Combining diffusion-weighted MRI with Gd-EOB-DTPA-enhanced MRI improves the detection of colorectal liver metastases

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Objectives: To compare the diagnostic accuracy of gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid (Gd-EOB-DTPA)-enhanced MRI, diffusion-weighted MRI (DW-MRI) and a combination of both techniques for the detection of colorectal hepatic metastases.

Methods: 72 patients with suspected colorectal liver metastases underwent Gd-EOB-DTPA MRI and DW-MRI. Images were retrospectively reviewed with unenhanced T_1 and T_2 weighted images as Gd-EOB-DTPA image set, DW-MRI image set and combined image set by two independent radiologists. Each lesion detected was scored for size, location and likelihood of metastasis, and compared with surgery and follow-up imaging. Diagnostic accuracy was compared using receiver operating characteristics and interobserver agreement by kappa statistics.

Results: 417 lesions (310 metastases, 107 benign) were found in 72 patients. For both readers, diagnostic accuracy using the combined image set was higher [area under the curve (Az)=0.96, 0.97] than Gd-EOB-DTPA image set (Az=0.86, 0.89) or DW-MRI image set (Az=0.93, 0.92). Using combined image set improved identification of liver metastases compared with Gd-EOB-DTPA image set ($p<0.001$) or DW-MRI image set ($p<0.001$). There was very good interobserver agreement for lesion classification ($\kappa=0.81$ – 0.88).

Conclusions: Combining DW-MRI with Gd-EOB-DTPA-enhanced T_1 weighted MRI significantly improved the detection of colorectal liver metastases.

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In patients with colorectal cancer, accurate assessment of the size, location and segmental distribution of liver metastases on a per-lesion basis is critical for treatment planning [1]. Accurate depiction of the size and distribution of liver metastases helps the selection of patients to undergo radical surgery [2, 3] or minimally invasive therapy, such as radiofrequency ablation (RFA) [4], chemoembolisation or radio-embolisation [5].

The image contrast in diffusion-weighted MRI (DW-MRI) is based on differences in the mobility of water between tissues [6]. In tumour tissues, such as liver metastases, water mobility is often more impeded compared with normal parenchyma. Hence, metastases appear to have high signal intensity on DW-MRI, facilitating their detection.

Compared with conventional T_2 weighted imaging, DW-MRI has been found to be superior for lesion detection in the liver [7–9]. When compared with contrast-enhanced MRI, DW-MRI had a higher diagnostic accuracy compared with superparamagnetic iron oxide (SPIO)-enhanced MRI [10] and similar diagnostic accuracy compared with gadolinium contrast-enhanced

imaging [11] for detecting colorectal liver metastases. DW-MRI has also been found to be more sensitive than fluorodeoxyglucose (18 FDG) positron emission tomography (PET) CT [12] for the same clinical indication. In another study, combining DW-MRI with T_1 weighted imaging after liver-specific contrast medium mangafodipir trisodium (MnDPDP) administration improved the diagnostic accuracy of colorectal liver metastases detection compared with either technique alone [13].

Gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid (Gd-EOB-DTPA; Eovist or Primovist; Bayer Schering Pharma, Berlin, Germany) is a relatively new hepatocyte-selective MR contrast medium that has been shown to be useful detecting liver metastases measuring <1 cm in diameter [14, 15]. Delayed T_1 weighted imaging in the hepatocellular phase of contrast enhancement at 20 min to several hours after contrast administration demonstrates metastases as T_1 hypointense lesions against the avidly enhancing liver parenchyma.

Both DW-MRI and Gd-EOB-DTPA-enhanced MRI are useful for the detection of liver metastases [7, 8, 14–16]. One study performed at 3 T compared the diagnostic performance of the two techniques for the identification of small (<2 cm) liver metastases [17]. Another study at 1.5 T independently compared the diagnostic performance of DW-MRI, dynamic phase MRI and hepatobiliary phase Gd-EOB-DTPA-enhanced MRI [18]. However,

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the possible incremental value of combining DW-MRI with Gd-EOB-DTPA-enhanced MRI for detecting colorectal metastases has not been reported. Hence, the aim of this study was to compare the diagnostic accuracy of Gd-EOB-DTPA-enhanced MRI, DW-MRI and a combination of both techniques for the detection of colorectal hepatic metastases.

Methods and materials

The study was approved by the institutional research and ethics committee. Signed informed consent was waived as the images were evaluated retrospectively.

Study population

Over the period of January 2008 to December 2009, 165 patients from our institution were consecutively evaluated by Gd-EOB-DTPA-enhanced MRI of the liver and DW-MRI. Of these, 89 patients had a known history of colorectal carcinoma and were referred for known or suspected liver metastases, to assess whether the liver disease was amenable for surgical resection. At our institution, Gd-EOB-DTPA-enhanced MRI and DW-MRI are performed routinely in this patient population to define the burden, location and distribution of liver metastases using a standardised imaging protocol.

