

## Detection of Hypervascular Hepatocellular Carcinoma with Non-enhanced Magnetic Resonance Imaging Including Diffusion-weighted Imaging

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MRI without DWI and US. However, a well-differentiated HCC or a nodule in S2 influenced by cardiac motion artifact may not be detected on DWI.

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**Key words:** Diffusion-weighted imaging; Hepatocellular carcinoma; Magnetic resonance imaging; Ultrasound

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### ABSTRACT

**AIM:** To evaluate the usefulness of non-enhanced magnetic resonance imaging (MRI) including diffusion-weighted imaging (DWI) for detecting hypervascular hepatocellular carcinomas (HCCs).

**METHODS:** A total of 121 consecutive patients with 149 initial HCCs definitely diagnosed by dynamic computed tomography underwent non-contrast MRI including DWI and ultrasound (US). Detection rates for hypervascular HCC were calculated for all non-enhanced MRI sequences including DWI and US. Then, the correlations between tumor negativity on DWI and other MRI sequences and tumor location were analyzed to clarify the characteristics of negative HCC on DWI.

**RESULTS:** The detection rates for HCC by US, all MRI sequences without DWI, and all MRI sequences including DWI were 85%, 91%, and 99%, respectively. The HCC detection rate was significantly higher by all MRI sequences including DWI than by US ( $p < 0.001$ ) and all MRI sequences without DWI ( $p < 0.001$ ). All negative HCCs on DWI were isointense or hyperintense on T1-weighted imaging ( $p < 0.001$ ). Negative HCCs on DWI showed significantly higher rates of positive chemical shift ( $p = 0.013$ ) on T1-weighted imaging and hypointense or isointense tumors on T2-weighted imaging ( $p < 0.001$ ). The HCC detection rate by DWI was 83% in S2, lower than in other segments.

**CONCLUSIONS:** The detection of hypervascular HCCs on non-enhanced MRI including DWI was superior to that on non-enhanced

### INTRODUCTION

Most early hepatocellular carcinomas (HCCs) and dysplastic nodules are arterial hypovascular on dynamic computed tomography (CT) or angiography, and these lesions have lower grade malignancy than arterial hypervascular, overt HCCs. Hypervascular HCCs should be treated because of their short doubling time and the risk of rapid progression<sup>[1]</sup>. Since recent progress in imaging analysis has brought earlier diagnosis of HCC, early HCC is not the critical factor affecting the survival rate. In the surveillance algorithm in Japan, when dynamic CT/magnetic resonance imaging (MRI) shows no findings of typical hypervascular hepatocellular carcinoma, if the tumor diameter is less than 2 cm, simply following the tumor by ultrasonography at intervals of 3 months is suggested<sup>[2]</sup>. Since there is a problem of lead-time bias and no evidence of survival benefit in the treatment of patients with hypovascular HCCs, treatment for tumors less than 2 cm is unnecessary. Therefore, it is more important that no hypervascular HCCs are missed on HCC screening than to detect hypovascular HCCs.

Surveillance for HCC is widely practiced and can generally be recommended using ultrasound (US) and tumor marker tests at 6-month intervals for groups at high risk for HCC<sup>[2]</sup>. However, there are blind spots on US, and the most difficult US examinations are in obese individuals with fatty liver disease and cirrhosis. US is non-invasive and highly specific, but it is insufficiently sensitive to detect

HCC in many cirrhosis patients or to support an effective surveillance program<sup>[3]</sup>. The sensitivity of unenhanced US alone is significantly lower than that of dynamic CT<sup>[4,5]</sup>.

