Comparison of two different diffusion weighted imaging sequences for detection of small hepatic metastases: monopolar and bipolar DWI sequences

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Aims and objectives

Diffusion-weighted imaging (DWI) has a potential role to play in the differentiation and evaluation of liver tumors on the basis of a high contrast between lesions and normal tissue. DWI can help direct the attention of the radiologist to findings that may otherwise be overlooked (1). It has been reported that gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)- or mangafodipir trisodium-enhanced magnetic resonance imaging (MRI) showed higher accuracy in the detection of small hepatic metastases than DWI, but the addition of DWI was useful (2, 3).

Because of the short T2 of the liver and the resulting low signal-to-noise-ratio, the diffusion encoding gradients need to be played in the shortest possible echo time. The single refocusing pulse of the Stejskal-Tanner monopolar (MP) sequence can lead to further shortening of the echo time. However, unbalanced MP gradients are known to generate stronger eddy current-induced distortions at high b values (4). In most previous liver diffusion studies, researchers used a twice-refocused bipolar (BP) diffusion sequence (5) that features intrinsic low eddy current artifacts, while BP shows a longer echo time than MP sequence.

In previous studies, there were comparisons of image quality and intravoxel incoherent motion in the normal liver between MP and BP DWI. However, to our knowledge, a direct comparison of the detection of hepatic metastases between two different DWI sequences has not been published in the literature. The aim of this study was to compare MP and BP sequences, and determine the better technique for the detection of small hepatic metastases (2cm or smaller).
Methods and materials

Patients

Eighty-eight patients underwent Gd-EOB-DTPA-enhanced MRI including DWI for the evaluation of hepatic metastasis at the Department of Radiology, Kyoto University Graduate School of Medicine, Kyoto, Japan, from January 2011 to October 2012.

Of the 88 patients, 65 were excluded from the study for the following reasons: one patient was undergoing chemotherapy; 2 patients had neither histological proof nor follow-up confirmation; 7 had large lesions of more than 2 cm; 14 had more than 5 lesions; 41 had no hepatic metastasis.

The remaining 23 patients (including 16 men and 7 women, aged 41-82 years, mean age: 67 years) were included in the final study. There were 17 patients with colorectal cancer, 4 with pancreatic cancer, one with gastric cancer, and one with breast cancer.

Lesion confirmation

Fifteen patients underwent definitive surgery with intraoperative ultrasonography (US), and 31 small hepatic metastases were confirmed histologically in these patients. The 15 visible small hepatic tumors in 8 patients for whom histopathological confirmation of disease was not available were considered to be hepatic metastases on the basis of tumor growth observed at follow-up examinations (performed 3-20 months after MRI). Tumor growth was defined according to Response Evaluation Criteria in Solid Tumors (RECIST) (7). There were no patients with hepatic cirrhosis in this study.

The presence or absence of hepatic metastases was decided based on consensus between two radiologists (R.Y. and H.I., with 8 and 24 years' experience, respectively, in gastrointestinal and hepatobiliary imaging). The two radiologists determined the presence or absence of metastases on the basis of findings obtained with contrast-enhanced CT, US, positron emission tomography (PET) using F-18 fluorodeoxyglucose (FDG), and MRI; findings obtained at follow-up US, CT, FDG-PET, or MRI; and findings obtained at definitive surgery that involved intraoperative US and serological examination.

As a result, 46 small hepatic metastases (size range: 0.3-2.0 cm; mean: 1.04 cm) in 23 patients were confirmed, and we also included 5 patients who were found to have no focal liver lesions to serve as a control group for lesion detectability (Table 1). Of the 23
patients, 8 had solitary lesions, 10 had two lesions, and the remaining 5 had three or more lesions (3 had three lesions, one had four lesions, and one had five lesions).

