Hepatobiliary phase imaging of gadoxetic acid-enhanced liver MRI: respiratory gating vs breath-holding for three-dimensional T1-weighted gradient echo imaging

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Aims and objectives

Contrast enhanced multi-row detector computed tomography (MDCT) and magnetic resonance imaging (MRI) are establishing roles as a primary diagnostic technique for evaluation of liver diseases, due to their high diagnostic sensitivity and specificity. But with the recent increasing concerns regarding the risks of radiation, the role of MR imaging is getting more important\(^1\). Several studies have demonstrated that Gd-EOB-DTPA enhanced MRI which demonstrated superior its diagnostic performance for detection of hepatocellular carcinoma (HCC) or colorectal liver metastases (CRLM) than MDCT due to its improved contrast between those liver malignancies and the background liver parenchyma\(^2\). However, one of the major challenges of MR imaging in the abdomen has centered on the problem of acquiring data from tissue that has high spatial displacement low-frequency movement, mostly caused by respiratory-dependent movement of the diaphragm\(^3\). Another limitation of MR compared with MDCT is its lower spatial resolution than MDCT\(^4\). Therefore, in order to further improve diagnostic performance of liver MRI with Gadoxetic acid, improving spatial resolution of T1-weighted imaging (T1WI) for depicting small focal liver lesions or or biliary ductal imaging fine anatomic details within reasonable acquisition time would be necessary\(^5\).

In order to obtain high resolution imaging for gadoxetic acid-enhanced liver MR imaging, breath-hold imaging technique using parallel imaging techniques with high acceleration factors, or respiratory triggered or gated T1-weighted imaging techniques could be used. Recently, there have been a few studies which demonstrated technical feasibility of respiratory triggered 3D T1-GRE sequence for hepatobiliary phase imaging of Gd-EOB-DTPA-enhanced MR imaging\(^6\)\(^-\)\(^9\). However, in those studies, only small numbers of patients\(^8\),\(^9\) or volunteers\(^6\) were included, and there have been no studies which demonstrate clinical feasibility of navigated T1-GRE sequence in large number of patients with focal and diffuse liver diseases.

Therefore, the purpose of this study was to determine whether navigated 3D T1W-GRE can improve image quality and diagnostic performance to detect focal liver lesions (FLLs) than breath-hold T1W-GRE during hepatobiliary phase (HBP) of gadoxetic acid-enhanced liver MRI.
Study Population and Standard of Reference

From July 2012 to December 2012, 414 consecutive patients underwent Gd-EOB-DTPA-enhanced liver MRI for assessing FLLs including hepatobiliary phase (HBP) imaging obtained by using both breath-hold LAVA sequence (BH-LAVA) and navigated LAVA (naviLAVA) sequence at 1.5T. Among them, T1-weighted dynamic sequences of 372 patients (M:F=256:116, mean age 61.1±9.2 years) who were older than 40 years (41~50 years [n=54]; 51~60 years [n=134]; 61~70 years [n=121]; and 71 years [n=63]) were reviewed by one attending radiologist (J.H.Y. with eight years of clinical experience) in the way described below. There were 309 patients (M:F=210:99, mean age 60.0±8.9 years) with sufficient breath-hold capacity and 63 patients with limited breath-hold capacity (M:F=46:17, mean age 65.7±9.4 years). Sixty-three patients with limited breath-hold capacity underwent liver MRI for following reasons: hepatocellular carcinoma (HCC) surveillance (n=53); liver metastasis surveillance (n=4); and FLL characterization (n=3). In those patients with limited breath-hold capacity, the clinical feasibility based on length of scan acquisition time of naviLAVA and qualitative analysis and diagnostic performance to detect FLLs were assessed. In patients with sufficient breath-hold capacity, overall image qualities of two scans were compared. Study flow chart was shown in Fig 1.
For assessing diagnostic performance to detect FLLs, multiple FLLs were identified in sixteen patients and one patient with more than thirty peribiliary cysts was excluded. The remaining 34 patients who had no FLLs were confirmed absence of FLLs on follow-up imaging studies, performed at least six months following the initial MR imaging. Total of 148 FLLs were identified in fifteen patients: nine patients had less than 5 FLLs (single FLL [n=4]; two FLLs [n=1]; three FLLs [n=1]; and four FLLs [n=3]); two patients had more than 10 FLLs (11 FLLs [n=1]; and 12 FLLs [n=1]); and four patients had more than 20 FLLs (21 FLLs [n=1]; 25 FLLs [n=1]; 26 FLLs [n=1]; and 32 FLLs [n=1]).

