Diagnostic Value of SPIO-mediated Breath-hold, Black-blood, Fluid-attenuated, Inversion Recovery (BH-BB-FLAIR) Imaging in Patients with Hepatocellular Carcinomas

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Purpose: We assessed the value of adding a breath-hold, black-blood, fluid-attenuated, inversion recovery (BH-BB-FLAIR) sequence with a small motion-probing gradient (b = 10 s/mm²) using superparamagnetic iron oxide (SPIO) to our present studies that utilize SPIO to detect hepatocellular carcinoma (HCC). We used inversion recovery (IR) in a FLAIR sequence to suppress signals from cysts and a low b-value to suppress vessel signals and provide higher signal to noise than that using high b-value diffusion-weighted imaging. Use of SPIO is expected to reduce the signal in both normal liver parenchyma and in most benign lesions.

Materials and Methods: In 19 patients, we reviewed 38 HCC nodules diagnosed by CT arteriportography (CTAP) and CT during hepatic arteriography (CTHA). We divided SPIO-mediated images into sets, those obtained with and without BH-BB-FLAIR. Six radiologists individually interpreted the 2 image sets and sorted them by their confidence levels for the presence of HCC, and we calculated the area under the receiver operating characteristic (ROC) curve (Az) for each image set.

Results: On images obtained with BH-BB-FLAIR after SPIO administration, 33 of the 38 HCC nodules appeared as areas of high signal and cyst signal was extinguished. The ROC analysis showed significantly higher Az values in the set with BH-BB-FLAIR (0.89) than in the set without (0.83).

Conclusions: Adding BH-BB-FLAIR to existing SPIO-mediated imaging protocols improved detection of HCC nodules and added only 24 s to the scan time.

Keywords: black blood, diffusion, liver, magnetic resonance, superparamagnetic iron oxide

Introduction

Diffusion-weighted imaging (DWI) has been used primarily to evaluate intracranial areas, particularly after acute ischemic stroke. However, body DWI has recently been used in other areas of the body, including the abdomen, e.g., liver and kidney; pelvis, e.g. prostate, uterus, colon, and rectum; lymph nodes; neck; and whole body. DWI is useful for discriminating malignant tumors by demonstrating a decrease in the apparent diffusion coefficient (ADC) that is probably attributable to high tumor cellularity. Current DWI methods employ either a large motion-probing diffusion gradient (high b-factor) to emphasize the effect of diffusion or a small gradient (low b-factor) to suppress the signals from vessels. Although DWI with a high b-factor is reported useful for detecting tumors in the liver, its disadvantages include image obscuration from artifacts and distortion and prolonged scan time when using...
Fig. 1. Concept of breath-hold, black-blood, fluid-attenuated inversion recovery (BH-BB-FLAIR) using superparamagnetic iron oxide (SPIO) for hepatocellular carcinoma (HCC). Upper route: Black blood (small motion-probing gradient) suppresses the signals from vessels with a high signal-to-noise ratio (SNR) and less distortion. Middle route: FLAIR suppresses the signals from cysts. Lower route: SPIO reduces the signal in the liver parenchyma and decreases the signal in hemangiomas. This simultaneous use causes the signal from HCC to stand out.
Table 1. Magnetic resonance imaging sequence parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TR*2 (ms)</th>
<th>TE*2 (ms)</th>
<th>FA*2 (degrees)</th>
<th>TI*2 (ms)</th>
<th>b-factor (s/mm²)</th>
<th>matrix</th>
<th>scan time (s)</th>
<th>comments</th>
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<tbody>
<tr>
<td>BH-BB-FLAIR*1 image</td>
<td>2380</td>
<td>80</td>
<td>90</td>
<td>920</td>
<td>10</td>
<td>128 × 128</td>
<td>24</td>
<td>single-shot spin-echo-type EPI*2</td>
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<tr>
<td>T₁-weighted image</td>
<td>165</td>
<td>2.4/4.8</td>
<td>75</td>
<td>—</td>
<td>—</td>
<td>192 × 256</td>
<td>31</td>
<td>dual-echo breath-hold gradient-echo</td>
</tr>
<tr>
<td>T₂-weighted image</td>
<td>3900</td>
<td>120</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>192 × 256</td>
<td>21</td>
<td>single breath-hold fast-spin-echo</td>
</tr>
<tr>
<td>T₂*-weighted image (fat suppressed)</td>
<td>4451–6426</td>
<td>80</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>256 × 384</td>
<td>75–110*3</td>
<td>fat-suppressed respiratory-triggered fast-spin-echo breath-hold gradient-echo</td>
</tr>
<tr>
<td>T₃*-weighted image</td>
<td>151</td>
<td>9</td>
<td>60</td>
<td>—</td>
<td>—</td>
<td>192 × 256</td>
<td>29</td>
<td>breath-hold gradient-echo</td>
</tr>
</tbody>
</table>

