Liver Imaging Reporting and Data System with MR Imaging: Evaluation in Nodules 20 mm or Smaller Detected in Cirrhosis at Screening US[1]

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Purpose: To evaluate the diagnostic accuracy of the Liver Imaging Reporting and Data System (LI-RADS) with magnetic resonance (MR) imaging for hepatic nodules 20 mm or smaller detected during ultrasonographic (US) surveillance in patients with cirrhosis.

Materials and Methods: Between November 2003 and January 2010, patients with cirrhosis with a newly US-detected solitary hepatic nodule 20 mm or smaller were included in this institutional ethics committee–approved study. All patients provided written informed consent before the study; the need to obtain consent for reanalysis of the data was waived. Patients underwent MR imaging and fine-needle biopsy (the reference standard). Nodules without pathologic confirmation were followed up with MR imaging every 6 months. A LI-RADS category was retrospectively assigned to nodules seen at MR imaging. The diagnostic accuracy for each LI-RADS category was described by sensitivity, specificity, and positive and negative predictive values with 95% confidence intervals.

Results: Final diagnoses of 133 nodules in 159 patients were as follows: 102 hepatocellular carcinomas (HCCs), three intrahepatic cholangiocarcinomas (ICCs), one neuroendocrine metastasis, and 27 benign lesions (median MR imaging follow-up, 95 months). None (0%) of five LI-RADS category 1 lesions, three (25%) of 12 category 2 lesions, 29 (69%) of 42 category 3 lesions, 24 (96%) of 25 category 4 lesions, and 44 (98%) of 45 category 5 lesions were HCCs. One category 3 lesion was ICC, one category 5 lesion was a neuroendocrine metastasis, and two (50%) of four lesions categorized as other malignancies were HCCs. In patients with nodules detected at surveillance US, LI-RADS category 4 criteria were as effective as category 5 criteria for HCC diagnosis. Combining both categories would improve sensitivity without impairing specificity or positive or negative predictive value for HCC diagnosis (42.3%, 98.2%, 97.8%, and 47.4% vs 65.4%, 96.4%, 97.1%, and 59.6%, respectively).

Conclusion: In patients with cirrhosis with US-detected nodules 20 mm or smaller, both LI-RADS category 4 and category 5 have high specificity for HCC. In addition, a relevant proportion of lesions categorized as LI-RADS category 2 or 3 or as other malignancies were HCCs. Thus, active diagnostic work-up, including biopsy to allow prompt treatment, is recommended in such patients.

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Imaging techniques are key in the diagnosis and treatment of hepatocellular carcinoma (HCC) (1,2). Diagnosis can be established by using imaging in patients with chronic liver disease if a nodule measuring 10 mm or larger exhibits a specific vascular profile characterized by homogeneous contrast material uptake in the arterial phase followed by contrast material washout during venous phases (1). This enhancement pattern has been shown in Europe, North America, and Asia (3–7) to bear a specificity of almost 100% and has become the noninvasive criterion for HCC diagnosis of several scientific societies (8–16).

The application of these imaging criteria relies on experienced radiologists together with state-of-the-art hardware and software for computed tomography (CT) and magnetic resonance (MR) imaging and standardized dynamic contrast material–enhanced imaging protocols. Ideally, imaging methods and reporting should be based in a standardized language that reflects the relevant findings. This would allow a common interpretation of the data by any physician. This is relevant in the setting of liver transplantation, because the diagnosis of HCC constitutes the indication for liver transplantation and the assignment of Model for End-Stage Liver Disease, or MELD, exception points. Regrettably, the reporting is usually heterogeneous among centers, potentially leading to incorrect nodule diagnosis, as was observed years ago in a retrospective analysis of the United Network for Organ Sharing (UNOS) database. This showed a false HCC diagnosis in 21% of the patients given priority because of an HCC registration (17). At that time, a mere "vascular blush" granted priority, and it became obvious that more accurate diagnostic criteria and homogeneous image reporting were needed. Such efforts had been already in place at the European Association for the Study of the Liver (EASL) in 2001 (18) and the American Association for the Study of Liver Diseases (AASLD) in 2005 (19). In 2008, the Organ Procurement and Transplantation Network (OPTN)/UNOS organized a consensus conference to develop a new policy for enlistment and priority allocation for patients with HCC. The resulting document gave recommendations regarding the minimum technical specifications for hardware for CT and MR imaging units, dynamic contrast-enhanced liver imaging protocols, mandatory diagnostic criteria for HCC on images, reporting requirements, and requirement for interpretation of images at an OPTN-approved transplantation center (20).

In 2008, the American College of Radiology convened a committee of radiologists to develop a system for standardizing the performance, interpretation reporting, and data collection of CT and MR imaging examinations of the liver in patients at risk for HCC. Version 1.0 of the resulting Liver Imaging Reporting and Data System (LI-RADS) was released online in 2011 and was updated in 2013 (21). LI-RADS addresses the full spectrum of liver lesions and pseudolesions ranging from benign to malignant. LI-RADS is aimed at categorizing nodules as category 1 (definitely benign), category 2 (probably benign), category 3 (intermediate probability of HCC), category 4 (probably HCC), or category 5 (definitely HCC). Findings with a high probability of being malignancies other than HCC are categorized as "other malignancies" (21). Ultimately, the system aims to give a stratified probability

Advances in Knowledge

- Using the Liver Imaging Reporting and Data System (LI-RADS) to categorize liver nodules, we found that in patients with cirrhosis with newly detected nodules that were 20 mm or smaller at screening US, LI-RADS category 4 criteria are as effective as LI-RADS category 5 criteria in registering a nodule as hepatocellular carcinoma (HCC).
- Combining LI-RADS categories 4 and 5 would substantially improve diagnostic sensitivity without impairing the specificity or positive or negative predictive value for HCC diagnosis (42.3%, 98.2%, 97.8%, and 47.4% vs 65.4%, 96.4%, 97.1%, and 59.6%, respectively).
- A relevant number of LI-RADS category 3 nodules (29 [69%] of 42) previously detected at screening US were HCCs, particularly those larger than 15 mm, but none smaller than 10 mm.