Total of 148 FLLs were identified based on all sequences and follow-up MRI and computed tomography by two attending radiologists (J.H.Y. and J.M.L. with 22 years of clinical experience): HCC (n=44; mean size, 2.45±3.65cm); metastasis (n=18; mean size 0.94±0.37cm); cyst (n=49; mean size 0.62±0.35cm); biopsy proven chronic inflammation (n=1; 1.1cm); hemangioma (n=1, 0.8cm); lipiodol uptake (n=2; 1.25±1.34cm); percutaneous ethanol injection treated lesion (PEIT defect, n=1; 1.1cm); dysplastic nodule (DN, n=32; 0.54±0.22cm).

Forty of 44 HCCs were diagnosed based on the noninvasive diagnostic imaging criteria for HCC of the American Association for the Study of Liver Diseases (AASLD) practice guidelines. The remaining four HCCs were confirmed by surgery. For metastasis, the diagnosis was established when FLLs showed interval growth in patients with underlying malignancies and the following findings: low T1 signal intensity and variable, high T2 signal intensity; and irregular borders with rim enhancement seen on MR dynamic images. In addition, hypermetabolic uptakes on FDG-PET images were also used as supporting evidence of metastases. The hemangioma diagnosis was made according to the bright signal intensity on T2W image and the typical enhancement pattern on CT or MR; and no interval change in the lesion size seen during a follow-up period of more than six months. Hepatic cysts were diagnosed when FLLs showed bright high SI on T2WI and no enhancement on dynamic phases. More than forty cirrhosis-related nodules were identified in explanted liver in two patients who underwent liver transplantation. Only five DNs were one-to-one matched by histological mapping of the specimen and MRI review and the remaining 27 DNs were not clearly matched.

Magnetic Resonance Imaging Acquisition

MR protocol

All patients underwent liver MR at 1.5T (Signa HDxt, GE Healthcare, Milwaukee, WI), using an 8-channel torso phased-array coil. Routine MR sequences consisted of a respiratory-triggered T2-weighted fast spin-echo, breath-hold T2-weighted single-shot...
fast spin-echo, breath-hold T1-GRE sequence, and breath-hold T1-weighted, dual echo spoiled gradient recalled echo sequence. T1W-imaging was performed in axial plane using the following imaging parameters: TR/TE= 6.6/ msec; flip angle (FA) 12°; matrix 320 × 224; slice thickness 4.8 mm; field of view (FOV) 300-350 mm depends on body size; and scan time, 18-20 seconds. Parallel imaging (array spatial sensitivity technique [ASSET], GE Medical Systems) with a reduction factor of two, was performed in an in-plane, phase-encoding direction. Dynamic 3D-fat suppressed (FS) T1-GRE sequences (liver acquisition with volume acceleration [LAVA], GE Healthcare) including arterial phase (AP), portal venous phase (PVP), delayed phase (DP), and hepatobiliary phase (HBP), were performed following injection of gadoxetic acid (Gd-EOB-DTPA; Eovist or Primovist; Bayer SheringPharma AG, Berlin, Germany). The standard dose of contrast agent was applied using intravenous bolus administration of 10 mL at a rate of 1.5 mL/s, and was immediately followed by a 20-mL saline flush through an antecubital venous catheter, using a power injector (Spectris Solaris® EP, MEDRAD Inc., Warrendale, PA, USA). HBP images were obtained 10 minutes and 20 minutes after contrast media injection.

**Hepatobiliary Phase Imaging using Navigated-LAVA**

HBP imaging obtained by using naviLAVA was performed 10~15 minutes after contrast media injection, followed by 20 minutes delayed HBP image acquisition by using BH-LAVA. Detailed scan parameters were summarized in Table 1.

