Additional Value of Diffusion-weighted MRI to Gd-EOB-DTPA-enhanced Hepatic MRI for the Detection of Liver Metastasis: the Difference Depending on the Experience of the Radiologists

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ABSTRACT

This retrospective study was to investigate whether adding diffusion-weighted imaging (DWI) to Gd-EOB-DTPA-enhanced MRI (EOB-MRI) improved the detection of liver metastasis in radiology resident and board-certified radiologist groups. It was approved by our institutional review board. We selected 18 patients with 35 liver metastases and 12 patients without liver tumors. Five board-certified radiologists and 5 radiology residents participated in the observer performance study. Each observer first interpreted T1- and T2-weighted-, plain-, arterial phase-, and hepatobiliary phase images and specified the location of the liver metastases. The software subsequently displayed the DWI images simultaneously and all participants repeated the reading. We used Jackknife alternative free-response receiver operating characteristic (JAFROC) analysis to compare the observer performance in detecting liver metastases. The mean values for the area under the curve (AUC) for EOB-MRI without and with DWI were 0.78 ± 0.13 [standard deviation: SD] and 0.87 ± 0.09, respectively, for the radiology residents, and the difference was statistically significant (p = 0.045). For the board- certified radiologists these values were 0.92 ± 0.02 and 0.96 ± 0.01, respectively, and the difference was not statistically significant (p = 0.092).

EOB-MRI with DWI significantly improved the performance of radiology residents in the identification of liver metastases.

Key words: *DWI, EOB-MRI, Liver metastases*

The accurate identification of liver metastasis is important for therapeutic planning in patients with neoplasms. The detection, quantification, and localization of liver metastases are crucial for the management of patients with colorectal liver metastasis because complete surgical resection of these metastatic foci prolongs the survival of surgery-eligible patients[14,17,22]. On the other hand, there is no indication for the surgical resection of liver metastases from pancreatic-, bile duct-, and lung cancer because the primary lesions grow rapidly and the prognosis is poor[16,19,23].

Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) allows the combined dynamic imaging of the liver and hepatocyte-specific imaging in one examination. Gd-EOB-DTPA-enhanced magnetic resonance imaging (EOB-MRI) may be a better imaging modality for the detection of liver metastases than standard Gd-enhanced MRI, contrast-enhanced computed tomography (CT), [18]FDG-PET, and contrast enhanced sonography[1,2,6,7,24,25].

Advances in diffusion-weighted imaging (DWI) have rendered it useful for the detection of focal liver lesions because it yields high-quality DWI scans of the liver[11,15,21]. In many institutions it is added to EOB-MRI for the survey of hepatic tumors. While some authors reported no statistically significant difference in the detectability of liver metastases between EOB-MRI without and with DWI[3,4,21], others found that the combined use of EOB-MRI and DWI improved their detectability[8,12,13]. We

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hypothesized that the clinical utility of adding DWI to EOB-MRI depended on the experience of the diagnostic radiologists. The purpose of this study was to investigate whether adding DWI to EOB-MRI improved the detection of liver metastasis for radiology resident and board-certified radiologist groups.

MATERIAL AND METHODS

This retrospective study was approved by our institutional review board; prior informed patient consent was waived.

Patient Selection

Two radiologists (W.F. and K.A.) with 5 and 27 years of experience, respectively, consensually reviewed the records of 59 patients with primary malignant tumors who had undergone both EOB-MRI and DWI in a survey of liver metastasis performed at our institute during the period from January 2009 to July 2012. Neither radiologist had participated in the observer performance study. Among the 43 patients with solid liver tumors 25 were excluded from further study: 6 harbored more than 6 liver metastases and it was difficult to perform an observer performance study; another 6 were receiving chemotherapy because findings of liver metastasis were modified, and 13 had liver metastases that exceeded 30 mm in maximum diameter, rendering lesion detection too easy in the observer performance test. Consequently, 18 patients with 35 liver metastases were included in this study: 10 were pathologically confirmed and in the other 8 confirmation was by CT, follow-up MRI, or ^{18}F-FDG-PET. In 12 of the original 59 patients the absence of liver tumors was confirmed on abdominal CT-, ^{18}F-FDG-PET/CT-, or by follow-up MRI scans acquired in at least 6-month intervals. These 12 patients without liver metastasis were included in this study. In 4 of the original 59 patients the absence of liver tumors could not be confirmed on other imaging modalities and they were excluded from the study. The background liv-

ers of all patients were normal. The primary cancer sites are summarized in Table 1.

