MAJOR PAPER

Gd-EOB-DTPA Enhanced MRI for Hepatocellular Carcinoma: Quantitative Evaluation of Tumor Enhancement in Hepatobiliary Phase

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(Received October 13, 2004; Accepted March 30, 2005)

Objective: The purpose of this study was to evaluate the utility of gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI) for the quantitative evaluation of hepatocellular carcinoma (HCC) and dysplastic nodules in the hepatobiliary phase.

Material and Methods: The subjects comprised 12 patients with 27 lesions (22 HCCs and 5 dysplastic nodules). Chemical-shift-selective fat-suppressed T1-weighted sequences were obtained before and 10, 20, and 40 min after the injection of Gd-EOB-DTPA. Quantitative analyses were performed with the enhancement ratio of the lesion and the contrast-to-noise (C/N) ratio.

Results: The enhancement ratios of the HCCs were 44.0 ± 36.5, 44.7 ± 46.8, and 47.7 ± 52.8 (%) at 10, 20, and 40 min, respectively, after the injection of Gd-EOB-DTPA. The enhancement ratios of the dysplastic nodules were 36.2 ± 34.3, 44.3 ± 37.3, and 40.1 ± 46.8 (%). The C/N ratios of the HCCs were 0.2 ± 6.6 for the precontrast image, and −9.2 ± 12.6, −9.9 ± 14.8, and −12.7 ± 15.7 at 10, 20, and 40 min, respectively, after the injection of Gd-EOB-DTPA. The C/N ratios of the dysplastic nodules were 1.4 ± 8.0, −13.7 ± 11.1, −13.3 ± 7.6, and −13.1 ± 10.4. No significant differences were found between the HCCs and the dysplastic nodules in the enhancement ratio and the C/N ratio. Only two HCCs showed a positive C/N ratio value, and these HCCs were pathologically confirmed to be a well differentiated and a moderately differentiated carcinoma, respectively.

Conclusion: HCCs and some of the dysplastic nodules showed hypointensity in the hepatobiliary phase in Gd-EOB-DTPA-enhanced MRI. No specific enhancement was observed, regardless of tumor differentiation.

Keywords: hepatocellular carcinoma, Gd-EOB-DTPA, MRI

Introduction

Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) is a new liver-specific contrast agent for magnetic resonance imaging (MRI). A bolus injection of Gd-EOB-DTPA enables tumor vascularity to be evaluated in a manner similar to evaluation with gadolinium-triamine pentaacetic acid (Gd-DTPA).1 Moreover, this contrast agent accumulates in normally functioning hepatocytes in the delayed phase (hepatobiliary phase1,2) which begins 20 min after injection and lasts until 40 min after injection. Thus, the liver parenchyma is enhanced; on the other hand, tumors appear as hypointense lesions because they do not possess normally functioning hepatocytes.2,3 Hepatocellular carcinoma is known to arise multicentrically in the case of virally induced liver cirrhosis, developing from dysplastic nodules into hepatocellular carcinoma.4,5 When considering the most appropriate therapeutic approach, it is important to distinguish between dysplastic nodules and hepatocellular carcinoma. A combination of CT (computed tomography) during arterial portography (CTAP) and CT
Fig. 1. A 80-year-old man with HCCs
A: CT hepatic arteriography revealed hypervascular lesions on liver segments 4 (arrowhead) and 8 (arrow).
B: CT arterial portography revealed that both lesions were perfusion defect.
C: The lesion on liver segment 8 (arrow) was clearly seen in a hepatobiliary phase image (40 min after injection of Gd-EOB-DTPA).
D, C, and D are consecutive images. The lesion on segment 4 was observed on CT hepatic arteriography and CT arterial portography but was difficult to visualize in the hepatobiliary phase image (arrowhead), due to the proximity of the heart. The other lesions were also seen (arrows).

hepatic arteriography (CTHA), as well as superparamagnetic iron oxide (SPIO)-enhanced MRI, has been performed to distinguish between these two entities. SPIO-enhanced MRI has been found deficient because SPIO accumulates in some well-differentiated hepatocellular carcinomas. However, CTAP and CTHA are too invasive for routine application. Although the data remain preclinical, specific enhancement with Gd-EOB-DTPA has been reported for the differentiation of hepatocellular carcinoma. Thus, Gd-EOB-DTPA-enhanced MRI was performed for the quantitative evaluation of dysplastic nodules and hepatocellular carcinoma in the hepatobiliary phase.

