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FULL PAPER

Detection of recurrent hepatocellular carcinoma after surgical resection: Non-contrast liver MR imaging with diffusion-weighted imaging versus gadoxetic acid-enhanced MR imaging

¹JI HYE MIN, MD, ²YOUNG KON KIM, MD, ³SEO-YOUN CHOI, MD, ²TAE WOOK KANG, MD, ²WOO KYOUNG JEONG, MD, ⁴KYUNGA KIM, PhD and ⁴HO-JEONG WON, MS

¹Department of Radiology, Chungnam National University Hospital, Chungnam National University College of Medicine, Daejeon, Korea

²Department of Radiology and Center for Imaging Science, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

³Department of Radiology, Soonchunhyang University College of Medicine, Bucheon Hospital, Bucheon, Republic of Korea

⁴Biostatistics and Clinical Epidemiology Center, Research Institute for Future Medicine, Samsung Medical Center, Seoul, Republic of Korea

Address correspondence to: MD Young Kon Kim

E-mail: youngkon0707.kim@samsung.com; jmyr@dreamwiz.com

Objective: To compare the diagnostic performance of non-contrast liver MRI to whole MRI using gadoxetic acid for detection of recurrent hepatocellular carcinoma (HCC) after hepatectomy.

Methods: This retrospective study analyzed 483 patients who underwent surveillance with liver MRI after hepatectomy for HCC (median time interval, 7.7 months). Non-contrast MRI set (T_1 - and T_2 weighted and diffusion-weighted images) and whole MRI set (gadoxetic acid-enhanced and non-contrast MRI) were analyzed independently by two observers. Receiver operating characteristic analysis was used (with the observers' individual observations and consensus) to detect recurrent HCC. The accuracy, sensitivity, and specificity were calculated.

Results: A total of 113 patients had 197 recurrent HCCs on first follow-up MRI. Although non-contrast MRI had fairly high sensitivity for recurrent HCC, there were significant

differences in sensitivity (94.7% vs 99.1%, $p = 0.025$) and accuracy (97.5% vs 99.2%, $p = 0.021$) between the two image sets (per-patients base analysis). However, in patients followed for ≥ 1 year after surgery, the diagnostic performance of non-contrast MRI and whole MRI were not significantly different ($p > 0.05$).

Conclusion: Non-contrast MRI may serve as an alternative follow-up method which can potentially replace whole MRI at least in selected patients followed up ≥ 1 year after surgery who have relatively lower risk of HCC recurrence.

Advances in knowledge: There is no consensus regarding the ideal imaging modality or follow-up interval after resection of HCC. Non-contrast MRI had comparable performance to that of gadoxetic acid-enhanced MRI in the detection of HCC recurrence during surveillance ≥ 1 year after surgery.

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most aggressive tumors that accounts for the third most common cause of cancer-related death.¹ One of the curative treatments for HCC is surgical resection. Unfortunately, the cumulative recurrence rate of HCC at 5 years after hepatic resection, including true recurrence (arising within the first 2 years after resection) and *de novo* tumors, exceeds 70%.^{2,3} Therefore, post-operative surveillance is important to manage recurrent tumors and improve patient survival. The goal of surveillance is to identify recurrent HCCs in their earliest stage, thereby enabling curative therapies with better outcomes and decreased mortality.⁴ A combined use

of tumor markers and imaging studies, such as multiphasic CT and MRI, is usually performed for post-operative surveillance of HCC. Nevertheless, there is no consensus regarding the ideal imaging modality or follow-up interval with consideration of clinical utility, cost effectiveness, and radiation risk.⁵ In addition, repeated examinations using contrast-enhanced CT or MRI might be a burden due to concerns regarding the development of contrast-induced nephropathy or nephrogenic systemic fibrosis in patients with renal insufficiency.⁶⁻⁹