In the surveillance algorithm in Japan, even if US does not visualize a nodule due to the poor visualization ability of US, contrast dynamic CT or dynamic MRI may be performed at intervals of 6 to 12 months<sup>[2]</sup>. However, contrast CT cannot be performed for patients with renal dysfunction or allergy to contrast media, the patients are exposed to high levels of radiation with CT, and there is a potential long-term carcinogenesis risk with repeated contrast CT<sup>[6,7]</sup>. In addition, patients with renal dysfunction are also exposed to the risk of nephrogenic systemic fibrosis by contrast dynamic MRI using a gadolinium-containing contrast agent<sup>[8]</sup>. Therefore, a safer imaging modality that misses fewer hypervascular HCCs than US should be used instead of contrast CT/MRI for HCC surveillance.

Diffusion-weighted imaging (DWI) is a non-invasive MRI technique that provides tissue contrast by measuring diffusion of water molecules in tissue. It has been reported to be useful in the detection of malignant tumors<sup>[9,10]</sup>. However, to the best of our knowledge, there have been few reports focusing on the detectability of HCC by non-enhanced MRI with added DWI. In the present study, whether non-enhanced MRI including DWI is superior to non-enhanced MRI without DWI and US in the detection of hypervascular HCCs was analyzed. Furthermore, the correlations between DWI and T1-weighted imaging (WI) or chemical shift on T1WI or T2WI were analyzed to clarify the characteristics of negative HCCs on DWI.

## METHODS

### Patients

Patients with initial hypervascular HCCs diagnosed by contrast dynamic CT were enrolled in the present study. Between October 2007 and October 2010, 121 consecutive patients with 149 initial hypervascular HCCs were examined by non-contrast MRI including DWI and US within 4 weeks from the diagnosis by contrast CT. Diagnostic criteria for HCC on contrast CT were defined as a nodule visualized as a high density area in the arterial phase and as a relatively low density area in the portal/equilibrium phase on the basis of the diagnostic algorithm for HCC in Japan<sup>[2]</sup>. The patients' characteristics are summarized in table 1.

**Table 1** Patients' characteristics.

Patients' characteristics	
Age (years)	70 (38-89)
Sex (male/female)	74/47
Etiology (HBV/HCV/both negative)	17/86/18
Fibrosis stage (F0/1/2/3/4/unknown)	2/3/10/32/68/6
Number of tumors	149
Solitary	98
Multiple	23
Tumor size (mm, range)	20 (8-130)
≤2 cm / >2 cm	82/67
Location of tumor (Segment 1/2/3/4/5/6/7/8)	2/12/13/16/24/22/17/43
AFP (ng/mL, range)	31.4 (1.4-23992.2)
AFP-L3 (% , range)	0.0 (0.0-99.5)
DCP (mAU/mL, range)	114 (5-113010)

HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein; AFP-L3, Lensculinaris agglutinin-reactive alpha-fetoprotein; DCP, Des-gamma-carboxyprothrombin. Values expressed as medians (range).

The fibrosis stage of the liver was evaluated by the METAVIR scoring system<sup>[11]</sup> using a core needle biopsy specimen or resected liver tissue. Written, informed consent was obtained from each enrolled patient, and the protocol was approved by the ethics committee of Wakayama Medical University.

### Technique and analysis

All contrast dynamic CT examinations for the definite diagnosis of hypervascular HCC with multi-detector row CT scanners (Aquilion16, Toshiba Medical Systems, Tochigi, Japan) with a section thickness of 5 mm were performed before enrollment in the present study. In addition to plain images, arterial phase images were obtained 40 seconds after the start of bolus administration. Portal and equilibrium phase images were obtained at 70 seconds and 180 seconds, respectively. All patients received a non-ionic iodinated contrast medium at a dose of 580 mgI/kg administered by an automated power injector for 30 seconds.