Materials and Methods

Subjects
Twelve patients from an original sample size of fifteen were included in the present study; these patients participated in phase III clinical trials conducted at our institute to investigate the use of Gd-EOB-DTPA. Three patients from the original selection of fifteen patients were excluded after entering the study because each had more than 10 nodules as confirmed by a combination of CTHA and CTAP. The 12 subjects included in the present analysis comprised 11 males and 1 female; the mean age was 67.8 years and the median age was 68 years. This clinical trial was approved by our institutional review board, and all patients provided their informed consent. This study was performed after confirmation of the presence of a liver lesion by ultrasound and CT. The patients with fewer than 10 lesions, all smaller than 5 cm, were included in this clinical trial. All patients had viral hepatitis (type B 1, type C 11).

The diagnosis of the liver lesions was based on comprehensive CTHA and CTAP examinations. Forty-eight lesions were hypervascular in nature on
Fig. 2. A 65-year-old man with dysplastic nodule and HCCs
A: CT hepatic arteriography revealed a hypovascular lesion on segment 8 (arrow) and 2 hypervascular lesions (arrowheads) on segments 7 and 8, respectively.
B: The hypovascular lesion was not visible on CT during arterial portography. Thus, this lesion could be diagnosed as a dysplastic nodule. The other lesions clearly revealed a perfusion defect; therefore, these lesions could be diagnosed as HCCs.
C: Two hypervascular HCCs (arrowheads) were clearly seen in hepatobiliary phase images (40 min after injection of Gd-EOB-DTPA).
D, C, and D are consecutive images. The dysplastic nodule on segment 8 was clearly seen in hepatobiliary phase images. The large arrow indicates a dysplastic nodule and the small arrow indicates a post-therapeutic nodule.

CTHA, and concomitant perfusion defects in CTAP led to a diagnosis of hepatocellular carcinoma. Among these lesions, seven were histopathologically confirmed (1 surgical specimen and 6 percutaneous biopsy) and were diagnosed as follows: 4 were well differentiated hepatocellular carcinomas and 3 were moderately differentiated hepatocellular carcinomas. Seven lesions were hypovascular on CTHA and isoperfusion comparing the surrounding liver parenchyma on CTAP led to a diagnosis of the lesion as dysplastic nodules. One sample was a pathologically confirmed lesion obtained by biopsy. Cases of nonuniform enhancement of the liver parenchyma due to liver cirrhosis were excluded. Careful consideration was given to non-tumorous perfusion defects on CTAP in order to achieve a diagnosis of hepatic lesions, according to previous reports. To avoid the partial volume phenomenon in the measurement of signal intensity, lesions with a diameter of less than 1 cm were excluded from the study. Finally, objective nodules comprised 22 hepatocellular carcinomas and 5 dysplastic nodules. From among these lesions, pathological confirmation was obtained for 7 hepatocellular carcinomas (4 well differentiated and 3 moderately differentiated) and 1 dysplastic nodule. The lesion size was defined as the largest diameter of the hypervascular or hypovascular area, as determined by CTHA. The lesion diameter was $20.1 \pm 9.9$ mm (mean ± standard deviation) in the cases of hepatocellular carcinoma, and $12.4 \pm 5.4$ mm in the cases of dysplastic nodules.