All 89 patients with colorectal cancer fulfilled the following inclusion criteria: (1) pathologically proven colorectal cancer; (2) CT/ultrasound/MRI/FDG-PET suspected or confirmed liver metastases; and (3) patients deemed potential candidates for surgery/minimally invasive therapies with or without neoadjuvant chemotherapy. However, the following exclusion criteria were also applied: (1) patients with a recent history (less than 3 months) of chemotherapy or minimally invasive treatment; and (2) contraindications to contrast administration. Hence, of the 89 patients who fitted the inclusion criteria, 13 patients were excluded from the study because of recent chemotherapy (9/13) or radio-frequency ablation (4/13). In addition, four patients underwent only unenhanced MRI owing to moderate renal impairment, for which contrast was withheld. Hence, our final study population comprised 72 patients (44 males, 28 females) with a mean age of 64.4 years (range 46–78 years).

MRI technique

MRI was performed on a 1.5T Siemens MR system (Avanto; Siemens Healthcare, Erlangen, Germany). A summary of the imaging sequences used is shown in Table 1.

Pre-contrast imaging

Axial in- and opposed-phase gradient-echo T_1 weighted, fat-suppressed turbo spin-echo T_2 weighted and half-Fourier acquisition single-shot turbo spin echo (HASTE) T_2 weighted imaging of the liver was performed.

DW-MRI was performed using a free-breathing, multiple averaging technique. Six b -values were employed

($b=0, 50, 100, 250, 500, 750 \text{ s mm}^{-2}$) to enable accurate apparent diffusion coefficient (ADC) values of liver metastases to be calculated, although quantitative ADC analysis was not performed as part of this study.

Post-contrast imaging

Following intravenous Gd-EOB-DTPA contrast administration (0.1 ml kg^{-1} body weight), dynamic contrast-enhanced axial T_1 weighted MRI was performed in arterial, portovenous and interstitial phases of contrast enhancement using a volume-interpolated breath-hold examination (VIBE). The dynamic contrast-enhanced images were used for clinical assessment but were not evaluated in this study.

In our clinical workflow, axial and coronal T_1 weighted delayed imaging in the hepatocellular phase is performed 1 h after contrast administration, according to protocol.

Image analysis

Two expert readers with more than 10 years of experience (AR, DMK) in hepatobiliary MRI and 5 years of experience in body DW-MRI evaluated the images independently, blinded to the clinical and pathological results. Image interpretation was performed in random order as three image sets separated by duration of 4 weeks to minimise recall bias, as follows:

- *Gd-EOB-DTPA image set.* This comprised the unenhanced T_1/T_2 weighted MR images and the hepatocellular phase Gd-EOB-DTPA enhanced T_1 weighted images.
- *DW-MRI image set.* This comprised the unenhanced T_1/T_2 weighted MR images and the DW-MRI images.
- *Combined image set.* This comprised the unenhanced T_1/T_2 weighted MR images, hepatocellular phase Gd-EOB-DTPA enhanced T_1 weighted images and DW-MR images.

For each focal liver lesion detected on each image set, the following were recorded:

- *Lesion size.* The maximum axial diameter of each metastasis was measured to the closest millimetre using the caliper tool on the PACS workstation (Sectra, Linköping, Sweden). This was measured on the Gd-EOB-DTPA-enhanced hepatocellular phase T_1 weighted image. On the DW-MRI image set, this was measured on the $b=750 \text{ s mm}^{-2}$ image.
- *Lesion location.* The location of each metastasis was recorded according to the Couinaud segmental anatomy of liver.
- *Lesion confidence score.* Each lesion detected was scored using a 5-point scale: 5, definite metastasis; 4, probable metastasis; 3, indeterminate; 2, probably not a metastasis; and 1, definitely not a metastasis.

The criteria used for defining whether a lesion was benign or metastatic on imaging took into consideration the high pre-test probability of metastatic disease and that none of the patients had a clinical history of liver cirrhosis.

Table 1. Liver MRI sequences performed before and after Gd-EOB-DTPA contrast administration

Imaging sequence	Repetition time (TR)	Echo time (TE)	Flip angle (degrees)	Field of view (mm)	Section thickness (mm)	Matrix size	Fat suppression	Parallel imaging factor	Receiver bandwidth (Hz per pixel)
Pre-contrast imaging									
Axial T_1 W GE	264	4.6 and 2.3	70	380	7	256 × 256	None	GRAPPA 2	390 and 400
Axial T_2 W TSE	4160	83	90	380	7	256 × 256	Chemical fat suppression	GRAPPA 2	260
Axial T_2 W HASTE	1000	241	150	380	7	256 × 256	None	GRAPPA 2	473
Axial EPI DW-MRI	5000	66	90	380	6	256 × 256	SPAIR	GRAPPA 2	1780
Post-contrast imaging									
Axial T_1 W 3D VIBE	5.7	2.6	10	380	3	256 × 256	SPAIR	GRAPPA 2	250
Axial and coronal T_1 W GE	100	4.6	70	380	7	256 × 256	None	GRAPPA 2	230

DW-MRI, diffusion-weighted MRI; EPI, echo-planar imaging; Gd-EOB-DTPA, gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid; GE, gradient echo; HASTE, half-Fourier acquisition single shot; SPAIR, spectral attenuated inversion recovery; T_1 W, T_1 weighted; T_2 W, T_2 weighted; TSE, turbo spin echo; VIBE, volume interpolated breath-hold examination.