With recent advances in image quality, diffusion-weighted imaging (DWI) has an emerging role in liver imaging, with

promising results for lesion detection and characterization.^{10–12} DWI can be easily implemented in routine protocols because it can be performed relatively quickly and does not require contrast injection. Previous reports have demonstrated adding DWI to standard MRI improved sensitivity for diagnosing HCC.^{10,11} Some researchers have shown that liver DWI ought to be a routine part of the MR evaluation for patients with rectal cancers by demonstrating its superiority over CT in the detection of liver metastasis.^{13,14} In addition, non-contrast MRI, including DWI, had a reasonable performance compared to that of standard MRI in the detection of HCC and cholangiocarcinoma with minimal compromise in sensitivity and negative predictive value in patients with chronic liver disease.³

Considering the high incidence of HCC and the further increasing role of MR studies for HCC assessment, it seems reasonable to assume that the number liver MR studies performed will further increase. Consequently, safety issues raised by the administration of gadolinium contrast agent such as nephrogenic systemic fibrosis and gadolinium accumulation in the brain seem to deserve further emphasis.¹⁵ The increasing financial cost burdened by the increasing number of MR studies is another issue that is not trivial. Therefore, we thought that it would be worthwhile to adopt a non-contrast MR method with quicker scanning capabilities not only to avoid gadolinium-associated complications, but also shorten the study time and consequently, reduce the cost of MRI. With these concepts in mind, we conducted this study to compare the diagnostic performance of non-contrast MRI [T_1 - and T_2 weighted (T_1 WI

and T_2 WI) images plus DWI] to that of whole MRI (gadoteric acid-enhanced imaging plus the non-contrast MRI set) with respect to their ability to detect intrahepatic HCC recurrence after hepatectomy.

METHODS AND MATERIALS

Patient selection

This retrospective study was approved by the Institutional Review Board. Written informed consent was waived. The study included 665 patients who underwent surveillance imaging after hepatectomy for HCC at Samsung Medical Center, Seoul, Korea, between August 2012 and September 2015. We reviewed the first follow-up liver MRI after hepatectomy (median time interval, 7.7 months; range, 0.6–47.8 months). Patients who met any of the following criteria were excluded: did not perform follow-up liver MRI ($n = 124$); received interventional treatments for recurrent HCCs between surgery and first follow-up liver MRI ($n = 49$); and extrahepatic metastasis detected on the first follow-up liver MRI ($n = 9$). Ultimately, a total of 483 patients were included in the final study population (Figure 1).

Imaging techniques

All MR images were acquired using a 3.0 T whole-body MR system (Intera Achieva 3.0 T, Philips Healthcare) with a 16-channel phased-array coil as the receiver coil. The baseline MR imaging included T_1 W turbo field-echo in-phase, opposed sequence and breathhold multishot T_2 WI, and a respiratory-triggered single-shot and heavily T_2 WI. The DWIs were acquired using respiratory-triggered single-shot echoplanar imaging with

Figure 1. Flow diagram of this study. HCC, hepatocellular carcinoma.

Table 1. MRI sequences and parameters

Sequence	TR/TE (ms)	Flip angle (degree)	Section thickness (mm)	Matrix size	Bandwidth (Hz/pixel)	Field of view (cm)	Acquisition time (s)
T_1 weighted-3D dual GRE	3.5/1.15–2.3	15	6	288 × 230	434.4	32–38	14
T_1 weighted-3D GRE	3.1/1.5	10	2	256 × 256	955.7	32–38	16.6
Breath-hold multishot T_2 weighted imaging	2161/70	90	5	324 × 235	235.2	32–38	55
Respiratory-triggered single-shot heavily T_2 weighted imaging	1573/160	90	5	320 × 256	317.9	32–38	120
Diffusion-weighted imaging	1600/70	90	5	112 × 112	14.5	32–38	126

2D, two-dimensional; 3D, three-dimensional; GRE, gradient echo; TE, echo time; TR, repetition time.

a b -value of 0, 100, or 800 s mm^{-2} . The apparent diffusion coefficient (ADC) was calculated using a monoexponential function using b -values of 100 and 800 s mm^{-2} . For gadoteric acid-enhanced imaging, we obtained the following imaging using a T_1 W three-dimensional turbo field echo sequence (T_1 high-resolution isotropic volume examination, eTHRIVE, Philips Healthcare): unenhanced, arterial-phase (20–35 s), portal phase (60 s), late-phase (3 min), and 20 min hepatobiliary phase (HBP). The time for the arterial phase was determined using an MR fluoroscopic bolus detection technique. Using a power injector, contrast agent was administered intravenously at 1 ml s^{-1} at a dose of 0.025 mmol kg^{-1} body weight, followed by a 20 ml saline flush. The detailed MR sequence parameters are shown in Table 1.

