Early Homogeneously Enhancing Hemangioma Versus Hepatocellular Carcinoma: Differentiation Using Quantitative Analysis of Multiphasic Dynamic Magnetic Resonance Imaging

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Abstract

The aim of this study was to determine the usefulness of quantitative analysis of multiphasic dynamic contrast-enhanced magnetic resonance (MR) imaging in differentiating early homogeneously enhancing hemangiomas from hepatocellular carcinomas (HCCs). Four-phased dynamic MR imaging at 10 sec (first phase of dynamic contrast-enhanced imaging, P1), 35 sec (second phase, P2), 60 sec (third phase, P3) and 300 sec (delay phase, P4) immediately after intravenous administration of 0.1 mmol/kg Gadolinium-DTPA was obtained with 1.5-T unit with breath-hold multisection FLASH (fast low angle-shot) sequence (TR/TE, 113-130 msec/4.1 msec; flip angle, 80°). Thirty-three HCCs and 18 hemangiomas, homogeneously enhanced on P1, were included in the study. The images were evaluated quantitatively (SNR, signal-to-noise ratio; and CNR, contrast-to-noise ratio of lesions). Quantitatively, mean CNR was higher for hemangiomas than for HCCs on all phases, and the difference in CNRs between hemangioma and HCCs was statistically significant on P3 and P4 (p < 0.0001). When the cutoff for CNR was set at a value of 7.00 on P3 and 1.00 on P4, sensitivity, specificity and accuracy were 94.4%, 93.9%, and 94.1% on P3, and 94.4%, 81.8%, and 86.3% on P4, respectively. There was no statistically significant difference in SNRs between HCC and hemangioma. The differential diagnosis between early, homogeneously enhancing hemangiomas and HCCs was more confidently made with CNRs of lesions on P3 and P4 in dynamic contrast-enhanced MR imaging.

Key Words: Liver, MR liver neoplasms, diagnosis liver neoplasms, MR magnetic resonance (MR), contrast enhancement

INTRODUCTION

Hemangioma is the most common benign tumor of the liver, and the diagnosis of hemangioma has often been established on the basis of MR imaging features. After bolus injection of contrast material, the majority of hemangiomas show a characteristic enhancement pattern on MR imaging: peripheral discontinuous nodular or globular enhancement on arterial phase image with progressive and centripetal enhancement. Although this pattern is diagnostic for the majority of hemangiomas, the pattern displayed can vary. We have sometimes encountered rapidly well-enhanced hemangiomas and have found it difficult to make a differential diagnosis from hypervascular solid tumor. While these hemangiomas used to be considered atypical and rare, hemangiomas showing homogeneous enhancement in the early phase are not that rare and tend to be observed in smaller lesions (≤ 10 mm in diameter). Also, 70-75% of small hepatocellular carcinomas (HCC, ≤ 30 mm in diameter) have shown homogeneous enhancement in the early phase. These hemangiomas tend to be hypechoic on ultrasonogram (predictability: 90%), which is also an atypical sonographic appearance of hemangioma. On T2-weighted images, hemangiomas have typically shown higher signal intensities than normal liver parenchyma and HCCs, corresponding to much longer T2 for hemangiomas than for HCCs. However, the signal intensities in the cases of small lesions can be greatly diminished by means of partial volume averaging, which may cause the lesion to resemble a solid mass. Thus, the differential diagnosis between early homo-
giously enhancing HCCs and hemangiomas is one of the main problems in contrast-enhanced dynamic CT and MR imaging. Consequently, it can be difficult to establish a conclusive diagnosis on the basis of a combination of MR imaging features related to T2-weighting and enhancement pattern, as well as sonographic appearance and enhancement pattern alone. In objectively differentiating these hemangiomas from hypervascular HCCs, there should be a difference in SNR or CNR, which are well known to be quantitative parameters in MR imaging. Therefore, the aim of this study was to determine the usefulness of quantitative analysis of multiphasic dynamic contrast-enhanced MR images in differentiating early homogeneously enhancing hemangiomas from HCCs.

