Three-Dimensional Dynamic Liver MR Imaging Using Sensitivity Encoding for Detection of Hepatocellular Carcinomas: Comparison With Superparamagnetic Iron Oxide-Enhanced MR Imaging

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Purpose: To assess the diagnostic performance of three-dimensional dynamic liver imaging with sensitivity encoding (SENSE), including double arterial phase images and increased resolution, by comparing it to superparamagnetic iron oxide (SPIO)-enhanced magnetic resonance (MR) imaging for the detection of hypervascular hepatocellular carcinoma (HCC).

Materials and Methods: Twenty-seven consecutive patients with 50 HCCs underwent Gd-BOPTA-enhanced dynamic imaging using SENSE and SPIO-enhanced MR imaging with at least a 24-hour interval between examinations. Using a three-dimensional gradient-echo technique applying SENSE, dynamic imaging consisting of double arterial phase-, portal phase- and delayed phase-images, was obtained. Using T2-weighted turbo spin-echo and T2*-weighted fast imaging with steady-state precession sequence, SPIO-enhanced MR imaging was obtained. For qualitative analysis, the diagnostic accuracy of both MR examinations for detecting the 50 HCCs was evaluated using the alternative free-response receiver operating characteristic method. Sensitivity and positive predictive value were also evaluated.

Results: The mean sensitivity and positive predictive value of three-dimensional dynamic imaging with SENSE were 91.3% and 89.2%, respectively, and those of SPIO-enhanced imaging were 77.3% and 92.6%, respectively. There was a significant difference in sensitivity between the two images (P < 0.05). The mean Az value of three-dimensional dynamic imaging with SENSE (0.97 ± 0.01) was significantly higher than that of SPIO-enhanced imaging (0.90 ± 0.02) (P = 0.00).

Conclusion: Three-dimensional dynamic liver MR imaging using SENSE for acquiring double arterial phase images is more efficient than SPIO-enhanced MR imaging for detecting HCCs.

Key Words: liver; MR; liver, neoplasms; MR, fast scan techniques; magnetic resonance (MR); contrast media

ADVANCES IN MAGNETIC resonance (MR) hardware and software allow faster scanning with reduced motion artifacts, which were previously responsible for the limited use of MR imaging for liver diseases. The use of localized phased-array body coils combined with the implementation of high-performance gradient systems result in rapid imaging acquisition with potentially no sacrifice in the signal-to-noise ratio (SNR) (1,2). However, due to the inherent limits of k-space speed, the overall acquisition time for MR imaging is still longer than that of multiphasic computed tomography (CT) imaging, which is routinely used for the evaluation of focal liver lesions. In addition, the resultant respiratory motion artifact with cardiac or vascular pulsation artifacts is one of the causes of degradation of the MR image quality.

Recently, the parallel acquisition technique was introduced as a method to reduce scan time with respect to standard Fourier imaging. Sensitivity encoding (SENSE), one of the parallel acquisition techniques, is based on the theory that receiver sensitivity has an encoding effect complementary to Fourier preparation and allows reduced acquisition time by means of arrays of multiple receiver coils with a resultant decrease in the number of measured echoes (3,4). There have been many studies regarding the clinical usefulness of SENSE, three-dimensional contrast-enhanced MR angiography (5), real-time cardiac imaging (6), and brain functional MRI (7). Recently, two clinical studies (8,9)
have demonstrated the efficacy of SENSE MR imaging for detecting hypervascular hepatocellular carcinoma (HCC) using multiphasic dynamic imaging.

Based on previous studies (10–12), superparamagnetic iron oxide (SPIO)-enhanced MR imaging is generally accepted as being useful for the detection of hepatic tumors, including metastasis and HCC, and is at least as accurate as CT during arterial portography, which is generally considered to be the most sensitive imaging modality for the detection of focal liver lesions. However, we know of no study that directly compares the diagnostic accuracy of dynamic MR imaging using SENSE to that of SPIO-enhanced MR imaging for the detection of focal liver lesions in the same patient groups using receiver operating characteristic (ROC) analysis. Accordingly, in this study we applied SENSE in a three-dimensional, T1-weighted gradient-echo sequence with a volumetric interpolation examination (volumetric interpolated breath-hold examination, VIBE: Siemens, Erlangen, Germany) (13) and acquired more upgraded dynamic images with double arterial phases and increased resolution by increasing the phase-encoding steps compared to those of conventional VIBE images. The purpose of this study was to assess the diagnostic performance of three-dimensional dynamic MR images with application of SENSE for the detection of HCC by comparing them with SPIO-enhanced MR images using alternative free-response ROC analysis with multiple observers.