On review of the Gd-EOB-DTPA enhanced image set, a lesion was deemed a definite metastasis if it was hypointense on unenhanced T_1 weighted image, showed mild hyperintensity on T_2 weighted (TE=80 ms) image but becoming isointense or near-isointense on the longer echo-time (TE=240 ms) T_2 weighted imaging; and showed hypointensity on the Gd-EOB-DTPA-enhanced MRI. A lesion was deemed definitely benign if it showed characteristics of a cyst or appeared hyperintense on the long echo-time T_2 weighted imaging (TE=240 ms). A lesion that appeared isointense or hyperintense to the liver in the hepatocellular phase of contrast-enhanced imaging was also classified as definitely benign.

On review of the DW-MRI image set, a focal liver lesion was considered malignant if it showed high signal intensity impeded diffusion on the high b -value image ($b=750 \text{ s mm}^{-2}$), together with T_1 hypointensity and mild T_2 hyperintensity. Lesions that were signal suppressed at higher b -values (e.g. 750 s mm^{-2}), and returned low T_1 signal intensity and high T_2 signal intensity on the long echo time (TE=240) T_2 sequence, were classified as benign [13]. In lesions deemed equivocal, a lesion that returned high signal on the ADC map supported the diagnosis of a benign lesion.

On the combined image set, lesions were ascribed to be malignant or benign if they fitted either imaging criteria as for the Gd-EOB-DTPA image set or the DW-MRI image set.

When the imaging results were compared with the reference standard, lesions that were not detected at imaging were classified as NS (not seen). The inter-observer agreement of lesion categorisation (1–5 and NS) between the two observers was compared using kappa statistics. When comparing the diagnostic performance of the three image sets, lesions not detected on the respective image sets (NS) were scored as definitely benign (score=1) for the purpose of receiver operating characteristic (ROC) analysis.

Imaging validation

The imaging findings were compared with the gold standard tests, which comprised surgery (mean of

3.6 months, range 0.5–4.5 months) with histopathology (36 metastases in 17 patients) and follow-up imaging (mean follow-up period of 16.2 months; range 9–28 months). The surgical resection rate reflected the general high sensitivity of our MRI technique in identifying small foci of metastases in unfavourable anatomical distribution, thus contraindicating surgery, and increasing utilisation of radiofrequency ablation for treatment (10/55 of non-surgical patients were treated with RFA).

Follow-up and comparison imaging included CT (72/72), MRI (42/72) and ^{18}F FDG-PET CT (40/72). Prior CT was available for review in 42 patients. On imaging review, the criteria used to determine a metastasis included (a) a lesion visible on current imaging but not visible on previous imaging using the same technique, (b) more than 20% increase or decrease of lesion size while the patient was receiving chemotherapy and/or (c) avid FDG tracer uptake within lesion on ^{18}F FDG-PET CT imaging. A lesion that was stable in size for more than 9 months at follow-up was deemed to be benign. Review was also undertaken by both observers to determine the reasons for missed lesions after imaging assessment was completed.

Statistical analysis

Statistical analysis was performed using Medcalc software v. 11.1 (Medcalc Inc, Mariakerke, the Netherlands). For each image set, ROC analysis was performed to determine the diagnostic accuracy by recording the area under the curve (Az) and the 95% confidence interval. Differences in the Az between image sets were compared using the variance z -test with the level of statistical significance set at $p < 0.016$ (Bonferroni correction applied for multiple comparisons within observers). Assuming that a lesion score of four or more indicated malignant disease, the diagnostic sensitivity and specificity for colorectal liver metastases were calculated for each image set on a per-lesion basis. Inter-observer agreement in lesion classification was compared by κ statistics for each image set. Values of $\kappa = 0.81$ –1.00 indicate very good agreement, $\kappa = 0.61$ –0.80 indicate good agreement, $\kappa = 0.41$ –0.60 indicate moderate

Table 2. Lesion detection by observers on evaluating the Gd-EOB-DTPA image set, DW-MRI image set and combined image set compared with reference standard