MATERIALS AND METHODS

Patients

From January 1996 to December 1997, 429 patients with suspected focal liver lesions were examined with MR imaging. Thirty-three patients with HCC and 18 patients with hemangioma were included in this study. Our subjects consisted of lesions with low signal intensities on unenhanced T1-weighted image and rapidly homogeneous enhancement on the first phase of multiphasic dynamic contrast-enhanced MR images. All the lesions ranged in size from 10 mm to 30 mm. The range in age was from 41 to 67 years (mean 54) in patients with HCC (22 men and 11 women), and from 31 to 65 years (mean 45) in patients with hemangioma (8 men and 10 women). The diagnosis of HCCs was established by percutaneous tissue core biopsy in 6 lesions, surgical resection in 5 lesions or combined assessment of their clinical manifestations, including elevation of serum alphafetoprotein level and angiographic finding in 18 lesions or definite tumor growth in 5 lesions. Tumor growth was defined as the increase in the longest dimension of tumors of more than 5 mm in diameter and determined by follow-up CT or MR images.

Four of 22 patients with hemangioma had chronic hepatitis (hepatitis B in 3 and hepatitis C in 1 patient). One patient had gall bladder carcinoma. The remaining 13 patients were asymptomatic, underwent ultrasonogram during a medical examination and were suspected of having liver tumors. Diagnosis of the hemangioma was established on the basis of typical findings (cotton wool appearance, mottled appearance) on hepatic angiography (HAG) in 5 lesions and tagged red blood pool scan in 16 lesions. The hemangioma in the patient with gall bladder carcinoma was surgically confirmed. All lesions showed typical MR imaging features related to T2-weighting and the absence of any increase in size over a period of at least 12 months. Since the majority of rapidly enhancing hemangiomas was hypoechoic on ultrasonogram, the sonographic feature was excluded from the diagnostic criteria.

MR imaging

MR imaging was performed with a 1.5-T superconducting system (Magnetom Vision; Siemens Medical System, Erlangen, Germany) with a phased-array multicoil. All MR images were obtained in the axial plane during breath holding. The unenhanced T1-weighted images by multisection fast low-angle shot sequence (TR/TE, 113–130 msec/4.1 msec; flip angle, 80°) and T2-weighted images by multishot turbo spin-echo sequence (3,540–4,000/138; echo train length, 29) were obtained, and then T1-weighted fat suppressed dynamic images were acquired at 10 sec (first phase of dynamic contrast-enhanced imaging: P1), 35 sec (second phase: P2), 60 sec (third phase: P3) and 300 sec (delay phase: P4) after the start of a bolus injection of 0.1 mmol/kg of gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany) into the antecubital vein. The matrix size was 117–140 × 256, and various fields of view were applied according to the patients size, ranging from 32 to 40 cm. A total of 12–15 sections with 8 to 10 mm section thickness and 2 mm interslice gap according to liver size on scout image were obtained. Breath-hold acquisition time of 16–19 sec was used.

Image analysis

For a set of unenhanced images for each phase of dynamic contrast-enhanced MR images, the signal intensities from lesions, adjacent normal liver parenchyma, and background were obtained with region of interest (ROI) measurement in the same locations by the same radiologist. Signal intensity measurement of the lesions was obtained by using the largest possible circular ROI. The normal liver parenchyma
adjacent to the lesion was measured with the same circular ROI that excluded artifacts and blood vessels. The background noise was measured with the largest possible circular ROI located ventrally to the patient's abdomen in the direction of the phase-encoding gradient. As quantitative parameters, we calculated signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) of lesions on each phase using the following equations: $\text{SNR} = \frac{\text{S}l\text{lesion} \cdot \text{SD}\text{noise}}{\text{CNR}} = \frac{\text{S}l\text{lesion} - \text{Sl}\text{liver}}{\text{SD}\text{noise}}$, where $\text{S}l\text{lesion}$ = signal intensity of lesion, $\text{Sl}\text{liver}$ = signal intensity of normal liver parenchyma, and $\text{SD}\text{noise}$ = standard deviation of the signal intensity of the background tissue without artifact. Unpaired Students $t$-test was performed to determine the statistically significant difference in SNR and CNR between hemangiomas and HCCs on each phase of dynamic MR images. A $p$-value of less than 0.001 was considered to be statistically significant.

