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Hepatocellular Carcinoma: Diagnostic Performance of Multidetector CT and MR Imaging—A Systematic Review and Meta-Analysis[1]

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Purpose: To perform a systematic review and meta-analysis of the diagnostic performance of computed tomography (CT) and magnetic resonance (MR) imaging as noninvasive modalities for evaluating hepatocellular carcinoma (HCC) in patients with chronic liver disease.

Materials and Methods: A search of the MEDLINE, EMBASE, and Cochrane Library databases was performed to identify studies providing per-patient or per-lesion diagnostic accuracies of multidetector CT and MR imaging for HCCs in patients with chronic liver disease. Studies published from January 2000 to December 2012 that used a reference standard based on histopathologic findings and/or findings at follow-up were included. Summary estimates of diagnostic accuracy were obtained by using a random-effects model with further exploration with meta-regression and subgroup analyses.

Results: Forty studies (six on multidetector CT, 22 on MR imaging, and 12 on both CT and MR imaging) were included. The studies evaluated a total of 1135 patients with multidetector CT and 2489 patients with MR imaging. The overall per-patient sensitivity of MR imaging was 88% (95% confidence interval [CI]: 83%, 92%), with a specificity of 94% (95% CI: 85%, 98%). The overall per-lesion sensitivity of MR imaging was higher than that of multidetector CT when the paired data of the 11 available studies were pooled (80% vs 68%, $P = .0023$). Gadoxetic acid–enhanced MR imaging showed significantly higher per-lesion sensitivity than MR imaging performed with other contrast agents (87% vs 74%, $P = .03$). Per-lesion sensitivity was significantly lower for HCCs smaller than 1 cm than that for HCCs 1 cm or larger ($P < .001$ for CT, $P = .02$ for MR imaging) and for those in explanted livers ($P = .04$ for CT, $P < .001$ for MR imaging).

Conclusion: MR imaging showed higher per-lesion sensitivity than multidetector CT and should be the preferred imaging modality for the diagnosis of HCCs in patients with chronic liver disease.

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Online supplemental material is available for this article.

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Received April 1, 2014; revision requested May 19; revision received September 13; final version accepted October 8. Supported in part by a grant from Bayer Healthcare, Korea and Seoul National University Bundang Hospital Research Fund, Korea (grant no. 02-2013-098). **Address correspondence to** J.M.L. (e-mail: *jmsh@snu.ac.kr*).

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Hepatocellular carcinoma (HCC) is the most common primary hepatic neoplasm and the third most frequent cause of cancer death worldwide (1,2), developing mostly (70%–90%) within a background of chronic liver disease (3). The 5-year cumulative incidence of HCC has been shown to range from 8% to 30% in patients with cirrhosis (4), and, when HCC is diagnosed after the onset of symptoms, it has been associated with a poor prognosis (5-year survival, <10%) (5). However, patient prognosis has been reported to improve to a 5-year survival rate of higher than 50% if the HCC can be diagnosed at an early stage, allowing curative treatment strategies such as resection, liver transplantation, or ablation (6).

Advances in Knowledge

- On a per-patient basis, the summarized sensitivity of MR imaging was comparable to that of CT (88% [95% confidence interval {CI}: 83%, 92%] vs 74%–100%) for the diagnosis of hepatocellular carcinoma (HCC); the summarized specificity of MR imaging was also comparable to that of CT (94% [95% CI: 85%, 98%] vs 81%–100%).
- On a per-lesion basis, the overall sensitivity of MR imaging was higher than that of CT (79% vs 72%), with statistical significance when comparing paired studies (MR imaging vs CT: 80% vs 68%; $P = .0023$).
- Summarized per-lesion sensitivity was significantly lower for HCCs smaller than 1 cm than for HCCs 1 cm or larger ($P < .001$ for CT, $P = .02$ for MR imaging) and for those in explanted livers ($P = .04$ for CT, $P < .001$ for MR imaging).
- Gadoxetic acid–enhanced MR imaging showed significantly higher per-lesion sensitivity than MR imaging performed by using other contrast agents (87% vs 74%, $P = .03$).

Currently, ultrasonography is widely used for the surveillance of HCCs, while computed tomography (CT) and magnetic resonance (MR) imaging are indicated for the characterization of focal lesions suspected of being HCCs. Indeed, recent guidelines from the American Association for the Study of Liver Diseases (7) and the Organ Procurement and Transplantation Network/United Network for Organ Sharing (8) allow the noninvasive diagnosis of HCCs on the basis of CT or MR imaging findings. HCCs smaller than 2 cm, however, have often shown discrepant enhancement patterns at dynamic CT and MR imaging, necessitating invasive procedures such as biopsy. Furthermore, a study by Forner et al (9) suggested that current CT and MR imaging criteria may be highly specific but may be insufficiently sensitive for diagnosing HCCs, because 30%–40% of patients with cirrhosis and HCCs could not be given an accurate diagnosis on the basis of the typical enhancement criteria of arterial enhancement and venous washout.

Although there have been several prospective studies that compare imaging tests for the diagnosis of HCCs (9–11), the results have been limited thus far by a small number of included patients. In addition, there have been no large-scale clinical trials verifying the new liver imaging policy guidelines for the imaging diagnosis of HCCs. In 2006, Colli et al (12) presented a systematic review of imaging studies for the diagnosis of HCCs published between 1966 and 2004. In their review, they reported that CT showed a sensitivity of 68% (95% confidence interval [CI]: 55%, 80%) with a specificity of 93% (95% CI: 89%, 96%), whereas MR imaging was more sensitive (81% [95% CI: 70%, 91%]) with comparable specificity (85% [95% CI: 77%, 93%]).

Implication for Patient Care

- MR imaging should be the preferred modality for evaluating HCCs in patients with chronic liver disease because it provides better per-lesion sensitivity than multidetector CT.

With recent advances in imaging technology such as the widespread use of multidetector CT and the use of hepatobiliary-specific agents including gadoxetic acid (Primovist; Bayer, Berlin, Germany), the diagnostic performance of these modalities may have improved and may require updating.

Therefore, we performed a systematic review and meta-analysis of the literature published in the past decade to obtain updated diagnostic performance values of CT and MR imaging for the detection of HCCs in patients with chronic liver disease.

Materials and Methods

This study was supported financially by Bayer Healthcare with a research grant. However, the authors had complete control of all data and information submitted for publication at all times.