**MATERIALS AND METHODS**

**Patients**

Between October 2002 and April 2003, 52 consecutive patients suspected of having HCC on previously performed ultrasonography or dynamic helical CT underwent three-dimensional dynamic imaging with the application of SENSE and SPIO-enhanced MR imaging. We excluded 25 of these patients for the following reasons: 12 had neither histologic proof nor a follow-up examination, seven had 10 or more HCCs, and six had massive or infiltrative HCCs. The remaining 27 patients (17 men, 10 women; mean age, 54 years) were enrolled in the study. Written informed consent was obtained from each patient before entry into the study, and the study was approved by the institutional review board of our hospital.

A total of 50 HCCs (size range 0.3–5 cm, mean 1.8 ± 1.3 cm) in 27 patients were included in this study. In all study patients, underlying viral-induced liver cirrhosis or chronic viral hepatitis (hepatitis B) was determined by clinical findings, a blood chemistry test (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, albumin, and globulin), and a hepatitis viral marker. Overall, 13 patients had solitary lesions, eight patients had two lesions each, four patients had three lesions each, and two patients had four lesions each.

The final diagnosis of HCC was proven by surgical specimen in nine patients, by core needle biopsy in 10, and in the remaining eight patients the final diagnosis was based on a combination of the clinical and radiologic criteria, including characteristic angiographic findings and iodized oil CT scans, three months or more of follow-up, tumor growth during subsequent follow-up imaging, and elevated serum alpha-fetoprotein level (over 400 ng/mL). Determination of the total number of HCCs in nine patients with 10 tumors who underwent hepatic surgery was made by intraoperative sonography and pathologic analysis of the surgical specimen in nine patients, by core needle biopsy in 10, and in the remaining eight patients the final diagnosis was based on a combination of the clinical and radiologic criteria, including characteristic angiographic findings and iodized oil CT scans, three months or more of follow-up, tumor growth during subsequent follow-up imaging, and elevated serum alpha-fetoprotein level (over 400 ng/mL). 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specimens. In 15 patients with 37 tumors who underwent transcatheter arterial chemoembolization, the standard of reference for the presence of HCC was the combined results of core needle biopsy, iodized oil CT scans after transcatheter arterial chemoembolization, and follow-up triphasic helical CT for more than six months. In the remaining three HCCs of three patients treated by radiofrequency thermal ablation, the diagnosis was based on the core needle biopsy and the six-month follow-up triphasic helical CT.

**MR Imaging**

All MR imaging was performed on a 1.5-T superconducting imager (Magnetom Symphony; Siemens, Erlangen, Germany) with a combination of phased array body coil and spine array coil for signal reception. SENSE with a reduction factor of two was applied in an in-plane phase encoding direction of three-dimensional dynamic imaging between two directions, i.e., the in-plane phase encoding direction and the partition direction. SENSE allowed acquisition of folded images in each receiver channel by reduced k-space sampling and then unwrapped them in the reconstruction process from a reference scan. All images were obtained in the axial plane.

Baseline MR images, including a respiratory-triggered T2-weighted turbo spin-echo (TSE) sequence, a breath-hold T2*-weighted fast imaging with steady-state precession (FISP) sequence, and a breath-hold T1-weighted fast low-angle shot (FLASH) sequence, were acquired. Respiratory-triggered T2-weighted TSE imaging was obtained using the following parameters: a
TR/TE of 3300–5500/85 msec; echo train length of 5; matrix of 256 × 512; and two signal averages. Breath-hold T2*-weighted FISP imaging was obtained using the following parameters: a TR/TE of 180/12; flip angle of 30°; matrix of 96 × 256; and a signal average. The long TE (12 msec) and lower flip angle (30°) were used for increasing sensitivity to field inhomogeneity induced by SPIO-administration and for decreasing T1 contrast, respectively (14,15). Breath-hold T1-weighted FLASH imaging was obtained with the following parameters: a TR/TE of 120/4; flip angle of 70°; matrix of 120 × 256; and a signal average. For all sequences, a 7-mm slice thickness was used with a 10% intersection gap and a field of view of 35–40 cm, depending on the size of the liver.