Navigated sequence was created by combining 3D T1-GRE sequence with a respiratory navigator echo. The navigation pulse consisted of cylindrical two-dimensional (2D) RF excitation pulses which were repeated in 200 msec for 20 msec. It included spectrally-selective partial fat inversion and segmented data acquisition. Parallel imaging (Auto-calibrating Reconstruction for Cartesian sampling [ARC], GE Medical Systems) with a reduction factor of 2.2 (2.0 in an in-plane, phase-encoding direction and 1.1 in an through-the-plane direction). The navigator was placed in the right hemidiaphragm and its width of the excitation was 10-20 mm and the length was 70-100 mm. A low 12° flip angle was used to avoid possible saturation in the imaging volume on HBP. Image acquisition was suspended when acquisition time of naviLAVA exceeded 10 minutes, to scan 20 minutes delayed HBP images. The cases with prolonged acquisition time were considered as ‘acquisition failure’ and reported by radiology technicians in charge of the scan.

<table>
<thead>
<tr>
<th></th>
<th>BH-LAVA</th>
<th>NaviLAVA</th>
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<tbody>
<tr>
<td>TR (msec)</td>
<td>6.0</td>
<td>4.9</td>
</tr>
<tr>
<td>TE (msec)</td>
<td>3.1</td>
<td>2.3</td>
</tr>
<tr>
<td>Flip angle (°)</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Fat suppression technique</td>
<td>Spectrally selective partial fat inversion</td>
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</table>
Fig. 2: Illustration of navigated LAVA. The black blocks indicate repetition of pulse sequence consisting of fat suppression (FS), T1-weighted images (T1W) and navigation pulse (NAV). Curved line indicates movement of diaphragm detected by navigation pulse and the solid line indicates threshold. Data acquired between two dashed lines (acceptance window) are only accepted and used for image reconstruction.

References: Department of Radiology, Seoul National University Hospital - Seoul/KR

Image Analysis

All image reviews were performed using a PACS (Maroview 5.4, Infinitt) and monitors with a spatial resolution of 1600 x 1200 (Totoku, Japan). Reviewers were allowed to adjust window level and width as they did in clinical practice.
Breathing hold capacity was estimated by one attending radiologist (J.H.Y.). Breath-hold capacity was assessed by two-point scale: 0, limited breath-hold capacity; 1, sufficient breath-hold capacity. Presence of motion artifact on PVP, DP indicated limited breath-hold capacity in our criteria. Motion artifact on AP only was not considered as limited breath-hold capacity due to possible contrast-medium induced transient dyspnea. In patients with limited breath-hold capacity, following items were qualitatively independently assessed by two attending radiologists (J.H.Y., E.S.L., with eight years of clinical experience): a) liver margin; b) liver vessel sharpness; c) presence of artifact; d) degree of fat suppression and e) overall image quality. Items were assessed by using three-point scale: score 1, suboptimal; score 2, blurry or presence of artifact/ incomplete fat suppression, but acceptable; and score 3, no presence of artifact, or complete fat suppression, with good image quality. After individual review, two reviewers reached consensus in a joint review session as their disagreements were minimal and, therefore, easily resolved. Finally, two radiologists (E.S.L., J.H.B. with 11 years of clinical experience) reviewed two HBP images in order to assess the diagnostic performance to detect FLLs. Each reviewer was requested to record the size, image number and location of the identified FLLs. In addition, qualitative scores of FLLs were recorded on three point scale: score 1, maybe present; score 2, probably present; and score 3, definitely present.

In patients with sufficient breath-hold capacity, naviLAVA images were compared with BH-LAVA by two reviewers (J.H.Y. and E.S.L.) in consensus. Images were compared side by side and overall image quality was scored using a five-point scale: score 1, definitely worse; score 2, slightly worse; score 3, similar image quality; score 4, slightly better quality; and score 5, definitely better image quality.

**Statistical Analysis**

For intra-individual comparison of the image quality, we performed a paired t-test. To analyze the diagnostic performance of BH-LAVA and naviLAVA to detect FLLs, a jackknife-alternative, free-response, receiver-operating-characteristic (JAFROC) analysis was performed using JAFROC software (JAFROC, version 4.2, [http://www.devchakraborty.com](http://www.devchakraborty.com)). The data of each reader were analyzed separately in order to avoid within-reader clustering. Figure of merit (FOM) was used to evaluate the diagnostic performance of each sequence: FOM is defined as the probability that lesions, including unmarked lesions, are rated higher than non-lesion marks on control MRI.