Implications for Patient Care

- In patients with a nodule 20 mm or smaller detected at surveillance US, the registration of a LI-RADS category 4 profile has a near-absolute specificity for HCC diagnosis, and thus there is no need to stratify or benefit to stratifying lesions between LI-RADS category 4 and category 5.
- In this population, LI-RADS category 3 lesions require biopsy, given the presence of a high proportion of atypical HCC, particularly in lesions larger than 15 mm.

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Abbreviations:
AASLD = American Association for the Study of Liver Diseases
EASL = European Association for the Study of the Liver
EORTC = European Organisation for Research and Treatment of Cancer
HCC = hepatocellular carcinoma
LI-RADS = Liver Imaging Reporting and Data System
OPTN = Organ Procurement and Transplantation Network
UNOS = United Network for Organ Sharing
VIBE = volumetric interpolated breath-hold examination

Author contributions:
Guarantors of integrity of entire study, A.D., A.F., C.A., J.B.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, A.D., A.F., M.R., C.A., J.B.; clinical studies, A.D., A.F., J.R., M.R., A.G.C., C.A.; experimental studies, A.G.C., C.A.; statistical analysis, A.F.; and manuscript editing, A.D., A.F., J.R., M.R., C.A., J.B.

Conflicts of interest are listed at the end of this article.

of HCC so that clinicians can gauge the benefits and risks of proceeding to a more invasive work-up or simply following the lesions.

The development of LI-RADS was based on the expert opinions of radiologists, surgeons, hepatologists, and pathologists and the need for congruence with the OPTN/UNOS recommendations. So far, to our knowledge, no external validation of the LI-RADS in a prospective cohort of patients with a biopsy-proven diagnosis has been published to demonstrate its intended value.

The aim of this study was to evaluate the diagnostic accuracy of LI-RADS with MR imaging for hepatic nodules 20 mm or smaller detected during ultrasonographic (US) surveillance in patients with cirrhosis with high risk for developing HCC who were included in a prospective study that began in 2003 (3,22–24).

Figure 1

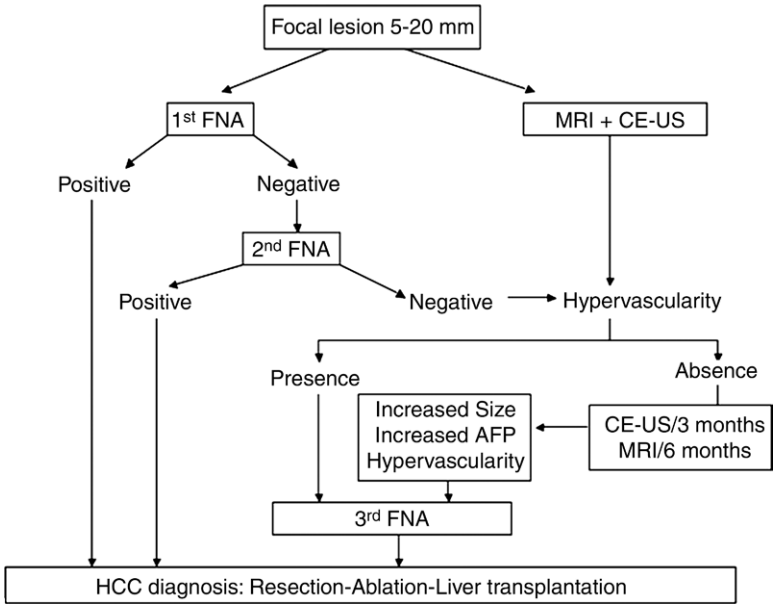

Figure 1: Diagnostic algorithm followed in the study. *AFP* = -fetoprotein, *CE-US* = contrast-enhanced US, *FNA* = fine-needle aspiration biopsy.

Materials and Methods

This study was approved by the Institutional Ethics Committee for Clinical Research of the Hospital Clinic of Barcelona. All patients provided written informed consent before enrollment in the study, and the need to obtain consent for reanalysis of the data was waived.

The study design and method have been described elsewhere (3,24) and are summarized in Figure 1. The study was initiated in November 2003, and the present assessment includes the patients recruited until January 2010 to ensure sufficient follow-up of patients with a nonmalignant diagnosis. Patients had Child-Pugh class A or B cirrhosis and no history of HCC but had a new solitary well-defined solid nodule between 5 and 20 mm that was detected at screening US. After we found that nodules smaller than 10 mm rarely correspond to a malignant nodule (3), the cutoff for further inclusion was set at 10 mm. Patients with contraindications to MR imaging or fine-needle biopsy were excluded. Data in part of the study population (n = 89) were previously reported to validate the noninvasive diagnostic criteria for HCC (3), and data in the whole population were used to show the limited value of the finding of intratumoral fat or peritumoral capsule to increase the diagnostic accuracy of MR imaging (24).

