Diagnostic efficacy of Gd-EOB-DTPA (Primovist)-enhanced MR imaging and CT for hepatocellular carcinoma

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Purpose

Hepatocellular carcinoma (HCC) is the most common primary liver cancer that is becoming more prevalent worldwide. HCC is the third leading cause of cancer death and responsible for more than 600,000 deaths annually. Therapeutic options for HCC have improved drastically over the last 10 years, including transcatheter arterial chemoembolization, transplantation, surgical resection, and local ablation. It is important to diagnose accurately the number, size, and location of hepatic lesions as well as to provide differential diagnosis thereof in order to choose the most appropriate treatment. Hence, imaging modalities must be able to provide correct diagnosis.

Recently, a variety of imaging modalities, including ultrasonography, computed tomography (CT), and magnetic resonance (MR) imaging have been used to detect and diagnose HCC. Multiphasic helical CT is widely used for hepatic follow-up because of its low invasivitiy, greater speed, high penetration within hospitals, and superior spatial and temporal resolution. Due to the development of a variety of tissue-specific MR contrast agents, such as superparamagnetic iron oxide (SPIO), which targets Kupffer cells, and gadobenate dimeglumine, which is taken up by hepatocytes, contrast material-enhanced MR imaging of the liver has begun to be considered a more accurate imaging modality than multiphasic helical CT [1, 2].

Recently, a revolutionary liver-specific MR contrast agent, gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (Primovist™; gadoxetic acid disodium or Gd-EOB-DTPA, Bayer Schering Pharma, Berlin, Germany), has been introduced for clinical imaging [3, 4]. Few studies have compared multiphase spiral CT and Gd-EOB-DTPA-enhanced MR imaging for the detection and characterization of HCC. Although the evaluation of its clinical efficacy is ongoing, Gd-EOB-DTPA-enhanced MR imaging potentially demonstrates pathophysiological characteristics of tumors.

The aim of this study is to compare dynamic-enhanced CT and Gd-EOB-DTPA-enhanced MR imaging in patients with focal liver lesions in terms of the detection of HCC. An aim of this study is also to consider whether we could extrapolate the degree of differentiation of the tumors.

Methods and Materials

Study Population
Between April 2007 and August 2009, 47 consecutive patients with suspected focal liver lesions were prospectively enrolled. Of these patients, **35 were men** (age range, 40-80 years; mean age, 67.8 years), and **12 were women** (age range, 47-76 years; mean age, 64.5 years). All patients underwent **triple-phase dynamic-enhanced CT and Gd-EOB-DTPA-enhanced MR imaging within 6 weeks**. Our hospital ethical committee reviewed and approved the study protocol. Informed consent was obtained from all patients. Exclusion criteria included clinically unstable conditions, severe renal impairments, and refusal to consent to the study.

### Liver-specific MRI contrast agent

Gd-EOB-DTPA is a gadolinium-based, paramagnetic, hydrophilic, ionic, highly watersoluble and diagnostic contrast agent with dual elimination routes; approximately 50% of the injected dose is taken up by functioning hepatocytes and excreted in bile, and the remaining 50% is eliminated by renal excretion. It produces high T1 relaxivity in liver tissue immediately after contrast administration. Dynamic and accumulation (hepatospecific) phase imaging also can be performed after bolus injection of Gd-EOB-DTPA. As a result, information of lesion vascularity and cell composition could be obtained. HCCs usually do not have function of hepatocytes so that the contrast effect of the lesions will appear as hypointense against healthy liver parenchyma in a T1 weighted image. All participants received a 0.025-mmol/kg body weight dose of a 0.25-mol/l gadoxetic acid solution administered via an antecubital vein with a flow velocity of 3 ml/s and flushed with 20 ml of 0.9% saline [3].

