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Staging of colorectal liver metastases after preoperative chemotherapy. Diffusion-weighted imaging in combination with Gd-EOB-DTPA MRI sequences increases sensitivity and diagnostic accuracy

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Abstract
Objectives To compare the diagnostic accuracy and sensitivity of Gd-EOB-DTPA MRI and diffusion-weighted (DWI) imaging alone and in combination for detecting colorectal liver metastases in patients who had undergone preoperative chemotherapy.
Methods Thirty-two consecutive patients with a total of 166 liver lesions were retrospectively enrolled. Of the lesions, 144 (86.8 %) were metastatic at pathology. Three image sets (1, Gd-EOB-DTPA; 2, DWI; 3, combined Gd-EOB-DTPA and DWI) were independently reviewed by two observers. Statistical analysis was performed on a per-lesion basis.
Results Evaluation of image set 1 correctly identified 127/166 lesions (accuracy 76.5 %; 95 % CI 69.3–82.7) and 106/144 metastases (sensitivity 73.6 %, 95 % CI 65.6–80.6). Evaluation of image set 2 correctly identified 108/166 (accuracy 65.1 %, 95 % CI 57.3–72.3) and 87/144 metastases (sensitivity of 60.4 %, 95 % CI 51.9–68.5). Evaluation of image set 3 correctly identified 148/166 (accuracy 89.2 %, 95 % CI 83.4–93.4) and 131/144 metastases (sensitivity 91 %, 95 % CI 85.1–95.1). Differences were statistically significant ($P<0.001$). Notably, similar results were obtained analysing only small lesions (<1 cm).
Conclusions The combination of DWI with Gd-EOB-DTPA-enhanced MRI imaging significantly increases the diagnostic accuracy and sensitivity in patients with colorectal liver metastases treated with preoperative chemotherapy, and it is particularly effective in the detection of small lesions.
Key Points
- *Accurate detection of colorectal liver metastases is essential to determine resectability.*
- *Almost 80 % of patients are candidates for neoadjuvant chemotherapic treatment at diagnosis. After chemotherapy, metastases usually decrease, and drug-induced liver steatosis may be present.*
- *The sensitivity of imaging is significantly inferior to that in chemotherapy-naïve patients.*
- *DWI combined with Gd-EOB-DTPA increases sensitivity in detecting small metastases after chemotherapy.*

Keywords Colorectal liver metastases · Chemotreated patients · Gd-EOB-DTPA enhanced MRI · DWI · Small lesions

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Introduction

In patients with colorectal liver metastases (CLM), surgical resection is still the only single treatment associated with a

chance for cure [1]. Nevertheless, in recent years, the integration of surgery into multimodal treatment protocols has resulted in 5-year survival rates approaching 60 % [2–4]. In addition, although 80 % of patients are not considered to be candidates for resection at the time of diagnosis [5], modern chemotherapeutic regimens permit a number of patients to have their disease converted from unresectable to resectable [6, 7]. Therefore, accurate detection and localisation of all metastatic deposits is essential to determine the resectability, which is now defined solely according to the possibility to obtain a radical (R0) resection [8]. However, staging the liver disease after chemotherapy is more difficult, and the sensitivity of preoperative imaging in such patients is significantly inferior to that observed in chemotherapy-naïve patients (CT: 65.3 % versus 87.5 %; PET 49 % versus 93.3 %, respectively) [9]. This has been attributed to the aspect of post-chemotherapy metastases that often have reduced contrast in respect to the liver and ill-defined borders [9]. Although these morphological characteristics might simply be the consequence of a decrease in tumour size to sub-centimetre diameters, frequently they are determined by a drug-induced steatosis [10], which modifies the imaging aspect of the liver parenchyma.

Thus, to improve the detection rate, novel contrast media and new imaging techniques should be utilised. In a previous study we reported that the accuracy and sensitivity of contrast-enhanced magnetic resonance (MRI) were significantly higher than those of spiral computed tomography (CT), with the largest difference observed in the detection of metastatic lesions of less than 1 cm [11]. In addition, we recently demonstrated the possibility to increase the MRI detection rate by using the liver-specific MRI contrast agent gadoxate disodium (Gd-EOB-DTPA) in the subset of patients who had undergone chemotherapy (83.2 % versus 64.5 % of CT respectively) [12].