Image set	Observer 1			Observer 2		
	No. of lesions detected (%)	No. of missed lesions (%)		No. of lesions detected (%)	No. of missed lesions (%)	
		Metastases	Benign		Metastases	Benign
Gd-EOB-DTPA image set	366/417 (87.8%)	39/310 (12.6%)	12/107 (11.2%)	364/417 (87.3%)	28/310 (9.0%)	25/107 (23.3%)
DW-MRI image set	373/417 (89.4%)	34/310 (11.0%)	10/107 (9.3%)	367/417 (88.0%)	31/310 (10%)	19/107 (17.8%)
Combined image set	404/417 (96.9%)	9/310 (2.9%)	4/107 (3.7%)	404/417 (96.9%)	11/310 (3.5%)	2/107 (1.9%)

DW-MRI, diffusion-weighted MRI; Gd-EOB-DTPA, gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid; No., number.

agreement, $\kappa=0.21$ – 0.40 indicate fair agreement and $\kappa<0.20$ indicate poor agreement.

Results

By the gold standard tests, 417 lesions were found in the 72 patients. Of these, 310 were metastases and 107 benign. The benign lesions comprised 93 cysts, 6 haemangiomas, 4 focal nodular hyperplasia and 4 post-radiofrequency ablation changes. The mean number of lesions per patient was 5.8 (range 1–28). 53.2% (222/417) of lesions were in the right lobe of the liver, while the remaining 46.8% (195/417) were in the left lobe.

The frequencies of lesion detection for the two observers on evaluating the Gd-EOB-DTPA image set, DW-MRI image set and combined image set are presented in Table 2.

Lesion size

The average mean lesion size measured on the Gd-EOB-DTPA T_1 weighted imaging and on the $b=750$ s mm⁻² imaging was 24.2 mm (range 3–76 mm). Of these, 169 lesions were ≤ 1 cm in diameter.

Lesion distribution

The distribution of lesions in the right and left lobe of liver that were detected or missed at image evaluation is summarised in Table 3.

Lesion confidence score

The diagnostic performance using Gd-EOB-DTPA image set, DW-MRI image set and the combined image sets by lesion scoring is summarised in Figure 1.

For both observers, the diagnostic accuracy on evaluation of combined image set was higher ($Az=0.96$, 0.97) than Gd-EOB-DTPA image set ($Az=0.86$, 0.89) or the DW-MRI image set ($Az=0.93$, 0.92). Combining DW-MRI with Gd-EOB-DTPA-enhanced imaging significantly improved the identification of liver metastases compared with reading of the Gd-EOB-DTPA image set (variance z-test, $p<0.016$) or the DW-MRI image set (variance z-test, $p<0.016$) on its own.

When evaluating the combined image set, using a lesion score of ≥ 4 to indicate metastatic disease resulted in a diagnostic sensitivity of 94.5% (95% CI: 91.4–96.8%) and diagnostic specificity of 97.2% (95% CI: 92.0–99.4%) for Observer 1, and a diagnostic sensitivity of 96.7% (95% CI: 94.1–98.4%) and diagnostic specificity of 97.2% (95% CI: 92.0–99.4%) for Observer 2.

There was very good interobserver agreement for lesion categorisation (lesion score 1 to 5 or NS) using the Gd-EOB-DTPA image set ($\kappa=0.81$; 95% CI: 0.75–0.86), DW-MRI image set ($\kappa=0.86$; 95% CI: 0.82–0.91) or combined image set ($\kappa=0.88$; 96% CI: 0.83–0.93).

Missed lesions

For both observers, evaluation of the combined image set resulted in the lowest number of missed lesions (Table 2). There was a larger proportion (59–70%) of missed lesions in the left lobe of liver when evaluating the DW-MRI image set (Table 3). The frequencies of missed lesions compared between observers are presented in Table 4.

The mean size of missed lesions using the Gd-EOB-DTPA image set, DW-MRI image set or combined image set was 7 mm (range 3–16 mm). Of the 67 missed by either observer on the Gd-EOB-DTPA image set, 54 (28 metastases, 26 benign lesions) were ≤ 1 cm in diameter.

Table 3. Distribution of detected and missed lesions in right and left lobe of liver on evaluating the Gd-EOB-DTPA, DW-MRI and combined image sets by observers

Lesion detection in liver	Observer 1			Observer 2		
	Gd-EOB-DTPA image set (%)	DW-MRI image set (%)	Combined image set (%)	Gd-EOB-DTPA image set (%)	DW-MRI image set (%)	Combined image set (%)
Right lobe ^a ($n=222$)						
Detected lesions	191 (86%)	204 (92%)	212 (95%)	196 (88%)	205 (92%)	217 (98%)
Missed lesions	31 (14%)	18 (8%)	10 (5%)	26 (12%)	17 (8%)	5 (2%)
Left lobe ^b ($n=195$)						
Detected lesions	175 (90%)	169 (87%)	192 (98%)	168 (86%)	162 (83%)	187 (96%)
Missed lesions	20 (10%)	26 (13%)	3 (2%)	27 (14%)	33 (17%)	8 (4%)

DW-MRI, diffusion-weighted MRI; Gd-EOB-DTPA, gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid.

