower sensitivity but higher specificity on MRI compared to contrast-enhanced CT. Diagnostic accuracy improved under the APASL and KLCA-NCC criteria, while no significant difference was observed between CT and gadoxetic acid-enhanced MRI when using LI-RADS. In all FLLs, APASL demonstrated the highest sensitivity (78.9%) but the lowest specificity (71.1%) on CT, whereas the other guidelines showed similar specificities (84.6–84.9%). For small FLLs (<20 mm), sensitivities and specificities were comparable between LI-RADS and KLCA-NCC guidelines (63.9–64.2%, 86.0–86.1%), while APASL exhibited higher sensitivity and lower specificity compared to the others. These findings suggest that the performance of gadoxetic acid-enhanced MRI relative to CT varies depending on the diagnostic criteria applied.

Our study supports the recommendations of AASLD, the latest European Association for the Study of the Liver (EASL) and APASL regarding the use of imaging studies as outlined in each guideline. Although the sensitivity of gadoxetic acid-enhanced MRI was lower than that of CT in our study, the diagnostic accuracy of the two methods did not differ significantly when applying LI-RADS. The AASLD and EASL guidelines do not express a preference

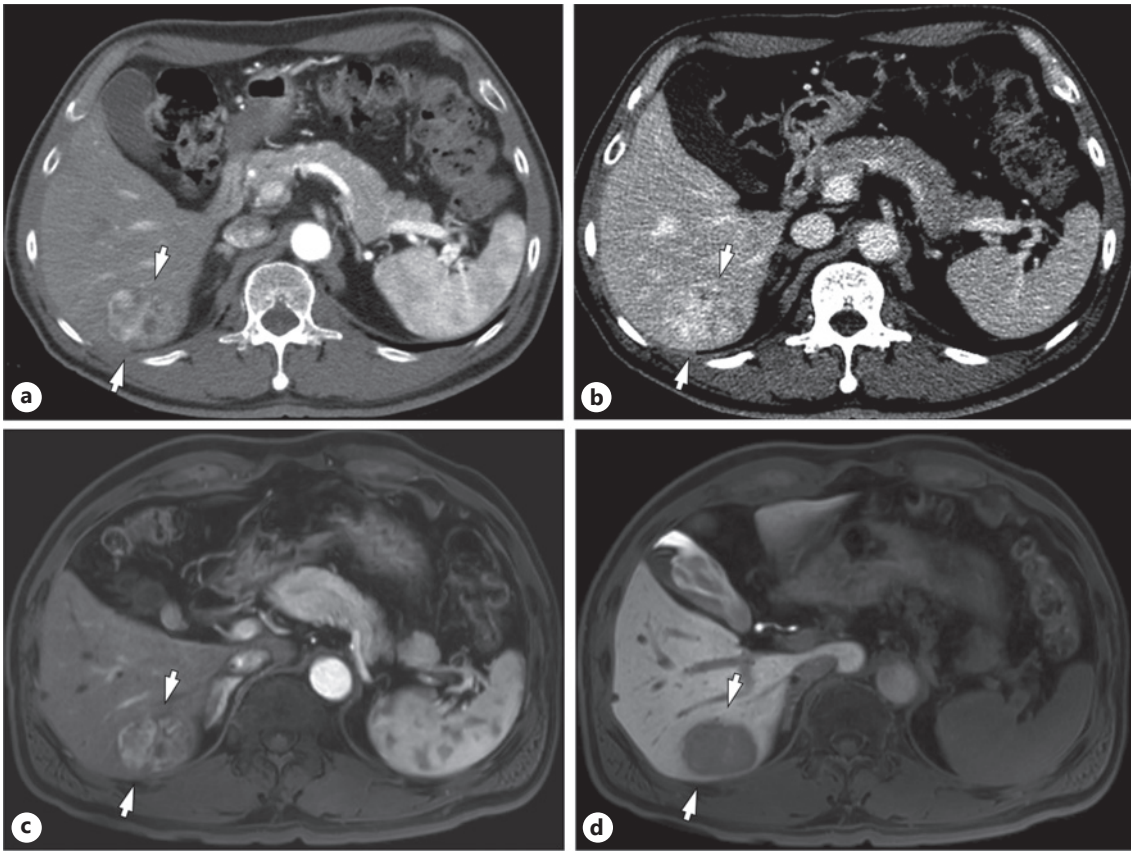

Fig. 4. A 57-year-old male patient with surgically diagnosed hepatocellular carcinoma (HCC). On CT, a 22.2 mm mass in segment 6 shows nonrim arterial hyperenhancement (APHE) in the arterial phase (**a**, arrows), while no washout is seen in the portal venous (not shown) and delayed phases (**b**, arrows). On gadoxetic acid-enhanced MRI, the mass presents nonrim APHE (**c**, arrows), absence