Detection of Hepatocellular Carcinoma Using Double-echo FLASH Sequence during the Hepatic Arterial Phase

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Purpose: The purpose of this study was to compare the performance of in-phase and opposed-phase gradient-recalled echo (GRE) pulse sequences in paramagnetic contrast-enhanced magnetic resonance (MR) imaging of hepatocellular carcinomas (HCCs) during the hepatic arterial phase.

Material and methods: Thirty-four patients with 84 lesions with known or suspected HCCs, nine of whom had a fatty liver, were examined with double-echo GRE techniques under 1.5T before and 30 s after injection of gadopentenate dimeglumine at a dose of 0.1 mmol/kg. Echo times were 2.4 ms (opposed phase) and 5.0 ms (in phase). Contrast enhancement of the HCC detected in both in-phase and opposed-phase images was evaluated. The liver signal-to-noise ratio (SNR), lesion-liver contrast-to-noise ratio (CNR), and enhancement ratio (ER) were calculated for the largest lesion of each patient.

Results: In dynamic gadolinium-enhanced images of the 84 HCCs, 81 (96.4%) were detected in both in-phase and opposed-phase images, two (2.4%) were detected in only in-phase images, and one (1.2%) was detected only in opposed-phase images. The liver SNR, CNR, and ER were 46.7 ± 16.1, 15.2 ± 10.3, and 0.637 ± 0.268 for in-phase images, and 48.9 ± 16.9, 16.3 ± 11.8, and 0.647 ± 0.309 for opposed-phase images, respectively. In patients with a fatty liver, the SNR, CNR, and ER were 46.0 ± 18.1, 21.7 ± 17.9, and 0.525 ± 0.231 for in-phase images, and 44.3 ± 18.7, 26.0 ± 21.3, and 0.793 ± 0.124 for opposed-phase images, respectively. No significant statistical differences were found between the in-phase and opposed-phase images.

Conclusion: Opposed-phase GRE imaging is equivalent to in-phase GRE sequences in patients with or without fatty liver for detection of HCC in dynamic gadolinium-enhanced images.

Keywords: MR imaging, liver, hepatocellular carcinoma, gradient echo

Introduction

Magnetic resonance (MR) imaging with T1-weighted gradient-recalled echo (GRE) pulse sequences during the hepatic arterial phase of contrast enhancement techniques provides better liver lesion detection and characterization, particularly for detection of hypervascular liver neoplasms.1-5 With most current MR imaging systems, the number of image sections that can be obtained with a given repetition time can be optimized with a gradient-echo technique with the shortest possible echo time. This approach reduces the effects of physiologic motion and section mis-registration and allows temporal resolution between different phases relative to the time of contrast agent administration. However, the shortest TE (time to echo) available in the GRE pulse sequence is occasionally the opposed-phase TE, in which images can be limited by a poor liver signal-to-noise ratio (SNR) in patients with fatty infiltration of the liver.6-8 Furthermore, we have noted that the signal intensity of some fatty tissues may actually decrease in opposed-phase MR images after administration of gadolinium chelates.9,10 The
technique of double-echo chemical shift gradient-echo MR imaging with the fast low-angle shot (FLASH) provides in-phase and opposed-phase images in a single breath-hold, and this technique is not compromised by slice mis-registration and time phase difference between breath-holds. Few reported studies have compared in-phase and opposed-phase images from dynamic MR imaging of hepatocellular carcinoma (HCC) with paramagnetic contrast agents in a T1-weighted GRE pulse sequence with a 1.0T system.\(^{11,12}\) However, we know of no study with a 1.5T system that changes the TEs of in-phase and opposed-phase images, the effect of chemical shift.

The purpose of this study was to compare the detectability of in-phase and opposed-phase images with double-echo FLASH in paramagnetic contrast-enhanced MR imaging of HCC during the hepatic arterial phase with a 1.5T system.

**Materials and Methods**

Thirty-four consecutive patients (30 men and four women, mean age 67.2 years) with 84 known or suspected HCCs were enrolled in the study. All patients had pre-existing liver cirrhosis or chronic hepatitis from the hepatitis B virus (n = 6) or hepatitis C virus (n = 28), nine of whom had a fatty liver. The diagnosis of HCC was verified by sonographically guided needle biopsy (26 lesions) or surgical biopsy (three lesions) within one month following MR imaging. For the remaining 55 lesions, the elevated serum tumor marker levels (alpha-fetoprotein > 50 ng/dl) and angiographic findings suggesting hypervascularity were used to confirm the presence of HCCs. Nine patients had one nodule, twelve had two nodules, four had three nodules, six had four nodules, and three had five nodules. The diagnosis of fatty liver was based on observation of the typical findings of ultrasound, CT (computed tomography) attenuation of less than 40 HU, and stability in serial CT scans after a minimum of six months.