Literature Search

A search of the MEDLINE, EMBASE, and Cochrane Library databases from January 2000 to December 2012 was performed to identify studies that reported per-patient or per-lesion diagnostic accuracies of CT and MR imaging for the diagnosis of HCCs in

Published online before print
10.1148/radiol.14140690 **Content codes:** CT GI MR

Radiology 2015; 275:97–109

Abbreviations:
CI = confidence interval
FLL = focal liver lesion
HCC = hepatocellular carcinoma
QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies 2
ROC = receiver operating characteristic

Author contributions:
Guarantors of integrity of entire study, Y.J.L., J.M.L., H.Y.L.; 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, Y.J.L., J.M.L., H.Y.L., B.H.P., Y.H.K., J.K.H.; clinical studies, J.K.H.; statistical analysis, Y.J.L., J.M.L., J.S.L., H.Y.L.; and manuscript editing, Y.J.L., J.M.L., Y.H.K., B.I.C.

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

patients with chronic liver disease. Reference lists from included original articles, available review articles, and proceedings of major meetings were also searched to identify additional eligible articles. The detailed search strategy with query terms is provided in Table E1 (online).

Inclusion and Exclusion Criteria

All search hits were evaluated for eligibility by two reviewers (H.Y.L. and B.H.P., with 5 and 6 years of experience, respectively, in data extraction in previously published retrospective and prospective studies), who screened the relevant titles and abstracts. An article was considered to be eligible if CT or MR imaging was evaluated in adult patients (18 years or older) with chronic liver disease who underwent an imaging study for the diagnosis of HCCs. Full-text reviews were performed for all potentially eligible studies.

Studies were included if all of the following inclusion criteria were met: *(a)* Multiphasic contrast material–enhanced CT or MR imaging, consisting of two or more phases, including arterial and venous delayed phases, was performed; *(b)* for CT, multiple detector rows (at least four) were used; *(c)* for MR imaging, contrast enhancement was achieved with a gadolinium agent; *(d)* a reference standard based on histopathologic examination of an explanted or resected liver or a biopsied specimen of a focal lesion and/or a clinical follow-up period of at least 6 months was used; *(e)* sufficient data were reported to allow the calculation of sensitivity and/or specificity; and *(f)* the published article was written in English. Studies were excluded if either of the following exclusion criteria were present: *(a)* The study involved fewer than 10 patients or *(b)* the study used a reference standard that was based on nonindex imaging studies such as ethiodized oil uptake at follow-up CT or enhancement patterns at CT hepatic arteriography or CT arterial portography. Disagreements in study selection between the two reviewers were resolved through discussion with a third reviewer (Y.J.L., an attending radiologist with 7 years of experience in the interpretation of body CT and MR imaging studies).

Data Extraction

The two reviewers (H.Y.L. and B.H.P.) who performed the initial literature search independently extracted relevant data regarding the study design characteristics and examination results using a standardized form. Reviewers were not blinded to the authors' affiliations or the journal name (13). All disagreements were resolved by consensus through discussion with the third reviewer (Y.J.L.).

The Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool was used to extract the appropriate study design characteristics of each study (14). The following study design characteristics were recorded: type of study design (case series, case control, cohort study, or randomized controlled trial), year of publication, country of origin, number of patients and HCC lesions, size range of HCC lesions, etiology of underlying chronic liver disease, and type of journal.

The basic technical characteristics of every imaging modality were extracted. For CT, we recorded the type of scanner, the section thickness, the use of iodinated contrast material, the kilovoltage, and the tube current. For MR imaging, we recorded the manufacturer of the MR imaging unit, the magnetic field strength, the type of coil, the type of contrast agent, the pulse sequences, and the section thickness.

Diagnostic criteria for the imaging tests were also extracted, including *(a)* the criteria to classify a test result as positive for HCC and *(b)* a diagnostic confidence scale. Details on the proportion(s) of patients and/or HCC lesions that had undergone surgery or biopsy, as well as the features used for histopathologic confirmation, were also recorded. In addition, the duration and means of clinical follow-up were obtained.

Study Quality Assessment

Study quality was assessed by two separate reviewers (J.M.L. and Y.J.L., attending radiologists for body imaging with 24 and 7 years of clinical experience, respectively) in consensus using the QUADAS-2 tool, which evaluates the risk of bias for four domains and the clinical applicability for three domains of the study characteristics. The QUADAS-2 tool was used as provided by the QUADAS-2 group.

Statistical Analysis

Two-by-two contingency tables for each imaging modality were extracted or reconstructed for every included study. If the included study reported data on more than one technical aspect of the same imaging modality, a contingency table was created for the most advanced technique (eg, the use of more dynamic enhancement phases or the use of the hepatobiliary phase in addition to the classic arterial and venous delayed phases). If diagnostic accuracy was compared between different observers, mean diagnostic accuracy was calculated and included. Sensitivity and specificity estimates were calculated on a per-patient basis. Only sensitivity estimates were calculated on a per-lesion basis owing to the intrinsic absence of true negative data.

A bivariate random-effects model and a hierarchical summary receiver operating characteristic (ROC) model were used to obtain summary estimates of sensitivity and/or specificity and corresponding 95% CIs (15). The hierarchical summary ROC plot was used for graphic representation. To compare the sensitivities and specificities of the two modalities, we used a z test for unpaired data. Studies comparing the diagnostic accuracy of CT and MR imaging within the same patient population were analyzed separately, to offer a more valid way of comparing imaging tests. The bivariate random-effects model was used to combine per-lesion sensitivity data in head-to-head comparison studies, and the z test for paired data was used to compare the pooled sensitivity between CT and MR imaging. The MIDAS module (16) for Stata, version 12.0 (Stata, College Station, Texas) (17) was used for the bivariate random-effects model and the hierarchical summary ROC

model. Proc NLMIXED in SAS, version 9.3 (SAS Institute, Cary, NC) was used to perform the z test for unpaired or paired data. $P < .05$ was considered to indicate a significant difference.

Heterogeneity Exploration and Subgroup Analysis

Heterogeneity was quantified by using the Q test, where $P < .05$ suggests significant heterogeneity (18–20). Factors that could affect diagnostic accuracy and cause heterogeneity were evaluated through subgroup analysis and meta-regression analysis. Such factors included the type of study design (case series, case control, cohort study, randomized controlled trial), use of an explanted liver as the only reference standard, size of the HCC lesion (a cutoff value of 1 cm or 2 cm), prospective study design for both patient selection and imaging evaluation, use of the hepatobiliary phase for MR image analysis, and use of gadoxetic acid for MR imaging. Details of the explored factors are provided in Table E2 (online). We considered factors to be explanatory of the observed heterogeneity in diagnostic accuracy if the corresponding regression coefficients were significantly different. Further subgroup analysis was planned for clinical settings with significantly different factors.