Diffusion-weighted MRI (DWI) is sensitive to the molecular diffusion of water in biologic tissues, and recent technical advancements have permitted obtaining high-quality DWI images of the liver. Colorectal liver metastases show high signal restricted diffusion on DWI compared with normal liver parenchyma. Using breath-hold single shot echo-planar (EPI) DWI with parallel imaging, Koh et al. [13] improved the mangafodipir trisodium MR imaging sensitivity and diagnostic accuracy. Nevertheless, robust evidence supporting the routine use of DWI is still lacking, in particular in the subset of chemo-treated patients with small metastatic lesions. Therefore, the purpose of this study was to determine the current role of DWI in the most challenging subset of patients, i.e. those treated with neoadjuvant or conversion chemotherapy, by comparing the diagnostic accuracy of Gd-EOB-DTPA MR imaging, DWI imaging and the combination of Gd-EOB-DTPA MR and DWI imaging in detecting colorectal liver metastases.

Methods

Study population

In the last 5 years, all patients evaluated at our institution for potentially resectable colorectal liver metastases had a thorough preoperative workup including a thoraco-abdominal CT and a Gd-EOB-DTPA-enhanced liver MRI. In all consecutive individuals in whom (1) a pathologically proven adenocarcinoma of the colon or rectum and (2) at least one liver lesion with CT characteristics diagnostic of liver metastasis, (3) treated with neoadjuvant or conversion chemotherapy, MRI was performed according to a specific protocol (see MRI protocol) including DWI sequences. All patients gave their informed consent before any imaging study. Between August 2009 and July 2011, 146 patients were resected for colorectal liver metastases. Out of these patients, 32 were eventually considered eligible for enrolment into the current study. Data collection and analysis were performed according to the national legislation and institutional guidelines conforming to the ethical standards of the Helsinki Declaration.

MRI protocol

MR examinations were performed using a 1.5-T MR system (Achieva, Philips Medical Systems) employing a SENSE body coil. Before contrast medium administration the following sequences, whose acquisition parameters are derailed in Table 1, were performed.

- Breath-hold T1-weighted axial section turbo spin-echo, in phase and out of phase; 40 sections through the liver were acquired in two 20-s breath-hold data acquisitions.
- Breath-hold T2-weighted axial sections, single shot; 27 sections through the liver were acquired in a 13-s breath-hold data acquisition.
- Breath-hold balanced weighted axial sections, turbo field echo; 36 sections through the liver were acquired in a 13-s breath-hold data acquisition.
- Triggered T2-weighted axial sections, turbo spin echo, high resolution; 30 sections through the liver were acquired in about 2 min 30 s.
- Breath-hold T2-weighted coronal sections, turbo spin echo; 25 sections through the liver were acquired in a 21-s data acquisition.
- SENSE DWI, axial section spin-echo, using two gradients, b value = 0, 300, 600 and b value=800 s/mm^2; 27 sections through the liver were acquired in two 40-s data acquisitions.

Then, a dynamic study was performed by 3D T1-weighted gradient echo sequences (THRIVE); 70 sections through the liver were acquired in about 1 min before and

Table 1 MRI acquisition parameters

1.5-T system	TR *(ms)*	TE *(ms)*	FOV *(mm)*	MATRIX *(r)*	TURBO factor	Slice thickness *(mm)*
T1 (in and out of phase)	146	4.3 and 2.6	405	168/256	2	4, gap 1
T2 axial single-shot	*12,615*	*100*	*415*	*260/400*	*64*	*7, gap 1*
BALANCED TFE	3.6	1.8	405	319/336	130	5, gap 1
T2 axial triggered	*2,084*	*100*	*375*	*244/512*	*130*	*6, gap 1*
T2 coronal TSE	10,302	100	375	204/384	130	6, gap 1
DWI (b=0, 300, 600, 800)	*4,092*	*0.0(63)*	*415*	*160/288*	*51*	*7, gap 1*
3D T1 gradient echo (arterial, portal venous and early hepatobiliary phases)	5.1	2.5	405	199/512	60	6, gap 3

after Gd-EOB-DTPA intravenous injection (dose of 0.1 ml/kg) during arterial (30″), portal (70″) and early hepatobiliary phase (120″) phases; 20 min after contrast medium administration, during the hepatospecific phase, 3D T1-weighted gradient echo sequences were performed (Fig. 1).