All MR imaging was performed with a 1.5T system (Vision; Siemens Medical Systems, Erlangen, Germany) before and 30, 60, 90, 120, and 240 s after injection of gadopentenate dimeglumine (Magnevist; Schering, Erlangen, Germany) at a dose of 0.1 mmol/kg. Double-echo FLASH MR imaging was performed with a TR (time to repeat) of 119 ms, double TEs of 2.4 ms (opposed-phase) and 5.0 ms (in-phase), and a flip angle of 70°. Imaging parameters included a 128 × 256 matrix, one excitation, and a field of view of 26 to 34 cm with a CP (circular polarized) body-array coil. Transaxial images were obtained with a 6-mm section thickness and a 1.2-mm section gap. Fifteen in-phase and 15 opposed-phase axial sections were acquired during a 17-s breath-hold.

To evaluate detection of contrast enhancement in the arterial dominant phase, unenhanced and contrast-enhancement dynamic MRI of the first phase were evaluated for each patient. Three radiologists (T.N., Y.Y., and Y.N.) in conference prospectively evaluated in-phase and opposed-phase images for lesion detection, number, size, and signal characteristics of the lesions during the hepatic arterial phase. The signal intensities (SI) of the liver, lesion, and background noise were measured with operator-defined regions of interest (ROI). For lesions, the largest possible ROI within the tumor was used. In patients with multiple lesions, only one representative lesion was evaluated. Liver SNRs—defined as liver SI divided by standard deviation of background noise—and lesion-liver contrast-to-noise ratios (CNR)—defined as (SI lesion minus SI liver) divided by the standard deviation of background noise—were calculated. The enhancement ratio (ER) of the lesion before and after administration of gadopentenate dimeglumine was calculated with the formula: ER = (SI lesion − SI pre-lesion)/SI pre-lesion. Quantitative data from all 34 patients were used. The results were tested for significance of differences between in-phase and opposed-phase values with the two-tailed paired Wilcoxon test (after performing a one-way analysis of variance). A p value of less than 0.05 was considered statistically significant.

**Results**

In the precontrast study, 23 lesions exhibited hypointensity and 61 lesions exhibited isosignal intensity relative to the surrounding liver in opposed-phase images, while 20 were hypointense and 64 exhibited isosignal intensity in in-phase images of the 84 HCCs. In the dynamic gadolinium-enhanced images, three lesions ranged from hypointense to isointense in opposed-phase images. No lesion ranged from hypointense to isointense in in-phase images. Twelve lesions were isointense in both in-phase and opposed-phase images (Table 1).

In dynamic gadolinium-enhanced images of 84 HCCs evaluated in a prospective review, 81 (96.4%) were detected in both in-phase and opposed-phase images, two (2.4%) were detected only in in-phase images (Fig. 1), and one (1.2%) was detected only in opposed-phase images (Fig. 2).

For quantitative analysis, Table 2 gives the...
Table 1. Signal intensity of HCCs of precontrast and arterial-dominant phase imaging in relation to surrounding liver

<table>
<thead>
<tr>
<th>Signal Intensity of Precontrast and Arterial-Dominant Phase</th>
<th>Opposed-phase</th>
<th>In-phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypo to iso</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Hypo to hyper</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Iso to iso</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Iso to hyper</td>
<td>49</td>
<td>52</td>
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Note: Numbers indicate number of nodules.

Fig. 1. Images of a biopsy-proven well-differentiated HCC obtained from a 75-year-old man. Unenhanced (a) opposed-phase (119/2.4) and (b) in-phase (119/5.0) FLASH MR images. The nodule (arrow) appears notably hypointense in the opposed-phase image and slightly hypointense in the in-phase image, thus proving intratumoral fat deposition. Dynamic gadolinium-enhanced (c) opposed-phase and (d) in-phase FLASH images obtained during the arterial phase. The lesion (arrow) is clearly detected in the in-phase image. However, the enhanced lesion appears isointense to the liver in the opposed-phase image.

values for the liver SNR, CNR, and ER in in-phase and opposed-phase images in all patients. No significant statistical differences were found between in-phase and opposed-phase images. For the nine patients with a fatty liver (Fig. 3), Table 3 gives the values for the liver SNR, CNR, and ER in in-phase and opposed-phase images. In patients with a fatty liver, CNR and ER were increased in opposed-phase images; however, the difference between in-phase and opposed-phase images was not statistically significant.