Publication Bias

To assess publication bias, we constructed funnel plots for each imaging modality on per-patient and per-lesion bases. The linear regression test was used to examine the asymmetry of the funnel plot. A significant regression coefficient ($P \leq .1$) was indicative of a correlation between the sample size and sensitivity, representing the likelihood of publication bias. All analyses of publication bias were performed by using Stata, version 12.0.

Results

Identification and Selection of Studies

The literature search yielded a total of 2856 references, of which only 194 were potentially relevant on the basis of their title and/or abstract. Among them, 40 studies (six on CT, 22 on MR imaging, and 12 on both CT and MR imaging) were ultimately included. The studies evaluated a total of 1135 patients with 1332 HCC lesions for CT (10,11,21–36) and 2489 patients with 2320 HCC lesions for MR imaging (9–11,22–24,26–29,33–35,37–57). The study selection process is shown in Figure 1. Details of the excluded studies are listed in Table E3 (online).

Figure 1

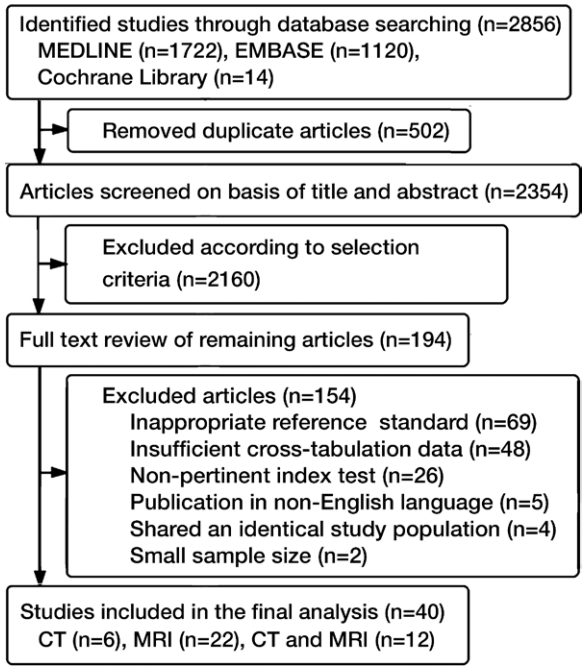

Figure 1: Study flow diagram.

Characteristics of Studies

All included studies except for one (37) had been conducted in single centers. There were no cohort studies or randomized controlled studies. Most studies were of the case-control design, including all eight studies on MR imaging and three studies on CT providing per-patient accuracy data, and 28 of 33 studies on MR imaging and 12 of 17 studies on CT providing per-lesion accuracy data. The important characteristics of the included studies are detailed in Tables 1 and 2. In brief, most studies included patients with documented underlying chronic liver disease, and in more than half of the studies, CT or MR imaging had been performed for the evaluation of known FLLs (13 of 18 studies for CT; 17 of 34 studies for MR imaging). The mean size of the HCC lesions was approximately 2 cm, ranging from 0.9 to 4.6 cm for CT and from 0.9 to 3.5 cm for MR imaging. The majority of studies included for CT (11 of 18) used scanners with 16 or more detector rows for all patients, while for MR imaging, the majority of studies (26 of 34) used a 1.5-T imaging unit for all patients. The hepatobiliary phase was used for MR imaging assessment in 12 studies, with 10 using gadoxetic acid for contrast enhancement. The reference standard depended solely on explanted livers in approximately one-third of the included studies (seven of 18 studies for CT; 11 of 34 studies for MR imaging).

The results of study quality assessment with the QUADAS-2 tool are summarized in Figure 2. There were no studies that were considered to be at low risk of bias for all domains. The fact that all included studies were of a

Table 1

Characteristics of Included Studies That Assessed the Diagnostic Accuracy of CT

Study	Study Design	No. of Detector Rows	Reference Standard	Underlying Disease	Ratio of Patients with HCC	No. of HCC Lesions	Mean Lesion Size (cm)
de Lédinghen et al (24)	Case control	4	Explant	Liver cirrhosis	21:34	54	1.8
Xiao et al (36)	Case series	16	Resection	Resectable HCC	56:56	67	4.6
Denecke et al (25)	Case control	4,16	Explant	Liver cirrhosis with HCC	31:32	76	2.7
Maetani et al (32)	Case control	8	Explant	Liver cirrhosis with HCC	41:41	134	2.1
Lee et al (29)	Case control	4–64	Explant	Liver cirrhosis	38:78	82	1.4
Luo et al (31)	Case control	16	HP	FLLs (liver cirrhosis in 72 of 77 patients)	77:139	77	3.3
Sangiovanni et al (33)	Case control	64	Fine-needle biopsy	Liver cirrhosis with FLLs	42:64	44	1.6
Kim et al 2009 (28)	Case series	16–64	Resection	HCC (chronic liver disease in 59 of 62 patients)	62:62	83	2.9
Di Martino et al (10)	Case control	64	HP for 53 lesions and follow-up for 56	Liver cirrhosis with suspected HCC	42:58	87	1.8
Luca et al (30)	Case control	16,64	Explant	Liver cirrhosis	57:125	131	2.09
Addley et al (21)	Case control	16,64	Explant	Liver cirrhosis	29:39	46	2.1
Akai et al (22)	Case series	64	Resection	Resectable HCC	34:34	52	2.6
Haradome et al (26)	Case control	16	HP	Liver cirrhosis	52:75	60	1.74
Hirakawa et al (27)	Case control	4	Explant	Liver cirrhosis with HCC	25:25	89	0.9
Khalili et al (11)	Case control	64	HP for 23 lesions and follow-up for 78	Liver cirrhosis with FLLs	NA:84	34	1.3
Sano et al (34)	Case series	16	Resection	Resectable HCC	64:64	96	1.27
Baek et al (23)	Case series	4–64	HP for 36 patients and follow-up for 15	Chronic liver disease with suspected HCC	51:51	73	2.98
Sersté et al (35)	Case control	4	Fine-needle biopsy	Chronic liver disease with FLLs	47:74	47	1.8

Note.—HP = histopathologic examination (explantation, resection, biopsy), FLL = focal liver lesion, NA = not available.

case series or case-control design introduced a high risk of bias for patient selection. The substantial risk of bias regarding patient flow and timing mainly arose from the fact that more than half of the included studies used a combination of histopathologic findings and clinical follow-up as reference standards, which may result in verification bias. There was also a considerable risk of bias regarding the reference standard, as most studies did not report whether or not the pathologist was blinded to the imaging test results.