*1 BH-BB-FLAIR = breath-hold black-blood fluid-attenuated inversion recovery  
*2 TR = repetition time; TE = echo time; FA = flip angle; TI = inversion time; EPI = echo-planar imaging  
*3 Dependent on respiratory rate
some nodules smaller than 3 cm in diameter.

**Establishing the reference standard**

By consensus, 2 radiologists from the Nagoya University Graduate School of Medicine with 3 and 21 years’ clinical experience in abdominal MR imaging determined as HCC–nodules that were apparent on CTAP in areas of partial or entire hypodensity that indicated absent intranodular portal supplies and that appeared on CTHA as areas of partial or entire hyperdensity that indicated increased intranodular arterial blood supply. Both radiologists retrospectively reviewed all MR images with an awareness of the CTHA and CTAP results and confirmed the presence of HCC nodules (n = 38) on MR images. Because nodules exceeding 3 cm in diameter were obvious in all images, they were excluded from this study.

**Set-up of image sets for evaluation**

From all images (32 slices × 8 sequences = 256 images), slice levels passing around the center of HCC lesions were selected from each sequence. Thirty-two positive slices included 27 with only one lesion, four with two, and one with three. In contrast, 60 slice levels from other subjects selected similarly at each positive slice level confirmed the absence of HCC. These images were divided into 2 image sets. One set without SPIO-BH-BB-FLAIR was included in the pre- and post- dual-echo T1W, T2W, and post-T2*W images, whereas the other set with SPIO-BH-BB-FLAIR was added to the post-SPIO BH-BB-FLAIR images to the former image set.

**Image analysis**

Six experienced radiologists with 3 to 14 years’ clinical experience (mean, 8 years) who were blinded to other imaging findings and final diagnoses interpreted the images in only one slice from each sequence. Each observer independently assessed the image sets at intervals of at least 4 weeks. Reading order was randomized, and the readers read half of each of the 2 image sets at each reading to avoid reading the same nodule twice at the same time. The readings were performed on a high-resolution liquid crystal display (2M-LCD × 2) monitor on a DICOM viewer.

Each observer reported the location of suspected malignant nodules by rough sketching and indicated the confidence level for nodule presence using a continuous rating scale from 0 (definite absence) to 1 (definite presence) of malignant nodules. Malignant nodules were defined as either a focal discrete, nodular area of high signal intensity relative to the surrounding liver parenchyma on BH-BB-FLAIR images obtained after SPIO administration or as a nodular area indicating lower uptake of SPIO than the surrounding liver parenchyma on T2W and T2*W images. However, each observer determined the final diagnosis, and no further evaluation was performed to differentiate HCC from other possible malignant tumors.

**Data analysis**

Each observer’s detection performance was assessed using receiver operating characteristic (ROC) analysis in which a binormal ROC curve was fitted to the individual observer’s confidence rating data from each reading session using a maximum likelihood estimation (MLE). We used the Metz LABROC4 algorithm to obtain MLEs of binomial ROC curves from the continuous ordinal-scale rating data. The area under the binomial ROC curve, Az, was used as an index of observer performance. To summarize the ROC curves for each test, the average ROC curves were obtained by averaging the binormal slope and intercept parameters of the individual observer’s ROC curves for each image set.

Our experimental design required statistical analysis of the differences between the 2 image sets. We performed analysis of variance (ANOVA) on the pseudo-values of Az computed using the jackknife-analysis method proposed by Dorfman’s group that was selected as the Dorfman-Berbaum-Metz (DBM) method.