Discussions

Many authors have studied the use of MR imaging in the diagnosis of HCCs, and rapidly advancing technology has expanded its use.1-5 The signal intensity of a small HCC relative to surrounding liver parenchyma is reported to have various patterns in T₁-weighted images (high, iso, and low intensity). Therefore, typical findings for small HCCs that have various cellular differentiations are limited, and a differential diagnosis from the benign cirrhotic nodule is not always easy solely
Fig. 2. Images of a HCC obtained from a 75-year-old woman
Unenhanced (a) opposed-phase (119/2.4) and (b) in-phase (119/5.0) FLASH MR images. The nodule (arrow) appears notably hypointense in the opposed-phase image and isointense in the in-phase image, thus proving intratumoral fat deposition.
Dynamic gadolinium-enhanced (c) opposed-phase and (d) in-phase FLASH images obtained during the arterial phase. In the opposed-phase image, the hypointense nodule (arrow) appears enhanced. However, the nodule is isointense to the liver in the in-phase image.

Table 2. Results of quantitative evaluation of in-phase versus opposed-phase images during arterial-dominant phase in all patients

<table>
<thead>
<tr>
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<th>In-phase</th>
<th>Opposed-phase</th>
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<td>SNR</td>
<td>46.7 ± 16.1</td>
<td>48.9 ± 16.9</td>
</tr>
<tr>
<td>CNR</td>
<td>15.2 ± 10.3</td>
<td>16.3 ± 11.8</td>
</tr>
<tr>
<td>ER</td>
<td>0.637 ± 0.268</td>
<td>0.647 ± 0.309</td>
</tr>
</tbody>
</table>

Note: Data are presented as mean ± SD. SNR: signal-to-noise ratio; CNR: contrast-to-noise ratio; ER: enhancement ratio.

Table 3. Results of quantitative evaluation of in-phase versus opposed-phase images during arterial-dominant phase in patients with fatty liver

<table>
<thead>
<tr>
<th></th>
<th>In-phase</th>
<th>Opposed-phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNR</td>
<td>46.0 ± 18.1</td>
<td>44.3 ± 18.7</td>
</tr>
<tr>
<td>CNR</td>
<td>21.7 ± 17.9</td>
<td>26.0 ± 21.3</td>
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<td>ER</td>
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Note: Data are presented as mean ± SD. SNR: signal-to-noise ratio; CNR: contrast-to-noise ratio; ER: enhancement ratio.

by means of static MR imaging for patients with a chronically damaged liver, whether or not the nodule is detected. Since the introduction of the high-resolution fast T1-weighted imaging technique, dynamic contrast-enhanced imaging has become possible, resulting in higher detection rates and easier tumor characterization. Previous studies have shown that the tumor detection rate of the arterial phase or sinusoidal phase was higher than that of the portal venous or non-equilibrium phase. In many of those studies, dynamic contrast-enhanced MR imaging of the liver with paramagnetic gadolinium chelates is best performed with T1-weighted GRE pulse sequences. This technique not only permits image acquisition with short scan times, thereby allowing dynamic scanning, but also provides greater T1-weighting in comparison with spin echo (SE) pulse sequences.
Fig. 3. Images of a HCC with fatty liver obtained from a 57-year-old man
Unenhanced (a) opposed-phase (119/2.4) and (b) in-phase (119/5.0) FLASH MR images. No
lesions are detected in either the in-phase or opposed-phase images.
Dynamic gadolinium-enhanced (c) opposed-phase and (d) in-phase FLASH images obtained during
arterial phase. Quantitative improvement in lesion-liver CNR was demonstrated in the opposed-
phase image.

due to the availability of shorter TE. The latter is
particularly useful in displaying the $T_1$ shortening
effects of paramagnetic contrast agents. To date,
MR researchers and manufacturers have concen-
trated on reducing the TE as much as possible.
However, so far insufficient attention has been paid
to the fact described by Dixon\textsuperscript{17} that variation of
the TE also determines whether the fat-water
components of a tissue being scanned are in-phase
or opposed-phase in the image. If, depending on
the field strength and the TE, a so-called opposed-
phase image results, severe problems may occur
with the interpretation of contrast enhancement in
those areas of the body where partial volume fat is
present.\textsuperscript{8,9} This article showed the effect of
opposed-phase sequences on the visibility of HCCs
by contrast enhancement in the arterial dominant
phase.