Overall Diagnostic Accuracy

Per-patient analysis.—Eight studies provided relevant data on MR imaging accuracy for per-patient analysis. The summary estimate of per-patient sensitivity of MR imaging was 88% (95% CI: 83%, 92%), with a specificity of 94% (95% CI: 85%, 98%). Substantial heterogeneity was revealed by the Q test for specificity ($P < .001$) but not for sensitivity ($P = .19$). We were not able to summarize the data on the diagnostic accuracy of CT, as only three studies were included (24,25,35). In those studies, however, the sensitivity ranged from 74% to 100%, while specificity ranged from 81% to 100%. Figure 3 shows the summary estimates of sensitivity and specificity of MR imaging with forest plots. The hierarchical summary ROC plot of MR imaging is shown in Figure E1 (online).

Per-lesion analysis.—Seventeen and 33 data sets were retrieved for CT and MR imaging analysis on a per-lesion basis, respectively. The overall per-lesion sensitivity of MR imaging was higher than that of CT when the sensitivity data of all included studies were pooled (79% [95% CI: 74%, 83%] vs 72% [95% CI: 75%, 84%]), although this difference was not statistically significant ($P = .605$). There was significant heterogeneity for the per-lesion sensitivities of both CT and MR imaging ($P < .001$ for both). Individual and summary estimates of per-lesion sensitivity for CT and MR imaging are shown with forest plots in Figure 4.

When we pooled the paired data of the 11 studies available for head-to-head comparison, MR imaging showed a significantly higher per-lesion sensitivity estimate of 80% (95% CI: 68%, 88%), compared with 68% (95% CI: 58%, 76%) for CT ($P = .0023$).

Heterogeneity Exploration

Per-lesion sensitivity estimates for the different subgroups are presented in Table 3. Case series studies showed significantly higher per-lesion sensitivity than case-control studies for both CT ($P = .01$) and MR imaging ($P < .001$). Sensitivity estimates were significantly lower when explanted livers were used as the sole reference standard for

Table 2

Characteristics of Included Studies That Assessed the Diagnostic Accuracy of MR Imaging

Study	Study Design	Magnetic Field Strength (T)	Reference Standard	Underlying Disease	Hepatobiliary Phase Imaging Used?	Ratio of Patients with HCC	No. of HCC Lesions	Mean Lesion Size (cm)
Ward et al (42)	Case control	1.0	HP	Liver cirrhosis	No	25:27	76	NA
de Lédinghen et al (24)	Case control	1.0	Explant	Liver cirrhosis	No	21:34	54	1.8
Pauleit et al (41)	Case control	1.5	HP for 24 lesions and follow-up for 19	Chronic liver disease	No	30:43	77	NA
Burrel et al (39)	Case control	1.5	Explant	Liver cirrhosis	No	29:50	76	1.8
Kim et al (40)	Case control	1.5	HP for 31 lesions and follow-up for 24	NA	No	55:55	103	2.5
Böhm et al (38)	Case control	1.5	HP	NA	No	10:50	34	NA
Bluemke et al (37)	Case control	1.5	HP	Hepatic resection	Yes (with GA)	33:169	33	NA
Hecht et al (46)	Case control	1.5	Explant	Liver cirrhosis	No	12:38	19	2.3
Giorgio et al (45)	Case control	1.5	Fine-needle biopsy	Liver cirrhosis with FLLs	No	48:73	48	1.8
Lauenstein et al (47)	Case control	1.5	Explant	Liver cirrhosis	No	27:36	36	NA
Forner et al (9)	Case control	1.5	Fine-needle biopsy	Liver cirrhosis with FLLs	No	60:89	60	1.4
Choi et al (44)	Case control	1.5	Explant	Liver cirrhosis	Yes (with GD)	23:47	41	2.2
Lee et al (29)	Case control	3.0	Explant	Liver cirrhosis	No	38:78	82	1.4
Kim et al 2009 (28)	Case series	3.0	Resection	HCC	Yes (with GA)	62:62	83	2.9
Di Martino et al (10)	Case control	1.5	HP for 53 patients and follow-up for 56	Liver cirrhosis with suspected HCC	Yes (with GA)	42:58	87	1.8
Khan et al (52)	Case control	1.5	HP for 71 patients and follow-up for 45	CLD	No	NA:80	74	2.2
Mita et al (50)	Case series	1.0	Fine-needle biopsy	Liver cirrhosis with FLLs	Yes (with GA)	29:29	34	1.27
Sangiovanni et al (33)	Case control	1.5	Fine-needle biopsy	Liver cirrhosis with FLLs	Yes (with GD)	42:64	44	1.6
Ahn et al (43)	Case control	1.5, 3.0	HP for 55 patients and follow-up for 58	Suspected HCC (liver cirrhosis in 56 of 59 patients)	Yes (with GA)	NA:59	84	2.8
Xu et al (51)	Case control	1.5	HP	Liver cirrhosis with FLLs	No	39:54	40	3.5
Akai et al (22)	Case series	1.5	Resection	Resectable HCC	Yes (with GA)	34:34	52	2.6
Becker-Weidman et al (48)	Case control	1.5	Explant	Chronic liver disease	No	35:101	58	2.0
Haradome et al (26)	Case control	1.5	HP	Liver cirrhosis	Yes (with GA)	52:75	60	1.74
Hardie et al (49)	Case control	1.5	Explant	Liver cirrhosis	No	21:37	31	1.9
Hirakawa et al (27)	Case control	1.5	Explant	Liver cirrhosis with HCC	No	25:25	89	0.9
Khalili et al (11)	Case control	1.5	HP for 23 patients and follow-up for 78	Liver cirrhosis with FLLs	No	NA:84	34	1.3
Sano et al (34)	Case series	1.5	Resection	Resectable HCC	Yes (with GA)	64:64	96	1.27
Yu et al (57)	Case control	1.5	Explant	Chronic liver disease	No	117:216	175	2.4
Baek et al (23)	Case series	3.0	HP for 36 lesions and follow-up for 15	Chronic liver disease with suspected HCC	Yes (with GA)	51:51	73	2.98
Sersté et al (35)	Case control	1.5	Fine-needle biopsy	Chronic liver disease with FLLs	No	47:74	47	1.8