^aRight lobe refers to segments VII, VIII, V, VI and I.

^bLeft lobe refers to segments IVa, IVb, II and III.

Figure 1. Receiver operating characteristic (ROC) curves showing the diagnostic performance of reading the gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid (Gd-EOB-DTPA) image set, diffusion-weighted MRI (DW-MRI) image set and combined image set by both observers. The area under each ROC curve (Az) was calculated and compared. Interpretation of the combined image set by readers showed significantly higher diagnostic accuracy compared with interpretation of the Gd-EOB-DTPA image set or the DW-MRI image set. Statistical comparison was made pairwise using the variance z-test with Bonferroni correction and results shown in box insert. A p -value < 0.016 was taken to be statistically significant.

Of the 59 lesions missed on the DW-MRI image set, 49 (26 metastases, 13 benign lesions) were ≤ 1 cm in diameter. Of the 21 lesions missed on the combined image set, 16 (3 metastases, 13 benign lesions) were ≤ 1 cm in diameter.

On evaluation of the Gd-EOB-DTPA image set, 37 lesions were missed by both observers, of which 26 were metastases and 11 were benign (9 cysts, 1 focal nodular hyperplasia and 1 haemangioma). Of the 26 metastases, 20 were found in retrospect to mimic intrahepatic vasculature on Gd-EOB-DTPA enhanced imaging (Figure 2) and 6 were obscured by motion artefacts.

On evaluation of the DW-MRI image set, 35 lesions were missed by both observers, of which 26 were metastases and 9 were benign (8 cysts, 1 focal nodular hyperplasia). Of the 26 metastases, 12 were not detected in the left lobe due to poor signal-to-noise ratio or artefacts (Figure 3), 6 were near isointense to the liver on DW-MRI (Figure 4) and 8 were located at the periphery of the liver (Figure 5).

When all the images were interpreted together as the combined image set, only five lesions were not visualised by both observers, which included two metastases and three benign lesions (two cysts, one focal nodular hyperplasia). One of the metastases and all benign lesions were obscured by artefacts, but were identified at contemporaneous CT or PET-CT examination. Another metastasis was identified at a follow up CT due to interval tumour growth.

In our study, two focal nodular hyperplasias mimicked the appearance of metastases on DW-MRI. These were shown to be benign by their contrast uptake on Gd-EOB-DTPA imaging. In addition, three mucinous metastases were incorrectly classified as cysts on Gd-EOB-DTPA-enhanced imaging, but showed high signal-impeded diffusion on DW-MRI. Interestingly, one haemangioma led to false positive results by both observers in all three image sets (Figure 6). Two small lesions < 5 mm were deemed false positives on the combined image set, although they showed impeded diffusion and low signal intensity on the hepatocellular phase Gd-EOB-DTPA-enhanced images. On review, these were not visible on the dynamic phase imaging, but showed no interval change for more than 12 months.

Discussion

Hepatocyte-specific contrast medium facilitates the detection of small metastases to the liver [15, 19, 20], because of the high contrast between the avidly enhancing normal liver parenchyma and the non-enhancing metastases in the hepatocellular phase of contrast uptake. Gd-EOB-DTPA is administered as an intravenous bolus, allowing dynamic scanning immediately after contrast administration. However, in the hepatocellular phase, there is intense T_1 enhancement of the

Table 4. Comparison of lesions missed by observers at image evaluation of Gd-EOB-DTPA image set, DW-MRI image set and combined image set

Image set	No. of lesions missed by either observer	No. of lesions missed by Observer 1 only	No. of lesions missed by Observer 2 only	No. of lesions missed by both observers
Gd-EOB-DTPA image set	67 (36)	14 (8)	16 (2)	37 (26)
DW-MRI image set	59 (39)	9 (8)	15 (5)	35 (26)
Combined image set	21 (9)	8 (7)	8 (0)	5 (2)

DW-MRI, diffusion-weighted MRI; Gd-EOB-DTPA, gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid; No., number. Number in parenthesis indicate metastases.

Figure 2. 56-year-old male with metastatic colorectal cancer. (a) Fat-suppressed axial T_1 weighted volume-interpolated breath-hold examination MR image at 60 min after gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid (Gd-EOB-DTPA) contrast administration. (b) Diffusion-weighted MRI (DW-MRI) axial image at b -value of 750 s mm^{-2} . Both T_1 weighted and DW-MRI images showed a large metastasis in the left lobe of liver (*). However, two small metastases (arrows) are seen with increased conspicuity on the DW-MR image. These metastases were missed on assessment of the axial Gd-EOB-DTPA-enhanced T_1 weighted images as they mimicked intrahepatic vasculature in the perihilar area of the liver.

normal liver, which increases the conspicuity of the hypointense metastases.