The final study population thus consisted of 30 patients (35 metastases). They were 18 men and 12 women ranging in age from 36 to 80 years (median 62.5 years). The age of the 18 patients (12 men, 6 women) with liver metastases ranged from 43 to 80 years (median 63.5 years). The mean tumor size of liver metastases was 14 mm. The patients without liver metastases were 6 men and 6 women aged from 36 to 75 years (median 61.5 years). There was no statistically significant difference in the age ($p = 0.498$ by the Mann-Whitney U-test) and sex distribution ($p = 0.458$ by the Fisher exact probability test) between patients with and without liver metastasis.

MRI and Contrast Enhancement Protocols

All MRI examinations were performed on a 1.5-T system using an 8-channel body phased array coil (Signa EXITE HD, GE Healthcare, Milwaukee, WI).

MRI scans were obtained in all patients and included T2-weighted fat-suppressed images. The scan parameters were TE 3700 msec, echo train length 20, flip angle 90°, matrix 288 × 192, slice thickness 8 mm, and gap 2 mm. For DWI they were TR 6000 msec, TE 74 msec, matrix 128 × 192, slice thickness 8 mm, gap 2 mm, and b factor = $0, 1000$ sec/mm^2. Dynamic study was with fat-suppressed T1-weighted gradient-echo imaging with liver acquisition with the volume-acceleration (LAVA) sequence (TR/TE 3.8/1.9 msec, flip angle 12°, field of view 36 cm, matrix size 320 × 192, slice thickness and interval 5 mm). During dynamic study each patient was given 25 μmol/kg (0.1 ml/kg) of Gd-EOB-DTPA as an intravenous bolus at the rate of 2 ml/sec. Flushing was with 20 ml saline delivered at a rate of 2 ml/sec using a power injector (Sonic Shot 50; Nemoto-Kyorindo, Tokyo, Japan). After pre-enhanced scanning we acquired four-phase Gd-EOB-enhanced scans of the liver during the arterial phase (AP), portal venous phase (PVP), transitional phase (TP), and hepato-

Table 1. Primary tumors of the 30 patients

Liver metastasis			
Yes		No	
Colorectal cancer	14	Colorectal cancer	5
Gastric cancer	1	Gastric cancer	1
Esophageal cancer	1	Esophageal cancer	1
Pancreatic cancer	1	Pancreatic cancer	2
Leiomyosarcoma of the inferior vena cava	1	Breast cancer	1
		Uterine cancer	1
		Gastrointestinal stromal tumor of the stomach	1
Total	18	Total	12

biliary phase (HBP). Scan timing for AP was determined by a test injection of 0.5 ml of Gd-EOB. Scanning during AP was at the aortic transit time calculated from injection images plus 7 sec after PVP. HBP scans were obtained 20 min after the start of the Gd-EOB injection. We defined TP as the 180 sec after the start of the Gd-EOB injection.

Observer Performance Study

Five board-certified radiologists and 5 radiology residents participated in the observer performance study. The board-certified radiologists had 11-15 years of experience (median 12 years) in hepatic MRI. The residents had 1-5 years of experience (median 2 years). The selected number of board-certified and resident observers was based on jack-knife alternative free-response receiver operating characteristic (JAFROC) analysis[10,18] with a significance level of 0.05, a power level of 0.90, and a case number of 40, with an anticipated effect size of 0.05. The required number of observers for each group was 5.

The sequential test method was applied in the observer performance study[9]. We used software developed by one of the authors (T.H.) for the observer performance study. It first juxtaposed T1- and T2-weighted images and the results of dynamic study (plain-, AP-, and HBP images) on a monitor screen. The images could be scrolled synchronously. Each observer first interpreted T1- and T2-weighted-, plain-, AP, and HBP images and specified the location of the liver metastases by marking them using a mouse. The readers then rated their confidence in the presence of a nodule on the right side of the screen. The software subsequently displayed the DWI images simultaneously on the screen and the radiologists repeated their reading and rating of the images. All radiologists read the 30 cases at random. No restriction was placed on the reading time.