### Imaging Protocols

For all participants, **dynamic-enhanced CT** was acquired using a 64-slice CT scanner within 6 weeks before or after Gd-EOB-DTPA-enhanced MR imaging. For triple-phase spiral CT, after an initial scout scan, images (120 kV; 140-375 mA; section thickness: 1 mm; table speed: 27 mm/sec; rotation: 0.5/sec; acquisition time: approximately 5 seconds; field of view: 300-425 mm) were acquired before administration of contrast material. A volume of 100 ml of nonionic contrast material was administered via an antecubital vein with a flow velocity of 3 ml/sec using a programmed CT injector. The scans were obtained **40, 60, and 120 seconds after the start of the injection** during the arterial, portal, and equilibrium phases, respectively.

**MR examinations** were performed at 1.5-T. After initial scout images, axial T2-weighted single-shot turbo spin-echo (TR = 403 msec; TE = 60 msec; 60° flip angle, 7-mm section thickness, 1-mm section gap), axial T1-weighted turbo spin-echo (TR = 500 msec; TE = 69 msec; 70° flip angle, 7-mm section thickness, 0.7-mm section gap), and axial diffusion-weighted echo-planar (TR = 1746 msec; TE = 72 msec; 7-mm section thickness, 1-mm section gap, 1000 sec/mm² b-value) images were obtained. Thereafter, Gd-EOB-DTPA
was administered intravenously and flushed with 20 ml of 0.9% saline. Arterial phase, portal venous phase, and equilibrium phase images were acquired 20, 60, and 120 seconds after contrast material administration with the same T1-weighted turbo spin-echo protocol described previously. The dynamic study was followed by a delayed-phase axial image 2.5 minutes after the injection of contrast material, and hepatospecific phase axial, sagittal, and coronal images 20 minutes later with the same protocol.

Image Interpretation

Two gastrointestinal radiologists (with 14 and 15 years of experience, respectively) independently reviewed all CT and MR images. The readers were blinded to clinical findings and results of the other imaging examination. Interpretations were reached by consensus.

Reference Diagnosis

The off-site interpretation of dynamic-enhanced CT images and Gd-EOB-DTPA-enhanced MR images were compared with the reference diagnosis, which was formed on site by means of interpretation of all available data for each patient. These data included all imaging data (findings on US, CT, and MR imaging), laboratory data, and histopathologic data as well as data from radiologic follow-up examinations. Follow-up examinations were part of the clinical routine and not part of the study protocol.

Statistical analysis

The sensitivity, specificity, and accuracy of dynamic-enhanced CT and Gd-EOB-DTPA-enhanced MR imaging were calculated by using the standard definitions. Confidence intervals were calculated for accuracy values on the basis of a 95% confidence level. The accuracies of dynamic-enhanced CT and Gd-EOB-DTPA-enhanced MR imaging for detection HCC lesions were determined, and differences between two modalities were evaluated by using the McNemar test. P values less than .05 were considered to indicate significant differences for all tests.

Results

Reference Standard Results

According to the reference standard, 24 patients had 58 HCCs, 8 patients had 16 metastases, 7 patients had 12 hemangiomas, 2 patients had 4 cysts, 2 patients had 2 hyperplastic nodules, and 2 patients had 20 cholangiocarcinomas. Histopathologic
information was available for deciding on reference diagnosis for 8 (7%) of 115 detected lesions.

**Lesion Detection and Characterization**

Dynamic-enhanced CT and Gd-EOB-DTPA-enhanced MR detected 43 and 54 lesions of HCC, respectively, with 39 of them detected by both modalities. There were 15 HCC lesions in 5 patients that were not detected by any observers at dynamic-enhanced CT but were revealed at Gd-EOB-DTPA-enhanced MR imaging (Fig. 1). These 5 patients had 11 other HCC lesions that were revealed by both modalities.