Fig. 1. MR image in a patient with hepatic hemangioma. Multiphase dynamic contrast-enhanced MR images obtained before (a) and at 10-sec (b), 35-sec (c), and 60-sec (d) and 300-sec (e) after the injection of contrast material. The lesion (arrow in a) shows rapid homogeneous enhancement on the arterial phase image in b, and prolonged enhancement on the later phases image in c, d, e.
Fig. 2. MR images in 2 patients with a hepatocellular carcinoma. Multiphasic dynamic contrast-enhanced MR images obtained before the injection of contrast material (a, c) and during the arterial phase (b, d). On the arterial phase, HCC in the first patient (arrow in b) shows homogeneously intense enhancement, whereas HCC in the second patient (arrow in d) was subtly enhanced, which resulted in low lesion to liver contrast, compared to HCC in the first patient. Dynamic MR images at 35 sec (e), 60 sec (f) and 300 sec (g) in the first case. The lesion demonstrates rapid wash-out of intratumoral contrast enhancement. This resulted in a rapid decrease of CNR of HCC and a considerable difference in CNRs between HCC and hemangioma existed in 60 sec and 300 sec images (e, f, g).
RESULTS

All of the hemangiomas immediately showed homogeneous enhancement with persistence of homogeneous enhancement at least in the delay phase after administration of contrast material (Fig. 1). There was no significant change in SNR despite of progression of phases, but there was a gradual decrease in the contrast of hemangiomas with respect to liver parenchyma because of a progressive increase of signal intensities of liver parenchyma accompanied by enhancement (Table 1). During dynamic MR imaging, HCCs also showed homogeneous enhancement, but variation in degree of enhancement on arterial phase (Fig. 2), and we observed two types of HCC lesions in degree of enhancement on the arterial phase. Fourteen-HCCs showed a rapid increase in enhancement accompanied with hyperintensity to liver parenchyma (Fig. 2, a and b). The other 19 HCCs with a slow and only subtle enhancement on the arterial phase, were iso- to hypointensity with respect to liver tissue (Fig. 2, c and d). As a result, the latter had statistically significant low CNR (1.03 ± 3.17) compared to that of hemangiomas (16.47 ± 8.43), and it could be easily distinguished from hemangioma. By contrast, the former with high CNR (15.76 ± 5.79) on the arterial phase could not be differentiated from hemangiomas by means of CNR. All HCCs revealed a substantial decrease in signal intensities on the later phase of dynamic imaging (Table 1) (Fig. 2, e, f and g).

By comparison, the majority of HCCs exhibited considerably lower signal intensities than those of hemangiomas, and mean CNRs were higher for hemangiomas than for HCCs on all phases of dynamic contrast-enhanced MR images (Fig. 3). The values of CNRs were higher on P1 and P2 compared to those

![Figure 3](image1.png)

**Fig. 3.** Quantitative evaluation of contrast to noise ratio (CNR) in early homogeneously enhancing hemangiomas and HCCs by using multiphasic dynamic contrast-enhanced MR imaging. Hemangiomas exhibit considerably higher CNR than that of HCCs. The difference in CNR between hemangiomas and HCCs was statistically significant on P3 and P4.

![Figure 4](image2.png)

**Fig. 4.** Distribution of CNR (mean ± standard deviation) in early homogeneously enhancing hemangiomas and HCCs on multiphasic dynamic contrast-enhanced MR images. The distribution of CNRs of hemangiomas and HCCs was overlapped on P1 and P2.