of portal washout (not shown) and presence of nontargetoid hepatobiliary phase defect (**d**, arrows). On CT, neither APASL nor KLCA-NCC can make a definite diagnosis for HCC radiologically, while it is "HCC" for APASL and "definite HCC" for KLCA-NCC on MRI. APASL, Asian Pacific Association for the Study of the Liver; KLCA-NCC, Korean Liver Cancer Association-National Cancer Center.

Table 4. Comparison of the presence of major features between CT and MRI

Major features	Presence on CT, %	Presence on MRI, %	Difference	*p* value
Nonrim APHE	72.4 (4,603/6,360) [70.4, 74.2]	72.5 (4,608/6,360) [70.6, 74.3]	−0.1 [−1.6, 1.4]	0.92
Nonperipheral washout[a]	70.3 (4,470/6,360) [68.5, 72.0]	63.3 (4,023/6,360) [61.3, 65.2]	7.0 [5.4, 8.7]	<0.001
Enhancing capsule (≥20 mm)[b]	47.5 (2,009/4,232) [45.3, 49.6]	44.6 (1,889/4,232) [42.5, 46.8]	2.8 [0.9, 4.7]	0.004

Values in parentheses are numerators/denominators and those in brackets are 95% confidence intervals. *p* value <0.05 indicates statistically significant differences between MRI and CT. APHE, arterial phase hyperenhancement. [a]Nonperipheral washout on portal venous or delayed phase on CT; nonperipheral washout on portal venous phase on MRI. [b]Assessed only in focal liver lesions ≥ 20 mm.

for either CT or MRI, acknowledging only minor differences in accuracy and considering other factors such as cost, site expertise, and technical complexity [1, 11]. Conversely, APASL showed a significant increase in sensitivity with MRI, which translates to enhanced diagnostic accuracy compared to CT. This finding aligns with the APASL guidelines, which recommend the use of gadoxetic acid-enhanced MRI over CT in facilities that