Gd-EOB-DTPA has been shown to improve the detection of small focal liver lesions $<1 \text{ cm}$ in diameter

compared with CT imaging [14, 15]. However, intrahepatic vessels and metastases both appear to have low signal intensity in the hepatocellular phase and, hence, small metastases lying adjacent to blood vessels may be

Figure 3. 48-year-old male with metastatic colorectal cancer. (a) Diffusion-weighted MRI (DW-MRI) $b=750 \text{ s mm}^{-2}$ image shows significant signal loss, especially over the left lobe of liver. No definite metastasis was identified. (b) Fat-suppressed axial T_1 weighted volume-interpolated breath-hold examination image at 60 min after gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid contrast administration shows a small lesion in the left lobe of liver (arrow). The metastasis was missed on evaluation of the axial DW-MRI image owing to signal loss over the left lobe of liver. Note incidental finding of haemangioma in the vertebral body (arrowhead).

Figure 4. 63-year-old female with metastatic colorectal cancer. (a) Axial fat-suppressed T_1 weighted volume-interpolated breath-hold examination image at 60 min after gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid contrast administration showed a metastasis in the caudate lobe of the liver (arrow). (b) The metastasis was isointense to the liver on the axial $b=750 \text{ s mm}^{-2}$ image. The lesion was missed when the diffusion-weighted MRI image set was assessed.

overlooked. In our study, 26 metastases were missed by both observers on the gadolinium-EOB-DTPA image set, of which 20 were found in retrospect to mimic intrahepatic vasculature.

DW-MRI is increasingly used in oncological imaging [6]. However, DW-MRI is sensitive to artefacts, which can degrade image quality and obscure lesion visualisation

[21]. The left lobe of the liver is prone to poorer signal-to-noise ratio and artefacts from cardiac motion, which results in spin dephasing. Air in the stomach may also induce susceptibility artefacts in the adjacent liver and gastric peristaltic motion can further compromise image quality. Not surprisingly, of the 26 metastases missed by both observers on the DW-MRI image set, a

Figure 5. 65-year-old female with metastatic colon cancer. (a) Fat-suppressed axial T_1 weighted volume-interpolated breath-hold examination image at 60 min after gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid contrast administration showed a small metastasis in the periphery of the liver (arrow). (b) The lesion was overlooked on diffusion-weighted MRI. In retrospect, the lesion was faintly visible as on this axial $b=750 \text{ s mm}^{-2}$ diffusion-weighted MRI image (arrowhead). Note several other metastases in both lobes of the liver.

Figure 6. 62-year-old male with metastatic colorectal carcinoma. False-positive findings on diffusion-weighted MRI (DW-MRI) and gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid (Gd-EOB-DTPA) enhanced MRI. (a) Axial diffusion-weighted MR image at $b=750 \text{ s mm}^{-2}$ and (b) axial hepatocellular phase Gd-EOB-DTPA-enhanced T_1 weighted volume-interpolated breath-hold examination image showed a small hyperintense focus in the left lobe of liver (arrows). The lesion was interpreted as likely to represent a metastasis by both techniques. However, follow up of the lesion for 18 months showed no interval change, while other metastases (not shown) in the liver regressed with chemotherapy. Retrospective review showed the lesion to return high signal intensity on the (c) long echo time ($TE=240 \text{ ms}$) axial T_2 weighted image and showed (d) uniform enhancement in the arterial phase of contrast enhancement (which were not assessed as part of this study). These appearances suggest the diagnosis of a haemangioma, which can mimic a metastasis. Note incidental finding of a renal cyst in the right kidney.

significant proportion (12/26) was due to poor visualisation in the left lobe. The number of false negatives could be reduced by using cardiac triggering at acquisition, which may improve left lobe visualisation [22], but at the expense of significantly increased acquisition time. Another potential pitfall on DW-MRI appears to be the detection of small lesions at the liver edge, which may be overlooked.

In our study, we found that although the diagnostic accuracy of interpreting the DW-MRI image set and Gd-EOB-DTPA image set were high for both observers, it was the combined reading of DW-MRI with Gd-EOB-DTPA imaging in the hepatocellular phase that resulted in the highest diagnostic accuracy ($Az=0.96, 0.97$). Interpretation of the combined image set significantly improved the identification of liver metastases compared

with the Gd-EOB-DTPA image set ($p < 0.001$) or the DW-MRI image set ($p < 0.001$). Combining DW-MRI with Gd-EOB-DTPA appears to minimise the disadvantages of individual techniques to increase identification of metastases missed by either technique alone. DW-MRI proved useful for identifying metastases lying close to intrahepatic vasculature, while the anatomical detail provided by Gd-EOB-DTPA-enhanced MRI was advantageous in regions prone to DW-MRI artefacts or at the liver periphery. In our study, when the techniques were combined, only 5/417 lesions were missed by both observers, attesting the enhanced efficacy of the diagnostic combination. In addition, very good interobserver agreement was found for the evaluation of all image sets.