### Table 1. Quantitative Analysis for Differentiation of Early Homogeneously Enhancing Hemangiomas from Hepatocellular Carcinomas (HCCs) on Multiphases of Dynamic Contrast-Enhanced MR Imaging by Using Contrast to Noise Ratio (CNR) and Signal to Noise Ratio (SNR)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hemangioma</th>
<th>HCC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNR of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1 (mean ± SD)</td>
<td>16.47 ± 8.43</td>
<td>7.57 ± 8.34</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>P2</td>
<td>13.76 ± 6.80</td>
<td>5.38 ± 6.18</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>P3</td>
<td>13.95 ± 5.89</td>
<td>−2.23 ± 7.63</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>P4</td>
<td>7.88 ± 6.83</td>
<td>−2.49 ± 4.11</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>SNR of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1</td>
<td>45.67 ± 19.37</td>
<td>41.10 ± 18.98</td>
<td>−</td>
</tr>
<tr>
<td>P2</td>
<td>45.91 ± 10.96</td>
<td>46.67 ± 19.17</td>
<td>−</td>
</tr>
<tr>
<td>P3</td>
<td>46.86 ± 14.03</td>
<td>48.77 ± 19.73</td>
<td>−</td>
</tr>
<tr>
<td>P4</td>
<td>38.43 ± 13.36</td>
<td>40.34 ± 19.40</td>
<td>−</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviations.
Of multiphasic dynamic contrast-enhanced MR imaging; P1, first phase; P2, second phase; P3, third phase; P4, fourth phase.
on P3 and P4, but the difference in CNRs between early homogeneously enhancing hemangiomas and HCCs was greater on P3 and P4 than on P1 or P2, which resulted in a statistically significant difference (p value < 0.0001) (Table 1). Since the CNRs of hemangiomas were highly maintained on P3 and P4, the rapid decrease in CNRs of HCCs on P3 and P4 could allow for a distinction between HCCs and hemangiomas. However, the CNRs in P1 and P2 were less helpful for differential diagnosis because of the overlapped distribution in values of CNR between HCCs and hemangiomas (Fig. 4).

SNRs of hemangiomas and HCCs were similar and there was no statistically significant difference in SNRs between hemangiomas and HCCs (Fig. 5 and Table 1). When the cutoff for CNR was set at a value of 7.00 on P3 and 1.00 on P4, 17 of 18 hemangiomas and 31 of 33 HCCs on P3, and 17 hemangiomas and 27 HCCs on P4 were categorized correctly. This resulted in a sensitivity of 94.4%, a specificity of 93.9% and an accuracy of 94.1% on P3, and 94.4%, 81.8% and 86.3% on P4, respectively.