Image analysis

Two gastrointestinal radiologists (W.K.J and T.W.K., with 15 and 10 years of experience, respectively) reviewed the MR images on a picture archiving and communication system (Centricity Radiology RA 1000; GE Healthcare, Chicago, IL). The reviewers knew that patients were at risk for intrahepatic HCC recurrence; however, they were unaware of the presence or location of liver lesions, or of the final diagnosis of hepatic lesions. The reviewers were allowed to review the pre-operative images for localization of pre-existing benign liver lesions such as hemangiomas. Image review consisted of two separate reviewing sessions with a 4-week interval between interpretations. The non-contrast MRI set (T_1 - and T_2 WI plus DWI) was presented randomly in a blinded manner at the first reading session. In the second session, the whole MRI set for each patient was presented randomly.

The diagnostic criteria for intrahepatic recurrent HCC on non-contrast MRI were a nodule with hypointensity on T_1 WI, mild to moderate hyperintensity on T_2 WI, and/or diffusion restriction on DWI.³ On gadoteric acid-enhanced MRI, arterial hyperenhancement and hypointensity on HBP with/without portal washout were considered HCC recurrence.^{10,16} A nodule with only arterial enhancement or hypointensity on HBP was also considered HCC recurrence when there was accompanying hyperintensity on T_2 WI and/or DWI.¹⁰ The final decisions were made by the subjective judgment of each observer with consideration of lesion clarity, shape, and size.

Intrahepatic tumor recurrence was classified using a 4-point scale: 1, probably a benign lesion; 2, possibly a benign lesion; 3, probably HCC recurrence; and 4, definitely HCC recurrence. Lesions that were not detected on MRI were given a rating of 0. Confidence scores of 3 and 4 represented diagnoses of intrahepatic HCC recurrence.

After independently evaluating both MRI sets, the two reviewers then jointly evaluated the scores until they reached a consensus, which was used for data analysis. In cases of disagreement, a third reviewer (J.H.M. with 9 years of abdominal imaging experience) was involved to reach a final consensus. Reviewers also determined the signal intensity of the hepatic lesions on MRI.

Reference standard of recurrent HCC

The diagnosis of recurrent HCC was based either on histopathological confirmation or on the clinical criteria,^{5,17,18} thoroughly evaluated by other radiologist (Y.K.K. with 18 years of abdominal imaging experience). The clinical diagnosis of HCC was based on its typical imaging hallmarks on two imaging techniques, with interval increase in size with increasing trend of serum alpha-fetoprotein in patients with suppressed hepatitis activity.¹⁸ The diagnosis of benign hepatocellular nodule was based on imaging findings and stability or interval decrease in size during at least 12 months of follow-up.

Statistical analysis

Continuous variables were compared parametrically using Student's t -test or non-parametrically using the Mann–Whitney U test. Categorical variables were compared using the χ^2 test or Fisher's-exact test, as appropriate.

The diagnostic performance of each imaging set was assessed using the jackknife alternative free-response receiver operating characteristic (JAFROC) software (JAFROC, v. 4.2; <http://www.devchakraborty.com>) with pairwise comparisons performed between imaging sets for each observer. The sensitivity, specificity, accuracy, positive-predictive value (PPV), and negative-predictive value (NPV) were calculated for each image set. We calculated 95% confidence intervals using Wilson's method to address the reliability of the results obtained from a sample.¹⁹ For

possible influence of lesion clustering on diagnostic accuracy, we used the generalized estimating equation method. McNemar's test was used to compare the sensitivity, specificity, and accuracy of two image sets. Bennett's test was used to compare PPV and NPV across image sets.²⁰ *p*-values < 0.05 were considered statistically significant. κ statistics were used to determine the inter-reviewer agreement for assessing MRI. Values of 0.8–1.0 were considered to reflect almost perfect agreement, 0.6–0.79 substantial, 0.40–0.59 moderate, 0.2–0.39 fair, 0–0.19 slight, and 0–1.0 poor.²¹ All statistical analyses were performed using SAS v. 9.4 (SAS Institute, Cary, NC) and R 3.3.2 (Vienna, Austria; <http://www.R-project.org/>).