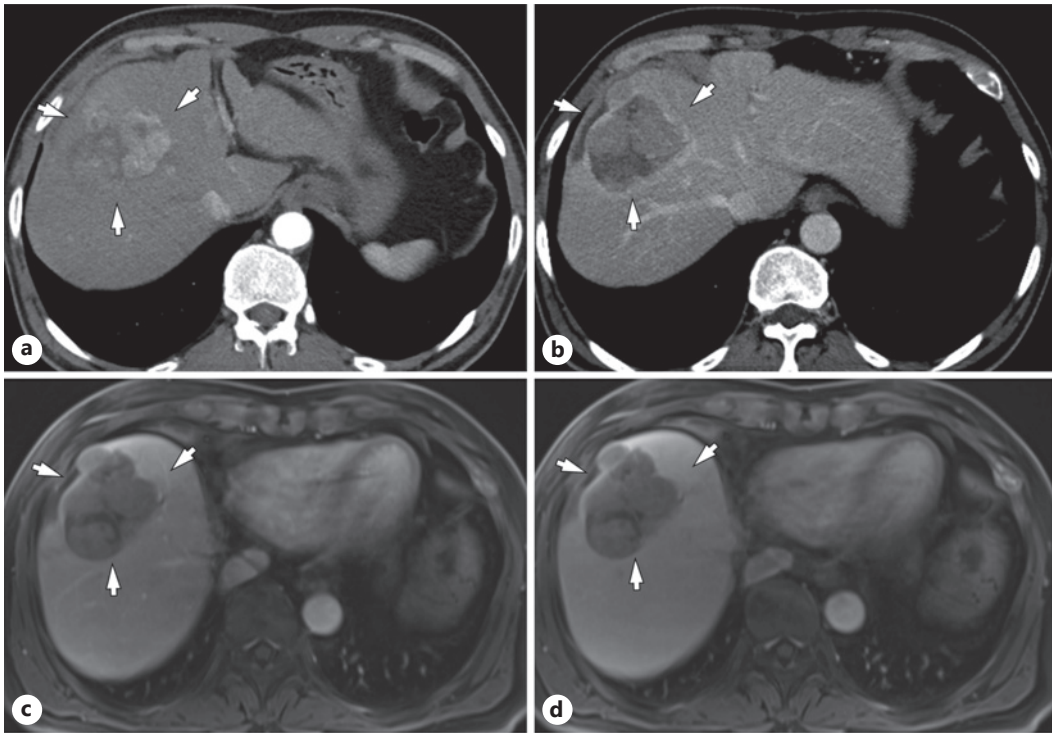

Fig. 5. A 61-year-old male patient with surgically confirmed hepatocellular carcinoma. On CT, 65.4 mm mass is in liver segment 4/8 with nonrim arterial phase hyperenhancement (APHE) (**a**, arrows). The mass shows nonperipheral washout and enhancing capsule in the delayed phase (**b**, arrows). On gadoxetic acid-enhanced MRI, the mass shows nonrim APHE (not shown), nonperipheral portal washout (**c**, arrows) and nontargetoid hypointensity on transitional phase (**d**, arrows). None of the reviewers perceived an enhancing capsule in a review session. On both CT and MRI, radiologic diagnosis is "HCC" for APASL, "definite HCC" for both KLCA-NCC and LI-RADS. APASL, Asian Pacific Association for the Study of the Liver; KLCA-NCC, Korean Liver Cancer Association-National Cancer Center.

Table 5. Changes in hepatocellular carcinoma diagnosis between CT and MRI in guidelines

Change of diagnosis between CT and MRI	LI-RADS	APASL	KLCA-NCC
"HCC" on both CT and MRI[a]	2,847 (44.8)	3,745 (58.9)	3,044 (47.9)
"Not HCC"[b] on CT but "HCC"[a] on MRI	590 (9.3)	1,185 (18.6)	863 (13.6)
"HCC"[a] on CT but "Not HCC"[b] on MRI	882 (13.9)	414 (6.5)	632 (9.9)
"Not HCC" on both CT and MRI[b]	2,041 (32.1)	1,016 (16.0)	1,821 (28.6)
Total	6,360 (100.0)	6,360 (100.0)	6,360 (100.0)

Values are number (percentage). APASL, Asian Pacific Association for the Study of the Liver; HCC, hepatocellular carcinoma, KLCA-NCC, Korean Liver Cancer Association-National Cancer Center; LI-RADS, Liver Imaging Reporting and Data System. [a]"LR-5" in LI-RADS, "HCC" in APASL and "definite HCC" in KLCA-NCC. [b]Non "LR-5" in LI-RADS, "Not HCC" in APASL and not "definite HCC" in KLCA-NCC.

have the necessary expertise [6]. Additionally, our results demonstrate higher sensitivity and accuracy with gadoxetic acid-enhanced MRI, supporting the APASL recommendation to use this method or contrast-enhanced ultrasound for FLLs that do not show APHE and washout on CT [6]. This also explains the preference for gadoxetic acid-enhanced MRI among physicians in Japan [12].

Our study results support the use of second-line examinations for FLLs that do not meet the noninvasive diagnostic criteria on first-line examination as outlined in all three guidelines. The incremental value of gadoxetic acid-enhanced MRI for inconclusive observations on CT varied depending on the guidelines: recategorization occurred in 22.4% of cases in LI-RADS, 32.2% in KLCA-NCC, and 53.8% in APASL. The PPV of recategorized observations was 89.5%, 83.0%, and 65.5%, respectively, which was related to the strictness of the diagnostic criteria on MRI in each guideline. CT also contributed to diagnosing HCCs for inconclusive observations on MRI, and the proportion of recategorized observations on CT was relatively consistent across guidelines: 30.2% in LI-RADS, 29.0% in APASL, and 25.8% in KLCA-NCC, with PPVs of 81.6%, 76.7%, and 71.0%, respectively. This consistency is likely related to the lower variation in diagnostic criteria between the guidelines with CT. Our study highlights the influence of different diagnostic criteria across guidelines on the value of second-line imaging for FLLs not meeting diagnostic criteria on first-line examinations, with varying incremental benefits of gadoxetic acid-enhanced MRI — emphasizing the need for guideline-specific approaches in selecting imaging modalities.