**Imaging protocols**

All MRI examinations were performed at 3 T using a commercially available MR system (Skyra; Siemens Medical Solutions, Erlangen, Germany) equipped with a spine matrix coil and body matrix coil. DWI using a single-shot spin-echo echo-planar imaging (EPI) sequence in the axial plane with respiration triggering using the PACE method (TE = monopolar sequence: 53 ms and bipolar sequence: 69 ms, ETL = 86, ETS = 0.52 ms, slice thickness = 5 mm, gap between slices = 1.3 mm, matrix size = 86 × 128, FOV = 35 cm, number of slices = 30, b factors = 1000 s/mm², GRAPPA factor = 2) was acquired between the dynamic and hepatocyte phases using Gd-EOB-DTPA (Fig.1). In this study, apparent diffusion coefficient (ADC) measurement was not performed because it fell outside the remit of this study.

Imaging analysis

**Quantitative Evaluation**

Quantitative evaluations were performed by a radiologist (A.F. with 12 years' experience). Regions of interest (ROIs) were drawn in the focal lesion and hepatic parenchyma at a commercially available DICOM viewer (YAKAMI Software, Kyoto, Japan) to measure signal intensity (SI) on DWI with a b value of 1,000 s/mm².

ROIs were created in each focal lesion and the adjacent liver parenchyma at the same site of the focal lesion with MP and BP sequences, and SI of each ROI was measured. Tiny structures, such as thin vessels of small cysts, were carefully excluded from the ROIs on the liver parenchyma. Because the standard deviation (SD) of the background noise could not be used to calculate the image signal-to-noise ratio (SNR) due to the use of the parallel imaging technique, relative contrast ratio (RCR) was calculated for each tumor as

$$\text{RCR} = \frac{SI_{\text{tumor}}}{SI_{\text{liver}}}$$

where the signal intensity of the liver parenchyma is $SI_{\text{liver}}$ and the corresponding signal intensity of the liver lesion is $SI_{\text{tumor}}$ (8). RCR with an undetectable lesion was scored one.

**Qualitative Evaluation**
Two image groups were assigned and statistically compared: MP and BP sequences. Two readers (H.S., and S.K. with 10, and 10 years' experience, respectively, in gastrointestinal and hepatobiliary imaging) interpreted the images independently. These two readers were not the two radiologists who had determined the presence or absence of tumors on the basis of radiological and pathological findings. They knew that the patients were at risk of hepatic metastases but were blinded to all other information about the patients' history, including the site of the primary tumor.

All data sets were anonymized and randomized. Analysis of the images was performed on a DICOM viewer. To minimize any learning bias, we scheduled a 4-week interval between the two interpretation sessions.

Each observer recorded the presence and segmental location of the lesions, assigning each a confidence level on a 5-point scale: 1 = definitely not present; 2 = probably not present; 3 = equivocal; 4 = probably present; 5 = definitely present. To achieve an accurate correlation between the findings of the scored lesions and those of the gold standard, each observer recorded the individual image number and segmental location and size of each lesion. For patients with multiple lesions in the same segment, the observers added information regarding the size and location of the lesion within each segment to avoid confusion in data analysis.

Distortions were assessed by two radiologists (R. Y. and H. I.) as a lesion's distortion score (LDS) using a four-point scale, ranging from 4 (minimal or no distortion) to 1 (excessive distortion), and an undetected lesion was given a rating of zero. Disagreements between reviewers were resolved by discussion.

In addition, a radiologist (A.F.) correlated the scored lesions with the reference standard on the basis of the description regarding the size and location of the lesion as a coordinator.

**Statistical analysis**

Statistical analysis was performed using Excel (2007; Microsoft Corporation, Redmond, WA, USA) with the add-in software Statcel (OMS, Tokyo, Japan).

