Detection of Hypervascular Hepatocellular Carcinoma: Comparison between Gadoxetic Acid-enhanced Magnetic Resonance Imaging and Diffusion Weighted Image

Suwannee Surattanasophon, M.D.*,, Sitthipong Srisajjakul, M.D.*, Wanwarang Teerasamit, M.D.***

*Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, **Department of Radiology, Saraburi Hospital, Saraburi 18000, Thailand.*

ABSTRACT

Objective: The purpose of the study was to determine if the gadoxetic acid-enhanced magnetic resonance (MR) imaging plus dynamic scans and diffusion-weighted (DW) imaging plus dynamic scans gives more sensitivity and accuracy in the diagnosis of hepatocellular carcinomas (HCCs).

Methods: The institutional review board approved this retrospective study and waived the requirement for informed consent. Forty-five cirrhotic patients with 101 HCCs underwent gadoxetic acid-enhanced MR-imaging and DW imaging at 3.0T between January 2012 and November 2013. Two sets of images were analyzed independently by two observers to detect HCC: a gadoxetic acid set (unenhanced, early dynamic, delayed and hepatobiliary phases) and a DW imaging set (unenhanced, early dynamic, delayed and DWI). Diagnostic accuracy, sensitivity, specificity, positive and negative predictive values were calculated.

Results: The accuracy of the gadoxetic acid set and DWI set were 88.5-89.2 and 62.8, respectively. The sensitivity of the gadoxetic acid set and DWI set were 93-96 and 57.4-64.3, respectively. No significant difference of positive predictive value between the two datasets was reported.

Conclusion: The gadoxetic acid set give more diagnostic accuracy and sensitivity to detect HCCs than the DWI set.

Keywords: Hepatocellular carcinoma, gadoxetic acid-enhanced magnetic resonance imaging, diffusion weighted image

INTRODUCTION

Most hepatocellular carcinomas (HCCs) develop in patients with underlying chronic hepatitis or cirrhosis. Carcinogenesis of HCCs are multistep processes, ranging from regenerative nodules and dysplastic nodules to classic HCC.

Gadolinium ethoxybenzyl diethylenetriamine pentacetic acid (gadoxetic acid disodium, Primovist; Bayer-Schering Healthcare, Berlin, Germany) is a liver-specific hepatocellular magnetic resonance (MR) imaging contrast agent that can provide comprehensive hemodynamic information during early dynamic phases

and improved lesion detection in the hepatobiliary phase (HBP) within a single examination. In the evaluation of patients suspected of having HCC, the most useful feature of gadoxetic acid is better depiction of HCC as hypointensity on the hepatobiliary phase HBP images than at equilibrium phase of conventional dynamic images, due to more obvious contrast image from surrounding hepatocyte uptake of normal liver parenchyma

Diffusion-weighted (DW) imaging has been applied increasingly to liver imaging, because it is easy to perform and no contrast agent is needed. The ability of DW imaging is to differentiate the basis of cellular density and architectural change in addition to vascularization.

Currently, we use both gadoxetic acid disodium contrast agent and DW imaging to detect and characterize liver nodules. Both of them can help us to evaluate whether a nodule is HCC from differences in hemodynamic changes and tissue diffusion of benign liver nodules and HCC. The recent study[1] reported that the combination of gadoxetic acid-enhanced MR imaging and DW imaging is helpful in the diagnosis of HCCs smaller than 1 cm. However, not every nodule exhibits the same result in both imagings, so this study was conducted to compare the diagnostic performance of gadoxetic acid enhanced-MRI and DW imaging for detection of HCC.