Of note, we observed that MRI showed lower sensitivity compared to CT while having higher specificity with LI-RADS. The lower sensitivity of gadoxetic acid-enhanced MRI compared to CT can be explained by two factors. The first is weak APHE, a known limitation of gadoxetic acid-enhanced MRI due to the small amount of administered contrast media and frequent transient motion during the arterial phase [13]. The second factor is the restriction of washout timing to the portal venous phase in LI-RADS. In our study, there was no difference in nonrim APHE between CT and gadoxetic acid-enhanced MRI. However, nonperipheral washout on portal or delayed phases was more pronounced on CT compared to portal nonperipheral washout on MRI. Therefore, the main reason for lower sensitivity in LI-RADS on MRI is likely the restriction of washout timing rather than weak APHE. Additionally, the presence of an enhancing capsule was more frequently observed on CT compared to MRI. It has been noted that the enhancing liver parenchyma may mask the enhancing capsule on gadoxetic acid-enhanced MRI [14]. Indeed, a study confirmed that the incidence of enhancing capsule was infrequent on gadoxetic acid-enhanced MRI compared with extracellular agent-enhanced MRI [15]. Therefore, if using the LI-RADS criteria, unless the washout timing is expanded to include the transitional phase or hepatobiliary phase, performing an additional gadoxetic acid-enhanced MRI after CT does not help improve diagnostic performance for identifying "definite HCC."

The lower sensitivity of LI-RADS on gadoxetic acid-enhanced MRI compared to CT in our study contrasts with previous findings. Several studies have indicated that MRI exhibits higher per-lesion sensitivity than CT, while maintaining similar specificity [2, 16–18]. This discrepancy may be due to the design of the meta-analyses in literature. Some did not involve direct head-to-head comparisons [18] did not differentiate between types of MRI contrast agents [17], included research conducted over extended periods using varying criteria for HCC diagnosis [16, 17], or did not specify the diagnostic criteria [2, 16]. Furthermore, there are discrepancies between meta-analyses: early meta-analyses reported that gadoxetic acid-enhanced MRI exhibited higher sensitivity than CT [2, 16], while a recent meta-analysis of studies using LI-RADS v2018 reported no significant differences in sensitivity and specificity between CT and gadoxetic acid-enhanced MRI for HCC diagnosis [18]. These discrepancies may be related to the inconsistent diagnostic criteria of the included studies [16] and/or the absence of a head-to-head comparison [18].

In a comparison of guidelines with CT, APASL demonstrated the highest sensitivity and the lowest specificity, a finding that aligns with the results from gadoxetic acid-enhanced MRI [8]. This can be attributed to the lack of LR-M features as exclusion criteria in APASL. Both LI-RADS and KLCA-NCC exhibited differences of approximately 1% in sensitivity, specificity, and accuracy with CT. Although the difference was minimal, KLCA-NCC showed slightly lower sensitivity and accuracy compared to LI-RADS. This discrepancy may be due to LI-RADS incorporating capsule appearance as a major feature, which is not considered in other guidelines. Our study findings indicate that KLCA-NCC and LI-RADS displayed similar sensitivity and specificity for small FLLs (<20 mm) with CT, supporting this hypothesis. It seems that FLLs ≥ 20 mm, which show capsule appearance but lack clear washout on CT, may have contributed to the observed performance differences among these three diagnostic criteria.