**Fig.** (Fig. 1) 80-year-old man with multiple HCCs. a. Gd-EOB-DTPA-enhanced arterial phase MR image shows two hypervascular nodules in segment four (arrow and arrowhead). b. Gd-EOB-DTPA-enhanced equilibrium phase MR image shows washout pattern of two nodules in segment four (arrow and arrowhead). c. Gd-EOB-DTPA-enhanced hepatobiliary phase MR image shows two hypointense nodules in segment four (arrow and arrowhead). d. Contrast-enhanced CT scan obtained in arterial phase shows moderately differentiated 2.8-cm-diameter hypervascular HCC in segment four (arrowhead). No lesion is detected dorsal side of this nodule. e. Contrast-enhanced CT scan obtained at equilibrium phase shows washout pattern of HCC in segment four.
(arrowhead). No lesion is detected on the dorsal side of this nodule (false negative lesion on CT).

References: T. Hasebe; Department of Radiology, Toho University Sakura Medical Center, Sakura, JAPAN

On the other hand, there were 4 HCC lesions in 2 patients that were not detected by any observers at Gd-EOB-DTPA-enhanced MR imaging but were revealed at dynamic-enhanced CT (Fig. 2). These 2 patients had 7 other HCC lesions detected by both modalities.

![Fig. (Fig. 2) 76-year-old man with multiple HCCs a. Contrast-enhanced CT scan obtained in arterial phase shows 1.5-cm-diameter hypervascular HCC in segment one (arrow). b. Contrast-enhanced CT scan obtained at equilibrium phase shows washout pattern of HCC in segment one (arrow). c. Gd-EOB-DTPA-enhanced arterial phase MR image shows hypervascular nodule in segment one (arrow). d. Gd-EOB-DTPA-enhanced equilibrium phase MR image shows no lesion in segment one (arrow). e. Gd-EOB-DTPA-enhanced hepatobiliary phase MR image shows no lesion in segment one (false negative lesion on MR imaging).](image-url)

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One patient had 1 false-positive lesion at Gd-EOB-DTPA-enhanced MR, and this was diagnosed as adenomatous hyperplasia at dynamic-enhanced CT (Fig. 3). Definitely, the lesion was proven at surgery as nodular hyperplasia.

**Fig.** (Fig. 3) 73-year-old woman with multiple HCCs. a. Gd-EOB-DTPA-enhanced arterial phase MR image shows no lesion in segment six (arrow). b. Gd-EOB-DTPA-enhanced equilibrium phase MR image shows washed out nodule in segment six (arrow). c. Gd-EOB-DTPA-enhanced hepatobiliary phase MR image shows hypointense nodule in segment six (arrow) (false positive lesion on MR imaging).

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One lesion, which was diagnosed as HCC by both modalities, showed a mixture of hypointensity and hyperintensity in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MR (Fig. 4). This lesion was a well-differentiated HCC containing bile pigment, what we call a "green hepatoma."
Fig.: (Fig. 4 73-year-old woman with multiple HCCs (same patient of Fig. 3). a. Gd-EOB-DTPA-enhanced arterial phase MR image shows hypervascular nodule in segment six (arrow). b. Gd-EOB-DTPA-enhanced equilibrium phase MR image shows weakly enhanced left inner part of the segment six mass (arrow). c. Gd-EOB-DTPA-enhanced hepatobiliary phase MR image shows a mixture of hypointense and hyperintense mass. d. Grossly, the left inner part of the mass has a green-brown color, and thus we designated it a "green hepatoma." e. The green-brown colored part was a well-differentiated HCC characterized by pseudoglandular formation containing bile pigment (HE stain, × 400).