Image interpretation and analysis

Two radiologists with 20 (SC) and 9 (MP) years of experience in abdominal MRI and hepatobiliary expertise independently reviewed all images without knowledge of any

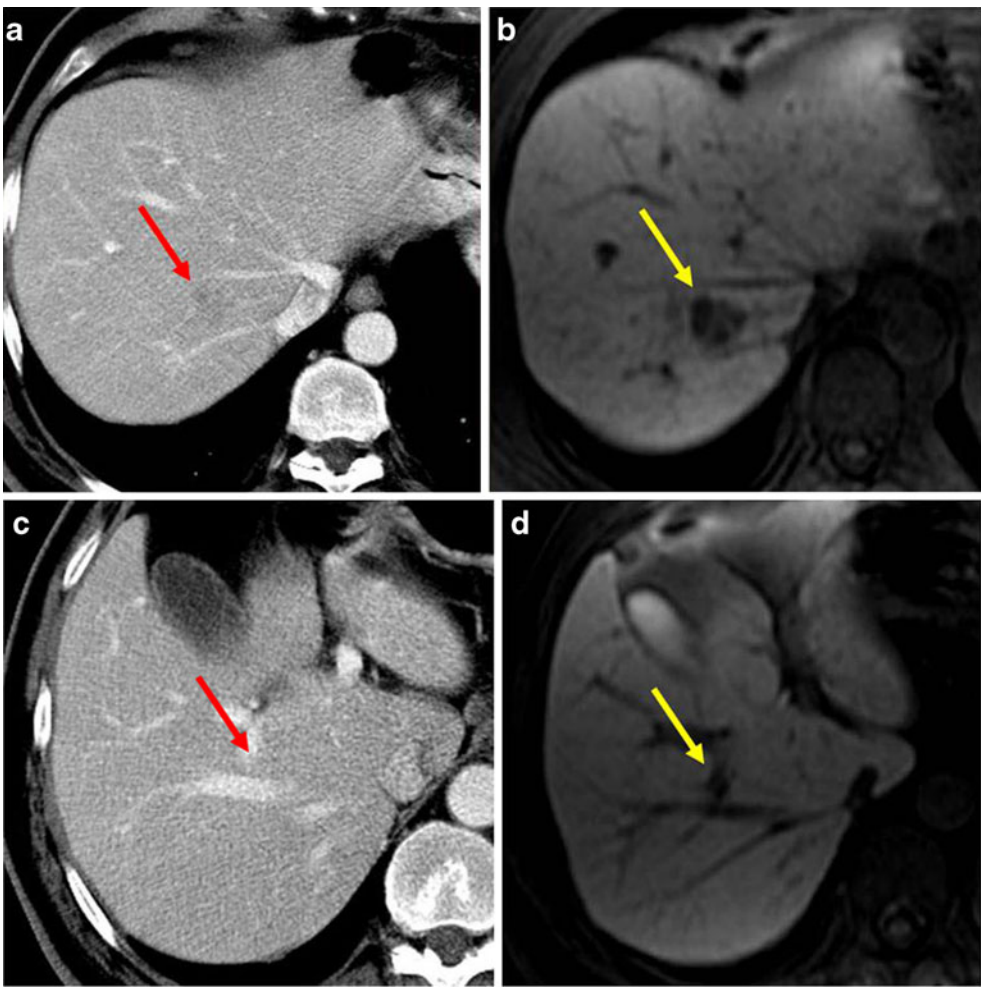

Fig. 1 Metastases slightly/not identified on CT (**a**, **c**) and well defined and detected on Gd-EOB-DTPA MRI (**b**, **d**)

clinical details. The MRI findings of metastatic lesions were then compared with permanent histopathology, which was our gold standard. Notably, the final tumour staging and the definitive type and extent of resection were defined on the basis of intraoperative ultrasound. In all patients all suspected metastatic lesions were removed. Therefore, only clear benign lesions (cysts and angiomas) at intraoperative ultrasound remained unresected. Three different sets of images were reviewed on a workstation during three separate readings sessions, with a 1-month interval between readings. Image sets were as follows:

- Image set 1: Unenhanced T1-/T2-weighted images were evaluated with Gd-EOB-DTPA-enhanced MRI images.
- Image set 2: Unenhanced T1-/T2-weighted images were evaluated with DWI images.
- Image set 3: Combined Gd-EOB-DTPA and DWI image set: Unenhanced T1-/T2-weighted images were assessed with Gd-EOB-DTPA-enhanced MRI and DWI images.