RESULTS

Patient demographics

The patient and lesion characteristics are shown in Table 2. The median time interval between initial liver resection and detection of intrahepatic recurrence was 7.8 months (range, 0.6–47.8 months). A total of 197 recurrent HCCs (median, 1.3 cm; range, 0.5–5.0 cm) were identified in 113 patients. 78 of these patients had a solitary lesion, while 35 had multiple lesions. Of the 197 HCCs, 147 were ≥ 1 cm in diameter (Figure 2), while the remaining 50 were <1 cm (Figure 3). Among 47 benign lesions in 43 patients (detected on either

Table 2. Characteristics of patients and lesions

	Patients with recurrent HCC (<i>n</i> = 113)	Patients without recurrent HCC (<i>n</i> = 370)	<i>p</i> -value
Age (yr) ^a	58 (32–80)	58 (26–85)	0.807
Male : Female	93 : 20	291 : 79	
Etiology			0.638
HBV	87 (77.0)	293 (79.2)	
HCV	11 (9.7)	26 (7.0)	
Others	15 (13.3)	51 (13.8)	
Liver cirrhosis	98 (86.7)	325 (87.8)	0.754
Extent of initial hepatectomy			0.122
Minor resection	62 (54.9)	235 (63.5)	
Major resection	51 (45.1)	135 (36.5)	
Child–Pugh class (at the time of MRI)			0.688
A	112 (99.1)	363 (98.1)	
B	1 (0.9)	7 (1.9)	
AFP (at the time of MRI) ^a	5.5 (1.3–38963.3)	2.8 (1.3–1628.9)	<0.001
Time interval between hepatic resection and first follow-up MRI ^a (months)	7.8 (0.6–47.8)	7.6 (0.6–45.5)	0.674
Time interval subgroup			0.556
<1 year	88 (77.9)	272 (73.5)	
1–2 years	18 (15.9)	76 (20.5)	
≥ 2 years	7 (6.2)	22 (6.0)	
Diagnosis method			0.029
Operation or biopsy	4 (3.5)	2 (0.5)	
Clinical diagnosis	109 (96.5)	368 (99.5)	
Lesion	<i>N</i> = 197	<i>N</i> = 47	
No. of lesions per patients (one/two/three/four/five lesions)	113 patients (78/11/8/7/9)	43 patients (41/0/2/0/0)	
Lesion size (cm) ^a	1.3 cm (0.5–5.0)	0.9 cm (0.4–1.5)	<0.001
Size subgroup			0.003
<1.0 cm	50 (25.4)	30 (63.8)	
≥ 1.0 cm	147 (74.6)	17 (36.2)	

AFP, alpha-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus.

Except where indicated, numbers in parentheses are percentages.

^aData are presented as median (range).

Figure 2. Recurrent hepatocellular carcinoma (1.2 cm), 17 months after left lateral sectionectomy in a 68-year-old male. A small recurrent tumor (arrow) shows hypointensity, arterial hyperenhancement, and hypointensity on (a) pre-contrast T_1 weighted image, (b) arterial phase, and (c) 20 min hepatobiliary phase images after administration of gadoxetic acid, respectively. Breath-hold T_2 weighted image shows (d) a nodular hyperintense lesion (arrow). This lesion (arrow) is hyperintense (e) on single-shot echoplanar diffusion-weighted imaging at $b = 800 \text{ s mm}^{-2}$ and (f) dark on the ADC map. This lesion was categorized as recurrent hepatocellular carcinoma by observers on both non-contrast and whole MRI set. ADC, apparent diffusion coefficient.

non-contrast or whole MRI), 17 were ≥ 1 cm in diameter, while the remaining 30 were < 1 cm. Pathological confirmation was made in four patients with recurrent HCC (surgery) and in two patients with high-grade dysplastic nodules (surgery and biopsy). Benign lesions proved to be regenerative or

dysplastic nodules ($n = 26$), nodular arteriportal shunts ($n = 8$), inflammatory lesions ($n = 8$), hemangiomas ($n = 4$), and adjacent vascular structure ($n = 1$). A total of 327 patients had no focal hepatic lesion on the first follow-up MRI.