The dynamic imaging (VIBE: Siemens) with SENSE and reduction factor of two was performed using the following parameters: a TR/TE of 4.3/2.0; flip angle of 12°; bandwidth of 450 Hz/pixel; matrix of 256 (read) × 135 (phase) × 44–46 (partition); effective slice thickness of 3.5–4 mm; and field of view of 32–35 cm. The determination of scan delay for image acquisition timing was achieved using the test bolus technique in which 1 mL of gadopentate dimeglumine was injected along with saline flushing and the vessel of interest (abdominal aorta) was scanned approximately once per second. Dynamic images consisting of early arterial (20 seconds), late arterial (30 seconds), portal (60 seconds), and equilibrium phases (180 seconds) were acquired after a bolus injection of 0.1 mmol/kg of gadopentate dimeglumine (Gd-BOPTA; MultiHance®, Bracco SpA, Milan, Italy). The contrast was injected into the antecubital vein using an automated injector (Spectris MR; Medrad Europe, Maastricht, The Netherlands), and a
20-mL saline flush followed the contrast injections. Early and later arterial phase imaging was performed consecutively during a single breath-hold for approximately 22 seconds; however, portal and equilibrium phase images were acquired during a single breath hold of 10–11 seconds.

After completion of the dynamic MR examination, SPIO-enhanced MR imaging was performed after at least a 24-hour interval. SPIO-enhanced imaging comprised the respiratory-triggered T2-weighted TSE sequence for high-resolution images and the breath-hold T2*-weighted FISP sequence to maximize the lesion-to-liver contrast (14,15) using the same parameters as those used in the baseline MR imaging. The SPIO agent (SHU-555-A; Resovist, Schering AG, Berlin, Germany), at a dose of 8 μmol of iron per kilogram of body weight, was rapidly injected intravenously through a 5-μm filter; imaging commenced approximately 10 minutes after the intravenous SPIO injection.

Image Analysis

For alternative free-response ROC analysis, MR images of all patients with HCCs were evaluated independently and separately by three gastrointestinal radiologists experienced in interpreting MR liver imaging in their daily clinical practice and who were unaware of the design of the present study. They knew that these patients had liver cirrhosis and were at risk for HCC but did not have any other information about the patients’ histories, laboratory results, findings of other imaging modalities, or final diagnoses. Two separate sets of images were analyzed, i.e., the dynamic images with SENSE (precontrast T1-weighted FLASH, two arterial, a portal, and an equilibrium phases) and the two sequences of SPIO-enhanced T2-weighted images (T2*-weighted and respiratory-triggered T2-weighted TSE images). To minimize any learning bias, the interval between the two readings was set at three weeks.

Each observer recorded the presence and segmental location of the lesions, assigning each a confidence level on a five-point scale: 1, definitely or almost definitely absent; 2, probably absent; 3, possibly present; 4, probably present; and 5, definitely or almost definitely present. To avoid a mismatch between the findings of the scored lesions by observers and the gold standard for determining the total number of lesions, each observer recorded the individual image number, the segmental location of all lesions, and the size of each lesion. In four patients with two lesions in one segment, the observers added further description of the size and location of the mass in each segment to avoid confusion in the data analysis.

Statistical Analysis

After blind reading of two images set by each observer, four hepatic cysts were excluded from the data analysis. Based on the reviews of the three observers, the alternative free-response ROC curve analysis was performed on a tumor-by-tumor basis (16). For each imaging set, an alternative free-response ROC curve was fitted to each observer’s confidence rating data using a maximum likelihood estimation program (ROCKIT 0.9B, http://www-radiology.uchicago.edu/krl/KRL-_ROC/) (17). The diagnostic accuracies of each imaging set and observer were determined by calculating the area under the alternative free-response ROC curve (A index, Az). The differences in the imaging sets in terms of the mean area under the alternative free-response ROC curves were statistically analyzed using the two-tailed Student’s t-test for paired data. A two-tailed P value less than 0.05 was considered to indicate a statistically significant difference.

The sensitivity and positive predictive value for dynamic imaging with SENSE and SPIO-enhanced imaging were then calculated. The sensitivity for each observer and each set of images was determined by the
number of lesions assigned level 4 or 5 from among the 50 HCC nodules. The comparison of sensitivity and positive predictive value between each image set were based on the Student’s t-test. A two-tailed P value less than 0.05 was considered significant.