We used a gray-scale monitor (model PA301A; NEC, Tokyo, Japan) with a spatial resolution of 2560 × 1600 for the observer performance study.

Statistical Analysis

We used JAFROC analysis to compare observer performance in detecting liver metastases with and without DWI. It takes into account the nodule location and allows evaluation of multiple lesions in each case. We applied the multiple-reader multiple-case (MRMC) design in the JAFROC analysis. To analyze MRMC-JAFROC data we employed Dorfman, Berbaum, and Metz (DBM)-MRMC[18] software provided by Chakraborty and Yoon (JAFROC 4.0, http://www.devchakraborty.com/index.php). We generated JAFROC curves by plotting the lesion localization fraction (LLF) against the false-positive fraction (FPF) and used the area under the curve (AUC) as the figure of merit for the detectability of liver metastases without and with DWI. We compared LLF and FPF, and the positive predictive value (PPV) for metastasis detectability without and with DWI using the two-tailed paired t-test. p values of less than 0.05 were considered to indicate statistically significant differences.

RESULTS

Random reader- and random case analysis showed that the mean AUC values for EOB-MRI without and with DWI were 0.78 ± 0.13 [standard deviation: SD] and 0.87 ± 0.09, respectively, for the radiology residents. The difference was statistically significant (p = 0.045) (Fig. 1 and Table 2). For the board-certified radiologists these values were 0.92
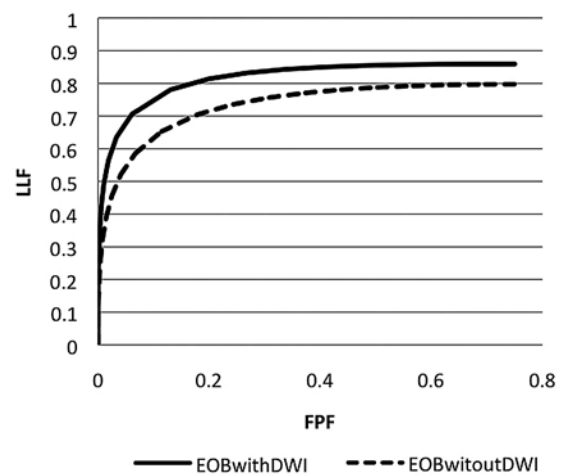

Fig. 1. JAFROC curves for residents detecting foci of liver metastasis on EOB-MRI without and with DWI.

The area under the curve for EOB-MRI with DWI was significantly larger than that without DWI (p = 0.045). Abbreviations: LLF, lesion localization fraction; FPF, false-positive fraction

Table 2. AUC for radiology residents and board-certified radiologists

	Radiology residents		Board certified radiologists	
	EOB-MRI		EOB-MRI	
	without DWI	with DWI	without DWI	with DWI
1	0.63	0.74	0.94	0.98
2	0.87	0.92	0.92	0.95
3	0.93	0.97	0.87	0.95
4	0.85	0.93	0.93	0.97
5	0.63	0.81	0.91	0.95
Mean (SD)	0.78 (0.13)	0.87 (0.09)	0.92 (0.02)	0.96 (0.01)
p value	0.045		0.092	

Abbreviations:
EOB-MRI, Gd-EOB-DTPA-enhanced MRI
DWI, diffusion-weighted MRI
AUC, area under the curve
SD, standard deviation

± 0.02 and 0.96 ± 0.01, respectively, and although the AUC values tended to be higher for EOB-MRI with DWI, the difference was not statistically significant (p = 0.092) (Fig. 2 and Table 2).

For the residents the mean LLF values for EOB without and with DWI were 0.71 ± 0.14 and 0.81 ± 0.01, respectively; the difference was statistically significant (p = 0.027, Table 3). For the board-certified radiologists these values were 0.85 ± 0.04 and 0.91 ± 0.01, respectively, and the difference was not statistically significant (p = 0.112) (Table 3).