MR Imaging

MR imaging was performed in all patients with a 1.5-T unit (Symphony, Siemens Medical Systems, Erlangen, Germany; or Signa, GE Medical Systems, Milwaukee, Wis) by using a phased-array torso coil for signal detection. Gadodiamide 0.5 mmol/L (Omniscan; Amersham Health, Madrid, Spain) was used in all studies. The technical aspects of imaging acquisition are summarized in Appendix E1 (online).

Image Interpretation

The first MR imaging study performed within 1 month after detection of a nodule at US was interpreted by two radiologists who were experienced in imaging of the liver (C.A. and J.R., with 25 and 8 years of experience in abdominal radiology, respectively). Disagreements were solved by consensus. A third radiologist (A.D., with 15 years of experience in abdominal radiology) who was not involved in the prospective image interpretation assigned a LI-RADS category (21) to all hepatic nodules seen at the first MR imaging examination. LI-RADS categories are category 1 (definitely benign), category 2 (probably benign), category 3 (intermediate probability of HCC), category 4 (probably HCC), and category 5 (definitely HCC). On the basis of their largest diameter, LI-RADS category 4 or 5 findings smaller than 20 mm are designated as A, and category 4 or 5 findings 20 mm or larger are designated as B. Findings with a high probability of being malignancies other than HCC are categorized as "other malignancies." In addition, the nodules were categorized as conclusive for HCC according to AASLD and EASL–European Organisation for Research and Treatment of Cancer (EORTC) guidelines if they were larger than 10 mm and displayed a specific vascular profile (contrast agent uptake during the arterial phase and washout in venous phases) (10,11). This assignment was based on the previous registered data and on a review of the images. All radiologists were unaware

of the results of the biopsy and the outcome of the patients.

The analysis was performed by taking into account only the target lesion initially detected at screening US. The following items obtained at MR imaging were separately evaluated in each target lesion: the greatest diameter (in millimeters) and the signal intensity in each sequence and in each phase of the dynamic study after intravenous contrast agent injection. The lesions were compared in terms of signal intensity with the liver parenchyma and were categorically classified as hyperintense, isointense, or hypointense at visual inspection. The occurrences of contrast material uptake during the arterial phase and washout in venous phases were specifically registered. Presence of fatty change was considered when there was a conclusive decrease in signal intensity between in-phase and opposed-phase images on T1-weighted gradient-echo images. A pseudocapsule was defined as a peripheral thin hyperintense band of enhancement identified on venous or delayed phase images obtained after gadodiamide injection and/or a peripheral thin hypointense band seen on unenhanced T1- and T2-weighted images (25).

Table 1

Characteristics of 133 Patients with a Visible Nodule at MR Imaging

Characteristic	All Patients	Patients with HCC	Patients with Non-HCC Nodules	*P* Value
No. of patients	133	102	31	
Age (y)	64 (37–83)	65 (37–83)	59 (44–77)	.571
Male patients	62 (37–83)	61 (37–83)	62 (44–74)	.874
Female patients	67.5 (45–77)	70 (45–77)	58 (47–77)	.004
M/F ratio	81:52	67:35	14:17	.046
Cause of cirrhosis*				.887
Hepatitis C virus	95	75	20	
Ethanol abuse	21	14	7	
Hepatitis B virus	9	7	2	
Cryptogenic	5	4	1	
Primary biliary cirrhosis	1	1	0	
Other	2	1	1	
Child-Pugh class A cirrhosis/class B cirrhosis*	119/14	91/11	28/3	.301
AST level (U/L)	70.5 (19–322)	81 (19–212)	55 (22–322)	.065
ALT level (U/L)	64.5 (11–537)	69 (11–313)	46 (15–537)	.589
AP level (U/L)	225.5 (93–2113)	231 (95–1002)	196 (93–2113)	.800
GGT level (U/L)	75 (12–1241)	80 (12–1241)	65 (15–301)	.124
Prothrombin time ratio (%)	79 (35–100)	78 (35–100)	85 (57–97)	.044
Bilirubin level (mg/dL)	1 (0.3–4.1)	1.1 (0.1–4.1)	1 (0.3–4.1)	.771
Platelet count (10^9/L)	100 (31–306)	99 (32–301)	106 (31–306)	.390
Albumin level (g/dL)	40 (26–49)	39 (26–48)	42 (30–49)	.007
α-Fetoprotein level (ng/mL)	8 (1–1154)	11 (1–1154)	5 (1–163)	.057

Note.—Unless otherwise specified, data are medians, with ranges in parentheses. ALT = alanine aminotransferase, AP = alkaline phosphatase, AST = aspartate aminotransferase, GGT = γ-glutamyl transpeptidase. To convert bilirubin level to Système International units (micromoles per liter), multiply by 17.1.

* Data are numbers of patients.

Statistical Analysis

Comparison of patients with HCC nodules and patients with non-HCC nodules within LI-RADS category groups and according to tumor size was performed by using the Student *t* test or the Mann-Whitney test for continuous variables and the χ^2 test or Fisher exact test for categoric variables. $P < .05$ was considered to indicate a significant difference. The diagnostic accuracy for each LI-RADS category was described by sensitivity, specificity, and positive and negative predictive values expressed with 95% confidence intervals. Calculations were performed with SPSS, version 20 (IBM, Chicago, Ill).