MRI acquisition
MR imaging was performed at 1.5T with a superconductive system (Symphony, Siemens, Erlangen, Germany). All MR images were obtained in the...
Fig. 3. A 78-year-old woman with a dysplastic nodule and HCC
A: CT hepatic arteriography revealed a hypovascular lesion on segment 8 (arrow).
B: This hypovascular lesion was not visible in CT during arterial portography. Thus, this lesion was diagnosed as a dysplastic nodule.
C: This chemical-shift-selective fat-suppressed T1-weighted image revealed that this lesion was hyperintense (arrow).
D: Hepatobiliary phase imaging (40 min after injection of Gd-EOB-DTPA) revealed no lesion.

axial plane with a CP (circular polarization) body array coil for the body. Unenhanced images were obtained with fast low-angle shot (FLASH) T1-weighted sequences (TR, 150 ms; TE, 4.5 ms; flip angle, 90°; matrix, 205 × 256; number of excitations, 1; field of view, 28–35 cm; acquisition time, 19 or 21 s) and chemical-shift-selective fat-suppressed T1-weighted sequences (TR, 150 ms; TE, 4.5 ms; flip angle, 90°; matrix, 205 × 256; number of excitations 1; field of view, 28–35 cm; acquisition time, 21 s). The latter sequences were limited in terms of the images obtained, such that image acquisition had to be performed twice in order to capture the entire liver. Chemical-shift-selective fat-suppressed T1-weighted turbo spin echo sequences (TR, 4300 ms; TE, 109 ms; flip angle, 180°; matrix, 187 × 256; number of excitations, 1–4; echo train length, 31) were obtained. All images were obtained with a slice thickness of 7 mm and a 1.4-mm intersection gap.

Dynamic study was performed after i.v. bolus injection of 25 μmol/kg of Gd-EOB-DTPA flushed with 20 ml of sterile saline solution from the antecubital vein. The injection of contrast media and sterile saline solution was performed manually. The scan delay time was 25 s, 70 s, and 5 min after initiation of contrast injection, and the images were obtained with FLASH sequences. Chemical-shift-selective fat-suppressed FLASH images were obtained 10, 20, and 40 min after initiation of contrast injection.

**CTHA, CTAP acquisition**

CTHA and CTAP were performed with a Suﬁda CT scanner (Shimazu, Kyoto, Japan). For CTAP, a total of 90 ml of Iopamidol (Iopamiron® 150, Japanese Schering, Osaka, Japan) was injected into the superior mesenteric artery at a rate of 2 ml per second immediately after the injection of 5 μg of prostaglandin E1 (Palux® inj, Taisho Pharmaceutical, Tokyo, Japan); the scan started 30 s after contrast injection. The imaging conditions were as follows: collimation, 5 mm; table speed, 7 mm per second; reconstruction, 7 mm; and helical scanning. For CTHA, a total of 15 ml of ioxilan...
Fig. 4.
A: Enhancement ratio of HCCs and dysplastic nodules
No significant difference was observed between HCCs and dysplastic nodules in terms of the enhancement ratio.

B: Contrast-to-noise ratio of HCCs and dysplastic nodules
No significant difference was observed between HCCs and dysplastic nodules with respect to contrast-to-noise ratio.

(Imageni® 300, Kyowa Hakko, Tokyo, Japan) was injected into the common hepatic artery at a rate of 1.5 ml per second; the scan was started five seconds after the contrast injection. Imaging was conducted twice, once for the cephalic half and once for the caudal half of the entire liver. The imaging conditions were as follows: collimation, 5 mm; table speed, 5 mm per second; reconstruction, 5 mm; and helical scanning.