The dynamic phase contrast-enhanced images were not included in this study as we wanted to specifically compare the hepatocellular phase imaging with DW-MRI. The study design would have been made considerably more complex had the dynamic phase images been included, as separate comparison of the arterial, portovenous and interstitial phases of enhancement would be desirable. Furthermore, we have reason to believe that the dynamic phase imaging is unlikely to be superior to hepatocellular phase imaging for the detection of liver metastases. Lowenthal et al [18] found that the dynamic phase images had a lower diagnostic accuracy ($Az = 0.76$) for metastases compared with the hepatocellular phase images ($Az = 0.89$). Dynamic phase images are time-critical, which could be degraded by breathing or movement artefacts, thus obscuring small lesions. However, if a lesion is visible on dynamic phase imaging, this could aid lesion characterisation by increasing confidence in the diagnosis of non-metastatic solid lesions (e.g. haemangioma or focal nodular hyperplasia).

There are limitations to our study. First, the study was conducted in a highly select population of patients with known or suspected liver metastases. As such, the pre-test probability was high. Nevertheless, this represents a clinically relevant group of patients where accurate detection and delineation of disease on a per-lesion basis are critical for management planning. However, it is uncertain to what degree current imaging findings could be applied to the general population.

Second, we only evaluated the diagnostic accuracy of Gd-EOB-DTPA in the hepatocellular phase of contrast enhancement. Theoretically, this could result in a negative bias towards diagnosis of metastases, since small benign non-hepatocellular lesions (e.g. adenoma, haemangioma, atypical focal nodular hyperplasia) may be indistinguishable from metastases in the hepatocellular phase. However, this was not observed, since the majority of benign lesions in our study were cysts. Indeed, it was likely that the small number of solid benign lesions in our study resulted in a bias towards higher diagnostic specificity. Even accepting this limitation, the overall diagnostic accuracy was still improved by combined reading of the DW-MRI with Gd-EOB-DTPA-enhanced imaging.

Third, the hepatobiliary phase imaging in our study was performed 1 h after contrast administration. As Gd-EOB-DTPA imaging protocols are now being optimised in many departments to improve workflow, it is now recognised that imaging post-contrast at 20 min may be

sufficient for good liver parenchymal enhancement [23]. It is thus likely that our study findings would be applicable to Gd-EOB-DTPA enhanced images acquired at 20 min after contrast administration.

Fourth, the number of patients who underwent surgical resection in our study population was small, but this reflected the high sensitivity of our current techniques in demonstrating small foci of disease in the liver in unfavourable anatomic locations, which contraindicated radical surgery.

Last but not least, for some patients there was a relatively long interval between imaging and surgery, and measuring lesion size change to determine malignancy may not be entirely accurate in patients receiving chemotherapy.

Conclusions

The combination of DW-MRI with Gd-EOB-DTPA-enhanced T_1 weighted MRI significantly improved the diagnostic accuracy of colorectal liver metastasis detection compared with parenchymal phase Gd-EOB-DTPA-enhanced imaging or DW-MRI. The routine use of DW-MRI with Gd-EOB-DTPA-enhanced MRI can be recommended to improve detection of liver metastases in patients with colorectal cancer.

References

1. Charnsangavej C, Clary B, Fong Y, Grothey A, Pawlik TM, Choti MA. Selection of patients for resection of hepatic colorectal metastases: expert consensus statement. *Ann Surg Oncol* 2006;13:1261–8.
2. Valls C, Andia E, Sanchez A, Guma A, Figueras J, Torras J, et al. Hepatic metastases from colorectal cancer: preoperative detection and assessment of resectability with helical CT. *Radiology* 2001;218:55–60.
3. Vogl TJ, Schwarz W, Blume S, Pietsch M, Shamsi K, Franz M, et al. Preoperative evaluation of malignant liver tumours: comparison of unenhanced and SPIO (Resovist)-enhanced MR imaging with biphasic CTAP and intra-operative US. *Eur Radiol* 2003;13:262–72.
4. Gillams AR, Lees WR. Five-year survival following radio-frequency ablation of small, solitary, hepatic colorectal metastases. *J Vasc Interv Radiol* 2008;19:712–17.
5. Denecke T, Ruhl R, Hildebrandt B, Stelter L, Grieser C, Stiepani H, et al. Planning transarterial radioembolization of colorectal liver metastases with yttrium 90 microspheres: evaluation of a sequential diagnostic approach using radiologic and nuclear medicine imaging techniques. *Eur Radiol* 2008;18:892–902.
6. Koh DM, Collins DJ. Diffusion-weighted MRI in the body: applications and challenges in oncology. *AJR Am J Roentgenol* 2007;188:1622–35.
7. Coenegrachts K, Delanote J, Ter Beek L, Haspelslagh M, Bipat S, Stoker J, et al. Improved focal liver lesion detection: comparison of single-shot diffusion-weighted echoplanar and single-shot T_2 weighted turbo spin echo techniques. *Br J Radiol* 2007;80:524–31.
8. Zech CJ, Herrmann KA, Dietrich O, Horger W, Reiser MF, Schoenberg SO. Black-blood diffusion-weighted EPI acquisition of the liver with parallel imaging: comparison with a standard T_2 -weighted sequence for detection of focal liver lesions. *Invest Radiol* 2008;43:261–6.
9. Parikh T, Drew SJ, Lee VS, Wong S, Hecht EM, Babb JS, et al. Focal liver lesion detection and characterization with