Results

One hundred fifty-nine patients (93 men; median age, 63 years; range, 37–83 years) with a conclusive diagnosis were included (24). Twenty-six nodules were not detected at MR imaging: 24 corresponded to benign lesions, and the remaining two corresponded to 12- and 13-mm moderately differentiated HCCs diagnosed at biopsy. Accordingly, LI-RADS categories were determined in the 133 target nodules identified at the first MR imaging examination after US detection (83.6% of the whole cohort). Table 1 summarizes the main patient characteristics. The final diagnoses in the 133 patients were 102 HCCs (76.7%), three intrahepatic cholangiocarcinomas (2.3%), one metastasis of a poorly differentiated neuroendocrine tumor (0.8%), and 27 benign lesions (20.3%) that were followed for a median of 95 months (range, 58–122 months) with US every 3 months and MR imaging every 6 months for at least 2 years to assure the absence of malignancy.

A malignant diagnosis was confirmed at pathologic examination in all nodules but one. This nodule was classified as a necrotic nodule at the time of biopsy. It vanished during follow-up and was initially reported as benign (3,24). However, it reappeared in the same location after 4 years of follow-up and displayed the typical HCC profile. After an initial successful ablation procedure, the patient developed local progression with multifocal intrahepatic spread.

LI-RADS Categories

The LI-RADS categories of the nodules are summarized in Table 2. Five lesions (3.8%) were classified as LI-RADS category 1, 12 (9%) as category 2, 42 (31.6%) as category 3, 25 (18.8%) as

category 4, and 45 (33.8%) as category 5. Four lesions (3.0%) were categorized as other malignancies.

All lesions classified as LI-RADS category 1 were benign. Three (25%) of 12 lesions classified as category 2 were ultimately diagnosed as HCCs. These lesions had diameters of 9, 10, and 10 mm.

Twenty-nine (69%) of 42 lesions classified as LI-RADS category 3 were HCCs, and one 14-mm nodule was diagnosed as an intrahepatic cholangiocarcinoma. The main characteristics of LI-RADS category 3 lesions are summarized in Table 3. For the 29 nodules with a final diagnosis of HCC, the median time from the MR imaging examination to the final diagnosis was 41 days. The LI-RADS category 3 lesions ultimately diagnosed as HCCs were larger (median size, 14 mm [range, 10–19 mm] vs 12 mm [range, 5–15 mm]; $P < .0001$) than non-HCC nodules (Figs 2, 3). None of the four LI-RADS category 3 lesions that were smaller than 10 mm were ultimately diagnosed as HCCs, but all lesions larger than 15 mm ($n = 12$) were found to be HCCs. Twenty of the 29 HCC nodules showed arterial phase hyperenhancement without washout or pseudocapsule. The remaining nine HCC nodules were hypo- or isoenhancing in the arterial phase. None showed washout but two had a pseudocapsule.

Twenty-five lesions were classified as LI-RADS category 4, and all but one were HCCs. Twenty-one of the 25 category 4 lesions were LI-RADS category 4A, because they were smaller than 20 mm and displayed arterial phase hyperenhancement and washout (Fig 4). The remaining four lesions were LI-RADS category 4B (≥20 mm); three displayed arterial phase hyperenhancement without washout or capsule, and one showed hypoenhancement in the arterial phase with a capsule. One arterial phase hyperenhancing nodule of 20 mm that was categorized as a LI-RADS category 4B lesion but in which the biopsy results were negative for malignancy disappeared during the work-up and did not reappear during a 100-month follow-up. This nodule was categorized as benign.

Table 2

LI-RADS Categories of the 133 Target Lesions Identified at Baseline MR Imaging

LI-RADS Category	Total No. of Lesions	Final Diagnosis		
		HCC Lesions	Non-HCC Malignant Lesions	Benign Lesions
1	5	0	0	5 (100)
2	12	3 (25)	0	9 (75)
3	42	29 (69)	1 (2)	12 (29)
4*	25	24 (96)	0	1 (4)
4A	21	21	0	0
4B	4	3	0	1
5†	45	44 (98)	1 (2)	0
5A	35	34	1	0
5B	10	10	0	0
Other malignancies	4	2 (50)	2 (50)	0

Note.—Data in parentheses are percentages. The LI-RADS categories are correlated with final diagnosis.

* Two of the 21 LI-RADS category 4A lesions were < 10 mm, with arterial phase hyperenhancement and washout. All were HCCs. The remaining 19 category 4A lesions were 10–19 mm, with arterial phase hyperenhancement and washout. All were HCCs. One of the four LI-RADS category 4B lesions was ≥ 20 mm, with arterial phase hypoenhancement and a capsule. It was an HCC. The remaining three category 4B lesions were ≥ 20 mm, with arterial phase hyperenhancement but no washout or capsule. Two of these lesions were HCCs and one was a benign nodule.

† The 35 LI-RADS category 5A lesions were 10–19 mm, with arterial phase hyperenhancement with washout and a capsule. Thirty-four of the lesions proved to be HCC, and one was a metastasis from a poorly differentiated neuroendocrine tumor. Seven of the 10 LI-RADS category 5B lesions were ≥ 20 mm, with arterial phase hyperenhancement, washout, and a capsule. All were HCCs. Of the three other category 5B lesions, one was ≥ 20 mm, with arterial phase hyperenhancement and washout. It was an HCC. The remaining two lesions were ≥ 20 mm, with arterial phase hyperenhancement and a capsule. Both were HCCs.