A biphasic relationship between lipid content
and signal intensity in an opposed-phase image has
been described previously.\textsuperscript{18,19} The short $T_1$
relaxation time of most CH$_2$ protons leads to their high
signal intensity in $T_1$-weighted images, so a small
amount of lipid produces a sufficient signal to
interfere destructively with the signal from a larger
amount of water. Conversely, predominately fatty
material loses very little signal intensity in opposed-
phase $T_1$-weighted images. Although fatty tissues
contain some water, the longer $T_1$ of water relative
to most CH$_2$ protons decreases the fraction of
signal intensity from water to less than the tissue
concentration of water. If the $T_1$ relaxation time of
water within fatty tissues were shorter, the fraction
of the signal intensity from water would be greater,
and the signal intensity loss in opposed-phase
images would be more substantial. Currently
available gadolinium chelates are distributed
throughout the extracellular space and facilitate the
relaxation of nearby water protons but have little
effect on intracellular lipid protons. Thus, adminis-
trations of these contrast agents increase the water
signal within fatty tissues, which eliminates the
signal from a greater number of lipid protons through destructive interference.\textsuperscript{8,9} Since in-phase
imaging is inconclusive for characterizing lesions
with fat, opposed-phase imaging can be very useful
in liver studies, not only because it improves lesion detectability, but also because it characterizes liver lesions for fat content and so reduces considerably the differential diagnosis of a focal liver lesion. In the present study, one HCC nodule was isointense to liver parenchyma and was therefore not seen in in-phase images, although they were well depicted in opposed-phase GRE images (Fig. 2). This can occur in fat-containing lesions when the lipid content is low. In these cases, in-phase images are relatively insensitive for identification of a fatty component; however, the cancellation effect between the water and fat protons produces a signal loss in opposed-phase images that renders the lesion visible (Fig. 2). In most cases of fatty liver, the relative loss of signal intensity in opposed-phase images should increase as the fat content of the liver increases. Thus, signal intensity in fatty liver is diminished in opposed-phase GRE images, resulting in a relatively lower signal intensity. However, HCCs are usually hyperintense in GRE images in the arterial-dominant phase, although opposed-phase images provide slightly greater lesion-liver contrast in patients with fatty infiltration of the liver in our study (Fig. 3).

Sugihara et al., who studied 107 HCCs with a field strength of 1.0T, noted that the mean sensitivity of opposed-phase imaging was higher than that of in-phase imaging. However, the difference between in-phase and opposed-phase imaging was not statistically significant. Our results in this study also suggest that no significant difference exists in detection sensitivity of HCCs between in-phase and opposed-phase dynamic MR imaging at a field strength of 1.5T. The chemical shift effect varies considerably, varying depending on proton Larmor frequencies (i.e., field strength). Thus, the chemical shift artifact in the opposed-phase images as a result of lipid and water signal cancellation in the overlapping region (etching artifact) with a 1.5T system is 1.5 times higher than that of a 1.0T system. This artifact appeared as a black rim surrounding the organ and degraded the image quality of the enhanced nodule at the liver edge. Conversely, the TEs of the in-phase and opposed-phase imaging with a 1.5T system are 1.5 times shorter than those of a 1.0T system. The sequence with the shorter TE should provide the higher SNR and greater enhancement with paramagnetic gadolinium chelates. In-phase imaging and opposed-phase imaging are complementary. The combination of in-phase and opposed-phase imaging not only increases the detectability of HCC but also characterizes the fatty metamorphosis of HCC.

Several potential criticisms of our study should be addressed. First, although histological confirmation of HCC was obtained in all cases, not all tumor nodules were biopsied or submitted for pathologic review after surgery. However, we attempted to address this point by forming a subset of data from patients for whom definitive surgery or follow-up angiographies proved total tumor burden. Second, our findings in patients with fatty liver were based on cross-sectional imaging findings and the lack of historical proof of fat fraction. Third, many of our patients had advanced cirrhosis with resultant focal fibrosis, nodular regeneration, and portal hypertension, all of which can diminish hepatic imaging. Therefore, our data may not necessarily be applicable to other hypervascular tumors in noncirrhotic patients. Finally, in-phase and opposed-phase images would ideally be obtained with theoretical TEs (e.g., a TE of 2.2 ms for opposed-phase and 4.4 ms for in-phase) with the double-echo FLASH technique. This could not be achieved with our double-echo FLASH sequence. However, for clinical applications, our principal aim was to compare the performance of in-phase and opposed-phase images, so we have not tried to correct the echo times.

In conclusion, this study shows that in-phase GRE imaging is equivalent to opposed-phase GRE sequences in patients with or without fatty liver in paramagnetic contrast-enhanced MR imaging of HCC during the hepatic arterial phase.

References