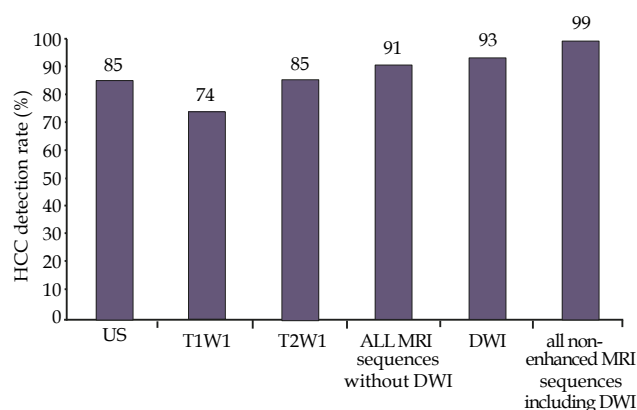
MRI scans were performed using a 1.5-Tesla MR imager (Intera 1.5 T, Philips Medical Systems, Best, The Netherlands). All patients underwent in-phase and out-of-phase axial T1-weighted imaging (T1WI) with breath-holding (FFE, TR=200 ms, TE=4.6 ms in-phase/2.3 ms out-of-phase, FA=80, slice thickness 4.5-5.5 mm, interslice gap 0 mm, matrix size 448×448, field of view 350), which was used as a breathing motion reduction technique. T2-weighted imaging (T2WI), respiratory trigger (SSTSE, TR=490 ms, TE=80 ms, FA=90, slice thickness 4.5-5.5 mm, matrix size 512×512, field of view 350) and DWI with the sensitivity encoding (SENSE) technique, respiratory trigger (SE-EPI, TR=1200 ms, TE=64 ms, FA=90, slice thickness 4.5-5.5 mm, matrix size 256×256, field of view 350) were also performed in all patients. The CHES fat suppression method was used for DWI. The b-factors were 50 and 800 sec/mm<sup>2</sup>.

Images obtained by MRI were independently analyzed without reference to CT images by one experienced radiologist and one experienced hepatologist who had more than 20 years of experience in liver imaging. Any disagreements in interpretation were resolved by consensus. If the HCC nodule diagnosed by contrast CT was detected on any non-enhanced MRI sequences by the interpreters, detection of that lesion was considered positive. The lesion's MRI signal intensity was visually compared with the surrounding liver and categorized as hyperintense, isointense, or hypointense. If the tumor intensity of out-of-phase T1WI was lower than that of in-phase T1WI, chemical shift was defined as positive. On DWI with a b-factor of 800 s/mm, hyperintense tumors were defined as positive. On T1WI (in-phase or out-of-phase) and T2WI, hypointense or hyperintense tumors were defined as positive.

An SSA-770A ultrasound system (Toshiba Medical Systems) with a PVT-674BT ultrasound probe or an S2000 Ultrasound Platform (Siemens Medical Systems, Erlangen, Germany) with a 4C1 convex probe was used. Tissue harmonic imaging was performed in B-mode. US was performed with reference to CT images to minimize the effect of sonographer skill. If the HCC nodule diagnosed by contrast CT was visualized on B-mode US by an expert sonographer who had 10 years of experience in liver imaging, detection of the lesion was considered positive.

### Statistical analysis

Values are expressed as means±standard deviation (SD). McNemar's test was used for comparing the detection rates for HCC among US, T1WI, T2WI, all non-enhanced MRI without DWI, DWI, and all non-enhanced MRI including DWI. Fisher's exact test was used for comparing the HCC detection rates by DWI according to tumor size and location, and the correlations between DWI and T1WI or chemical shift using T1WI or T2WI were analyzed using Fisher's exact test. A p value less than 0.05 was considered significant. All analyses were performed using the SPSS 19.0 software package (SPSS, Inc., Chicago, IL, USA).



**Figure 1** Comparison of HCC detection rates. Although there is no significant difference in the HCC detection rate between all non-enhanced MRI sequences without DWI and US ( $p=0.137$ ), the HCC detection rate is significantly higher by all non-enhanced MRI sequences including DWI than by US ( $p<0.001$ ) and by all non-enhanced MRI sequences without DWI ( $p<0.001$ ).