Table 3

MR Imaging Features of Lesions Classified as LI-RADS Category 3

Feature	All Nodules ($n = 42$)	HCCs ($n = 29$)	Non-HCC Nodules ($n = 13$)
Size (mm)*			
<10	4 (10)	0	4 (31)
10–15	26 (62)	17 (59)	9 (69)
16–20	12 (29)	12 (41)	0
Arterial phase hyperenhancement	32 (76)	20 (69)	12 (92)
Washout	0	0	0
Capsule	2 (5)	2 (7)	0
Intralesional fat	3 (7)	2 (7)	1 (8)

Note.—Data in parentheses are percentages. Percentages may not add up to 100% because of rounding.

* $P < .0001$.

Forty-five lesions were classified as LI-RADS category 5 lesions, and all but one were HCCs. Thirty-five LI-RADS category 5 lesions were category 5A (<20 mm with arterial phase hyperenhancement, washout, and capsule). The only false-positive result corresponded to an 18-mm hepatic metastasis from a poorly differentiated neuroendocrine tumor. Ten LI-RADS category 5 lesions were category 5B (≥20 mm at MR imaging); seven had arterial phase hyperenhancement, washout, and capsule; one had arterial phase hyperenhancement and washout; and two had arterial phase hyperenhancement and capsule. All 10 were HCCs.

Figure 2

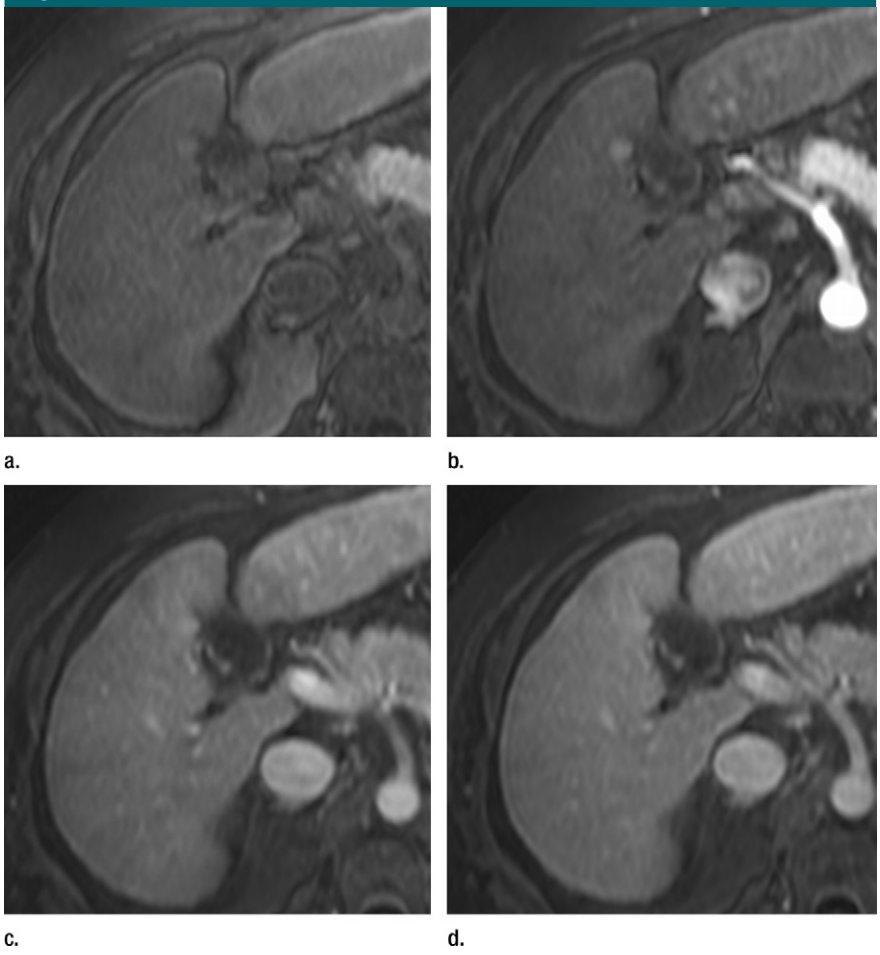

Figure 2: **(a–d)** Axial fat-suppressed T1-weighted volumetric interpolated breath-hold examination (VIBE) MR images of the liver obtained in 50-year-old woman with alcoholic cirrhosis (**a**) before and (**b–d**) after contrast agent administration in the (**b**) arterial, (**c**) portal venous, and (**d**) delayed phases. There is a 10-mm nodule in segment V adjacent to the gallbladder that is slightly hyperintense on **a** and shows arterial phase hyperenhancement on **b** without washout or pseudocapsule on **c** and **d**. A LI-RADS category of 3 was assigned. This nodule corresponds to a regenerative nodule that has remained stable for 83 months as of this writing.

The four lesions classified as other malignancies were two intrahepatic cholangiocarcinomas and two HCCs that displayed atypical findings.

Diagnostic Accuracy of LI-RADS for HCC Diagnosis

The diagnostic accuracies for HCC diagnosis of the LI-RADS proposal are summarized in Table 4. Considering only those lesions classified as LI-RADS category 5, the LI-RADS proposal yielded sensitivity, specificity, and positive and negative predictive values of 42.3%, 98.2%, 97.8%, and 47.4%, respectively, for confident HCC diagnosis in nodules detected during US surveillance in cirrhosis. Considering LI-RADS categories 4 and 5 together as definitive for HCC, the sensitivity, specificity, and positive and negative predictive values were 65.4%, 96.4%, 97.1%, and 59.6%, respectively.