As shown in Table 4, for the residents the mean FPF values for EOB without and with DWI were 0.33 ± 0.19 and 0.35 ± 0.19, respectively, and the difference was not statistically significant (p = 0.607). For the board-certified radiologists these
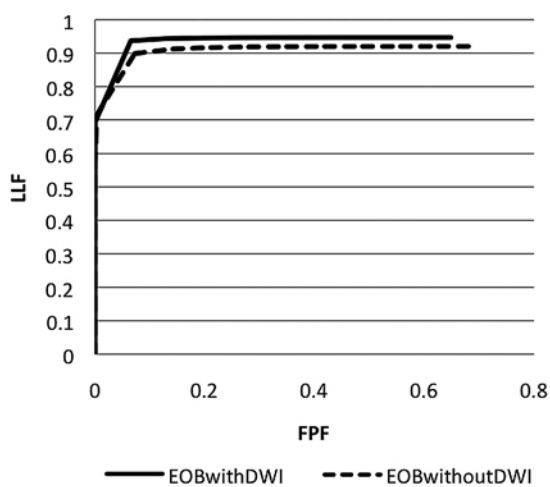
Table 4. FPF for EOB-MRI with and without DWI for all readers

	Radiology residents		Board certified radiologists	
	EOB-MRI		EOB-MRI	
	without DWI	with DWI	without DWI	with DWI
1	0.42	0.42	0.00	0.00
2	0.25	0.33	0.17	0.17
3	0.00	0.00	0.08	0.08
4	0.50	0.50	0.08	0.17
5	0.50	0.50	0.00	0.00
Mean (SD)	0.33 (0.19)	0.35 (0.19)	0.07 (0.06)	0.08 (0.07)
p value	0.607		0.374	

Abbreviations:
EOB-MRI, Gd-EOB-DTPA-enhanced MRI
DWI, diffusion-weighted MRI
FPF, false-positive fraction
SD, standard deviation

Fig. 2. JAFROC curves for board-certified radiologists detecting foci of liver metastasis on EOB-MRI without and with DWI.

There was no statistically significant difference in the area under the curve between EOB-MRI with DWI and without DWI (p = 0.092).

Table 3. LLF for radiology residents and board-certified radiologists

	Radiology residents		Board certified radiologists	
	EOB-MRI		EOB-MRI	
	without DWI	with DWI	without DWI	with DWI
1	0.54	0.69	0.86	0.91
2	0.86	0.91	0.89	0.91
3	0.83	0.89	0.77	0.89
4	0.8	0.86	0.89	0.91
5	0.54	0.69	0.83	0.91
Mean (SD)	0.71 (0.14)	0.81 (0.01)	0.85 (0.04)	0.91 (0.01)
p value	0.027		0.112	

Abbreviations:
EOB-MRI, Gd-EOB-DTPA-enhanced MRI
DWI, diffusion-weighted MRI
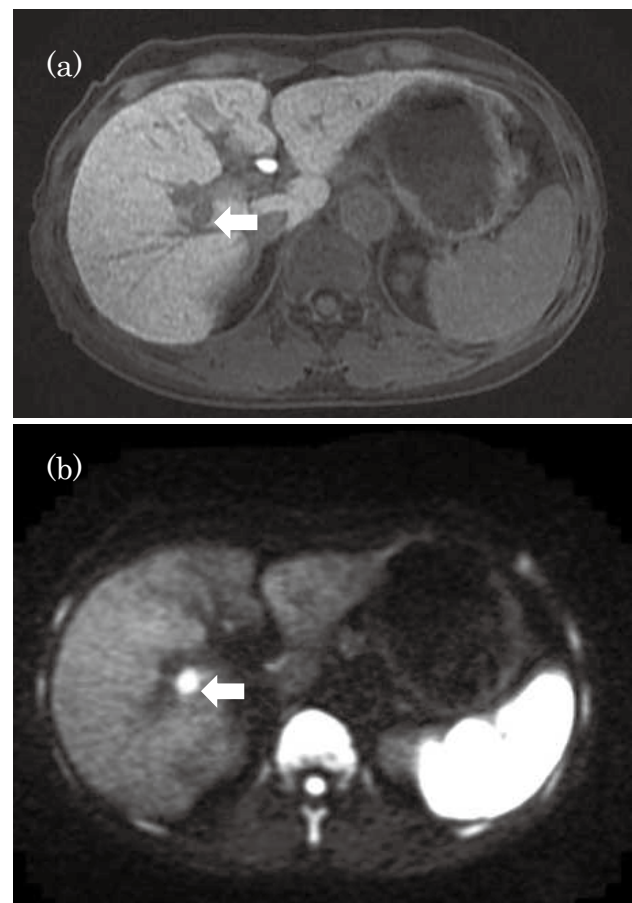LLF, lesion localization fraction; SD, standard deviation

Fig. 3. A 53-year-old woman with liver metastasis from colon cancer.