## RESULTS

### HCC detection rate

The detection rates for hypervascular HCCs by US, T1WI (in-phase or out-of-phase), T2WI, all MRI sequences without DWI, DWI, and all non-enhanced MRI sequences including DWI were 85% (127/149), 74% (111/149), 85% (126/149), 91% (136/149), 93% (139/149), and 99% (148/149), respectively (Figure 1).

The HCC detection rate was significantly higher by all non-enhanced MRI sequences including DWI than by all non-enhanced MRI sequences without DWI ( $p<0.001$ ). Although there was no significant difference in the HCC detection rate between all non-enhanced MRI sequences without DWI and US ( $p=0.137$ ), the HCC detection rate by all non-enhanced MRI including DWI was also significantly higher than that by US ( $P<0.001$ ). The reasons for invisible HCCs on US were blind spots ( $n=18$ ) such as multiple reflections at the liver surface and under the lung or bowel, obesity ( $n=3$ ), and isoechoic tumor ( $n=1$ ). However, one remaining lesion (18 mm in S8) that was undetected on all non-enhanced MRI including DWI was visualized by US.

The HCC detection rates by DWI according to tumor size were 90% for  $\leq 2$  cm and 97% for  $> 2$  cm. There was no significant difference in the HCC detection rate by DWI according to tumor diameter ( $p=0.186$ ). The HCC detection rates according to tumor location were as follows: S1, 100%; S2, 83%; S3, 100%; S4, 94%; S5, 96%; S6, 91%; S7, 100%; and S8, 88%. The HCC detection rate was lower for S2 than for the other segments, but there was no significant difference in the HCC detection rate by tumor location ( $p=0.429$ ).

### Negative HCCs on DWI

Ten HCCs were negative on DWI. Table 2 shows the correlation between DWI and in-phase T1WI. All negative HCCs on DWI were isointense or hyperintense on T1WI ( $p<0.001$ ).

Table 3 shows the correlation between DWI and chemical shift using T1WI; 6 of 10 negative HCCs were positive for chemical shift. The rate of positive chemical shift was significantly higher in the negative HCCs on DWI than in the positive HCCs on DWI ( $p=0.013$ ).

Table 4 shows the correlation between DWI and T2WI; 6 of 10 negative HCCs were hypointense or isointense on T2WI. The rate of hypointense or isointense tumors was significantly higher in the negative HCCs on DWI than in the positive HCCs on DWI ( $p<0.001$ ).

**Table 2** Correlation between DWI and in-phase T1WI.

	In-phase T1WI			<i>p</i> -value
	Hypointense ( $n=77$ )	Isointense ( $n=57$ )	Hyperintense ( $n=15$ )	
DWI-positive ( $n=139$ )	77 (55%)	51 (37%)	11 (8%)	$<0.001$
DWI-negative ( $n=10$ )	0	5 (50%)	5 (50%)	

DWI: diffusion-weighted imaging; T1WI: T1-weighted imaging.

**Table 3** Correlation between DWI and chemical shift using T1WI.

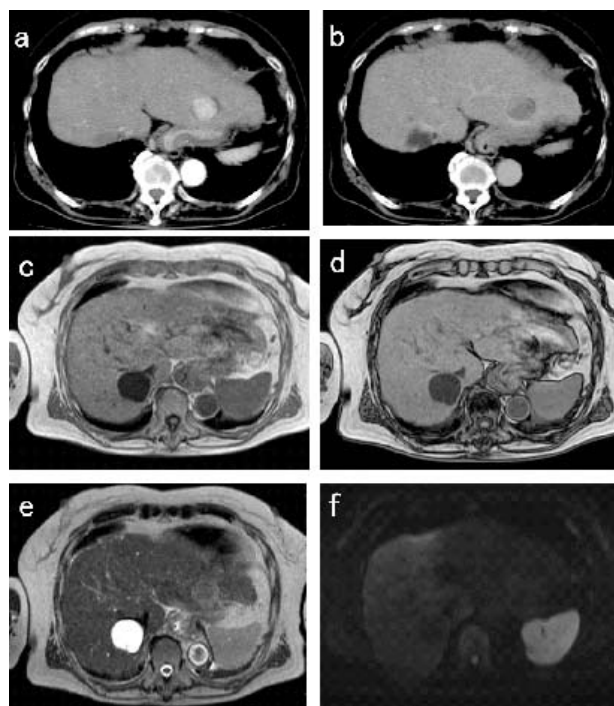
	Chemical shift		<i>p</i> -value
	Positive	Negative	
DWI-positive ( $n=139$ )	30 (22%)	109 (78%)	0.013
DWI-negative ( $n=10$ )	6 (60%)	4 (40%)	