Relationship between LI-RADS Category 4 and 5 Lesions and AASLD/EASL Criteria

As per the LI-RADS definitions, the majority of nodules classified as LI-RADS category 4 (21 of 25), as well as most LI-RADS category 5 lesions (43 of 45), did exhibit the specific arterial phase hyperenhancement and washout that is the core profile of the AASLD and EASL criteria (10,11). Their application in nodules 10 mm or larger to diagnose HCC in our series (their LI-RADS category would correspond to LI-RADS category 4A [n = 19] or LI-RADS category 5A [n = 35] in nodules < 20 mm and to LI-RADS category 5B in nodules ⩾ 20 mm [n = 8]), yielded sensitivity, specificity, and positive and negative predictive values of 58.6%, 98.2%, 98.4%, and 55.7%, respectively.

A total of seven lesions that did not meet AASLD criteria but were categorized as LI-RADS category 4 or 5 were ultimately diagnosed as HCC. Two lesions of 9 mm each (smaller than the 10-mm cutoff) displayed arterial contrast material uptake and washout, being categorized as LI-RADS category 4A. Two lesions of 27 and 21 mm displayed arterial contrast material uptake without washout or capsule and were classified as LI-RADS category 4B lesions. One lesion of 20 mm was hypoenhancing but showed a capsule and thus was classified as LI-RADS category 4B. Finally, two 20-mm lesions displayed arterial contrast material uptake and pseudocapsule, without washout, and were classified as LI-RADS category 5B.

Discussion

Our results show that in patients with a nodule 20 mm or smaller detected at surveillance US, the findings that correspond to LI-RADS category 4 at MR imaging have a specificity of 98.2%. Thus, there is no need to distinguish or benefit to distinguishing between LI-RADS category 4 and category 5. Considering only LI-RADS category 5 as conclusive for HCC diagnosis, the current LI-RADS proposal would miss a relevant number of HCCs that otherwise would be confidently diagnosed by using the AASLD criteria (10). Indeed, if both LI-RADS category 4 and category 5 are combined as definitely indicating HCC, the specificity is maintained but the sensitivity is substantially increased, to 65%.

Figure 3

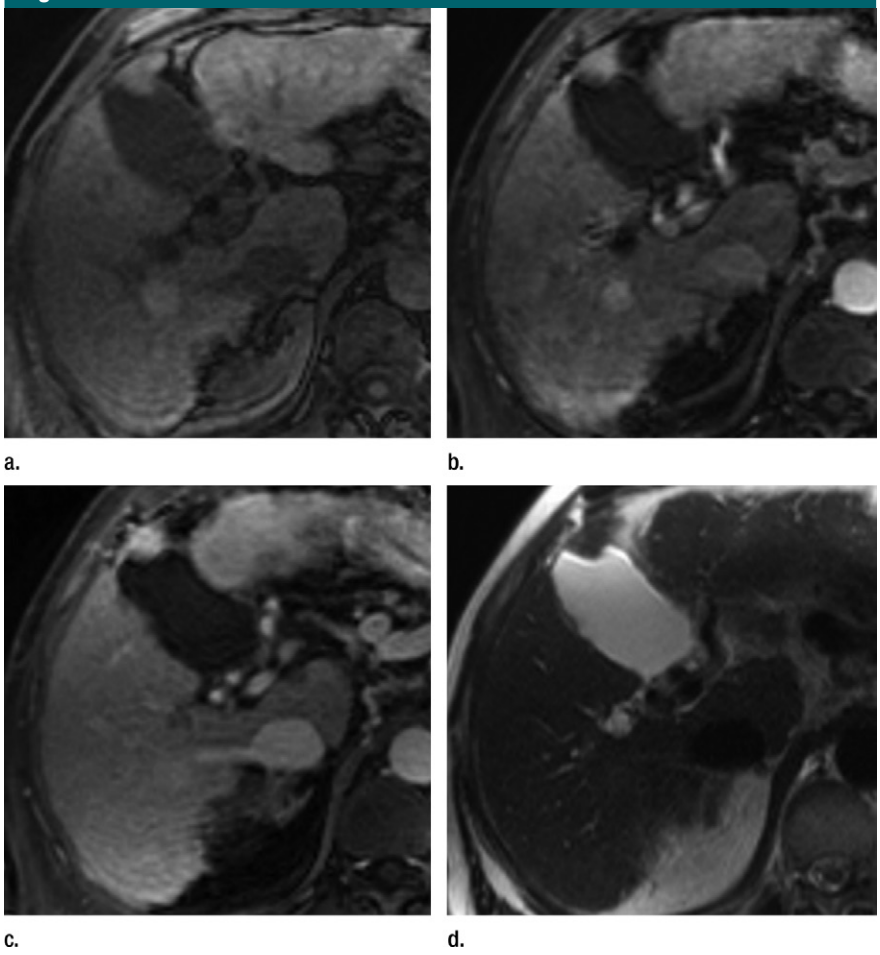

Figure 3: **(a–c)** Axial fat-suppressed T1-weighted VIBE MR images of the liver obtained in 72-year-old man with cirrhosis caused by chronic hepatitis C virus infection (**a**) before and (**b, c**) after contrast material administration in the (**b**) arterial and (**c**) portal venous phases. **(d)** Axial T2-weighted half-Fourier rapid acquisition with relaxation enhancement MR image. There is a 17-mm nodule in segment VI adjacent to the gallbladder that is slightly hyperintense on **a** and shows arterial phase hyperenhancement on **b** without washout or pseudocapsule on **c**; the nodule is not seen on **d**. A LI-RADS category of 3 was assigned. Fine-needle biopsy revealed a well-differentiated HCC.