The differences between the RCRs obtained from MP and those from BP were evaluated statistically using Wilcoxon's signed rank test. A $P$-value of $< 0.05$ was considered to indicate a significant difference. For calculation of the detection sensitivity, the presence of lesions was dichotomized. Lesions with a score of 1 or 2 were "not present" and lesions with a score of 3-5 were rated as "present". Significant differences in detection rates of liver lesions using the two group's image sets, were evaluated with the related-samples McNemar test for each reader.
Comparison of the LDS of distortions with each lesion between the MP and BP sequence datasets was performed with the non-parametric Wilcoxon's signed ranks test.
Table 1: Forty-six small hepatic metastases (size range: 0.3-2.0 cm; mean: 1.04 cm) in 23 patients were confirmed, and we also included 5 patients who were found to have no focal liver lesions to serve as a control group for lesion detectability (Table 1). Of the 23 patients, 8 had solitary lesions, 10 had two lesions, and the remaining 5 had three or more lesions (3 had three lesions, one had four lesions, and one had five lesions).
Fig. 1: Schematic sequence diagrams show diffusion preparation followed by a single-shot echo-planar imaging readout. RF = radiofrequency, TE = echo time. (a) When using MP diffusion encoding, a minimum echo time of 53 msec is required. (b) When using BP diffusion encoding, an echo time as low as 69 msec can be achieved.

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Results

Quantitative Evaluation

The means and SDs of RCR are presented in Table 2. The RCR with BP showed significantly higher values than with MP (P=0.013).

Qualitative Evaluation

Detection sensitivity of liver lesions

The detection sensitivity for the two readers and datasets are shown in Table 3. One reader detected significantly more hepatic lesions on assessing with BP compared with MP (Fig.2). The detection sensitivities of the other reader was higher with BP than MP, but there was no significant difference.

Fig. 2: Small hepatic metastasis at S5 from colon cancer in a 42-year-old man. (a) BP demonstrates small metastasis at S5 with no distortion (arrow). (b) On MP, a small metastatic lesion at S5 shows marked distortion.

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Distortion score of lesions

The results of analysis are presented in Table 4. LDS was significantly better with BP than MP (p=0.002) (Fig.3).
**Fig. 3:** Two small hepatic metastases from gastric cancer in a 70-year-old man. (a) BP clearly shows two metastases at S7 (arrow) and S1 (arrowhead). (b) On MP, one lesion at S1 (arrowhead) is clearly visualized, but the other lesion at S7 (arrow) is not clear.

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Fig. 3: Fig.3: Two small hepatic metastases from gastric cancer in a 70-year-old man. (a) BP clearly shows two metastases at S7 (arrow) and S1 (arrowhead). (b) On MP, one lesion at S1 (arrowhead) is clearly visualized, but the other lesion at S7 (arrow) is not clear.

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Fig. 2: Fig.2: Small hepatic metastasis at S5 from colon cancer in a 42-year-old man. (a) BP demonstrates small metastasis at S5 with no distortion (arrow). (b) On MP, a small metastatic lesion at S5 shows marked distortion.

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Table 2: The RCR with BP showed significantly higher values than with MP (P=0.013).

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**Sensitivity for the detection on a per-lesion basis for the two individual readers using two method image sets.**

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<tr>
<th>Reader</th>
<th>Monopolar</th>
<th>Bipolar</th>
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<tr>
<td>Reader1</td>
<td>76.1%(35/46)</td>
<td>84.8%(39/46)</td>
</tr>
<tr>
<td>Reader2*</td>
<td>65.2%(30/46)</td>
<td>78.3%(36/46)</td>
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*Statistically significant change (p=0.04) in detection sensitivity

Table 3: One reader detected significantly more hepatic lesions on assessing with BP compared with MP. The detection sensitivities of the other reader was higher with BP than MP, but there was no significant difference.

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<th>Monopolar</th>
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<tr>
<td></td>
<td>2.80±1.03</td>
<td>3.39±0.87</td>
<td>0.002*</td>
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</table>

* Values are means ± SD.

* P value indicates a significant difference.