MATERIALS AND METHODS

Patient Selection

In this retrospective study, the sample size was determined on the basis of the primary hypothesis: that the difference in sensitivity with the use of gadoxetic acid-enhanced MR imaging and DW imaging was 10%. Therefore, the appropriate sample size was 62 true-positive lesions, which ensured a power of 80% and a significance level of 0.05.[2]

Our study had institutional review board approval, and the requirement for informed consent was waived. We retrospectively reviewed our institutional database for liver MR imaging reports in patients suspected of having HCC, between 1 January 2012 and 1 November 2013. MR imaging was performed to rule out or confirm HCC because of possible focal hepatic lesions found at ultrasonography or CT.

The inclusion criteria for the patient group were: (a) HCCs that had been proved at surgical resection; (b) liver nodules that showed early arterial enhancement and wash-out on portovenous phase or delayed imaging; and (c) no transarterial chemoembolization (TACE) for HCC treatment before the MR examination. A total of 45 patients (29 men and 16 women with age range, 38-84 years) with 101 HCCs (mean size, 2.06 cm; range, 0.5-12.7 cm) fitted the inclusion criteria. We also selected 12 consecutive participants who had undergone liver MR imaging but had no identifiable HCCs to serve as a control group. Liver cirrhosis associated with hepatitis B virus was diagnosed in 32 patients, and 19 patients had hepatitis C virusinduced liver cirrhosis, while 5 patients had alcoholic induced cirrhosis and 1 patient had cryptogenic cirrhosis.

Reference Standards

A composite reference standard was used to diagnose or rule out HCC (Table 1). A diagnosis of HCC required one or more of the following criteria: histologic confirmation (liver biopsy, resection, and transplantation), or demonstration of substantial growth at a minimum imaging follow-up of 12 months, or characterization of early arterial enhancement with wash-out on portovenous phase or delayed phase according to American Association for the Study of Liver Disease (AASLD). Diagnosis of hemangiomas and other benign lesions were based on imaging findings and stability for at least 12 months of follow-up.

MR Imaging

Twenty seven MR images were acquired by using a 3.0-T whole-body MR system (Ingenia 3.0-T; Philips Healthcare, Best, the Netherlands) and 18 MR images were acquired by using a 3.0-T whole-body MR system (Achieva 3.0-T; Philips Healthcare, Best, the Netherlands). The MR protocol included a

TABLE 1. Reference standard.

	HCC No. = 101	Benign lesions No. = 39
Patients total = 57	45	12
Size (cm)		
Mean	2	2
Range	0.5-12.7	0.6-13.1
No. of lesions per patient		
Mean	1.7	4.5
Range	(1-5)	(1-15)
Surgery		
Lesions (%)	8 (14.0)	0(0)
Biopsy		
Lesions (%)	1 (1.75)	3 (5.2)

T1-weighted dual fast field echo in-phase and opposed-phase sequence, a T2-weighted with fat suppression, a T2-weighted turbo spin echo, and coronal single shot T2-weighted sequence. DW images were acquired before the administration of gadoxetic acid by using a respiratory-triggered single-shot echo-planar imaging sequence with b values of 0, 150, and 500 sec/mm^2. A spectral attenuated inversion-recovery technique was used for fat suppression on DW images. The apparent diffusion coefficient was calculated by using a monoexponential function with b values of 150 and 500 sec/mm^2 to minimize perfusion effects

The MR contrast agent used was gadoxetic acid (Primovist$^®$; Bayer-Schering Healthcare, Berlin, Germany) which was administered at 0.1 mL/kg bodyweight (equivalent to 25 μmol/kg bodyweight). The post-contrast images were acquired during the arterial phase (30 seconds), portovenous phase (70 seconds), 120 seconds and delayed phases (5 minutes) after gadoxetic acid administration, and the hepatobiliary phase was also achieved after 20 and 30 minutes.