Figure 3. Recurrent hepatocellular carcinoma (0.8 cm), 6 months after wedge resection in a 65-year-old male. A small recurrent tumor (arrow) shows hypointensity, arterial hyperenhancement, and hypointensity on (a) pre-contrast T_1 weighted image, (b) arterial phase, and (c) 20 min hepatobiliary phase images after administration of gadoxetic acid, respectively. Breath-hold T_2 weighted imaging shows (d) a nodular hyperintense lesion (arrow) despite its small size. This lesion (arrow) is hyperintense (e) on single-shot echoplanar diffusion-weighted imaging at $b = 800 \text{ s mm}^{-2}$. This lesion was categorized as recurrent hepatocellular carcinoma by observers on both the non-contrast MR and whole MRI set.

Diagnostic performance in the detection of recurrent HCC

In the per-patient-based analysis for the detection of recurrent HCCs, whole MRI was superior to non-contrast MRI with regard to sensitivity (non-contrast vs whole MRI, $p = 0.025$) and accuracy ($p = 0.021$) on the consensus analysis. We also found the same trend in the individual analysis ($p = 0.005$ and 0.004 for R1; $p = 0.008$ and 0.011 for R2) (Table 3). In the per-lesion-based analysis, the sensitivities of whole MRI were better than were those of non-contrast MRI in both the consensus data ($p = 0.048$) and the individual data, $p = 0.005$ for R1; $p = 0.018$ for R2). With regard to the accuracy in per lesion-based analysis, there were only significant differences in the individual analysis ($p = 0.032$ for R1; $p = 0.028$ for R2), not in the consensus analysis ($p = 0.248$) (Table 4).

However, in the population that was followed for ≥ 1 year, we found no significant differences in any of the six diagnostic values including sensitivity (1–2 years after surgery, 88.9% vs 100.0%; ≥ 2 years after surgery, 100.0% of both imaging) between the two MRI sets for both the individual and consensus data. In contrast, in the population with a follow-up period < 1 year, the sensitivity of whole MRI was higher than that of non-contrast MRI (90.9 vs 96.6% $p = 0.025$ for R1; 94.3 vs 98.9%, $p = 0.046$ for R2) in the individual reading; however, the sensitivities did not differ in the consensus reading (95.5 vs 98.9%, $p = 0.083$) (Table 5, Table A1).

In the patient-based analysis, we found a higher NPV with whole MRI than non-contrast MRI for both individual analysis (97.1% vs 99.2%, $p = 0.005$ for R1; 97.9% vs 99.7%, $p = 0.009$ for R2) and consensus analysis (98.4% vs 99.7%, $p = 0.026$) (Table 3).

False negative lesions

One recurrent HCC with 0.7 cm in size was not verified by observers on either non-contrast or whole MRI sets. A retrospective review of this lesion revealed tiny arterial enhancement and hypointensity on HBP; however, this was not observed on non-contrast MRI. The lesion was confirmed as recurrent HCC by interval increase in size on the next follow-up MR image.

Five HCCs in five patients were not verified by any observer on non-contrast MRI, but were clearly discerned on whole MRI. On retrospective review, these lesions were faintly hyperintense on T_2 WI and DWI ($n = 2$), while the others were not depicted on non-contrast MRI set ($n = 3$). Three of these five lesions were in subcapsular area. The remaining two lesions were isointense relative to the surrounding liver parenchyma on non-contrast MRI, probably due to localized bile stasis (Figure 4) or poor hepatic function (Child-Pugh B) (Table A2).