Focal liver lesions identified at review of each image set were assessed by individual observers for lesion (1) site (the location of each lesion was recorded. An anatomical description and slice position of each lesion were also noted to facilitate subsequent lesion matching and comparison); (2) size (the largest axial diameter of each lesion was measured in millimetres); and (3) characteristics (a lesion was deemed metastatic if it showed low T1 signal intensity, heterogeneous and slightly variable high T2 signal intensity, appeared hypointense 20 min after contrast administration and had high signal intensity on DWI images) (Fig. 2). In case of discrepancies between readers in the identification and localisation of lesions, the MRIs were re-evaluated by both readers together in a reading session.

Statistical analysis

The primary endpoint of the study was the overall diagnostic accuracy, defined based on per-lesion analysis, as the sum of true-positive and true-negative results. Of note, we evaluated only metastatic lesions that were the sole lesions that were systematically removed. Secondary endpoints were sensitivity, specificity, and positive and negative predictive value (PPV and NPV) on a per-lesion basis. Results were reported as point estimates and 95 % confidence intervals (95% CIs). The effect of the size of the lesion on the sensitivity of image sets was assessed using the chi-square test for trend, whereas the comparison between values of sensitivity and specificity of the image sets was performed using the McNemar test. Differences were considered

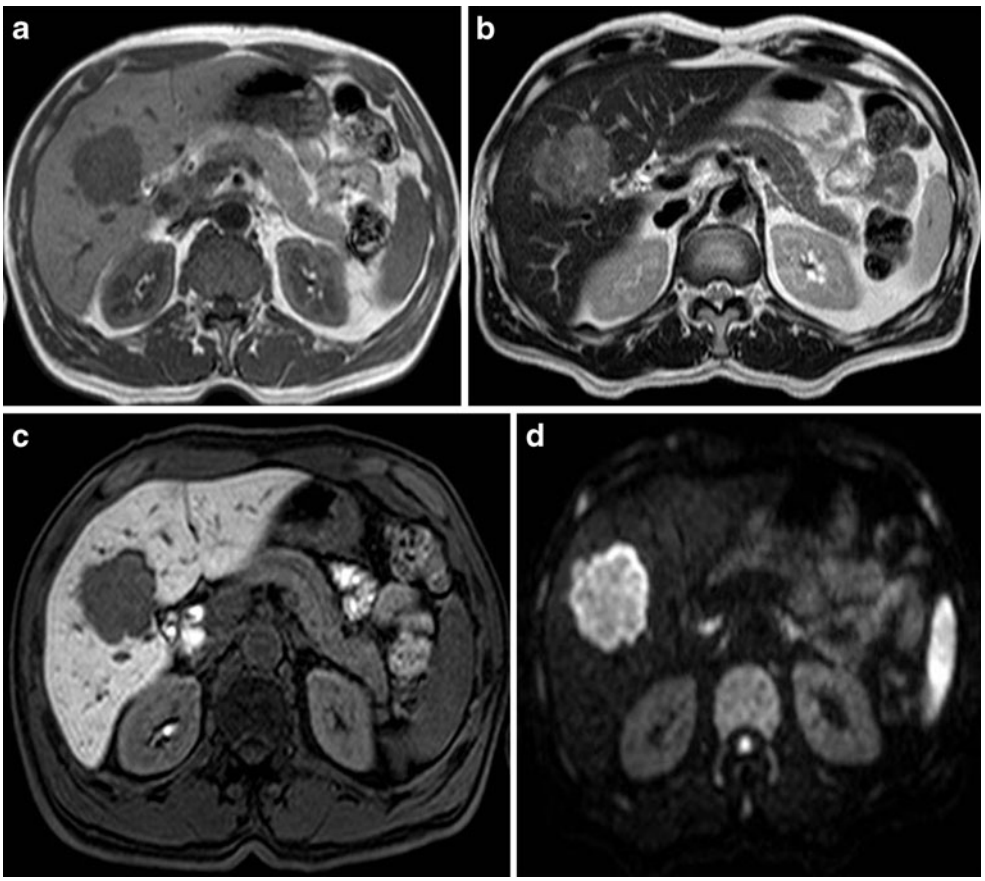

Fig. 2 Metastasis appearance on T1-weighted (**a**), T2-weighted (**b**) and during hepatospecific phase imaging (**c**) and DWI (**d**)

significant at a *P*-value of <0.05. Statistical analysis was performed using SAS software version 9.1.

Results

In all, 32 consecutive patients [24 male and 8 female; median age 65 years, (range 45–78)] were eventually operated on and formed the study cohort. A total of 166 lesions were detected. Of these, 144 (86.7 %) were metastases, whereas the remaining 22 (13.3 %) were considered, at intraoperative ultrasound, as benign lesions (cysts and/or angiomas), albeit for these latter lesions a histological diagnosis was not available. The median size of the metastatic lesions was 9 mm, ranging from 2 to 80 mm; 75 lesions (52.1 %) were smaller than 1 cm, 37 (25.7 %) were in the range of 10–20 mm, and the remaining 32 (22.2 %) were bigger than or equal to 20 mm. Most lesions were located in the right lobe.