We calculated localization accuracy rate, probability of correct localization (PCL), and ratio of all images of malignant nodules correctly indicated on rough observer sketches regardless of confidence rates. We then estimated 95% confidence intervals using the maximum likelihood method for the binormal model. $P < 0.05$ was accepted as significant.

**Results**

Quality of all images acquired using BH-BB-FLAIR was considered readable with less susceptibility to artifacts and distortion.

According to our estimation, images obtained with BH-BB-FLAIR following SPIO administration depicted 33 of 38 HCC nodules as areas of high signal and the remaining five as areas of iso- or low signal; the nodules were apparently not detected using other MR sequences (Figs. 2–4). Five nodules shown as areas of partial hypodensity on CTAP and partial hyperdensity on CTHA were presumed to be on the step of well differentiated HCC during hepatocarcinogenesis. On the images obtained with BH-BB-FLAIR after SPIO administration, three of these 5 nodules appeared as areas of high signal (Fig. 4), the other two were not shown, and the signal of the cyst was extinguished.
Fig. 2. Images from a 63-year-old man with hepatocellular carcinoma (HCC) (a) Breath-hold, gradient-echo prior to superparamagnetic iron oxide (SPIO) administration, T1-weighted image (in-phase). (b) Following administration of SPIO, respiratory triggered, fat-suppressed, fast-spin-echo T2-weighted image. (c) Breath-hold, gradient-echo, T2*-weighted image. (d) Breath-hold, black-blood, fluid-attenuated, inversion recovery (BH-BB-FLAIR) image. (e) Computed tomographic (CT) arteriortography (CTAP). (f) CT during hepatic arteriography (CTHA). Large classical HCC (arrowheads, a-f) in Segment 8 and small HCC in Segment 4 (arrows, c-f) are depicted on CTAP (e) and CTHA (f). The large lesion is apparent on all images, whereas the nodule in Segment 4 is so small that it is difficult to identify on conventional magnetic resonance (MR) imaging (a-c). Conversely, this small nodule is distinct and can be easily identified on BH-BB-FLAIR (d).

We observed significant differences in Azs between the 2 image sets. Table 2 lists the results of the DBM ANOVA conducted on Azs for the 2 sets. This overall ANOVA showed statistically reliable effects of the 2 image sets on reader diagnostic performances ($P<0.05$). Statistically reliable differences in diagnostic performance were found among the 92 cases ($P<0.001$). No statistically reliable differences were found among the 6 observers ($P=0.6126$). Figure 5 depicts the average ROC curves for the 2 image sets, showing the curve for the set obtained with BH-BB-FLAIR after SPIO administration to be superior to that of the set without.

Although some observers noted statistically reliable differences in PCL in the 2 image sets (Fig. 6), the relationship between PCL values and the 2 sets differed among the 6 observers, and no general tendency was recognized regarding this relationship.

**Discussion**

Identifying the exact number and location of HCC nodules optimizes treatment strategies. CTAP and CTHA have high detection rates for HCC, and their combined use has been firmly established for successfully diagnosing HCC and enables evaluation of the blood supply for histologically grading HCC malignancy. Consequently, CTHA and CTAP have been adopted as reference standards. Nevertheless, it is difficult to justify their use for screening because their disadvantages include radiation exposure, risk of allergic reaction and anaphylactic shock associated with using an iodine contrast material, invasiveness of selective injection in the superior mesenteric and celiac artery, and bleeding from the puncture canal.

SPIO is a tissue-specific MR imaging contrast medium that is taken up by Kupffer cells in the liver and has thus been used to detect hepatic tumors.
Fig. 3. Images from a 74-year-old man with multiple cysts and hepatocellular carcinoma (HCC)
(a) Prior to administration of superparamagnetic iron oxide (SPIO), breath-hold, gradient-echo T1-weighted image (in-phase). (b) Following administration of SPIO, respiratory-triggered, fat-suppressed, fastspin-echo, T2-weighted image. (c) Breath-hold, gradient-echo, T2*-weighted image. (d) Breath-hold, black-blood, fluid-attenuated, inversion recovery (BH-BB-FLAIR) image. (e) Computed tomographic arteriopography (CTAP). (f) CT during hepatic arteriography (CTHA) injected into the right hepatic artery. A classical HCC (arrows, b-f) in Segment 8 and multiple cysts in the entire liver are depicted on CTAP (e) and CTHA (f). Because the signal from this lesion is low and the signals from multiple cysts are obvious on (b), it is difficult to identify the lesion. In (d), similarly to (c), the lesion shows high intensity, and the multiple cysts show a decrease in signal. However, because this nodule shows much higher intensity than the surrounding parenchyma, it is more easily identified on BH-BB-FLAIR (d) than on (c). The area of high intensity on BB-BH-FLAIR (arrowhead, d) is presumed to be edema or non-specific inflammation of the Glisson’s sheath.