(a) In the hepatobiliary phase of EOB-MRI a 10-mm metastatic focus was identified near vessels (*arrow*). Its size was almost the same as that of adjacent vessels.

(b) On DWI the metastatic nodule revealed high signal intensity (*arrow*). Nine of the 10 readers detected this lesion on DWI.
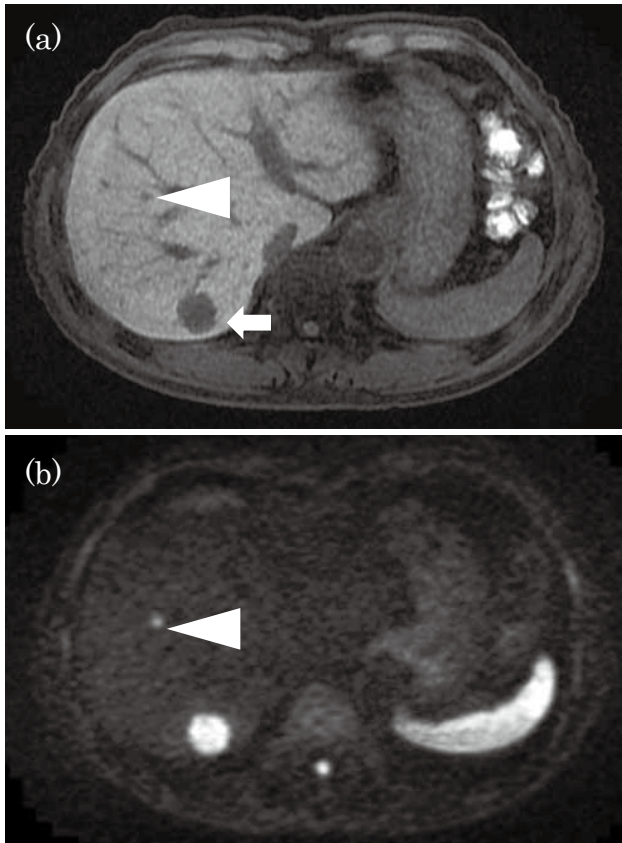
Fig. 4. A 64-year-old man with liver metastases from colon cancer.

(a) In the hepatobiliary phase of EOB-MRI metastases were identified in segments 7 (*arrow*) and 8 (*arrowhead*). The size of the lesion in segment 7 was 3 mm. Because the nodule was small it could be overlooked on the EOB-MRI scan.

(b) On DWI the 3 mm metastatic nodule showed high signal intensity (*arrowhead*). This rendered its detection easy.

Fig. 5. A 75-year-old woman with liver metastases from colon cancer who had undergone resection of the right lobe due to liver metastasis.

(a) In the hepatobiliary phase of EOB-MRI a 10-mm metastatic lesion was observed at the margin of resection (*arrow*). It was difficult to detect on the EOB-MRI scan without DWI.

(b) Combining DWI with EOB-MRI facilitated its detection (*arrow*).

values were 0.07 ± 0.06 and 0.08 ± 0.07, respectively, and the difference was not statistically significant ($p = 0.374$).

Representative cases are shown in Figs. 3-5.