The interobserver agreement of the image quality assessment of various items was evaluated using the weighted kappa test. A # value of 0 indicated poor, 0.01-0.20 slight, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 good, and 0.81-1.00 excellent agreement. All statistical analyses were performed using commercially available software (IBM SPSS, version 21, SPSS Inc., IBM Company, Armonk, NY, USA; Medcalc, version 12, Medcalc Software, Mariakerke, Belgium), and a $P$-value less than 0.05 was considered to indicate a significant difference.
Results

Image acquisition for assessing clinical feasibility of navigated T1WI

In total 63 patients with limited breath-hold capacity, there were 13 patients in whom acquisition time of naviLAVA exceeded 10 minutes. Thirteen patients consisted of nine men and four women (mean age 71.2±10.9 years). There was no acquisition failure in patients with sufficient breath-hold capacity.

Image quality between BH-LAVA and naviLAVA in patients with limited BH capacity

In qualitative analysis on 50 patients with limited breath-hold capacity, overall image quality was better in naviLAVA than in BH-LAVA (2.78±0.95, 2.42±0.81, \( P<0.005 \)) (Fig. 3). NaviLAVA showed better liver margin than BH-LAVA (2.36±0.72, 2.04±0.53, respectively, \( P<0.001 \)). There were no significant differences of hepatic vessel sharpness and degree of artifact between two images (Table 2, \( P>0.05 \)). However, with regard to fat suppression, BH-LAVA showed better result than naviLAVA (2.82±0.44, 2.14±0.57, respectively, \( P<0.001 \)): in 33 of 50 patients (66%), naviLAVA showed localized incomplete fat suppression in the left flank in consensus review (Fig. 4).

Both reviewers showed fair to moderate interobserver agreement (#=0.36~0.59) in all evaluated items and good agreement (#=0.62) in hepatic vessel sharpness on BH-LAVA image (Table 2).

<table>
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<th>Interobserver agreement</th>
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<tr>
<td></td>
<td>BH-LAVA</td>
<td>naviLAVA</td>
</tr>
<tr>
<td>Liver margin</td>
<td>2.04±0.53</td>
<td>2.36±0.72</td>
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<tr>
<td>Hepatic vessel sharpness</td>
<td>2.10±0.93</td>
<td>2.32±1.11</td>
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<tr>
<td>Degree of Artifact</td>
<td>2.04±0.45</td>
<td>2.08±0.60</td>
</tr>
<tr>
<td>Degree of fat suppression</td>
<td>2.82±0.44</td>
<td>2.14±0.57</td>
</tr>
<tr>
<td>Overall image quality</td>
<td>2.42±0.81</td>
<td>2.78±0.95</td>
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</table>

BH-LAVA  naviLAVA  
Reviewer 1  Reviewer 2  
Reviewer 1  Reviewer 2
Lesion Detection

On BH-LAVA HBP images, reviewer 2 (E.S.L.) detected 93 FLLs including two pseudolesions and reviewer 3 (J.H.B.) detected 86 FLLs including two pseudolesions. The number of detected FLLs increased on naviLAVA images: reviewer 2 detected 132 FLLs including one pseudolesion and reviewer 3 detected 123 FLLs. The number of detected FLLs and characteristics were summarized in Table 4.

In reviewer 2, 44 FLLs (mean size 0.78±0.71cm) were additionally detected on naviLAVA: HCC (n=13; mean size 1.23±1.06cm); metastases (n=3; mean size 1.13±0.45cm); cysts (n=11; mean size 0.49±0.36cm); lipiodol uptake (n=1; 0.3cm); and DNs (n=16; mean size 0.54±0.28cm). However, four FLLs which were seen on BH-LAVA were not detected on naviLAVA: cyst (n=3); and DN (n=1). Two pseudolesions were not seen on naviLAVA, which were presumed as vascular end-on. Instead, one pseudolesion was detected on naviLAVA which was regarded as heterogeneous liver parenchymal enhancement. Therefore, total 40 FLLs were additionally detected on naviLAVA by reviewer 2.