False positive lesions

Overall, 10 lesions were misclassified as recurrent HCCs on either non-contrast or whole MRI by the two observers. One lesion was misclassified as HCC on both image sets, but was actually a vascular structure (as evident on follow-up imaging). There were five false-positive lesions on non-contrast MRI which had mild to moderate hyperintensity on T_2 WI and DWI with/without hypointensity on T_1 WI. However, they were proven to

Table 3. Diagnostic performance of detection of recurrent HCC by patient ($n = 483$)

	Modality	TP	TN	FP	FN	Az value (95% CI)	Sensitivity	Specificity	Accuracy	PPV	NPV
R1	Non-contrast MRI	102	367	3	11	0.897 (0.816,0.979)	90.3	99.2	97.1	97.1	97.1
	Whole MRI	110	369	1	3	0.977 (0.937,1)	97.4	99.7	99.2	99.1	99.2
	p -value ^a					0.003	0.005	0.317	0.004	0.294	0.005
R2	Non-contrast MRI	105	367	3	8	0.877 (0.787,0.966)	92.9	99.2	97.7	97.2	97.9
	Whole MRI	112	368	2	1	0.959 (0.900,1)	99.1	99.5	99.4	98.3	99.7
	p -value ^a					0.009	0.008	0.564	0.011	0.509	0.009
Consensus	Non-contrast MRI	107	364	6	6	0.972 (0.951,0.993)	94.7	98.4	97.5	94.7	98.4
	Whole MRI	112	367	3	1	0.994 (0.985,1)	99.1	99.2	99.2	97.4	99.7
	p -value ^a					0.027	0.025	0.257	0.021	0.234	0.026

CI, confidence interval; FP, false-positive; FN, false-negative; HCC, hepatocellular carcinoma; NPV, negative-predictive value; PPV, positive-predictive value; R1, reviewer 1; R2, reviewer 2; TN, true-negative; TP, true-positive.

^a p -value for difference of each factor of diagnostic performance between non-contrast vs Whole MRI.

Table 4. Diagnostic performance of detection of recurrent HCC by lesion ($n = 571$)

	Modality	TP	TN	FP	FN	Az value (95% CI)	Sensitivity	Specificity	Accuracy	PPV	NPV
R1	Non-contrast MRI	185	371	3	12	0.949 (0.921, 0.977)	93.9	99.2	97.4	98.4	96.9
	Whole MRI	194	372	2	3	0.987 (0.972, 1)	98.5	99.5	99.1	99.0	99.2
	p -value ^a					0.002	0.005	0.725	0.032	0.695	0.006
R2	Non-contrast MRI	188	371	3	9	0.962 (0.938, 0.986)	95.4	99.2	97.9	98.4	97.6
	Whole MRI	196	371	3	1	0.994 (0.985, 1)	99.5	99.2	99.3	98.5	99.7
	p -value ^a					0.007	0.018	1.000	0.028	0.950	0.020
Consensus	Non-contrast MRI	191	368	6	6	0.972 (0.950, 0.993)	97.0	98.4	97.9	97.0	98.4
	Whole MRI	196	369	5	1	0.994 (0.985, 1)	99.5	98.7	99.0	97.5	99.7
	p -value ^a					0.026	0.048	0.804	0.248	0.777	0.050

CI, confidence interval; FP, false-positive; FN, false-negative; HCC, hepatocellular carcinoma; NPV, negative-predictive value; PPV, positive-predictive value; R1, reviewer 1; R2, reviewer 2; TN, true-negative; TP, true-positive.

^a p -value for difference of each factor of diagnostic performance between non-contrast vs Whole MRI.

Table 5. Diagnostic performance of detection of recurrent HCC by patient according to follow-up period (consensus data)