DISCUSSION

The mean AUC value obtained by the radiology residents, but not the board-certified radiologists, was significantly larger on EOB-MRI scans with, than without DWI. This indicates that with respect to the detection of hepatic metastatic foci the combination of EOB-MRI and DWI was more useful to the less experienced residents. The LLF was higher for EOB-MRI with, than without DWI, in both observer groups; the LLF increase was larger for the residents than for the more experienced radiologists. There was no significant difference in the FPF between EOB-MRI without and with DWI in either group of readers, suggesting that
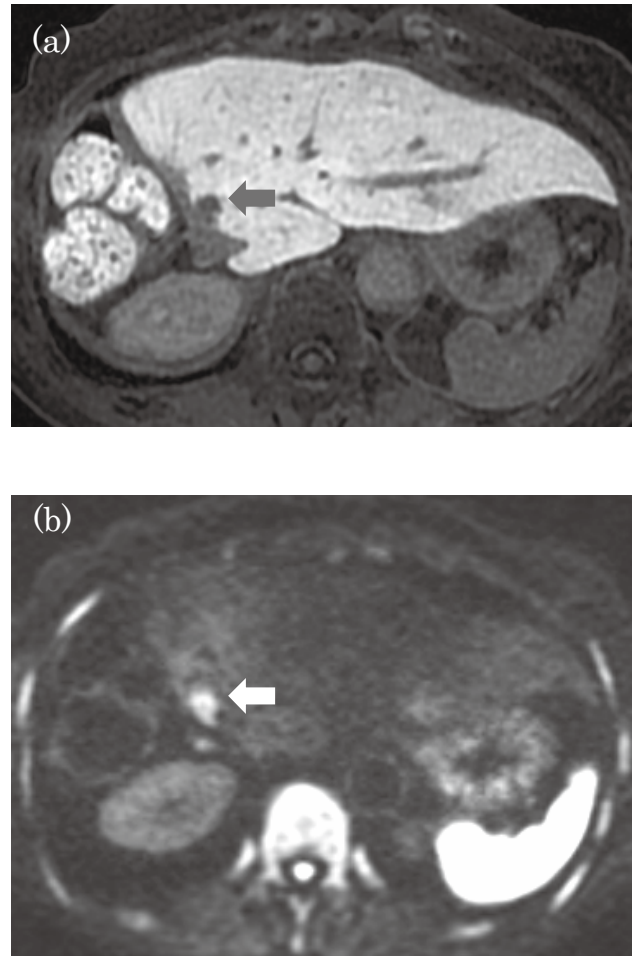
this played a role in the performance of the residents.

Although the diagnostic performance of EOB-MRI is excellent, small liver metastases near thin hepatic vessels may be overlooked because both the metastatic foci and the vessels appear as a low-intensity area on EOB-MRI scans obtained during HBP. Experienced radiologists are skilled in the analysis of the MR anatomy. However, radiology residents lack experience and may find it difficult to distinguish between metastatic foci and small vessels. On DWI scans, the signal intensity of the hepatic vessels and the surrounding liver parenchyma is lower than that of metastatic nodules[15,21]. This may account for the ability of even less-experienced radiologists to identify these lesions (Fig. 3). However, even board-certified radiologists may find it difficult to differentiate small metastatic foci from hepatic vessels on single- or thick-slice EOB-MRI scans acquired during HBP (Fig. 4).

Therefore, data sets of consecutive and thin slices are needed for the interpretation of HBP-EOB-MRI. Irrespective of the level of experience, it may be difficult for readers to differentiate lesions whose diameter is less than the slice thickness.

The detection of liver metastases on the surface of the liver can be problematic on EOB-MRI scans (Fig. 5). Especially the differentiation in hepatectomized patients between dimples and metastatic foci on the stump of the residual liver is very difficult on EOB-MRI scans. However, DWI distinguishes these nodules as high-intensity areas and facilitates their identification.

In our study, as in earlier investigations[3,8,21], the PPV on EOB-MRI scans with and without DWI was almost the same. The characterization of small lesions depicted in the HBP is somewhat difficult and they may be misdiagnosed as metastatic. These diagnostic errors may not be corrected by the addition of DWI because of its low spatial resolution and the presence of artifacts[21]. We posit that this explains why the addition of DWI failed to improve the PPV for the detection of liver metastases. Also, high-intensity DWI lesions, e.g. hemangiomas, may be confused with metastases.

Despite numerous reports on the combined use of EOB-MRI and DWI for the detection of liver metastases[3,4,8,12,13,20,21], its diagnostic significance remains to be determined. We cannot directly compare our findings with those of others because the design of the observer performance test varies among studies. However, in most of the earlier reports only a small number (2 to 3) of radiologists participated in the observer performance tests and the results were not subjected to optimal statistical analysis. As we used robust JAFROC analysis[5,10] and confirmed the statistical power with respect to the number of observers and cases, we think that the results of our observer performance test are valid.