Table 2 (continues)

Table 2 (continued)

Characteristics of Included Studies That Assessed the Diagnostic Accuracy of MR Imaging

Study	Study Design	Magnetic Field Strength (T)	Reference Standard	Underlying Disease	Hepatobiliary Phase Imaging Used?	Ratio of Patients with HCC	No. of HCC Lesions	Mean Lesion Size (cm)
Park et al 54)	Case control	3.0	HP for 218 patients and follow-up for 105	Chronic liver disease with suspected HCC	Yes (with GA)	130:260	179	1.4
Le Moigne et al (53)	Case control	1.5	HP	Liver cirrhosis with FLLs	No	53:62	66	1.4
Park et al (55)	Case control	1.5	Explant	Liver cirrhosis	No	33:52	72	1.5
Rimola et al (56)	Case control	1.5	Fine-needle biopsy	Liver cirrhosis with FLLs	No	103:159	103	1.5

Note.—HP = histopathologic examination (explantation, resection, biopsy), GA = gadoxetic acid, GD = gadobenate dimeglumine, NA = not available.

both CT (P = .04) and MR imaging (P < .001). For small HCC lesions, sensitivity estimates were lower for both CT and MR imaging, with a significant difference for lesions measuring less than 1 cm (P < .001 for CT, P = .02 for MR imaging) compared with lesions measuring 1 cm or greater. There was also a significant difference for lesions measuring less than 2 cm compared with lesions measuring 2 cm or greater for CT (P = .02). The sensitivity estimate was significantly higher for studies where more than half of the patients had HCCs for MR imaging (P < .001). The sensitivity estimate was significantly lower for the five MR imaging studies with a prospective design (9,33,39,48,56) (P < .001). There was only one study of CT with a prospective design (33), which reported a sensitivity of 44%; however, a statistical comparison was not possible. Studies in which the hepatobiliary phase was used at MR imaging analysis showed a significantly higher estimate of per-lesion sensitivity (P = .01). In particular, the use of gadoxetic acid for contrast-enhanced MR imaging yielded the best per-lesion sensitivity among the three MR imaging parameters, with an estimate of 87% with statistical significance (P = .03). Other subgroup factors, including Child-Pugh class, number of CT detector rows (<16 vs ≥16), and magnetic field strength, did not show statistically significant differences.

Subgroup Analysis

As considerable heterogeneity was revealed, additional subgroup analysis was performed to assess two different clinical settings: *(a)* Studies where MR imaging or CT was used as the initial diagnostic tool for FLLs detected during surveillance in consecutive patients with chronic liver disease or liver cirrhosis and *(b)* studies where findings in the explanted liver were used as the sole reference standard.

Initial diagnosis of FLLs in consecutive patients.—All of the included studies were of a case-control design. There was only one study (35) that provided relevant accuracy data for per-patient analysis, and it reported a sensitivity of 81% and a specificity of 85% for MR imaging and a sensitivity of 74% and a specificity of 81% for CT. On a per-lesion basis, 12 studies were included for MR imaging (9–11,26,33,41,43,45,51–53,56) and four studies were included for CT (10,11,26,33). The summary estimate of the per-lesion sensitivity of MR imaging was 76% (95% CI: 66%, 84%), with significant heterogeneity (P < .001). Similar trends were found for other subgroup factors, but these did not show statistical significance (Table E4 [online]). For CT, the summarized per-lesion sensitivity was 60% (95% CI: 49%, 71%), with significant heterogeneity (P = .03). The sole prospective study (33) showed a lower sensitivity than the other three studies (44% vs 66% [95% CI: 59%, 73%]), but the difference was not significant. Head-to-head comparison of four studies with available data (10,11,26,33) demonstrated significantly higher per-lesion sensitivity for MR imaging than for CT (74% [95% CI: 62%, 84%] vs 63% [95% CI: 48%, 75%], P = .0018).

Findings in explanted livers as the sole reference standard.—All of the included studies were of a case-control design. There were seven studies that provided appropriate MR imaging data for per-patient analysis, with a summarized sensitivity of 89% (95% CI: 84%, 93%) and specificity of 95% (95% CI: 86%, 98%). Significant heterogeneity was observed for specificity (P < .001) but not for sensitivity (P = .21). For CT, only two studies were available for per-patient analysis, with a sensitivity and specificity of 81% and 85% (24), and 100% and 100% (25), respectively. On a per-lesion basis, 11 studies were included for MR imaging (24,27,29,39,44,46,48,49,55,57) and seven studies for were included for CT (21,22,25,27,29,30,32). The summary estimate of per-lesion sensitivity for MR imaging was 69% (95% CI: 66%, 73%), with significant heterogeneity (P < .001). The summarized per-lesion sensitivity for CT was 64% (95% CI: 49%, 77%), with significant heterogeneity (P < .001). Sensitivities for lesions smaller than 2 cm were significantly lower for both MR imaging (55% vs 95%, P = .02)

Figure 2

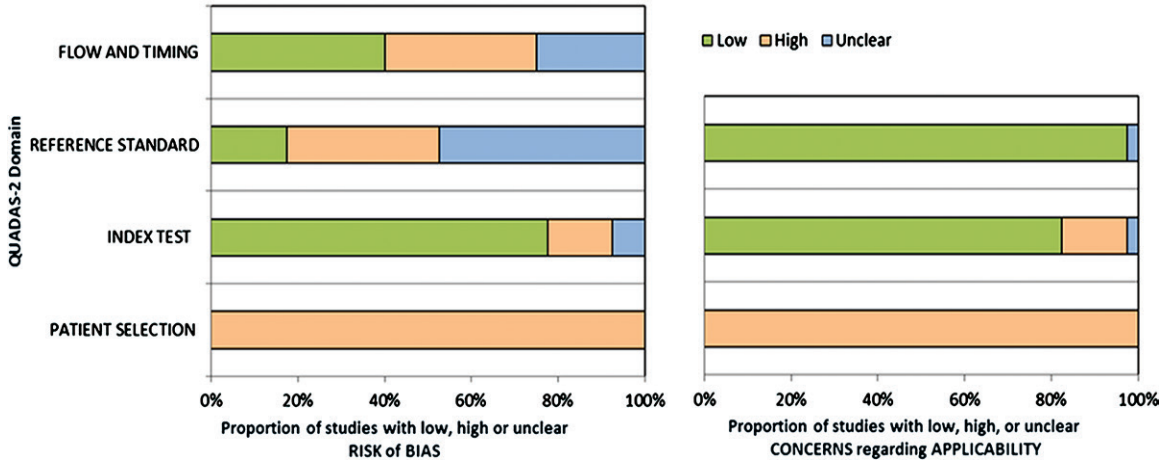

Figure 2: Grouped bar charts show results of study quality assessment with QUADAS-2 tools. The charts show the cumulative results of the 40 included studies in terms of the risk of bias (left) and concerns regarding applicability (right) according to each QUADAS-2 domain.