Image analysis
The contrast-to-noise (C/N) ratio and the enhancement ratios for each lesion diagnosed as either hepatocellular carcinoma or dysplastic nodule were calculated, and a quantitative evaluation was performed in order to investigate the utility of these modalities in differentiating these two entities. The signal intensity (SI) of the liver parenchyma and the lesion were measured before the injection of the contrast agent and 10, 20, and 40 min after the initiation of the injection of contrast media in T1-weighted images with fat suppression. The SI of the liver parenchyma was calculated by setting a circular region of interest (ROI), while avoiding vascular structures. When liver lesions were measured, the ROI was set as the entire lesion. In cases of non-visualized lesions, the measurement location was determined with anatomical structures, such as the vasculature, as a point of orientation. The standard deviation (SD) of the background noise was also determined by backtracking in the encoding direction and locations without artifacts were selected. The C/N ratio and enhancement ratios were calculated with the following formula:

$$C/N \text{ ratio} = \frac{(SI \text{ of tumor}-SI \text{ of liver})}{\text{SD of background noise}}$$

$$\text{Enhancement ratio} = \frac{[SI \text{ after enhancement}-SI \text{ before enhancement}]}{SI \text{ before enhancement}} \times 100$$

Comparisons of HCCs and dysplastic nodules with respect to the C/N ratio and the enhancement ratio were performed with Student's t-test. A two-tailed P-value of less than 0.05 was considered significant.

Results
Fifteen nodules were detected with precontrast MRI. In the hepatobiliary phase, 25 lesions were detected (Figs. 1, 2); however, two lesions were not visualized (Fig. 3). These two lesions were dysplastic nodules. Both lesions showed hyperintensity in the precontrast T1-weighted image.

The C/N ratios and the enhancement ratios in the hepatobiliary phase are shown in Fig. 4. The enhancement ratios of the HCCs were $44.0 \pm 36.5\%$ (mean ± standard deviation), $44.7 \pm 46.8\%$, and $47.7 \pm 52.8\%$ at 10, 20, and 40 min, respectively, after injection of contrast media. The corresponding ratios of the dysplastic nodules were $36.2 \pm 34.3\%$, $44.3 \pm 37.3\%$, and $40.1 \pm 46.8\%$, respectively. The enhancement ratios of the liver parenchyma were $64.6 \pm 28.4$, $70.9 \pm 30.7$, and $77.4 \pm 41.2$ respectively. No significant difference was recognized between HCCs and dysplastic nodules. The enhancement ratios were increased in almost all of the HCCs (Fig. 1) and dysplastic nodules (Figs. 2, 3), as compared with those of the precontrast images.

The C/N ratios of the HCCs were $0.2 \pm 6.6$, $-9.2 \pm 12.6$, $-9.9 \pm 14.8$, and $-12.7 \pm 15.7$ at precontrast, and at 10, 20, and 40 min, respectively, after the injection of contrast media. The corresponding ratios of the dysplastic nodules were $1.4 \pm 8.0$, $-13.7 \pm 11.1$, $-13.3 \pm 7.6$, and $-13.1 \pm 10.4$, respectively. No significant difference was observed between the HCCs and the dysplastic
nodules. The C/N ratios had negative values in almost all of the lesions, but only 2 lesions had a positive value in the entire hepatobiliary phase. These 2 lesions were pathologically diagnosed by biopsy, and these diagnoses determined the presence of well-differentiated HCC (Fig. 5) and moderately differentiated HCC (Fig. 6).

Discussion

It is possible to detect hypervascular HCCs in the arterial dominant phase with Gd-EOB-DTPA; moreover, Gd-EOB-DTPA appears as equally capable as Gd-DTPA at such detection. However, some problems remain with the imaging of liver lesions, including optimal arterial phase acquisition and non-tumorous staining. This contrast material is transported to hepatocytes, thus enabling image acquisition at the hepatobiliary phase. The optimal timing of the hepatobiliary phase is a long duration, and problems associated with the optimal timing may be resolved. Although the usefulness of the detection of hypervascular HCCs has been reported, neither hypovascular lesions nor lesions with weakly increased arterial flow have been evaluated to date. These latter nodules are difficult to evaluate in dynamic studies with Gd-DTPA.