Image Analysis

All images were evaluated independently by two gastrointestinal radiologists: observer 1 (S.S., with 7 years of experience), observer 2 (W.T., with 6 years of experience), who were blinded to whether the patients had HCC. The image review consisted of two reviewing sessions for two image sets, with a 2-week interval between image reviews. At the first reading session, the observers were randomly given either the gadoxetic acid set (unenhanced T1- and T2-weighted images and arterial, portal, 5 minute delay, and 20-or 30-minute HBP images) or the DW imaging set (unenhanced T1- and T2-weighted images, arterial, portal, 5 minute delay and DW images) from the HCC and control groups. In the second session,
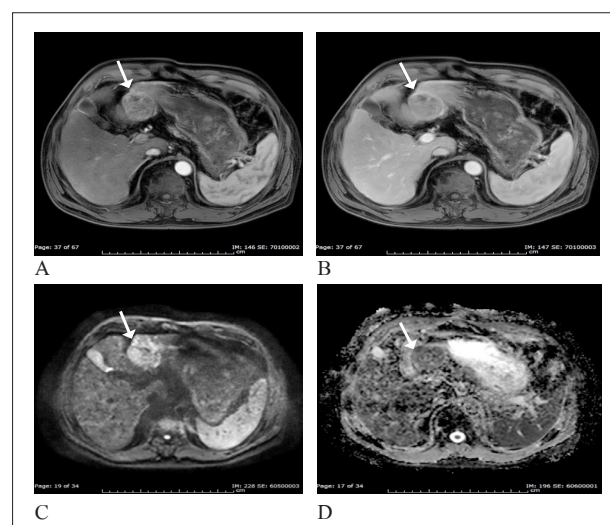

Fig 1. A 65-year-old-man with hepatitis B cirrhosis and HCC (arrow in a-d). Axial arterial phase image (A) and delayed phase (B). Axial DWI image at b = 600 s/mm2 shows hyperintensity (C) and hypointensity on ADC (D) indicating restricted diffusion. Liver surgery confirmed moderate differentiated HCC.

observers received the image set they had not reviewed.

The diagnostic criteria for HCCs on the gadoxetic acid-enhanced images were a nodule showing enhancing foci during the arterial phase, washout during the portal venous phase or 5-minute delayed phase, and hypointensity during HBP. A lesion was diagnosed as HCC on DWI when it was hyperintense on $b = 50$ or $150 \ sec/mm^2$ images, and remained hyperintense on $b = 600$ or $500 \ sec/mm^2$ images (Fig 1), and showed an apparent diffusion coefficient that was lower than or equal to that of the liver parenchyma.

Statistical Analysis

Descriptive statistical analyses were performed by using statistical software (MedCalc version 11.4, MedCalc Software, Mariakerke, Belgium; SPSS version 18.0, SPSS, Chicago, III). Among the 101 HCCs, the sensitivity for each set of images was evaluated according to the number of lesions with the pathological proven HCCs or typical early arterial enhancement with rapid wash-out on portovenous or delayed phase. The specificities and positive and negative predictive values of the sets of images were also calculated.

Inter-reader variability among the two readers for lesion detection was assessed using an un-weighted statistic. Values of 0.4 or less were considered to indicate positive, but poor agreement, while those of 0.41-0.75 and greater than 0.75 indicated good and excellent agreement, respectively. The diagnostic accuracy, sensitivity, specificity, positive and negative predictive values (PPV and NPV) of the two sets of images in the diagnosis of HCC were assessed. Diagnostic accuracy was calculated as the number of lesions confirmed to be HCC at the reference standard (both true-positive and true-negative findings).

RESULTS

Sensitivity and Specificity

The Gadoxetic acid enhanced-MRI set yielded significantly higher mean sensitivity and accuracy for all HCCs (96% and 89.2%, 93% and 88.5% for reader 1 and 2, respectively) than did the DWI-MRI set (64.3% and 62.8%, 57.4% and 62.8% for reader 1 and 2, respectively). Accuracy of HCCs identification was not significantly different between the two observers.

The specificities among the gadoxetic-acid and DWI sets were 70% and 58.9% for reader 1, and 69.7% and 75% for reader 2, respectively.