	Modality	TP	TN	FP	FN	Az value (95% CI)	Sensitivity	Specificity	Accuracy	PPV	NPV
<1 year ($n = 360$)	Non-contrast MRI	84	267	5	4	0.975 (0.953, 0.998)	95.5	98.2	97.5	94.4	98.5
	Whole MRI	87	269	3	1	0.992 (0.98, 1)	98.9	98.9	98.9	96.7	99.6
	p -value ^a					0.098	0.083	0.414	0.096	0.387	0.084
1–2 years ($n = 94$)	Non-contrast MRI	16	76	0	2	0.943 (0.865, 1)	88.9	98.7	96.8	94.1	97.4
	Whole MRI	18	76	0	1	1 (1, 1)	100.0	100.0	100.0	100.0	100.0
	p -value ^a					0.155	0.500	1.000 ^a	0.250	0.330	0.163
≥2 years ($n = 29$)	Non-contrast MRI	7	22	0	0		100.0	100.0	100.0	100.0	100.0
	Whole MRI	7	22	0	0		100.0	100.0	100.0	100.0	100.0
	p -value ^a					N.A	N.A	N.A	N.A	N.A	N.A

CI, confidence interval; FP, false-positive; FN, false-negative; HCC, hepatocellular carcinoma; N.A, not applicable; NPV, negative-predictive value; PPV, positive-predictive value; R1, reviewer 1; R2, reviewer 2; TN, true-negative; TP, true-positive.

^a p -value for difference of each factor of diagnostic performance between non-contrast vs Whole MRI.

Figure 4. Recurrent hepatocellular carcinoma (1.1 cm), 19 months after central hepatectomy in a 68-year-old male. A small recurrent tumor (arrow) shows slight hypointensity, arterial hyperenhancement, and hypointensity on (a) pre-contrast T_1 weighted image, (b) arterial phase, and (c) 20 min hepatobiliary phase images after administration of gadoxetic acid, respectively. This lesion was categorized as recurrent hepatocellular carcinoma by both observers on the whole MRI set. However, breath-hold T_2 weighted imaging shows (d) segmental hyperintensity (arrows) with no focal lesion at the corresponding area. There is a hyperintense, dilated bile duct (arrowheads) within the segment. Inferiorly, there is intrahepatic bile duct dilatation in the remnant right lobe due to stricture (not shown here). (e) Single-shot echoplanar diffusion weighed imaging at $b = 800 \text{ s mm}^{-2}$ also shows segmental hyperintensity of the obstructed liver segment (arrows). This lesion was missed by both observers using non-contrast MRI.

be inflammatory lesions including eosinophilic abscesses ($n = 4$) and a tiny sclerosing hemangioma ($n = 1$). Similarly, four lesions in two patients were misclassified as HCCs on whole MRI given subtle arterial hyperenhancement and hypointensity on HBP, with hyperintensity on DWI and T_2 WI. These four lesions were confirmed as dysplastic nodule ($n = 1$) or inflammatory lesions ($n = 3$) by biopsy. The dysplastic nodule was a 1.4-cm-sized fat-containing lesion on T_1 WI, with hypointensity on HBP and faint DWI hyperintensity (Table A2).

Interobserver agreement

The κ -values for per-patient-based analysis between the two observers were 0.92 for the non-contrast MRI set and 0.97 for the whole MRI set. The κ -values for per-lesion-based analysis were 0.93 for the non-contrast MRI set and 0.97 for the whole MRI set. These κ -values reflect excellent interobserver agreement with regard to the presence of intrahepatic HCC recurrence.

DISCUSSION

Our study demonstrates that whole MRI has significantly higher sensitivity than non-contrast MRI in the surveillance for recurrent HCC after surgery in both patient-based and lesion-based analysis. However, the diagnostic performance of non-contrast MRI was fairly high (sensitivity 94.7% and accuracy 97.5% for per patient-based consensus analysis). The sensitivity of non-contrast MRI in this study was higher than that from a previous meta-analysis showing 88% overall per-patient sensitivity and higher overall per-lesion sensitivity of MRI than that of multi-detector CT (80 vs 68%, $p = 0.0023$).²² Interestingly, non-contrast MRI had comparable performance to that of whole MRI in the detection of recurrent HCC in a selected cohort of patients

followed for ≥ 1 year. Therefore, our study provides an important information regarding establishment of a strategy for selecting imaging modalities for surveillance after HCC resection.