SPIO-enhanced MR imaging reflects numbers and function of Kupffer cells. It has been reported that the number of Kupffer cells decreases in HCC nodules and that SPIO-enhanced MR imaging is useful for estimating HCC histological grading.26,27 However, the detection rate of small HCC nodules on SPIO-enhanced MR imaging is reported to be inferior to that of other dynamic modalities,28 possibly attributable, in part, to the residual signals of vessels and cysts. Therefore, the detection rate of small HCCs using SPIO-enhanced MR imaging must be improved.

Diffusion-weighted imaging of the liver is divided roughly into a method utilizing a high b-factor (b > 400)3,13 and one employing a low b-factor (black-blood liver imaging) (b < 100).16–18 Use of a high b-factor may permit differentiation of benign from malignant tumors to further estimate the degree of HCC differentiation but may be ineffective for detecting small lesions resulting from gross artifacts caused by breathing and peristalsis as well as severe distortion from the boundary surface of air to parenchyma.29 The method employing a low b-factor (small MPG) is less susceptible to artifacts and distortion.29,30 In addition, because many liver tumors and vessels have high signal on FSE T2W images, it is difficult to distinguish small tumors from the signals of the portal and hepatic veins in the liver. Distinguishing small tumors from these veins is certainly possible when comparing contiguous slices in up and down views, but it is very time-consuming. Suppressing vessel signal with a small
Fig. 4. Images from a 77-year-old man with hepatocellular carcinoma (HCC)

(a) Schematic illustration shows localization of the liver nodules. (b) Prior to administration of superparamagnetic iron oxide (SPIO), breath-hold, gradient-echo, T₁-weighted image (in-phase). (c) Breath-hold, gradient-echo, T₂*-weighted image. (d) Breath-hold, black-blood, fluid-attenuated, inversion recovery (BB-BH-FLAIR) image. (e) Computed tomographic arteriography (CTAP). (f) CT during hepatic arteriography (CTHA). Nodule #1 in Segment 7 and nodule #4 in Segment 5 show the absence of stain on CTAP (e) and increased staining on CTHA (f). These findings indicate the absence of an intranodular portal supply on CTAP (e) and increased intranodular arterial blood supply on CTHA (f). They are diagnosed as classical HCC. Nodules #2 and #3 in Segment 7 indicate the partial or complete absence of staining on CTAP (e) and partially increased stain on CTHA (f). These findings indicate the partial or complete absence of an intranodular portal supply and partially increased intranodular arterial blood supply. They are presumed to be well differentiated HCC. Nodule #5 in Segment 4 indicates decreased but not absent stain on CTAP (e) and decreased stain on CTHA (f). These findings indicate decreased but not absent intranodular portal blood flow and decreased intranodular arterial blood supply. They are presumed to represent a high-grade dysplastic nodule. Nodules #1 through #4 are depicted in high intensity on (d). Nodule #5 cannot be detected on magnetic resonance (MR) images. A nodule in Segment 3 is not contained in the slice in (d), but these nodules are depicted in high intensity in another slice (not shown).