Positive predictitive value (PPV) among the gadoxetic acid and DWI sets were 88.9% and 80.2% for reader 1 and 87.8% and 85.2% for reader 2, respectively.

Overall of the 101 HCC nodules, fifty-five (55.5%) and ninety-three (92%) were identified on DWI-MRI and gadoxetic-acid enhanced MRI by the two observers, respectively.

False Negative

There were 4 HCCs that were not verified on the gadoxetic acid set by any observer. These lesions show partial uptake of gadoxetic acid (Fig 2). However, these four lesions were discerned on the DWI set.

There were 36 HCCs that were not verified on DWI-MRI by any observer, and a review of these lesions showed that all of these lesions were less than 2 cm (0.5-1.8 cm).

There were 32 HCCs that were not verified by any observers on the DWI set but were clearly discerned on the gadoxetic acid set (Fig 3).
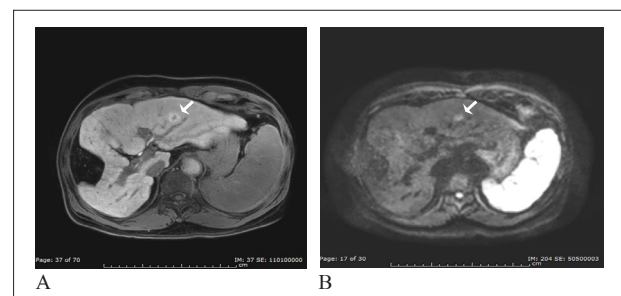

Fig 2. A 57-year-old man was diagnosed benign nodule from HBP phase due to partially gadoxetic uptake (arrow in A) and the lesion depicted hyperintensity on DWI (arrow in B). Angiography showed early arterial enhancement and rapid wash-out, thus, TACE was consequently performed
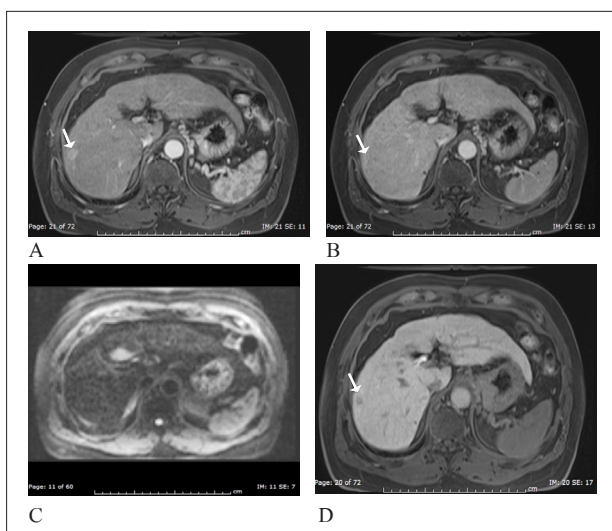
Fig 3. A 78-year-old woman with hepatitis B cirrhosis with small HCC. Axial arterial phase (A) and portovenous phase (B) showed obvious enhancement and faint wash-out of the lesion (arrow in A and B) DWI (C) showed no hyperintense lesion. HBP MR image (D) obtained 20 minutes after administration of gadoxetic acid, revealed hypointense nodule corresponding with arterial enhancing lesion (arrow in D).

False Positive

There were 10 nodules (for reader 1 and 2) which were interpreted to be HCCs on the DWI set. Seven lesions were not changed in their sizes during one to two years and they were verified as benign lesions. One lesion was biopsied and the histological analysis revealed inflammation. Two lesions were hemangiomas.

Interobserver Agreement

The kappa values for the two observers were 0.746 (from 0.635 to 0.858) and 0.879 (from 0.784 to 0.973) for DWI set and the gadoxetic-acid enhanced set, respectively, which indicated good and very good interobserver agreement with 95% confidence interval.