Hardie et al reported that non-contrast MRI has moderate sensitivity for HCC detection in transplanted liver compared to gadolinium-enhanced MRI (53.5% vs 82.5%), implying diagnostic value of non-contrast MRI when gadolinium cannot be administered.²³ In a study which analyzed patients who underwent surgical resection, Kim et al reported that the Az value of the non-contrast MRI (mean, 0.906) was not inferior to that of the gadoxetic acid-enhanced whole MRI (mean, 0.924) for detecting HCC and cholangiocarcinoma ($p > 0.05$).²⁴ The previous study²⁴ and our current study both demonstrated considerably high sensitivity of non-contrast MRI for detecting HCC (92.2–93.0% and 97.0%, respectively). Given the fact that a vast number of patients are subjected to MRI for either HCC screening or recurrence surveillance after treatment, the result of our study implies that non-contrast MRI can be exploited to shorten MR examination time, reduce study cost, and relieve patient inconvenience by avoiding gadolinium administration. Newly developed non-HCC tumors are unlikely in patients who underwent HCC resection; therefore, such tumors are not often considered in the differential of new solid liver lesions. Therefore, our study might have been biased resulting in an increased likelihood of identifying liver lesions as HCC recurrences, leading to a higher sensitivity than reported in previous studies. Other reasons for the disparity between our findings and those of former studies are differences in patient selection. Most of our study population was classified as Child–Pugh A. We also used different imaging techniques and higher field strength (3.0 T) compared

to those of other studies. Another possible cause might be the recent improvement in DWI and T₂WI quality. In particular, improvements in multichannel surface receiver coils, gradient technology, and echoplanar imaging, as well as the introduction of parallel imaging enable high quality DWI to be obtained using a signal-shot.²⁴

There is a high incidence of HCC recurrence during the first 2 years after resection.^{25–27} Most early recurrences within 1 year of resection are thought to be due to tumor dissemination and tend to be biologically aggressive.^{28,29} In contrast, late recurrences are mainly attributable to *de novo* carcinogenesis, which are more likely curable.²⁹ Recently, Kim et al reported that the detection rate of recurrent HCC using gadoxetic acid-enhanced MRI was higher than that of multidetector CT in patients followed for ≥1 year after hepatectomy.⁵ These findings are in close agreement to those of another previous study.²² Given that the diagnostic performance of recurrent HCC in our study did not differ using two imaging modalities in patients followed for ≥1 year, our study is partly in line with prior findings³ that demonstrated a comparable diagnostic performance between non-contrast and whole MRI for detection of hepatic malignancy (mostly HCC) in patients with chronic liver disease. Interestingly, in consensus reading, there were also no differences in the five diagnostic values, including sensitivity, between the two images. This finding was also found in the population with a follow-up period of <1 year. Of six missed HCCs with non-contrast MRI, four lesions were assigned a score of 1 or 2, which reflect that characterizing a lesion is more challenging than localizing it when using non-contrast MRI. Therefore, it is reasonable to recommend non-contrast MRI for surveillance in selected patients followed for ≥1 year after HCC surgery, followed by contrast-enhanced CT or MRI for characterization when a lesion is detected.

This study has several limitations. First, we included heterogeneous cohorts with various follow-up periods and no pre-defined MRI surveillance policy, although most patients were followed up every 3 months during the first 2 years, and every 6 months thereafter. However, it was not our intention to establish a post-operative surveillance strategy for HCC patients. Instead, our study compared the diagnostic performance between non-contrast and whole MRI. Nevertheless, this retrospective study serves as the first step toward fully understanding the value of non-contrast MR in long-term post-operative HCC surveillance. Second, our data come from a single institution with a single MR protocol. Therefore, our data might not be readily generalizable to other institutions. In addition, the image quality of DWI and T2WI could be variable across MR systems resulting from different field strengths and from different vendors due to different gradient linearity and eddy current. Our results require further validation to be reproducible in a 1.5T system and heterogeneous patient population.

In conclusion, non-contrast MRI including DWI had comparable performance to that of whole MRI using gadoxetic acid in the detection of late intrahepatic HCC recurrence during post-operative surveillance. Non-contrast MRI may serve as an alternative follow-up method which can potentially replace whole MRI at least in selected patients ≥1 year after surgery who have relatively lower risk of HCC recurrence.

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