DWI: diffusion-weighted imaging; T1WI: T1-weighted imaging.

**Table 4** Correlation between DWI and T2WI.

	T2WI			<i>p</i> -value
	Hypointense ( $n=1$ )	Isointense ( $n=23$ )	Hyperintense ( $n=125$ )	
DWI-positive ( $n=139$ )	0	18 (13%)	121 (8%)	$<0.001$
DWI-negative ( $n=10$ )	1 (10%)	5 (50%)	4 (40%)	

DWI: diffusion-weighted imaging; T2WI: T2-weighted imaging.

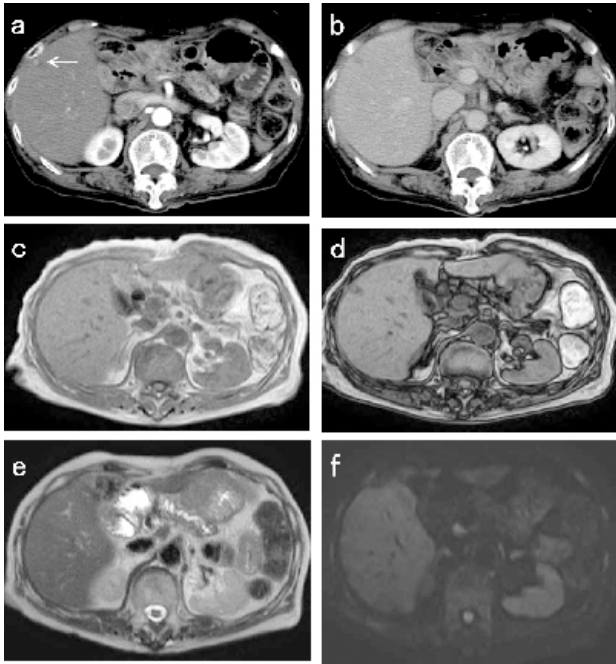


**Figure 2** A case of undetectable HCC on DWI due to cardiac motion artifact. The 3-cm HCC in segment 2 is stained during the arterial phase on contrast CT (a), and tumor stain washout is shown during the equilibrium phase (b). However, the tumor is unclear on both in-phase (c) and out-of-phase (d) T1WI and is slightly hyperintense on T2WI (e). The tumor is not depicted on DWI due to cardiac motion artifact (f).

Overall, 7 of 10 negative HCCs on DWI were visualized on US, and 2 of 3 nonvisualized HCCs on US were located in S8, in the blind spot by the lung. The remaining one was a small, 1-cm HCC located deeply in S6. A case of undetectable HCC located in S2 due to cardiac motion artifact is shown in figure 2, while a case of undetectable, well-differentiated HCC on DWI is shown in figure 3.