It may be argued that our population, as well as that in other studies (4–6), includes patients in whom a prior US examination has revealed a nodule, and this is a setting that differs from a setting in which such a prior finding would not be in place. A previous US observation of the nodule would increase the pretest probability and prime a higher positive predictive value, but should not affect specificity. In any case, our results endorse the proposal to consider as a LI-RADS category 5 lesion a US-detected nodule that shows arterial phase hyperenhancement and washout at CT or MR imaging. This is the most recent modification introduced in LI-RADS in 2014 (26), as documented in a recent publication in which one the authors of our study (J.B.) was part of the advisory board for the last LI-RADS version, which incorporates the existence of a prior positive US result to grade LI-RADS category 4 nodules as conclusive for HCC (27). Future studies will be needed to assess if nodules with the same pattern in patients at risk, but in whom US is not available (or does not depict a nodule), would be able or not to be confidently diagnosed as HCC. If a dynamic pattern is specific, it is unlikely to have a lower diagnostic accuracy depending on the availability of US prior to MR imaging.

The attempt to achieve congruency between LI-RADS and OPTN/UNOS classification, where the diagnostic criteria were intentionally not optimized to achieve maximum sensitivity for HCC detection but rather attempted to increase the specificity of HCC diagnosis, explains the low sensitivity for LI-RADS category 5 even if it includes additional parameters other than those related to contrast material dynamics. The presence of peritumoral capsule, moderate hyperintensity at T2-weighted imaging, intralesional fat, or delayed hypointensity may favor malignancy (28–30). However, as we have previously demonstrated (24), these additional parameters do not significantly increase diagnostic accuracy. The presence of pseudocapsule has been described in hepatic adenoma (31) and metastasis (32), and thus, these lesions could be classified as LI-RADS category 5 lesions. Similarly, growth of a lesion is not specific for HCC, as this can be seen in other malignancies as well.

Interestingly, we observed a clinically relevant number of HCCs among LI-RADS category 2 lesions (three of 12). The sample size of this category was small, and larger studies should further explore this scenario. LI-RADS categorizes these lesions as probably benign and does not recommend additional studies except continuing routine surveillance (21). This recommendation is in conflict with most scientific guidelines dealing with HCC diagnosis (10–15,33,34). Even if additional studies would reduce the risk of HCC to around 5%–10% in LI-RADS category 2 nodules, this should not be neglected. In that sense, the Breast Imaging Reporting and Data System for breast cancer screening recommends active diagnostic work-up when the likelihood of cancer is 2%. Thus, even a 5%–10% risk would be a clinical concern and would likely merit further evaluation. Our finding of 25% HCCs in LI-RADS