Our study has some limitations. First, as we assessed EOB-MRI and DWI in combination with unenhanced T1- and T2-weighted images, the true diagnostic value of EOB-MRI with DWI is unclear. Nonetheless, in the clinical setting, combined imaging modalities are used to obtain a diagnosis. Second, we did not characterize non-metastatic lesions such as cysts and hemangiomas. None of our 30 patients presented with hemangioma. It is difficult to differentiate between metastatic liver nodules and hemangiomas on EOB-MRI with DWI and further studies that include patients with benign lesions such as hemangiomas are needed. Third, we adopted the sequential test method[9] in the observer performance study because the completion of all reading sessions was very time-consuming; this may have introduced bias into our results. We are planning to carry out another study in which the first session consists of the observer performance test using only the EOB-MIR scans and the second session, performed after an appropriate interval, includes EOB-MRI scans with DWI.

In conclusion, EOB-MRI with DWI significantly improved the performance of radiology residents in the identification of liver metastases.

REFERENCES

1. **Ashbury, J.E., Taylor, S.A., Tse, M.Y., Pang, S.C., Louw, J.A., Vanner, S.J., et al.** 2014. Biomarkers measured in buccal and blood leukocyte DNA as proxies for colon tissue global methylation. Int. J. Mol. Epideiol. Genet. **5**: 120-124.

2. **Chen, L., Zhang, J., Zhang, L., Bao, J., Liu, C., Xia, Y., et al.** 2012. Meta-analysis of gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced magnetic resonance imaging for the detection of liver metastases. PloS one. **7**: e48681.

3. **Chung, W.S., Kim, M.J., Chung, Y.E., Kim, Y.E., Park, M.S., Choi, J.Y., et al.** 2011. Comparison of gadoxetic acid-enhanced dynamic imaging and diffusion-weighted imaging for the preoperative evaluation of colorectal liver metastases. Journal of magnetic resonance imaging : JMRI. **34**: 345-353.

4. **Donati, O.F., Fischer, M.A., Chuck, N., Hunziker, R., Weishaupt, D. and Reiner, C.S.** 2013. Accuracy and confidence of Gd-EOB-DTPA enhanced MRI and diffusion-weighted imaging alone and in combination for the diagnosis of liver metastases. Eur. J. Radiol. **82**: 822-828.

5. **Hillis, S.L., Berbaum, K.S. and Metz, C.E.** 2008. Recent developments in the Dorfman-Berbaum-Metz procedure for multireader ROC study analysis. Acad. Radiol. **15**: 647-661.

6. **Hofmann, J.N., Hosgood, H.D., 3rd, Liu, C.S., Chow, W.H., Shuch, B., Cheng, W.L., et al.** 2014. A nested case-control study of leukocyte mitochondrial DNA copy number and renal cell carcinoma in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. Carcinogenesis **35**:1028-1031.

7. **Kim, Y.K., Lee, Y.H., Kwak, H.S., Kim, C.S. and Han, Y.M.** 2010. Detection of liver metastases: Gadoxetic acid-enhanced three-dimensional MR imaging versus ferucarbotran-enhanced MR imaging. Eur. J. Radiol. **73**: 131-136.

8. **Kim, Y.K., Lee, M.W., Lee, W.J., Kim, S.H., Rhim, H., Lim, J.H., et al.** 2012. Diagnostic accuracy and sensitivity of diffusion-weighted and of gadoxetic acid-enhanced 3-T MR imaging alone or in combination in the detection of small liver metastasis (</= 1.5 cm in diameter). Invest. Radiol. **47**: 159-166.

9. **Kobayashi, T., Xu, X.W., MacMahon, H., Metz, C.E. and Doi, K.** 1996. Effect of a computer-aided diagnosis scheme on radiologists' performance in detection of lung nodules on radiographs. Radiology **199**: 843-848.

10. **Kocyigit, A., Selek, S., Celik, H. and Dikilitas, M.** 2011. Mononuclear leukocyte DNA damage and oxidative stress: the association with smoking of hand-rolled and filter-cigarettes. Mutat. Res. **721**:

136-141.