In reviewer 3, 43 FLLs (mean size 0.74±0.61cm) were additionally detected on naviLAVA: nine HCCs (mean size 1.05±1.0cm); five metastases (mean size 0.73±0.15cm); eighteen cysts (mean size 0.62±0.39cm); and eleven DNs (mean size 0.55±0.24cm). Four FLLs were not detected on naviLAVA, albeit with they were detected on BH-LAVA: one HCC; one metastasis and two cysts. Two pseudolesions which were presumed as hepatic vessel end-on (n=1) and heterogeneous liver parenchymal enhancement (n=1) were not seen on naviLAVA. Consequently, reviewer 3 detected 39 additional FLLs on naviLAVA.

<table>
<thead>
<tr>
<th>Liver margin</th>
<th>2.16±0.62</th>
<th>2.08±0.49</th>
<th>2.40±0.67</th>
<th>2.14±0.67</th>
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<tr>
<td>Hepatic vessel sharpness</td>
<td>2.26±1.03</td>
<td>2.01±0.95</td>
<td>2.42±1.11</td>
<td>2.14±0.94</td>
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<td>Degree of Artifact</td>
<td>2.12±0.48</td>
<td>2.02±0.35</td>
<td>2.10±0.65</td>
<td>1.97±0.45</td>
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<td>Degree of fat suppression</td>
<td>2.74±0.53</td>
<td>2.30±0.54</td>
<td>2.14±0.53</td>
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<td>Overall image quality</td>
<td>2.62±0.75</td>
<td>2.46±0.73</td>
<td>2.88±1.00</td>
<td>2.65±0.90</td>
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<th>Identified lesion on MRI†</th>
<th>Reviewer 1</th>
<th>Reviewer 2</th>
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<tr>
<td>BH-LAVA</td>
<td>naviLAVA</td>
<td>BH-LAVA</td>
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<td>Metastases (n=18)</td>
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<tr>
<td>HCC (n=44)</td>
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<tr>
<td>HCC (n=44)</td>
<td>31</td>
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<tr>
<td>Condition</td>
<td>BH-LAVA</td>
<td>navILAVA</td>
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<td>-------------------</td>
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<tr>
<td>Cysts (n=49)</td>
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<tr>
<td>Hemangioma (n=1)</td>
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<td>Lipiodol uptake (n=2)</td>
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<td>PEIT defect (n=1)</td>
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<td>Inflammation (n=1)</td>
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<td>1</td>
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<td>DN (n=32)</td>
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<td>23</td>
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<tr>
<td>Pseudolesion‡</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Total (n=148)</td>
<td>91 (61.5%)</td>
<td>131 (88.5%)</td>
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</table>

**Image quality between BH-LAVA and navILAVA in patients with sufficient BH capacity**

In patients with sufficient breath-hold capacity, overall image quality was similar with that of BH-LAVA in 157 of 309 (50.8%) patients, better in 95 of 309 (30.7%: slightly better in 55 patients and definitely better in 40 patients) patients and worse in 57 of 309 patients (18.4%: slightly worse in 18 patients and definitely worse in 39 patients). In patients with worse image quality, motion artifact was prominently noted on navILAVA images than on BH-LAVA images (Fig. 5).
**Fig. 4:** Figure 3 (b). HBP images of a 73-year-old man with surgically confirmed hepatocellular carcinoma (HCC). HBP image obtained by BH-LAVA sequence (a) showed blurry margins of the liver and HCC (arrowheads) and significant motion artifact. On HBP images obtained by naviLAVA (b), liver margin, hepatic vessel and HCC (arrowheads) were clearly demonstrated without significant motion artifact.

**References:** Department of Radiology, Seoul National University Hospital - Seoul/KR
Fig. 3: Figure 3 (a). HBP images of a 73-year-old man with surgically confirmed hepatocellular carcinoma (HCC). HBP image obtained by BH-LAVA sequence (a) showed blurry margins of the liver and HCC (arrowheads) and significant motion artifact. On HBP images obtained by naviLAVA (b), liver margin, hepatic vessel and HCC (arrowheads) were clearly demonstrated without significant motion artifact.

References: Department of Radiology, Seoul National University Hospital - Seoul/KR
**Fig. 8:** Figure 5 (b). HBP images of a 65-year-old woman with liver cirrhosis. In comparison with BH-LAVA image (a), motion artifact (arrowheads) was significantly noted on naviLAVA images (b) and deteriorated image quality.