DISCUSSION

The diagnosis of hemangioma has often been established on the basis of MR imaging features, especially those related to T2-weighting and the pattern of contrast material enhancement. However, since some hemangiomas are enhanced homogeneously in the early phase of dynamic contrast-enhanced images, differentiating these hemangiomas from hypervascular tumors such as HCC, hepatic adenoma, focal nodular hyperplasia and some hepatic metastasis is often a problem. Thus, extremely rapid enhancement can create confusion in differential diagnosis and it may be difficult to establish a conclusive diagnosis on the basis of enhancement pattern alone. Although these hemangiomas used to be considered atypical, previous study has reported that they are not very rare. Moreover, since HCC and hemangioma have been the most frequent hepatic tumors, it is important to differentiate these hemangiomas from hypervascular HCCs, especially for treatment implications. In a previous study using two-phase dynamic incremental computed tomography (CT), the difference in the attenuation value between these hemangiomas and HCCs was reported. In our study, the attenuation or enhancement values in the arterial dominant phase were greater for early homogeneously enhancing hemangiomas than HCCs, aside from differentiating by enhancement pattern in the parenchymal phase. Similarly, for quantitative differential diagnosis of these hemangiomas from hypervascular HCCs on dynamic MR image, there should be a difference in SNR or CNR between hemangiomas and HCCs. In our study as well, early homogeneously enhancing HCCs exhibited lower CNR than that of hemangiomas on later phases, as well as the arterial phase of dynamic MR imaging. The CNR value of hemangioma was highest on the arterial phase among 4 phases of dynamic MR imaging, which was similar to the result of a previous study by Hanafusa et al. In contrast, the CNR of lesions on the arterial phase in our study did not prove to be helpful for lesion differentiation as demonstrated by overlapped distribution in the CNR values of HCCs and hemangiomas. There are reliable reasons for the difference in results between our study and that of Hanafusa et al. In quantitative analyses of early homogeneously enhancing hemangiomas and HCCs for the differential diagnosis, Hanafusa et al. used two-phase dynamic CT, whereas we used dynamic MR imaging consisting of 4 phases. The injection of highly concentrated contrast agent over a short time and fast image acquisition in the arterial dominant phase are 2 of many advantages of dynamic MR imaging, compared to CT scan. Therefore, in the depiction of hemodynamic change in regard to enhancement and the contrast between lesions and liver.
parenchyma, there were inevitable differences between MR and CT imaging. In addition to the difference in study modality, we evaluated patients with 4 phases, which provided more subdivided dynamic imaging, including the early arterial phase. In contrast, Hanafusa et al. did not obtain the later phase beyond the parenchymal phase and the scanning time of each phase was broadly ranged (arterial: 33–62 sec, parenchymal: 89–142 sec). As a consequence, the variable phases were presumably subsumed into one phase. The different result for the arterial phase, whether or not it was helpful for differential diagnosis, may also be explained by the different composition in cases of HCC. In this study, HCCs showed interlesional variability in the degree of enhancement on P1 and P2. Some HCCs with subtle enhancement in the early phase of dynamic imaging had low CNRs and could be differentiated from hemangiomas, while other HCCs with very high CNR due to rapid and strong enhancement in the early phase could not be distinguished from hemangiomas, which made CNR of the arterial phase less helpful in differential diagnosis. The variable increase in the enhancement of small HCCs has been known, which may be related to their variability in tumor vascularity and histopathologic differentiation, although it was demonstrated in the study using gadobenate dimeglumine enhanced dynamic MR imaging. In our study, the maximum contrast between hemangioma and HCC was obtained on the P3 and P4 rather than P1 or P2, because CNRs of HCCs were considerably lower than those of hemangiomas on P3 and P4. The rapidly reduced CNR of HCCs on P3, P4 might be resulted from the combined effect of the wash-out of contrast enhancement from the tumor and a considerable increase in the enhancement of liver parenchyma which was contrast to the CNR of hemangiomas that remained relatively high on P3 and P4. Indeed, the CNRs of hemangiomas on P3 and P4 were statistically higher than those of HCCs, and therefore they may be used as a quantitative parameter for differential diagnosis. In our results, however, there was no difference in SNRs between hemangiomas and HCCs, which suggests that the CNR of lesions provide comparable diagnostic information.

The difference in signal intensities on T2-weighted images is well known to be useful for the characterization of focal lesions on MR imaging: hemangiomas, which have a much longer T2 than HCC tend to stay bright on heavily T2-weighted images at long TEs. However, some investigators have advocated the acquisition of gadolinium-enhanced images for accurate discrimination of nonsolid benign lesions (hemangiomas or cysts) from solid malignant tumors. Since rapidly enhancing hemangiomas tend to be small, these signal intensities can be greatly diminished by means of partial volume averaging, which may cause the lesion to resemble a solid mass. This can be especially severe in the case of a small lesion located at the dome of the liver where the relatively high signal intensity of the lesion is reduced because of averaging with the signal void from pulmonary air. In addition, a pseudoglandular type of HCC can demonstrate the marked T2-prolongation, which may create a pitfall in using T2 to correctly differentiate between HCC and hemangioma. Therefore, in making a differential diagnosis, multiphasic dynamic contrast-enhanced MR imaging can improve lesion characterization and increase confidence. When an assured diagnosis is not obtained by T2-weighted images, the usefulness of dynamic MR imaging will be greatest. Our results suggest that the signal intensity measurement of lesions on dynamic contrast-enhanced MR imaging allowed us to make the differentiation between hepatic tumors and that the most accurate quantitative measurement was the calculation of CNR of the lesion, but not SNR. The value of quantitative analysis using CNR could be very worth while in differential diagnosis between lesions smaller than 3 cm in diameter.

In conclusion, the differential diagnosis between early homogeneously enhancing hemangiomas and hypervascular HCCs could be more confidently made with CNRs of lesions on MR images obtained at 60 sec and 300 sec, among multiphasic dynamic contrast-enhanced imaging. CNR on dynamic contrast-enhanced MR imaging could be a useful quantitative parameter in characterizing the rapidly enhancing hemangioma.

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