- diffusion-weighted MR imaging: comparison with standard breath-hold T_2 -weighted imaging. *Radiology* 2008;246:812–22.
10. Nasu K, Kuroki Y, Nawano S, Kuroki S, Tsukamoto T, Yamamoto S, et al. Hepatic metastases: diffusion-weighted sensitivity-encoding versus SPIO-enhanced MR imaging. *Radiology* 2006;239:122–30.
11. Hardie AD, Naik M, Hecht EM, Chandarana H, Mannelli L, Babb JS, et al. Diagnosis of liver metastases: value of diffusion-weighted MRI compared with gadolinium-enhanced MRI. *Eur Radiol* 2010;20:1431–41.
12. Coenegrachts K, De Geeter F, ter Beek L, Walgraeve N, Bipat S, Stoker J, et al. Comparison of MRI (including SS SE-EPI and SPIO-enhanced MRI) and FDG-PET/CT for the detection of colorectal liver metastases. *Eur Radiol* 2009;19:370–9.
13. Koh DM, Brown G, Riddell AM, Scurr E, Collins DJ, Allen SD, et al. Detection of colorectal hepatic metastases using MnDPDP MR imaging and diffusion-weighted imaging (DWI) alone and in combination. *Eur Radiol* 2008;18:903–10.
14. Zech CJ, Herrmann KA, Reiser MF, Schoenberg SO. MR imaging in patients with suspected liver metastases: value of liver-specific contrast agent Gd-EOB-DTPA. *Magn Reson Med* 2007;6:43–52.
15. Hammerstingl R, Huppertz A, Breuer J, Balzer T, Blakeborough A, Carter R, et al. Diagnostic efficacy of gadoxetic acid (Primovist)-enhanced MRI and spiral CT for a therapeutic strategy: comparison with intraoperative and histopathologic findings in focal liver lesions. *Eur Radiol* 2008;18:457–67.
16. Soyer P, Boudiaf M, Place V, Sirol M, Pautrat K, Vignaud A, et al. Preoperative detection of hepatic metastases: comparison of diffusion-weighted, T_2 -weighted fast spin echo and gadolinium-enhanced MR imaging using surgical and histopathologic findings as standard of reference. *Eur J Radiol* 2010;80:245–52.
17. Shimada K, Isoda H, Hirokawa Y, Arizono S, Shibata T, Togashi K. Comparison of gadolinium-EOB-DTPA-enhanced and diffusion-weighted liver MRI for detection of small hepatic metastases. *Eur Radiol* 2010;20:2690–8.
18. Lowenthal D, Zeile M, Lim WY, Wybranski C, Fischbach F, Wieners G, et al. Detection and characterisation of focal liver lesions in colorectal carcinoma patients: comparison of diffusion-weighted and Gd-EOB-DTPA enhanced MR imaging. *Eur Radiol* 2011;21:832–40.
19. Kim KW, Kim AY, Kim TK, Park SH, Kim HJ, Lee YK, et al. Small (≤ 2 cm) hepatic lesions in colorectal cancer patients: detection and characterization on mangafodipir trisodium-enhanced MRI. *AJR Am J Roentgenol* 2004;182:1233–40.
20. Bartolozzi C, Donati F, Cioni D, Procacci C, Morana G, Chiesa A, et al. Detection of colorectal liver metastases: a prospective multicenter trial comparing unenhanced MRI, MnDPDP-enhanced MRI, and spiral CT. *Eur Radiol* 2004;14:14–20.
21. Le Bihan D, Poupon C, Amadon A, Lethimonnier F. Artefacts and pitfalls in diffusion MRI. *J Magn Reson Imaging* 2006;24:478–88.
22. Nasu K, Kuroki Y, Sekiguchi R, Kazama T, Nakajima H. Measurement of the apparent diffusion coefficient in the liver: is it a reliable index for hepatic disease diagnosis? *Radiat Med* 2006;24:438–44.
23. Akimoto S, Mori H, Fujii T, Furuya K. Optimal scan timing for Gd-EOB-DTPA enhanced liver dynamic MR imaging. [In Japanese.] *Nippon Hoshasen Gijutsu Gakkai Zasshi* 2009;65:626–30.