## DISCUSSION

Abdominal DWI images have improved with the appearance of the extremely fast, spin-echo, echo planar, imaging method, and they



**Figure 3** A case of undetectable, well-differentiated HCC on DWI. The 1-cm HCC in segment 5 (arrow) is stained during the arterial phase on contrast CT (a), and tumor stain washout is shown during the equilibrium phase (b). The tumor is isointense on in-phase T1WI (c), hypointense on out-of-phase T1WI (d), and isointense on T2WI (e). The tumor is not depicted on DWI (f). The tumor is diagnosed as a well-differentiated HCC with fatty change on MRI.

can be applied to the liver<sup>19</sup>. DWI is already reported to be superior to standard T2WI in detecting focal liver lesions<sup>12-14</sup>. Zech *et al.*<sup>13</sup> suggested that the black-blood effect was the reason for this. On DWI, signals such as background liver parenchyma, blood vessels, and bile ducts are inhibited by high b value images. The contrast-to-noise ratio becomes higher secondarily, and small lesions or lesions near blood vessels can be easily confirmed. In the present study, the hypervascular HCC detection rate was a high 93% with DWI, significantly better than with standard T2WI or T1WI. Nasu *et al.*<sup>15</sup> reported a hypervascular HCC detection rate of 91.2%, about the same as the results of the present study. However, DWI has the disadvantages of a low signal-to-noise ratio, low spatial resolution, and susceptibility to effects from motion artifacts due to breathing, intestinal peristalsis, and heartbeat. It is thus possible that a tumor cannot be detected based on its size or location<sup>16-18</sup>. In the present study, how tumor size and location affect HCC detection on DWI was investigated. In a comparison of the HCC detection rate by tumor size, the detection rate of small HCCs  $\leq 2$  cm was a high 90%, showing no significant difference in comparison with the detection rate for HCCs  $> 2$  cm. Vandecaveye *et al.*<sup>19</sup> concluded that DWI provided higher sensitivity and a higher positive predictive value for the detection of HCCs  $< 2$  cm than conventional contrast MRI. Yu *et al.*<sup>20</sup> reported that the addition of DWI to contrast-enhanced MRI was superior in detecting small intrahepatic metastases. Thus, DWI is thought to be useful in detecting small overt HCCs. Meanwhile, looking at the detection rate by tumor location, the HCC detection rate was found to be lowest (83%, 10 of 12 lesions) in the S2 region, which is most strongly susceptible to artifact effects from the heartbeat. The lesion detection rate is thought to be lowered because of heart motion artifacts, and care should be exercised in interpreting such images.

Another possible reason that tumors are not detected with DWI is

the histological characteristics of the tumor. With DWI, the image of diffusion of water molecules within the tissue is obtained, and diffusion is affected by the tissue properties of cellular architecture and density, as well as the microcirculation<sup>16</sup>. In well-differentiated HCCs, since the state of water in the extracellular space closely resembles that in normal liver cells, the signal contrast enhancement is poor on DWI<sup>10</sup>. With T1WI and T2WI, on the other hand, histological features such as fat or metal deposits and water content are depicted well. Many dysplastic nodules and well-differentiated HCCs present as hyperintensity or isointensity on T1WI and isointensity or hypointensity on T2WI. Typical moderately to poorly differentiated HCCs present as hypointensity on T1WI and hyperintensity on T2WI. Distinguishing between well-differentiated and moderately differentiated types is possible from the signal intensity on standard MRI<sup>21-24</sup>. On examining the relationship between DWI and T1WI detection in the present study, all DWI-negative HCCs presented as hyperintensity or isointensity without showing hypointensity on T1WI. On examining the relationship with chemical shift, 60% of DWI-negative HCCs was positive for chemical shift, and the percentage in which fat deposits were seen was significantly higher than with DWI-positive HCCs. As for the relationship with T2WI, the percentage of DWI-negative HCCs that did not present as hyperintensity was significantly higher than that of DWI-positive HCCs. Thus, it may be said that detection on DWI is difficult for HCCs that are histologically well-differentiated, even in the case of hypervascular HCCs. As indicated in the preceding, when using DWI for HCC screening, it is important to have a good understanding of the effects of artifacts and level of histological differentiation.