It is known that SPIO accumulates in some HCCs. SPIO-enhanced MRI is of limited use in the evaluation of HCCs, because this type of examination alone is not sufficient to determine a therapeutic strategy for the treatment of HCCs, as the degree of tumor vascularity remains unvisualized. Gd-EOB-DTPA is a liver-specific contrast material that has a different mechanism of activity from that of SPIO; therefore, it is expected to distinguish dysplastic nodules from HCCs.
In this study, some dysplastic nodules revealed a level of hypointensity in the hepatobiliary phase similar to that of HCCs. No significant quantitative difference was observed between HCCs and dysplastic nodules in terms of the enhancement ratios and the C/N ratio. Gd-EOB-DTPA is known to accumulate in normal, functioning hepatocytes; therefore, a lack of normal accumulation in dysplastic nodules indicates a lack of normally functioning hepatocytes. All lesions recognized as hypointense in the hepatobiliary phase that are diagnosed as HCCs are associated with the possibility of a misdiagnosis. When a combination of CTHA and CTAP is used, the blood supply remains quite informative for the evaluation of the malignancy of liver lesions, while Gd-EOB-DTPA-enhanced MRI provides additional diagnostic clues, namely, the level of hepatocyte function and their excretion. The two lesions diagnosed here as dysplastic nodules according to CTHA and CTAP were not detected in the hepatobiliary phase, but three lesions were detected with this approach. This finding may indicate the possibility of a classification of tumor grade, independent of the blood supply, for dysplastic nodules. Further evaluation is required for evaluation of biological malignancy in dysplastic nodules exhibiting hypointensity in the hepatobiliary phase.

HCCs showed less enhancement than the liver parenchyma in the hepatobiliary phase. The liver parenchyma exhibited strong enhancement and liver lesions were found to be relatively hypointense. In a previous study, well-differentiated HCCs were more enhanced than the surrounding liver parenchyma in the hepatobiliary phase; thus, Gd-EOB-DTPA has the potential to be applicable to the differentiation of tumors. However, it has been reported that positive enhancement in the hepatobiliary phase is not dependent on tumor differentiation. Both previous reports noted here
were experimental studies. Vogle et al. reported that specific hepatobiliary enhancement was not observed in any HCCs, regardless of tumor grade. In this study, greater tumor enhancement was observed in pathologically confirmed, well-differentiated HCC and moderately differentiated HCC than in the surrounding liver parenchyma; therefore, tumor differentiation was not found to contribute to specific hepatobiliary enhancement. It should be noted, however, that the present study employed only a small sample.

In this study, fat-suppressed FLASH was used in the hepatobiliary phase. However, Reimer et al. reported that fat-suppressed T1-weighted FLASH did not improve lesion conspicuity as compared to T1-weighted FLASH. The majority of the subjects in that study had metastatic lesions, whereas all of our subjects had HCCs; thus, fat-suppressed T1-weighted FLASH was used in the present study. It is well known that HCCs contain an adipose component; therefore, this type of sequence facilitated the present evaluation of lesion enhancement.

The present study was limited in that only a small number of subjects were considered, as it was a phase 3 clinical trial; moreover, only a small number of cases were confirmed pathologically. It is also difficult to confirm that every HCC node observed by biopsy arose due to viral hepatitis and cirrhosis. Recently, advances in radiological imaging modalities have aided the process of diagnosis. From this perspective, angiography-assisted CT is considered a reliable modality for the diagnosis of HCC; therefore, the present results are considered reliable.

In conclusion, HCCs and some dysplastic nodules show hypointensity in the hepatobiliary phase in Gd-EOB-DTPA-enhanced MRI. No difference in enhancement was observed between HCCs and dysplastic nodules in the hepatobiliary phase. Thus, specific enhancement may not be observed, regardless of tumor differentiation.

References