11. **Koh, D.M., Brown, G., Riddell, A.M., Scurr, E., Collins, D.J., Allen, S.D., et al.** 2008. Detection of colorectal hepatic metastases using MnDPDP MR imaging and diffusion-weighted imaging (DWI) alone and in combination. Eur. Radiol. **18**: 903-910.

12. **Koh, D.M., Collins, D.J., Wallace, T., Chau, I. and Riddell, A.M.** 2012. Combining diffusion-weighted MRI with Gd-EOB-DTPA-enhanced MRI improves the detection of colorectal liver metastases. Br. J. Radiol. **85**: 980-989.

13. **Lowenthal, D., Zeile, M., Lim, W.Y., Wybranski, C., Fischbach, F., Wieners, G., et al.** 2011. Detection and characterisation of focal liver lesions in colorectal carcinoma patients: comparison of diffusion-weighted and Gd-EOB-DTPA enhanced MR imaging. Eur. Radiol. **21**: 832-840.

14. **Malafosse, R., Penna, C., Sa Cunha, A. and Nordlinger, B.** 2001. Surgical management of hepatic metastases from colorectal malignancies. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. **12**: 887-894.

15. **Nasu, K., Kuroki, Y., Nawano, S., Kuroki, S., Tsukamoto, T., Yamamoto, S., et al.** 2006. Hepatic metastases: diffusion-weighted sensitivity-encoding versus SPIO-enhanced MR imaging. Radiology **239**: 122-130.

16. **Okano, K., Maeba, T., Ishimura, K., Karasawa, Y., Goda, F., Wakabayashi, H., et al.** 2002. Hepatic resection for metastatic tumors from gastric cancer. Ann. Surg. **235**: 86-91.

17. **Pawlik, T.M., Schulick, R.D. and Choti, M.A.** 2008. Expanding criteria for resectability of colorectal liver metastases. The oncologist **13**: 51-64.

18. **Pedersen, K.S., Bamlet, W.R., Oberg, A.L., de Andrade, M., Matsumoto, M.E., Tang, H., et al.** 2011. Leukocyte DNA methylation signature differentiates pancreatic cancer patients from healthy controls. PloS one. **6**: e18223.

19. **Sakamoto, Y., Ohyama, S., Yamamoto, J., Yamada, K., Seki, M., Ohta, K., et al.** 2003. Surgical resection of liver metastases of gastric cancer: an analysis of a 17-year experience with 22 patients. Surgery **133**: 507-511.

20. **Shimada, K., Isoda, H., Hirokawa, Y., Arizono, S., Shibata, T. and Togashi, K.** 2010. Comparison of gadolinium-EOB-DTPA-enhanced and diffusion-weighted liver MRI for detection of small hepatic metastases. Eur. Radiol. **20**: 2690-2698.

21. **Tajima, T., Akahane, M., Takao, H., Akai, H., Kiryu, S., Imamura, H., et al.** 2012. Detection of liver metastasis: is diffusion-weighted imaging needed in Gd-EOB-DTPA-enhanced MR imaging for evaluation of colorectal liver metastases? Jap. J. Radiol. **30**: 648-658.

22. **Van den Eynde, M. and Hendlisz, A.** 2009. Treatment of colorectal liver metastases: a review. Rev. Recent. Clin. Trials. **4**: 56-62.

23. **Wang, Z. and Chen, J.Q.** 2011. Imaging in assessing hepatic and peritoneal metastases of gastric cancer: a systematic review. BMC gastroenterology **11**: 19.

24. **Zech, C.J., Herrmann, K.A., Reiser, M.F. and Schoenberg, S.O.** 2007. MR imaging in patients with suspected liver metastases: value of liver-specific contrast agent Gd-EOB-DTPA. Magn. Reson. Med. Sci. **6**: 43-52.

25. **Zhang, Y., Su, H.J., Pan, K.F., Zhang, L., Ma, J.L., Shen, L., et al.** 2014. Methylation status of blood leukocyte DNA and risk of gastric cancer in a high-risk chinese population. Cancer Epidemiol. Biomarkers Prev. **23**: 2019-2026.