The HCC detection sensitivity with US in the present study, despite being done with reference to CT images, was 85%, significantly lower than the HCC detection sensitivity of 99% with non-enhanced MRI with DWI. The reasons for invisible HCCs on US in the present study were mainly blind spots, such as the liver surface and under the lung or bowel, as well as obesity and isoechoic HCC. Kim *et al.*<sup>25</sup> demonstrated that the percentage of visible HCCs on planning US before radiofrequency ablation was 74.7%, and smaller tumors, subphrenic location of the tumor, liver cirrhosis, and macronodular cirrhosis were independent predictors of invisible HCC. This is a limitation of US. In HCC surveillance without reference to CT images, the HCC detection sensitivity with US would probably be even lower. DWI is one of the non-contrast-enhanced MRI sequences, and DWI is not normally used alone. In the present study, the detection rate of hypervascular HCCs when DWI was added to standard non-contrast-enhanced MRI was 99%. Even for HCCs that cannot be detected with DWI alone, detection can be reliably done using other MRI sequences. Current HCC surveillance is centered on regular US every 3-6 months<sup>2,26</sup>, but many tumors are overlooked, and the low detection sensitivity is a problem. However, HCC that could not be detected on non-contrast-enhanced MRI including DWI was detected on US. Therefore, it seems that, by combining non-contrast-enhanced MRI including DWI with US, detection of nearly all cases of hypervascular HCC that can be diagnosed with contrast-enhanced CT would become possible, and a noninvasive routine test that does not overlook tumors may be achieved. However, while HCC detection sensitivity may be improved with the combined use of US and non-contrast-enhanced MRI, cost effectiveness may become a problem.

The present study had some drawbacks. First, the analysis of the detection rate for each imaging modality was not carried out blind. Although the analysis of MRI images was done without reference to

CT images, US was performed with reference to CT images. Since US diagnosis is contingent on sonographer skill, a study protocol in which US was performed with reference to CT images was developed to minimize the effect of sonographer skill. This might have resulted in a significant bias in the results of the detection rate for each diagnostic parameter. The detection rate of hypervascular HCC by US was probably overestimated. Even if US were performed blind, the hypervascular HCC detection rate by US would be significantly lower than that by non-enhanced MRI including DWI. Second, the apparent diffusion coefficient (ADC) map and values were not evaluated in the present study, because the aim of the present study was not the differential diagnosis of malignancy, but its detection. Third, in the present study, the specificity of hypervascular HCC detection by non-enhanced MRI with DWI could not be evaluated, because subjects with benign tumors were not included. Fourth, the gold standard of HCC diagnosis in the present study was not histology, but dynamic CT. Since the sensitivity of HCC diagnosis by dynamic CT is not very high, there is a selection bias. However, since the specificity of HCC diagnosis by dynamic CT is very high<sup>[3]</sup>, only patients with hypervascular HCCs were selected. The results of the present study do not indicate that non-enhanced MRI including DWI is superior to US in the detection of hypovascular HCCs. With respect to the detection rate for hypovascular early HCCs and borderline lesions such as dysplastic nodules, it is likely that non-enhanced MRI including DWI will be inferior to US. However, in the detection of hypervascular HCCs, non-enhanced MRI including DWI was superior to US, which is mainly used in the present HCC surveillance. Fifth, since only HCC patients were analyzed in the present study, one cannot conclude that non-enhanced MRI including DWI might be useful in HCC screening. However, since non-enhanced MRI including DWI is non-invasive, it should be clarified whether non-enhanced MRI, rather than US, should have the central role in surveillance, or whether combined non-contrast-enhanced MR and US should have the central role. For this, a large-scale, randomized, controlled trial should be done.

In conclusion, the detection of hypervascular HCCs on non-enhanced MRI including DWI was superior to that on non-enhanced MRI without DWI and US. However, since a well-differentiated HCC or a nodule in S2 influenced by cardiac motion artifact may not be detected on DWI, care should be exercised in interpreting non-enhanced MRI including DWI.

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