Our study had several limitations. First, there was an inevitable bias due to the retrospective nature of the study. We attempted to mitigate this by utilizing a large, multi-institutional dataset. Second, we did not employ the most recent KLCA-NCC guidelines (v2022). However, since the criteria for "definite HCC" remained consistent between v2018 and v2022, this would not have altered the study results. Third, we did not include clinically diagnosed malignancies, potentially introducing an incorporation

bias. Fourth, we included benign FLLs only if they demonstrated stability or decreased size over a 2-year follow-up period as this provided reasonable confirmation of their benign nature. While this strict criterion helped ensure diagnostic certainty, it may have led to the exclusion of some benign lesions that lacked adequate follow-up duration, potentially affecting HCC prevalence in study population. Lastly, the study population predominantly consisted of individuals with hepatitis B viral infection, which may not accurately represent the geographic variations in the etiology of underlying liver diseases.

In conclusion, the incremental value of gadoxetic acid-enhanced MRI following CT varies depending on the noninvasive diagnostic criteria applied. Limiting the evaluation of washout to the portal venous phase decreases the sensitivity of gadoxetic acid-enhanced MRI relative to CT.

Acknowledgments

We appreciate the statistical advice from the Medical Research Collaborating Center at Seoul National University Hospital and Seoul National University College of Medicine.

Statement of Ethics

This study was approved by the Institutional Review Board of all participating institutions. The first IRB approval was obtained on September 13, 2018 from Seoul National University Hospital (No.: H-1809-030-969) and then approved across all participating hospitals including, Samsung Medical Center, Korea University Guro Hospital, Seoul National University Bundang Hospital, Seoul St. Mary's Hospital, Korea University Anam Hospital, Severance Hospital, Konkuk University Hospital, Chung-Ang University Hospital, Kyung Hee University Hospital, Gangnam Severance Hospital. The institutional Review Boards waived the requirement of informed consent due to its retrospective study design.

Conflict of Interest Statement

Jeong Min Lee was a member of the journal's Editorial Board at the time of submission. J.H.Y. Consulting fees from AIRS Medical, Bayer; honoraria from Bayer, Guerbet, Philips Healthcare, Siemens Healthineers. W.C. No relevant relationships. Y.K.K. No relevant relationships. C.H.L. No relevant relationships. J.W.K. No relevant relationships. B.J.P. No relevant relationships. J.Y.C. No relevant relationships. S.K. No relevant relationships. H.S.P. No relevant relationships. E.S.L. Research grants from Biomedical Research Institute, Chung-Ang University Hospital, Canon Medical System; honoraria for lectures from the Korean Society of Radiology, Korean Association of Study for Intestinal Disease; support for meetings from Korean Society of Abdominal Radiology. J.S.Y. No relevant relationships. S.J.P. No relevant relationships. M.W.Y. No relevant relationships. M.J. No relevant relationships. J.I.C. Grants from Guerbet Korea, Samsung Medison; consulting fees from Bayer Korea; support for meetings from Bayer Korea. J.M.L. Grants from Bayer, Guerbet, Siemens Healthineers, Philips, GE HealthCare, CMS, Siemens Healthineers, Starmed, RF Medical; consulting fees from Bayer, Samsung Medison, Starmed; payment or honoraria for lectures from Bayer, Samsung Medison, Starmed, Philips Healthcare, GE HealthCare; associate editor for Liver Cancer.

Funding Sources

This work is financially supported by Bayer (grant No SNUH-1809-030-969). The funder had no role in the design, data collection, data analysis, and reporting of this study. The authors had complete control of the data and information submitted for publication at all times.

Author Contributions

All authors had access to the study data and had reviewed and approved the final manuscript. Study concept/design and Data interpretation: all authors. Data acquisition: Jeong Min Lee, Young Kon Kim, Chang Hee Lee, Won Chang, Joon-Il Choi, Beom Jin Park, Jin-Young Choi, Hee Sun Park, Eun Sun Lee, Jeong-Sik Yu, Seong Jin Park. Data analysis. Jeong Hee Yoon, Jeong Woo Kim, Seung-Seob Kim, Myung-Won You. Drafting of the manuscript: Jeong Hee Yoon, Won Chang. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: Myoung-jin Jang. Obtained funding: Jeong Min Lee. Study supervision: Jeong Min Lee, Joon-Il Choi.

Data Availability Statement

Individual patient data are not shared or made publicly available due to protections around the sharing of private health information in accordance with each institution's policies. The statistical analysis plan and results are available from the corresponding authors upon a reasonable request.

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