and CT (42% vs 87%, P = .01). No statistically significant subgroup factor could be found (Table E5 [online]). Head-to-head comparison of the three studies with available data (24,25,29) showed higher per-lesion sensitivity for MR imaging than for CT (72% [95% CI: 56%, 84%] vs 59% [95% CI: 42%, 74%]), without statistical significance (P = .225).

Publication Bias

A low likelihood of publication bias for MR imaging analysis on a per-patient basis (P = .764) and for CT analysis on a per-lesion basis (P = .12) was observed from the linear regression test of funnel plot asymmetry. However, there was evidence of a high likelihood of publication bias for MR imaging analysis on a per-lesion basis (P = .008).

Discussion

In our meta-analysis, we evaluated the diagnostic accuracy of CT and MR imaging for HCCs in patients with chronic liver disease. Our results show that, on a per-lesion basis, MR imaging is generally more sensitive than CT for diagnosing HCCs (79% vs 72%). The difference was significant in a head-to-head comparison of studies with paired diagnostic accuracy data for MR imaging and CT (80% vs 68%, P = .0023). The overall sensitivity estimates for CT and MR imaging have not substantially increased from those in the previous meta-analysis of Colli et al published in 2006 (12), which reported sensitivities of 68% for CT and 81% for MR imaging. However, that study did not separately analyze the data on a per-patient and a per-lesion basis and relied mostly on per-patient data. We evaluated 38 studies, with little overlap between the included studies (only two MR imaging studies), on both a per-patient and per-lesion basis. The inclusion of a per-lesion analysis is important, as information regarding the performance of a test in localizing disease can also be obtained. Moreover, we used more recently developed statistical methods of combining the studies (ie, the hierarchical summary ROC model or the bivariate random-effects model). On the basis of our study results, MR imaging should be the preferred modality for evaluating HCCs in patients with chronic liver disease because it provides better per-lesion sensitivity than multidetector CT. Furthermore, our data suggest promising evidence of improved sensitivity for MR imaging when hepatobiliary phases are used, especially when contrast enhancement is achieved with the use of gadoxetic acid, which showed the highest per-lesion sensitivity among the three MR imaging parameters, with an estimate of 87%. This superiority of gadoxetic acid is likely to be due to the fact that it is readily transported into the hepatocytes by the organic anion-transporting polypeptide family, with approximately 50% of the administered dose undergoing hepatobiliary excretion, which is much higher than the excretion rate (5%) of gadobenate dimeglumine (58).

With regard to the impact of tumor size on the diagnosis of HCCs, a confident diagnosis of HCC in subcentimeter hepatic nodules has been considered not to be feasible (7,9,33). This is in keeping with our results, which showed markedly decreased sensitivity estimates for subcentimeter HCCs compared with lesions 1 cm or larger. The per-lesion sensitivity estimate was even lower for CT (31% vs 82%), compared with MR imaging (48% vs 88%) in these subcentimeter lesions. The relatively higher per-lesion sensitivity estimate for MR imaging compared with that for CT for subcentimeter HCCs may even be further increased with the use of hepatobiliary contrast agents, particularly gadoxetic acid.

The summarized per-lesion sensitivity estimate was significantly lower in studies that used findings in explanted livers as the sole reference standard for both CT (64% vs 77%, P = .04) and MR imaging (73% vs 81%, P <