DISCUSSION

Hepatocarcinogenesis is a multifactorial process that includes changes in architecture, cellular density, hepatocyte function, and Kupffer cell numbers or function. The diagnostic imaging of HCCs by combining gadoxetic acid and DW imaging have potential because they concern hemodynamic changes, hepatocyte function, and tissue diffusitivity.

Our study results demonstrated that the sensitivities for the detection of HCCs in the gadoxetic-acid enhanced set were significantly higher than the DWI set (96% and 64.3%, respectively). Gadoxetic-acid enhanced MR imaging improves the detection of HCCs especially small-sized HCCs because of obvious contrast of the hypointense lesion on the hepatobiliary phase HBP from surrounding hepatocyte uptake of normal liver parenchyma. In our study, large numbers of hypointense nodules at HBP (30 nodules for reader 1 and 28 nodules for reader 2) were noticeably detected, and not compatible with the number of morphologic features of typical HCCs. Thus, there were some hypointense nodules at HBP that did not correspond with the characteristics of early arterial enhancement and rapid wash
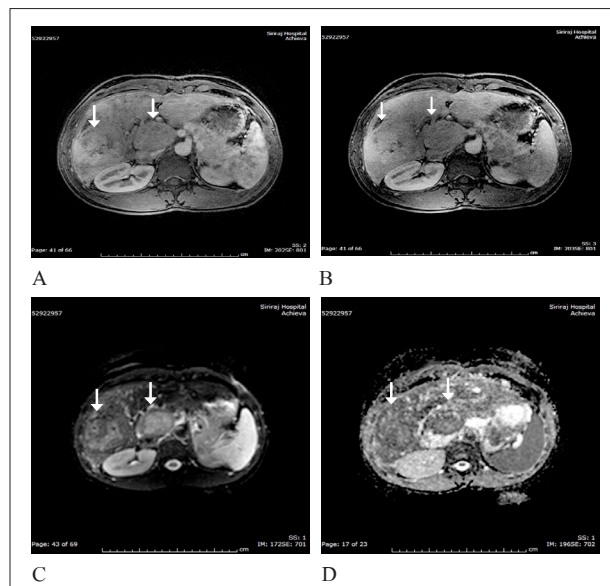

Fig 4. A 46-year-old man with large liver masses (arrows in A-D). The MR contrast-enhanced axial image obtained during the arterial (A) shows arterial enhancement with partially wash-out on portovenous phase (B). DWI (C) shows hyperintensity in some portion of the mass with slightly hypointense on ADC (D). This lesion was biopsied and the pathological result is inflammatory lesion. The lesion is unchanged in size in the next one and a half year- follow up CT scan.
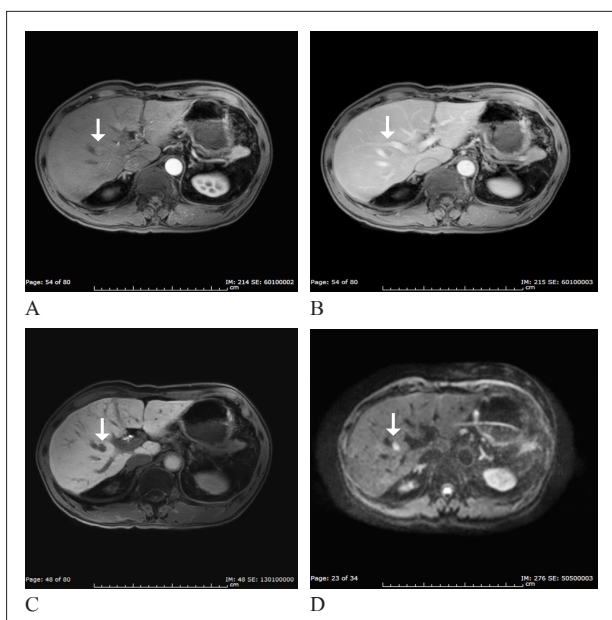
Fig 5. A 58-year-old-man with hepatitis C cirrhosis and small HCC (arrow in A-D). The MR contrast-enhanced axial image obtained during the arterial phase (A) showing subtle arterial enhancement and wash-out on portovenous phase (B). HBP MR image obtained 20 minutes after administration of gadoxetic acid (C) the lesion can easily missed due to it is very closed to noncontrast-filled hepatic vein. DWI (D) shows obvious lesion from hyperintense during relative hypointensed background.