References: T. Hasebe; Department of Radiology, Toho University Sakura Medical Center, Sakura, JAPAN

Statistical analysis

On a per lesion basis, the sensitivity, specificity, and accuracy of dynamic-enhanced CT for detection of HCC were 74%, 100%, and 91%, respectively. The diagnostic sensitivity, specificity, and accuracy of Gd-EOB-DTPA-enhanced MR imaging were 93%, 98%, and 96%, respectively. The sensitivity of the Gd-EOB-DTPA-enhanced MR imaging was statistically higher in detection of HCC than that of dynamic-enhanced CT (p = .0218). Additionally, the accuracy of the Gd-EOB-DTPA-enhanced MR imaging was statistically higher in detection of HCC than that of dynamic-enhanced CT (p < .001). The positive predictive value and negative predictive value were 100% (43 of
43) and 79% (57 of 72), respectively, for dynamic-enhanced CT and 98% (54 of 55) and 93% (56 of 60), respectively, for Gd-EOB-DTPA-enhanced MR.

Discussion

With its superior spatial and temporal resolution, multidetector CT (MDCT) has resulted in improved detection and characterization of focal liver lesions. For the diagnosis of HCC, MDCT proved to be a robust and reliable tool. On the other hand, it has often been debated whether MRI is the most sensitive and specific technique for evaluating the liver.

Gd-EOB-DTPA is a novel liver specific MR contrast agent with the characteristic property of acting as both an extracellular and a hepatocyte-targeted agent. Although some studies have compared multiphase spiral CT and Gd-EOB-DTPA-enhanced MR imaging for the detection and characterization of HCC, the outcomes of the studies were different. A recent study revealed a trend of Gd-EOB-DTPA-enhanced MR imaging being able to detect hepatic lesions more accurately than multiphase spiral CT in blinded reading, although results did not reach statistical significance. More noteworthy was the revealed superiority of differential diagnosis for Gd-EOB-DTPA-enhanced MR imaging over CT. Another multicenter trial showed that the proportion of correctly characterized lesions with Gd-EOB-DTPA-enhanced MR imaging was significantly higher than the proportion of correctly characterized lesions with the use of biphasic CT. However, the limitation of this trial regarding lesion characterization was the highly selected patient population having suspected malignant lesions [6]. In addition, the last study indicated that Gd-EOB-DTPA-enhanced MR imaging and triple-phase MDCT exhibit similar diagnostic performance in the preoperative detection of HCC.

We hypothesized that the diagnostic accuracy of Gd-EOB-DTPA-enhanced MR imaging could outperform that of dynamic-enhanced CT for the detection of HCC. Our study was definitively designed to assess the ability of detection of HCC in both modalities. We included all patients with suspected focal liver lesions with or without hepatic disease including hepatitis and liver cirrhosis, not only those with suspected malignancy.

Our results with Gd-EOB-DTPA-enhanced MR imaging with 93% sensitivity were significantly better than those with dynamic-enhanced CT (74%). This contrast was confirmed by blinded reading without the use of clinical findings or results of other imaging examinations. Additionally, our results for accuracy in diagnosis of both modalities can be compared favorably with published clinical studies involving a large sample of lesions (more than 50). Such findings may result from the higher tumor-to-liver contrast possible with hepatocyte-selective MR imaging. The 15 false negative lesions in 5 patients on CT were detected in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MR imaging with a lack of uptake of the agent area and showed very weak enhancement in the arterial phase of Gd-EOB-DTPA-enhanced MR imaging. In these 5 patients,
dynamic-enhanced CT studies were performed only ten days earlier than Gd-EOB-DTPA-enhanced MR imaging on average. In consequence of these 15 lesions with no washout pattern in the equilibrium phase at dynamic-enhanced CT, observers could not diagnose HCCs.

Conversely, there were four lesions in 2 patients that were detected only at dynamic-enhanced CT and not detected at Gd-EOB-DTPA-enhanced MR imaging. Those nodules were hypervascular HCCs that, when compared with the liver parenchyma at dynamic-enhanced CT, showed early enhancement during the arterial phases and a washout pattern during the equilibrium phase. When we retrospectively reviewed the four missed lesions at Gd-EOB-DTPA-enhanced MR imaging, all lesions were isointense in the hepatobiliary phase. According to a previous study, moderately or poorly differentiated HCC shows no enhancement in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MR imaging, whereas highly differentiated HCC, by contrast, may show enhancement in the hepatobiliary phase [9]. Considering all information, including tumor vascularity and signal intensity in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MR imaging, could lead to more accurate diagnosis and degree of differentiation of tumors.