To assess interobserver agreement for the evaluation of two imaging modalities, we calculated the kappa statistic for multiple observers (18). Agreement between blinded observers is reported below in terms of kappa values, i.e., those greater than 0 indicating a positive correlation. Kappa scores >0.41 are considered to show moderate agreement; those >0.61, good agreement; and those >0.81, very good agreement (19). The level for statistical significance was P < 0.05. The statistical analyses were performed using SPSS 8.0 computer software (SPSS Inc., Chicago, IL).

RESULTS

For all 50 HCCs, the calculated Az values for each observer with SPIO-enhanced images and the dynamic imaging with SENSE are shown in Table 1. All three observers achieved superior diagnostic capability with dynamic imaging with SENSE to SPIO-enhanced images; in addition, the mean areas under the ROC curves of both MR examinations were significantly different (mean Az on dynamic imaging with SENSE, 0.972; mean Az on SPIO-enhanced imaging, 0.903; P = 0.00).

The sensitivities and positive predictive values for each observer and for each modality were calculated, and the mean values were also determined (Table 2). The mean value as well as the individual value of the sensitivity for dynamic imaging with SENSE were sig-
SIGNIFICANTLY HIGHER THAN THOSE OF THE SPIO-ENHANCED IMAGES \( (P < 0.05, \text{Table 2}) \). NONE OF THE OBSERVERS DETECTED TWO LESIONS ON EITHER SPIO-ENHANCED IMAGES OR ON DYNAMIC IMAGING WITH SENSE; NOR COULD EITHER OF THESE LESIONS BE SEEN ON RETROSPECTIVE REVIEWING. THESE LESIONS WERE SMALLER THAN 5 MM IN DIAMETER AND WERE CONFIRMED BY SURGICAL RESECTION. ON SPIO-ENHANCED IMAGES, NINE SMALL (0.4–1.0 CM) LESIONS WERE NOT DETECTED BY ANY OF THE OBSERVERS BUT THEY WERE ALL DETECTED ON DYNAMIC IMAGING WITH SENSE (Fig. 1). TWO SMALL NODULAR HYPERVASULAR HCCs WERE CLEARLY DEPICTED ON THE EARLY ARTERIAL PHASE OF DYNAMIC IMAGING WITH SENSE RELATIVE TO OTHER PHASES OF DYNAMIC IMAGING (Fig. 2). TWO 0.5–0.8 CM LESIONS WERE NOT DETECTED BY ANY OBSERVERS ON DYNAMIC IMAGING WITH SENSE BUT WERE DETECTED ON SPIO-ENHANCED IMAGES (Fig. 3). RETROSPECTIVE ANALYSIS OF THE MISSED LESIONS SHOWED THAT FOUR OF THE NINE MISSED LESIONS WERE MISSED FOR VESSELS ON SPIO-ENHANCED IMAGING: THE OTHER FIVE LESIONS SHOWED DECREASED SIGNAL INTENSITY ON SPIO UPTAKE. ON DYNAMIC IMAGING WITH SENSE, TWO LesIONS WERE MISSED THAT WERE CONFIRMED BY PERCUTANEOUS BIOPSY AND LIPIDOL CT, RESPECTIVE, AND WHICH SHOWED ISOSIGNAL INTENSITY TO THE SURROUNDING LIVER PARENCHYMA.

In terms of positive predictive values, no significant difference was found between the dynamic imaging with SENSE and the SPIO-enhanced imaging (89.2 vs. 92.6%). For all observers, 14 false-positive findings on SPIO-enhanced imaging and 11 false-positive findings on dynamic imaging with SENSE were found. On SPIO-enhanced imaging, all false-positive lesions were smaller than 1 cm in diameter and were attributed to hepatic vessels (10 cases) and fibrosis (four cases). ON DYNAMIC IMAGING WITH SENSE, ALL FALSE-POSITIVE LESIONS...
were attributed to the arterioporal shunts (nine cases) or vessels (two cases), and two were misdiagnosed by all observers and were not confirmed at surgery, thus indicating false-positive lesions.

For SPIO-enhanced and dynamic imaging with SENSE, the kappa values for the three observers were 0.756–0.882, thus indicating either good or very good inter-observer agreement with regard to the presence of lesions (Table 3).