Well differentiated HCC is an early stage of multistep hepatic carcinogenesis. Although DWI using a high b-value is expected to be the optimal method to detect malignancies, such as tumors in other regions, DWI does not clearly depict well differentiated HCCs. Perhaps this results from the lack of a T₂ shine-through effect as well as a similar ADC as that of the surrounding liver parenchyma. The T₁ value of well differentiated HCC is reported shorter than that of the surrounding liver parenchyma. Therefore, as we expected, well differentiated HCCs can be visualized on BH-BB-FLAIR images, which affect T₂ shine-through and the character of a T₁W image. However, it is difficult to detect some well differentiated HCCs on BH-BB-FLAIR because they have T₁ and T₂ values resembling those of the surrounding liver parenchyma and the uptake ability of SPIO. Treatment for HCC includes resection; transplantation; regional therapeutic procedures, such as transcatheter arterial infusion therapy or transcatheter arterial embolization (TAE); percutaneous ethanol instillation; chemotherapy; and radiofrequency ablation. Because therapy is chosen based on the number and range of nodules, it is important to detect small or well differentiated HCC nodules and determine possible malignancy.

It is also necessary to differentiate benign lesions, such as cysts and hemangiomas, that are often seen in the liver. In this study, we applied an IR pulse in FLAIR to suppress signals from cysts. Simple cysts...
Table 2. Analysis of variance of 2 sets for areas under the binormal receiver operating characteristic (ROC) curves

<table>
<thead>
<tr>
<th>Source*</th>
<th>Degree of freedom</th>
<th>Mean Square</th>
<th>F ratio</th>
<th>Probability value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>1</td>
<td>0.9185</td>
<td>5.2415</td>
<td>0.0481 &lt; 0.05</td>
</tr>
<tr>
<td>C</td>
<td>91</td>
<td>1.0249</td>
<td>10.0504</td>
<td>0.0000</td>
</tr>
<tr>
<td>R</td>
<td>5</td>
<td>0.0729</td>
<td>0.7148</td>
<td>0.6126</td>
</tr>
<tr>
<td>T × C</td>
<td>91</td>
<td>0.1319</td>
<td>1.5707</td>
<td>0.0016</td>
</tr>
<tr>
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<td>1.5160</td>
<td>0.1833</td>
</tr>
<tr>
<td>R × C</td>
<td>455</td>
<td>0.1020</td>
<td>—</td>
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</tr>
<tr>
<td>T × R × C</td>
<td>455</td>
<td>0.0840</td>
<td>—</td>
<td>—</td>
</tr>
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</table>

* T = image sets; C = cases; R = readers

Fig. 5. Composite receiver operating characteristic (ROC) curve of 6 observers. Definitions of 2 sets with and without superparamagnetic iron oxide (SPIO) breath-hold, black-blood, fluid-attenuated, inversion recovery (BH-BB-FLAIR) are given in Table 2. Area under the ROC curve (Az) = estimated means of Az ± 95% confidence intervals for each image set.

Fig. 6. Localization accuracy rates (PCL's) ± their 95% confidence intervals for each observer and for each image set. PCL is the ratio of all malignant nodule images having nodules correctly reported on a rough sketch by the observer regardless of confidence rate. The 95% confidence intervals were estimated using the maximum-likelihood method for the binormal model.

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Most HCC nodules develop in patients with liver cirrhosis. However, in late-stage cirrhosis, uneven uptake of iron oxide particles caused by the decreased activity of Kupffer cells results in poor lesion conspicuity on SPIO-enhanced MR imaging.37,39,40 However, SPIO-enhanced MR imaging with BH-BB-FLAIR suppresses signal obstacles and synergistically utilizes the difference between T1 and T2 values to improve lesion conspicuity.

Our study has several limitations. First, the design was retrospective, and the patient population was small. Second, the gold standard of this study was the consensus interpretations with the CTHA and CTAP results, and all lesions were not histopathologically confirmed; therefore, the actual sensitivity of detecting HCC could be overestimated by a reduced number of false-negative lesions. Third, BH-BB-FLAIR imaging provides rather blurred images, low spatial resolution, and distortion owing to the use of echo-planar imaging.
Conclusions

BH-BB-FLAIR imaging after SPIO administration is an excellent method for visualizing HCC nodules. Interpreting images thus obtained along with other SPIO-mediated images improved detection of HCC, and addition of BH-BB-FLAIR adds only 24 s to existing protocols for SPIO-mediated studies. The resultant suppression of signals from vessels and cysts makes it easy for radiologists to identify lesions.

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References

21. Metz CE, Herman BA, Shen JH. Maximum likelihood estimation of receiver operating characteris-