**Table 4:** LDS was significantly better with BP than MP (p=0.002).

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Conclusion

The accurate detection of hepatic metastases, especially small hepatic metastases, is clinically important because it may significantly affect the choice of therapeutic approach in many cases (8). MRI, especially single-shot EPI DWI, can obtain high lesion-to-liver contrast even without a contrast agent. Recently, abdominal DWI has become widely used for cancer patients because it can provide additional information for lesion detection, especially in the detection of hepatic metastasis (9,10). In this study, DWI of the liver was performed with two different approaches: an MP sequence which can shorten the echo time, and a BP sequence which can reduce eddy current.

The present study demonstrates that, the RCR was significantly higher with the BP sequence. This finding may be a result of the fact that, the signal of each hepatic tumor in MP comprised the real signal of the hepatic tumor and the signal of adjacent structures due to eddy-current-induced distortion compared with BP.

The detection sensitivity of one reader was significantly higher with the BP sequence, and the other reader showed a higher detection sensitivity with the BP rather than MP sequence, but without statistical significance. The present study also demonstrates that reading a BP sequence improves eddy-current-induced image distortion in small liver metastases compared to the MP sequence. This result suggests that lesion distortion influences lesion detection sensitivity.

Rosenkrantz et al. reported a higher sensitivity with reduced distortion DWI in comparison with the detection of prostate cancer using only DWI (11). Also, it has been reported that the image quality of hepatic parenchyma in BP DWI is better than with the MP sequence by reducing eddy-current-induced distortion (12). However, to our knowledge, the association between the lesion distortion in DWI and lesion detection sensitivity has not been previously reported in the peer-reviewed literature.

It is assumed, with the BP sequence, that the distortion of lesions within liver parenchyma is reduced compared with using the MP sequence. This may provide a reason why the distortion of the boundaries of the tumor to the surrounding liver parenchyma led to blurring of the lesion’s shape; therefore, the distortion lesions may be overlooked.

Chung et al. reported that the detection sensitivity of small liver metastases (#2 cm) using DWI is lower compared with larger metastases (#2 cm) (13). Although the detection sensitivity fell in response to the influence of the eddy current induced artifact since our study targeted small liver metastasis (#2 cm), the distortion due to the eddy current might not influence the detection sensitivity of larger lesions (#2 cm).
The diffusion-encoding gradients need to be set at the shortest possible echo time because of the short T2 of the liver. Also, since the liver is relatively a homogeneous organ in the abdomen, it was thought that liver metastases could not be easily influenced by eddy current-induced distortion. Therefore, it was expected that the detection sensitivity with MP might be higher than with BP, but, actually, BP was higher than MP. Since other organs in the abdomen have a longer T2 and more heterogeneous parenchyma than the liver, the higher detection rate of metastasis with BP might show the same tendency in other organs.

Only one lesion on bipolar DWI was not depicted because of physiological movement-related artifacts. The lesion was very small (7 mm in diameter) and was located in the superior portion of the lateral segment. This area is where images can be markedly distorted by air in the lungs and intestinal tract, and signal loss might occur because of cardiac motion (14,15). It might be described only with MP because SI of lesions with MP was high compared with BP.

Our study had several limitations. Firstly, our sample size was small, reflecting our initial experience. Secondly, not all lesions were compared and confirmed with surgical specimens. Thirdly, 14 patients found to have more than 5 focal hepatic lesions were excluded. A relatively large number of patients were excluded, leading to a potential selection bias. Fourthly, DWI was acquired after the administration of Gd-EOB-DTPA to shorten the examination time, and this may have had some effects on ADC values. However, a recent paper reported that ADCs of focal hepatic lesions were not significantly different between before and after the administration of a contrast agent and that DWI after Gd-EOB-DTPA administration can be used as a substitute for unenhanced DWI at 3.0 T without compromising CNR and ADC of focal hepatic lesions (16). Finally, we have not compared these DWI sequences with other sequences regarding their ability to detect and characterize liver lesions because our aim was only to objectively compare the image quality with the two DWI sequences.

In conclusion, the BP DWI sequence reduced eddy current more than the MP DWI sequence, being an acceptable sequence for the detection of small liver metastases, since the detection sensitivity of small liver metastases is related to lesion distortion due to the eddy current.
References