DISCUSSION

Parallel imaging acquisition techniques (3,4,20), i.e., recently developed MRI software, were introduced to reduce scan time, thereby indicating that increased temporal resolution is possible on dynamic imaging. SENSE, one of the parallel imaging methods, allows substantial reduction of scan time by decreasing the number of measured echoes. (3,4). However, by reducing the number of measured echoes and the non-optimum weighting of the array coil elements, the SNR in SENSE images is decreased according to the square-root of acquisition time and is inversely proportional at least equal to the square root of the reduction factor (4). Therefore, SENSE is appropriate only when the faster imaging acquisition should be given much more weight relative to the SNR concerns. For detection of hypervascular tumors such as HCC, it is important to obtain appropriate arterial phase imaging on gadolinium chelate-enhanced dynamic MR imaging; this was well-documented in the study of Yoshioka et al (8).

In our study on alternative free-response ROC analysis, three-dimensional dynamic imaging including double arterial phase imaging using SENSE showed...
higher diagnostic accuracy than SPIO-enhanced T2-weighted images for detecting HCCs. This superior diagnostic accuracy of dynamic imaging could be attributed to several factors. First, we acquired successive double arterial phases of dynamic images during a single breath-hold, which, we believe, contributed to the higher diagnostic performance of the dynamic imaging than that of the SPIO-enhanced imaging for detecting HCC. An exactly timed arterial phase is essential for improving the detectability and accurate characterization of hypervascular HCCs on dynamic MR imaging. Given that double arterial phase imaging has less risk of failure to obtain exactly timed arterial phase images, it may have a great advantage over dynamic imaging with a single arterial phase for detecting hypervascular HCC. In this aspect, our results agree with those of previous studies regarding double arterial phase dynamic images including CT or MR imaging (8,21–23) for detecting HCC. Second, the use of the three-dimensional VIBE technique with SENSE, which provides thinner slice thickness (3.5–4.0 mm) compared to two-dimensional gradient echo images (6–8 mm) might contribute more to its higher diagnostic capability than SPIO-enhanced imaging (24,25). A high spatial resolution imaging modality is extremely advantageous for the early detection and accurate evaluation of small liver lesions. Last, in this study, 0.1 mmol/kg of gadopentate dimeglumine was used for the dynamic MR imaging. Given that the T1 shortening effect of gadopentate dimeglumine is double that of other gadolinium chelates (26), the image quality of the dynamic imaging with 0.1 mmol/kg of gadopentate dimeglumine may be similar to that of double-dose gadolinium chelate (21,27).

Figure 3. A 47-year-old woman with two nodular HCCs in the dome of the liver. The early arterial phase (a) and late arterial phase (b) of the three-dimensional dynamic imaging with SENSE after administration of gadopentate dimeglumine show a single enhancing mass (arrow) in segment VII. c: Equilibrium phase imaging obtained three minutes after contrast injection shows a single low-signal intensity lesion (arrow) at the same location in b. d: A SPIO-enhanced, breath-hold T2*-weighted fast image obtained with steady state precession reveals another daughter nodule (long arrow) as well as the main mass (arrow). e: Iodized oil CT shows two nodular lipiodol uptakes consistent with the SPIO-enhanced image.
The application of SENSE in dynamic imaging with VIBE allows time between each phase due to the considerable reduction of scanning time for each dynamic phase (from the original 20 seconds to 10 seconds), whereby acquisition of the higher phase encoding steps (from the original 120 to 135–140) and the resultant increased spatial resolution imaging was then possible. As a result, the application of SENSE makes it possible to acquire upgraded three-dimensional dynamic MR images with higher temporal resolution by reducing the scanning time. This results in acquisition of double arterial phases and higher spatial resolution by trading reduced scan time for a larger matrix relative to conventional dynamic images. Furthermore, we shortened the bandwidth (490 → 450 Hz/pixel) and the partition of the VIBE sequence for the dynamic MR imaging, which could compensate for the SNR penalty for reducing the scan time using SENSE and increased in-plane resolution to some degree.

This study has some limitations. Relatively small numbers of the study patients had both surgical and histopathologic proof of HCC. Therefore, some false-positive or false-negative lesions might have been included in this study. However, in our study, at least the six-month follow-up imaging studies were part of the inclusion criteria, and these strict criteria may provide firm evidence for the true-negative segments in this study.

In conclusion, high temporal resolution by application of SENSE allowed room for three-dimensional dynamic images to be upgraded by the acquisition of two successive arterial phases and increased in-plane resolution without degradation of image quality. This observation demonstrates that double arterial phase
three-dimensional dynamic MR imaging using SENSE is useful for detecting focal liver lesions.

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