Figure 3

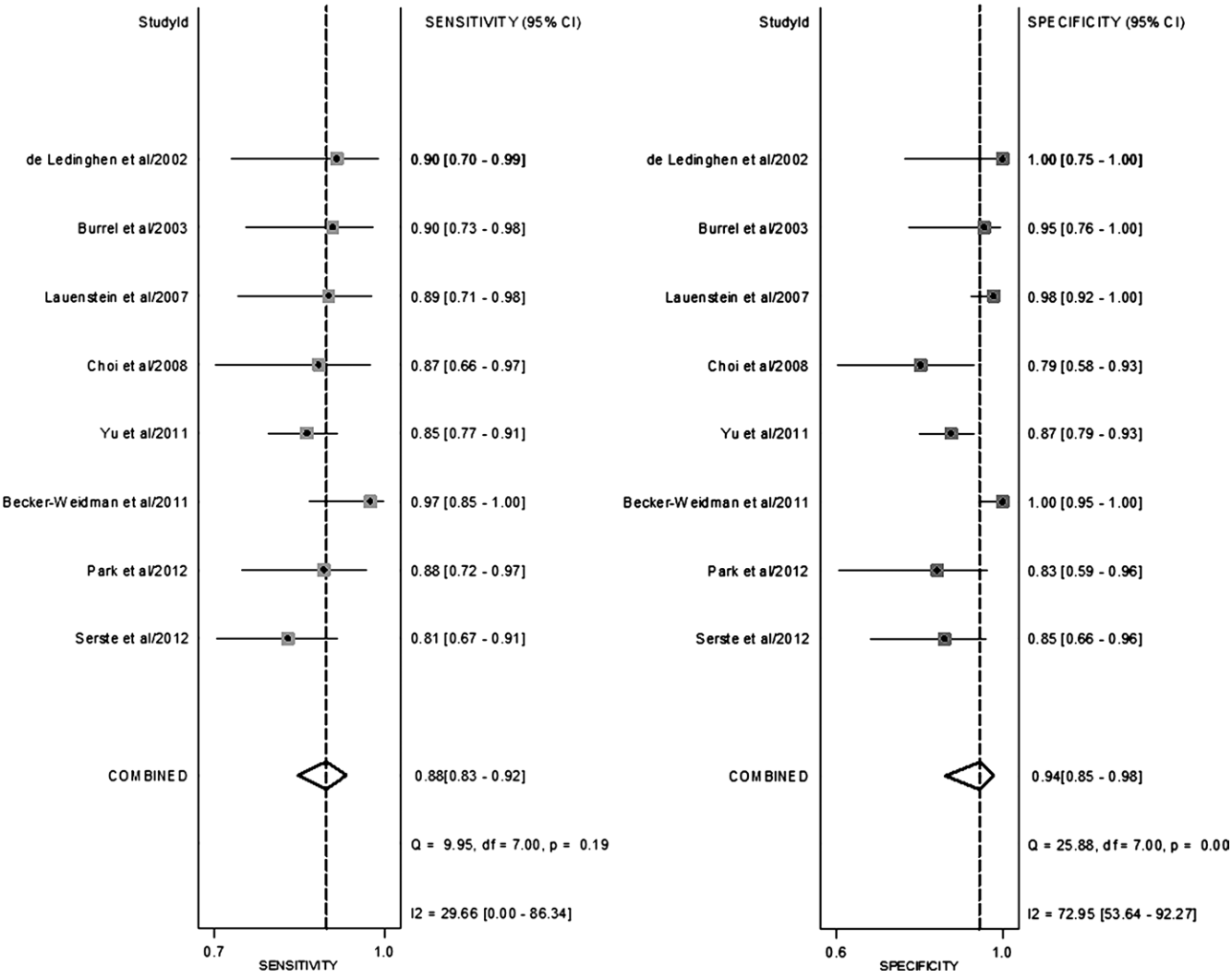

Figure 3: Forest plots of studies included for the per-patient diagnostic accuracy of MR imaging show individual and summarized sensitivity (left) and specificity (right) estimates for the per-patient diagnosis of HCCs, with corresponding heterogeneity statistics at the bottom right corners. The *Q* statistic is a measurement of heterogeneity in which the *P* value is derived from a χ^2 test. $P < .05$ indicates significant heterogeneity. Squares = individual study point estimates. Horizontal lines = 95% CIs. Dashed line and rhombus = summarized estimate and its 95% CI. The 2012 study by Park et al is the study published in *Hepatology* (55).

.001). This finding may be explained by the fact that patients undergoing liver transplantation are more likely to have advanced liver cirrhosis, with more severe morphologic distortions of segments and greater numbers of benign cirrhosis-related nodules (59). It is well known that disease severity will affect sensitivity (15); however, we could not find statistically significant differences between patients with Child-Pugh class A disease and those with Child-Pugh class B or C disease for both CT and MR imaging. This may be due to the roughness of Child-Pugh classification itself in reflecting hepatic function. Nevertheless, the lower sensitivity estimates for patients undergoing liver transplantation seem to reveal the effect of disease severity to some extent.

Our meta-analysis had several limitations. There were a limited number of studies (one for CT, five for MR imaging) that reported diagnostic accuracy data collected in a prospective manner. This resulted in a major methodologic limitation of including many studies with retrospective patient data collection. Pooling such suboptimal retrospective results may have caused a bias toward increased diagnostic sensitivity (60). Another important potential bias of our study was that both patients known to have HCCs on the basis of findings at prior imaging tests or treatment and those suspected of having HCCs were included, despite the fact that these two patient populations had different