Figure 4

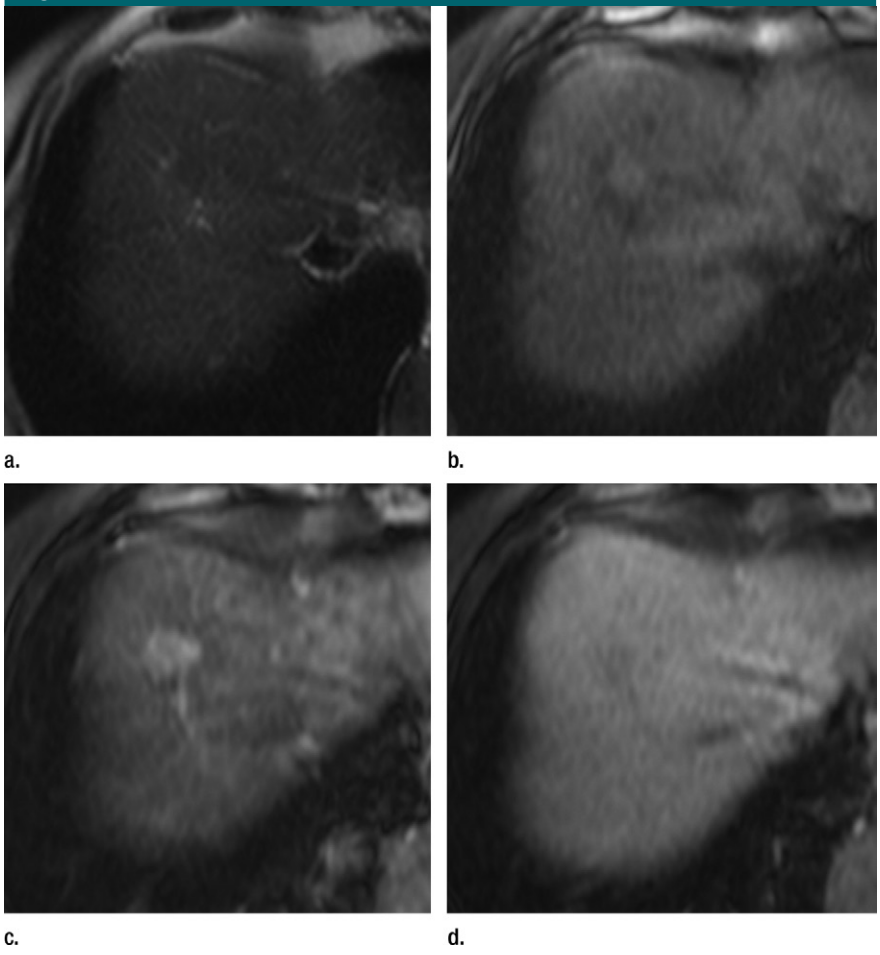

Figure 4: **(a–d)** Axial MR images in 76-year-old man with cirrhosis caused by chronic hepatitis C virus infection. **(a)** T2-weighted half-Fourier rapid acquisition with relaxation enhancement image. **(b–d)** Fat-suppressed T1-weighted VIBE images of the liver (**b**) before and (**c, d**) after contrast agent administration in the (**c**) arterial and (**d**) delayed venous phases. There is an 18-mm nodule in segment VIII that is slightly hypointense on **a** and is hyperintense on **b**. The nodule shows arterial phase hyperenhancement on **c**, with washout on **d**. A LI-RADS category of 4A was assigned. Fine-needle biopsy revealed a well-differentiated HCC.

category 2 lesions is of concern, but it should be kept in mind that our population was patients with cirrhosis undergoing US surveillance, and the sample size of this category was small.

This HCC likelihood is even more relevant for LI-RADS category 3 lesions. This category involved almost one-third of our cohort, and 69% of these lesions corresponded to HCC. While this is a very high proportion of HCC, other authors (4,6) have reported a similar incidence in these patients. Nevertheless, the high proportion of HCC in LI-RADS category 3 lesions is different from that in a recent retrospective study (35), where only four (6%) of the 69 lesions were categorized as probable or definitive HCCs after 1 year of follow-up. The retrospective design of that study is at risk for a selection bias that would explain the unexpected low rate of malignant disease. In addition, it did not use biopsy as the reference standard, and this implies a risk of underdiagnosis. Finally, that study did not use conventional gadolinium contrast agent but rather gadoxetic acid. In that regard, LI-RADS, version 2103.1, which we used to categorize lesions, applies only to CT and MR imaging performed with extracellular contrast agents.

In our series, only three lesions smaller than 10 mm (two 9-mm nodules classified as LI-RADS category 4A and one 9-mm nodule classified as LI-RADS category 2) were ultimately diagnosed as HCCs. This finding reinforces the AASLD and EASL-EORTC guidelines recommendation not to engage into further examinations on detection of a nodule smaller than 10 mm except close follow-up with US (10,11). None of the four LI-RADS category 3 nodules smaller than 10 mm were ultimately diagnosed as HCC. By contrast, all LI-RADS category 3 lesions larger than 15 mm were ultimately diagnosed as HCC. Thus, the current 20-mm cutoff to define probabilities may be inaccurate and may constitute a limitation of the LI-RADS proposal as currently defined. Probably the cutoff should be better set at 10 mm if LI-RADS aims to deliver information about HCC probability according to profile. Because of this high probability that a new lesion detected in patients with cirrhosis that is classified as a LI-RADS category 3 lesion corresponds to an HCC, an active diagnostic work-up should be strongly recommended if we are intending to diagnose and treat the HCC at a very early stage.

Our study had limitations. Prospective findings were recorded after consensus interpretation by two experienced radiologists. This somewhat limits generalizability. LI-RADS categories were assigned by one radiologist, and very recently other authors have shown a substantial variation in liver observation reporting by both experts and novices when standardized reporting schema are used (36). As previously mentioned, the LI-RADS categorization system is still being modified. These changes will have to incorporate the findings of robust, prospective investigations. Obviously, recommendations for a standardized technique for image acquisition and reporting will be helpful both in practice and in research. However, successful incorporation of any

Table 4

Summary of Diagnostic Accuracies for Confident HCC Diagnosis in Nodules Detected during US Surveillance in Patients with Cirrhosis

	No. of Nodules				Diagnostic Performance (%)			
Diagnostic Criteria	TP	FN	FP	TN	Sensitivity	Specificity	PPV	NPV
LI-RADS category 5	44	60	1	54	42.3 (33.3, 51.9)	98.2 (90.4, 99.7)	97.8 (88.4, 99.6)	47.4 (38.4, 56.5)
LI-RADS category 4 and 5	68	36	2	53	65.4 (55.8, 73.8)	96.4 (87.7, 99)	97.1 (90.2, 99.2)	59.6 (49.2, 69.1)
AASLD criteria*	61	43	1	54	58.6 (48.6, 67.3)	98.2 (90.4, 99.7)	98.4 (91.4, 99.7)	55.7 (45.8, 65.1)

Note.—Data in parentheses are 95% confidence intervals. FN = false-negative, FP = false-positive, NPV = negative predictive value, PPV = positive predictive value, TN = true-negative, TP = true-positive.

* Nodules ≥ 10 mm that displayed the specific vascular pattern of contrast agent uptake during the arterial phase followed by contrast agent washout during the venous phases.

proposal in clinical practice will happen only if it provides useful information for decision making.

In conclusion, if US screening in high-risk patients with cirrhosis shows a new lesion that is larger than 10 mm, a categorization of LI-RADS 4 or 5 at subsequent MR imaging is highly specific for HCC, and thus, in this specific population, there is no need to distinguish between LI-RADS category 4 and category 5. In addition, a relevant proportion of these newly detected nodules at screening US classified as LI-RADS category 3 lesions are HCCs, justifying an active diagnostic work-up, including biopsy. However, prospective studies are still needed to validate our findings.

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