A false positive lesion in Gd-EOB-DTPA-enhanced MR imaging shows a washout pattern in the dynamic phase and hypointensity in the hepatobiliary phase. The observers diagnosed as well differentiated HCC using Gd-EOB-DTPA-enhanced MR imaging, but pathological findings after surgery indicated nodular hyperplasia. A previous study reported that some dysplastic nodules show hypointensity in the hepatobiliary phase in a manner similar to HCCs [2]. Concurrently, no significant difference was observed between HCCs and dysplastic nodules in terms of enhancement ratio in the hepatobiliary phase. Dysplastic nodules are considered to be consistent with adenomatous hyperplasia by the International Working Party of the World Congress of Gastroenterology, and nodular hyperplasia is classified as belonging to the regenerative lesions group and not the dysplastic lesions group. Another study revealed only 2% of focal nodular hyperplasia lesions show hypointensity in the hepatobiliary phase [3]. Such false positive lesions indicate that nodular hyperplasia could also show hypointensity in the hepatobiliary phase, so that all lesions recognized as exhibiting hypointensity in the hepatobiliary phase that are diagnosed as HCCs or precancerous lesions could lead to misdiagnosis and overtreatment of benign lesions.

Moreover, we noted a "green hepatoma" lesion that showed paradoxical uptake of the agent in the hepatobiliary phase. Some studies have reported that some kinds of lesions show hyperintensity in the hepatobiliary phase. In the analysis of liver-specific enhancement with Gd-EOB-DTPA, hepatocyte-selective uptake was observed 10 and 20 minutes after injection in subset of focal nodular hyperplasia, adenoma, cystadenoma, and highly differentiated HCC, although moderately or poorly differentiated HCCs show
no uptake, with the tumor appearing hypointense to the normal liver parenchyma [9]. Meanwhile, another study reported all degrees of differentiated HCC involve the possibility of the appearance of isointensity or hyperintensity in relation to the normal liver parenchyma in the hepatobiliary phase [7]. These studies have not referred to bile producing HCC, "green hepatoma," so that the correlation between bile stasis and uptake of the agent has not been clarified.

In the first place, Gd-EOB-DTPA is transported into hepatocytes via \textbf{Oatp1} organic anion transporting polypeptides in rats [12] and excreted into bile via multidrug resistance-associated protein 2 (\textbf{MRP2}) [13]. A recent work that investigated the characteristics of such Gd-EOB-DTPA-positive HCCs in the hepatobiliary phase clarified the relation between enhancement ratios and expression levels of the \textbf{OATP1B3} protein [14]. This transporter is expressed in the human liver, having a function of bringing drugs from sinusoid into hepatocytes. Almost no expression of OATP1B3 was observed in most HCCs that did not show uptake of Gd-EOB-DTPA, and expression of MRP2 was neither correlated with enhancement ratios nor bile production. MRP2 is localized in the canalicular membrane and secretes non-bile salt organic anions into bile [15]. \textbf{MRP3} is localized in the basolateral membrane [16, 17] and transports bile salts and xenobiotic compounds [18, 19]. In a previous study, MRP2 immunostaining was observed in 87% (33/38) of HCC samples and MRP3 was detected in all HCC samples examined [20] (Fig. 5).
Fig.: (Fig. 5) The metabolic pathway of Primovist.

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MRP3 is also involved in drug transport, and there is a need for new investigation of the relationship between expression levels of the MRP3 and uptake of Gd-EOB-DTPA, so that a determinate quantity of residual Gd-EOB-DTPA in tumor cells could potentially be used to predict the response to chemotherapy.

**Limitations**

There are some limitations that need to be acknowledged and addressed regarding the present study.