Figure 4

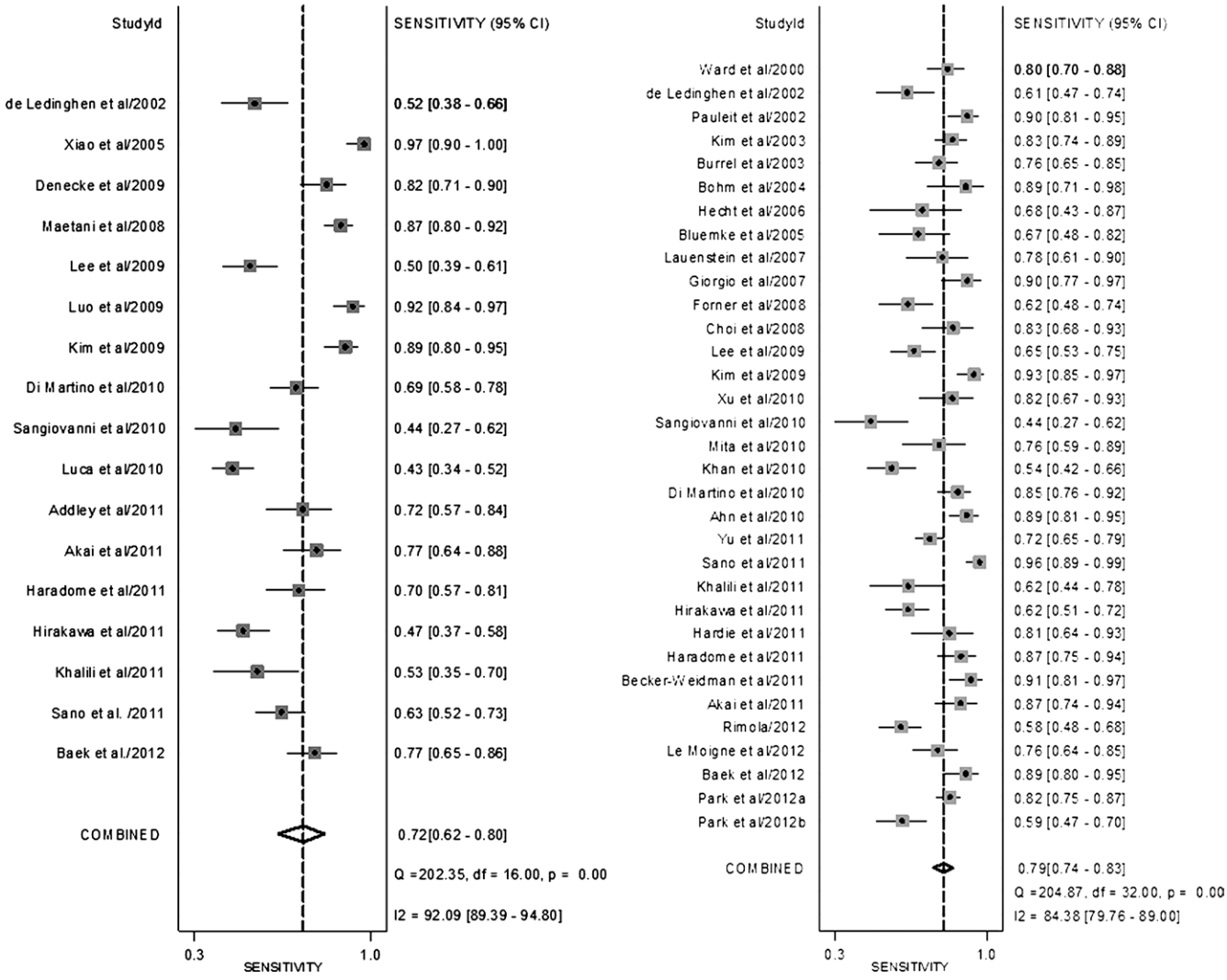

Figure 4: Forest plots of studies included for the per-lesion diagnostic sensitivity of CT and MR imaging show individual and summarized sensitivity estimates for the per-lesion diagnosis of HCC for CT (left) and MR imaging (right), with corresponding heterogeneity statistics at bottom right corners. The *Q* statistic is a measurement of heterogeneity in which the *P* value is derived from a χ^2 test. $P < .05$ indicates significant heterogeneity. Squares = individual study point estimates. Horizontal lines = 95% CIs. Dashed line and rhombus = summarized estimate and its 95% CI. *Park et al/2012a* = reference 54; *Park et al/2012b* = reference 55.

pretest probabilities and thresholds for diagnosis. It would have been more desirable to study the effect of differential verification on diagnostic accuracy. However, this was not possible because of the use of a composite reference standard, consisting of histopathologic examinations and clinical follow-up. Nevertheless, such a composite reference standard may better reflect the daily clinical practice of diagnosing HCCs in patients with chronic liver disease, as surgical resection or biopsy is not always possible or accurate. The effect of the study design was shown to be significant for per-lesion analysis of sensitivity, with higher values for case series than for case-control studies for both MR imaging (90% vs 76%, $P < .001$) and CT (84% vs 66%, $P = .01$). Therefore, it is crucial that future studies adopt study designs that can better control biases and provide higher levels of evidence such as cohort studies and randomized controlled trials.

Finally, considerable heterogeneity was observed for per-lesion analysis for both CT and MR imaging. This was mainly caused by the variation in several study design characteristics, patient characteristics (eg, disease severity, lesion size), technical aspects (eg, use of hepatobiliary phase or gadoxetic acid, different diagnostic thresholds of readers), and the reference standard

Table 3

Sensitivity Estimates for Each Subgroup on a Per-Lesion Basis

Subgroup	Summarized Sensitivity for MR Imaging (%)	*P* Value	Summarized Sensitivity for CT (%)	*P* Value
Type of study design		<.001		.01
Case series	90 (84, 96) [*n* = 5]		84 (73, 94) [*n* = 5]	
Case-control study	76 (71, 81) [*n* = 28]		66 (55, 77) [*n* = 12]	
Explanted liver as the only reference standard		<.001		.04
Yes	73 (65, 82) [*n* = 11]		64 (49, 79) [*n* = 7]	
No	81 (76, 86) [*n* = 22]		77 (67, 87) [*n* = 10]	
Lesion size (cm)				
<1	48 (35,60) [*n* = 12]		31 (12,49) [*n* = 7]	
≥1	88 (84, 92) [*n* = 17]	.02	82 (71, 93) [*n* = 9]	<.001
<2	62 (53, 72) [*n* = 21]		48 (40,56) [*n* = 12]	
≥2	95 (92, 99) [*n* = 12]	.08	92 (79, 97) [*n* = 8]	.02
Child-Pugh class		.6		.93
A	82 (75, 89) [*n* = 11]		79 (68, 90) [*n* = 8]	
B or C	68 (63, 73) [*n* = 5]		53 (48,58) [*n* = 5]	
Unclassified	74 (70, 77) [*n* = 17]		78 (73, 83) [*n* = 4]	
Frequency of HCC (%)		<.001		.1
<50	74 (65, 83) [*n* = 12]		57 (31, 83) [*n* = 3]	
≥50	81 (74, 87) [*n* = 15]		76 (67, 85) [*n* = 14]	
Prospective study design		<.001		NA
Yes	55 (35, 75) [*n* = 5]		44 [*n* = 1]	
No	84 (78, 90) [*n* = 22]		70 (67, 72) [*n* = 16]	
No. of CT detector rows				NA
<16	NA		72 (66, 78) [*n* = 3]	
≥16	NA		70 (68, 73) [*n* = 14]	
Magnetic field strength (T)		.08		
<3.0	77 (72, 82) [*n* = 28]		NA	
3.0	85 (77, 93) [*n* = 5]		NA	
Hepatobiliary phase imaging		.01		
Yes	84 (79, 90) [*n* = 12]		NA	
No	75 (69, 80) [*n* = 21]		NA	
Use of gadoxetic acid				
Yes	87 (83, 92) [*n* = 10]	.03	NA	
No	74 (69, 79) [*n* = 23]		NA	

Note.—Data are numbers of studies, with 95% CIs in parentheses. NA = not applicable.

used. To overcome the heterogeneity of our data, we used both the hierarchical summary ROC model and the random-effects model. Because the 95% CIs were not substantially wide, we believe that these results are valuable. However, the heterogeneity in this type of diagnostic study still remains a point of concern.

In conclusion, MR imaging has higher overall per-lesion sensitivity estimates than CT and can be more potent with the use of hepatobiliary-specific MR contrast agents, even in challenging situations such as end-stage liver disease and lesions smaller than 1 cm. Therefore, MR imaging should be the preferred imaging modality over CT for the diagnosis of HCC in patients with chronic liver disease.

Acknowledgments: We thank Chris Woo, BA, for his editorial assistance. We also thank Yun Ku Cho, MD, for his critical review and helpful comments.

Disclosures of Conflicts of Interest: Y.J.L. Activities related to the present article: received a grant from Bayer Healthcare, Korea. Activities not related to the present article: none to disclose. Other relationships: none to disclose. **J.M.L.** Activities related to the present article: received a grant from Bayer Healthcare, Korea. Activities not related to the present article: is a consultant for Siemens Healthcare; has received grants from GE Healthcare, Donseo Medical, CMS, Acuzen, Starmed, and RF MEDICAL. Other relationships: none to disclose. **J.S.L.** disclosed no relevant relationships. **H.Y.L.** disclosed no relevant relationships. **B.H.P.** disclosed no relevant relationships. **Y.H.K.** disclosed no relevant relationships. **J.K.H.** disclosed no relevant relationships. **B.I.C.** Activities related to the present article: none to disclose. Activities not related to the present article: has received a grant from Samsung Electronics. Other relationships: none to disclose.

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