out on portovenous or delayed phase, and particularly the small lesions which frequently depicted only arterial enhancement. These lesions cannot totally exclude the possibility of HCC because some of them might transform into hypervascular HCC in the future. DWI did not detect 36 HCC on 101 (35.6%), which are also reported by Muhi et al,[3] and 50% of the well-differentiated HCCs were not visible on DWI. The visibility of these HCCs may be related to relatively low structural atypia at histopathologic evaluation.

The study of Xu et al,[4] demonstrated significantly higher sensitivity of breath-hold DWI combined with dynamic phase MRI compared with dynamic phase MRI alone for detection of HCCs ≤ 2 cm (in a small study population). The other studies of Park et al, and Kim et al,[5,6] suggest that DWI could only slightly increase

sensitivity and diagnostic accuracy of MRI in the detection of HCC. Recently, there has been the study of Michele et al,[7] which reported no effectiveness of DWI to improve the diagnostic accuracy in the detection of small HCCs.

There were a considerable number of false negative lesions (43 and 36 lesions for reader 1 and 2, respectively) on DW imaging because the cirrhotic liver could cause restricted diffusion resulting in difficulty to identify HCC. DW imaging also has limitations, including limited spatial resolution and echoplanar image (EPI) related artifacts which may obscure the visualization of the lesions. The kappa value which represented interobserver agreement of DWI and the gadoxetic acid enhanced sets were 0.746 and 0.879 indicating good and very good, respectively.

This means DWI is more variable in interpretation than the gadoxetic-acid enhanced MRI and gives more different results in different readers. In our study, some benign liver lesions can exhibit hyperintensity on DWI (Fig 4), thus, we do not recommend to use DWI alone to differentiate the solid liver tumors in the first diagnosis. Nevertheless, DW imaging has advantages to improve the detection of small HCCs by reducing the number of mischaracterized lesions and by gaining more confidence to diagnose equivocal lesions (Fig 5). Vandercaveye et al,[8] reported sensitivity and specificity values of 91.2% and 82.9% for DWI (b=600), and 67.6% and 61% for morphological imaging, respectively. These results suggest that DWI can potentially be used as an alternative in those cases where gadolinium contrast medium is contraindicated.

However, our study has some limitations. First, our patient population was not a surveillance population, and the majority of patients in our study had at least one known or possible HCC nodule prior to surveillance examination. Higher sensitivity might have spuriously been recorded.

Second, pathological confirmation of HCC was obtained for only 9 of 101 nodules (9%). This was due to the small size of the nodules

in some patients and some typical nodules had been treated by TACE (transarterial chemo-embolization) or RFA (radiofrequency ablation).

Third, we use two different 3T-MRI machines to examine these patients which caused the different quality of images. The newcoming technique is able to reduce the noise and artifact and give the better images than the older technique.

Fourth, some HCCs showed isointense or hyperintense relative to the background liver signal intensity on the HBP phase, which indicated substantially higher levels of OATP1B3 (also known as OATP8) and MRP3 expression than those with hypointense signals relative to normal livers[9]. Thus, these HCCs might be missed in interpretation for this study.

Finally, we did not establish the ADC value for liver masses. Thus, we were unable to differentiate HCC from benign lesions in cases where the nodules showed subtle hypointensity on ADC. This limitation was one of the causes of some amount of false positive nodules in our study.

In conclusion, we have demonstrated that the dynamic gadoxetic acid-enhanced MRI with hepatobiliary phase showed significantly higher sensitivity and accuracy than DWI plus dynamic phase.

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