1. First, **not all lesions were pathologically confirmed**, so it is possible that some small lesions were present and were missed with both imaging modalities. This could lead to a loss of diagnostic accuracy in the results from both modalities.

2. Second, we evaluated the diagnostic accuracy of CT and MR imaging in the detection of HCC in **patients with suspected focal liver lesions**, which can lead to higher diagnostic performance.
3. Third, for the 7 patients with false-negative lesions, other multiple HCC lesions detected, so **there is not necessarily an influence on therapeutic strategy** if it is possible to find HCC lesions in addition using both modalities. For instance, the same treatment would be recommended for 4 or more HCC lesions according to the Evidence-Based Practice Guidelines proposed by the Japan Society of Hepatology.

4. Fourth, the sensitivity and the accuracy of Gd-EOB-DTPA-enhanced MR for HCC were significantly better than those of dynamic-enhanced CT, although **there were some HCC lesions detected only at dynamic-enhanced CT**. Gd-EOB-DTPA-enhanced MR was unable to serve as a perfect alternative to dynamic-enhanced CT because the correct number and size of HCC lesions influence the therapeutic strategy.

Images for this section:

![Figure 1](image_url)

**Fig. 1**: (Fig. 1) 80-year-old man with multiple HCCs. a. Gd-EOB-DTPA-enhanced arterial phase MR image shows two hypervascular nodules in segment four (arrow and arrowhead). b. Gd-EOB-DTPA-enhanced equilibrium phase MR image shows washout
pattern of two nodules in segment four (arrow and arrowhead). c. Gd-EOB-DTPA-enhanced hepatobiliary phase MR image shows two hypointense nodules in segment four (arrow and arrowhead). d. Contrast-enhanced CT scan obtained in arterial phase shows moderately differentiated 2.8-cm-diameter hypervascular HCC in segment four (arrowhead). No lesion is detected dorsal side of this nodule. e. Contrast-enhanced CT scan obtained at equilibrium phase shows washout pattern of HCC in segment four (arrowhead). No lesion is detected on the dorsal side of this nodule (false negative lesion on CT).

**Fig. 2:** 76-year-old man with multiple HCCs. a. Contrast-enhanced CT scan obtained in arterial phase shows 1.5-cm-diameter hypervascular HCC in segment one (arrow). b. Contrast-enhanced CT scan obtained at equilibrium phase shows washout pattern of HCC in segment one (arrow). c. Gd-EOB-DTPA-enhanced arterial phase MR image shows hypervascular nodule in segment one (arrow). d. Gd-EOB-DTPA-enhanced equilibrium phase MR image shows no lesion in segment one (arrow). e. Gd-EOB-DTPA-enhanced hepatobiliary phase MR image shows no lesion in segment one (false negative lesion on MR imaging).
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**Fig. 4:** (Fig. 4) 73-year-old woman with multiple HCCs (same patient of Fig. 3). a. Gd-EOB-DTPA-enhanced arterial phase MR image shows hypervascular nodule in segment
six (arrow). b. Gd-EOB-DTPA-enhanced equilibrium phase MR image shows weakly enhanced left inner part of the segment six mass (arrow). c. Gd-EOB-DTPA-enhanced hepatobiliary phase MR image shows a mixture of hypointense and hyperintense mass. d. Grossly, the left inner part of the mass has a green-brown color, and thus we designated it a "green hepatoma." e. The green-brown colored part was a well-differentiated HCC characterized by pseudoglandular formation containing bile pigment (HE stain, × 400).

Fig. 5: (Fig. 5) The metabolic pathway of Primovist.
Conclusion

In conclusion, the results of this study indicate that **Gd-EOB-DTPA-enhanced MR imaging is more sensitive and accurate than dynamic-enhanced CT for detection of HCCs.** Lesion vascularity and signal intensity in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MR imaging could lead to more accurate diagnosis, including degree of differentiation of HCC, and it could allow selection of the optimal treatment.

References


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