**References:** Department of Radiology, Seoul National University Hospital - Seoul/KR
Fig. 7: Figure 5(a) HBP images of a 65-year-old woman with liver cirrhosis. In comparison with BH-LAVA image (a), motion artifact was significantly noted on naviLAVA images (b) and deteriorated image quality.

References: Department of Radiology, Seoul National University Hospital - Seoul/KR

Fig. 5: Figure 4(a). HBP images of a 56-year-old man who was treated for HCC in S7/8. Compared to HBP image obtained by BH-LAVA sequence (a), naviLAVA with free-breathing (b) showed clearer liver margin (white arrowheads), but incomplete fat suppression in the left abdominal subcutaneous layer (black arrowheads).

References: Department of Radiology, Seoul National University Hospital - Seoul/KR
Fig. 6: Figure 4(b). HBP images of a 56-year-old man who was treated for HCC in S7/8. Compared to HBP image obtained by BH-LAVA sequence (a), naviLAVA with free-breathing (b) showed clearer liver margin (white arrowheads), but incomplete fat suppression in the left abdominal subcutaneous layer (black arrowheads).

References: Department of Radiology, Seoul National University Hospital - Seoul/KR
Conclusion

HBP images of hepatocyte-specific contrast enhanced liver MRI plays an important role for FLL detection. However, image quality of HBP is significantly degraded in patients with limited breath-hold capacity or cannot follow instructions during the examination. In this study, we observed that navigated T1WI (naviLAVA) showed better FLL detection and overall image quality than breath-hold T1WI (BH-LAVA) in patients with limited breath-hold capacity. Therefore, we believe that naviLAVA may be beneficial for lesion detection and for providing HBP images with better quality in patients with limited breath-hold capacity.

We observed improved diagnostic performance to detect FLLs on naviLAVA with higher spatial resolution in free-breathing manner than BH-LAVA. It was different from the recent study reporting that navigated T1WI did not improve lesion detectability (7). One reason for difference might be different navigation method. We used navigator gating method whereas navigator triggering was used in prior study. In navigator gating, respiratory information is updated every 200 msec, to the contrary navigator triggering dose not check respiratory status for 1500-1900 msec once it triggers an inversion recovery pulse. Therefore, we assume that navigator-gating is more resistant to motion than navigator-triggering and provide better images than navigator-triggering free-breathing method. Another reason for discrepant results was due to study population. We evaluated diagnostic performance of HBP images using naviLAVA in patients with limited breath-hold capacity, and relatively poor image quality of HBP, whereas breath-hold capacity was not assessed in prior study (7). In this study, most patients with sufficient breath-hold capacity showed either similar (50.8%, 157 of 309) or better (30.7%, 95 of 309) image quality we also noted that approximately 12% of patients (39 of 309) with sufficient breath-hold capacity showed definitely worse image quality due to prominent motion artifact. Therefore, navigated T1-weighted HBP may play complementary role instead of complete replacement, due to relatively higher rate of image quality decrease. In addition, study which includes high proportion of patients with sufficient breath-hold capacity may underestimate clinical value of free-breathing, navigated T1-weighted HBP images.

Our study has several limitations. First, this is a retrospective study, and it has an inevitable selection bias. Second, we used imaging-based standard of reference for lesion detection which might overestimate diagnostic performance of HBP images in our study, especially considering that HBP images showed better lesion detectability than other modalities, it may be the biggest limitation in this study. However, every metastasis and benign lesions such as cysts cannot be confirmed in clinical practice. Furthermore, the purpose of this study was comparison of diagnostic performance of two T1WI, not an assessment of accuracy in HBP images. In addition, thorough image reviews were performed by two attending radiologists in consensus on multiple modalities to minimize dependency on HBP images. Third, we only performed qualitative evaluation due to T1WI
used parallel imaging on BH-LAVA. Finally, the prospective study including patients with severely compromised breath-hold capacity is needed. Despite of these limitations, we believe that the study result is valuable because we investigated clinical feasibility of navigated T1WI and revealed beneficiary population by obtaining HBP using navigation technique.

In conclusion, navigated T1WI improved image quality and lesion detectability of HBP images than breath-hold T1WI in patients with limited breath-hold capacity.
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