Image set 1 correctly identified 127 out of 166 lesions (accuracy: 76.5 %; 95% CI 69.3–82.7 %), 106 out of 144 metastases (sensitivity 73.6 %; 95 % CI 65.6–80.6 %) and 21 out of 22 benign lesions (specificity 95.4 %; 95 % CI 77.2–99.9 %). The 38 missed lesions had a median diameter of 5 mm, ranging from 2 to 10 mm. Sensitivity increased from 52.7 % for lesions sized <10 mm to 100 % for those measuring ≥20 mm (P<0.0001). There was only one false-positive result for a PPV of 99.1 % (106/107, 95 % CI 94.9–100 %) and a NPV of 35.6 % (21/59, 23.6–49.1 %) (Figs. 3, 4 and 5).

Image set 2 correctly identified 108 out of 166 lesions (accuracy: 65.1 %; 95 % CI 57.3–72.3 %), 87 out of 144 metastases (sensitivity 60.4 %; 95 % CI 51.9–68.5 %) and 21 out of 22 benign lesions (specificity 95.4 %; 95% CI 77.2–99.9 %). The 38 missed lesions had a median diameter of 5 mm, ranging from 2 to 11 mm. Sensitivity increased from 33.3 % for lesions sized <10 mm to 100 % for those measuring ≥20 mm (P<0.0001). There was only one false positive. Therefore, the PPV was 98.9 % (87/88 95 % CI 93.8–1.00 %), whereas the NPV was 26.9 % (21/78, 17.5–38.2 %) (Figs. 3, 4, 5).

Image set 3 correctly identified 148 out of 166 lesions (accuracy: 89.2 %; 95 % CI 83.4–93.4 %), 131 out of 144 metastases (sensitivity 91.0 %; 95 % CI 85.1–95.1 %) and 17 out of 22 benign lesions (specificity 77.3 %; 95 % CI 54.6–92.2 %). The 13 missed lesions had a median diameter of 4 mm, ranging from 3 to 6 mm. Sensitivity increased from 83.3 % for lesions sized <10 mm to 100 % for those measuring ≥20 mm (P=0.001). There were five false positives; thus, the PPV was 96.3 % (131/136, 95% CI 91.6–98.8 %), whereas the NPV was 56.7 % (21/78, 17.5–38.2 %) (Figs. 3, 4, 5).

The diagnostic accuracy of set 3 is significantly better than that in both set 1 and set 2 (P<0.0001). The sensitivity of set 1 is significantly better than that in set 2 (P=0.003). Consistent results have been found for sensitivity. Table 2 summarises the reported results.

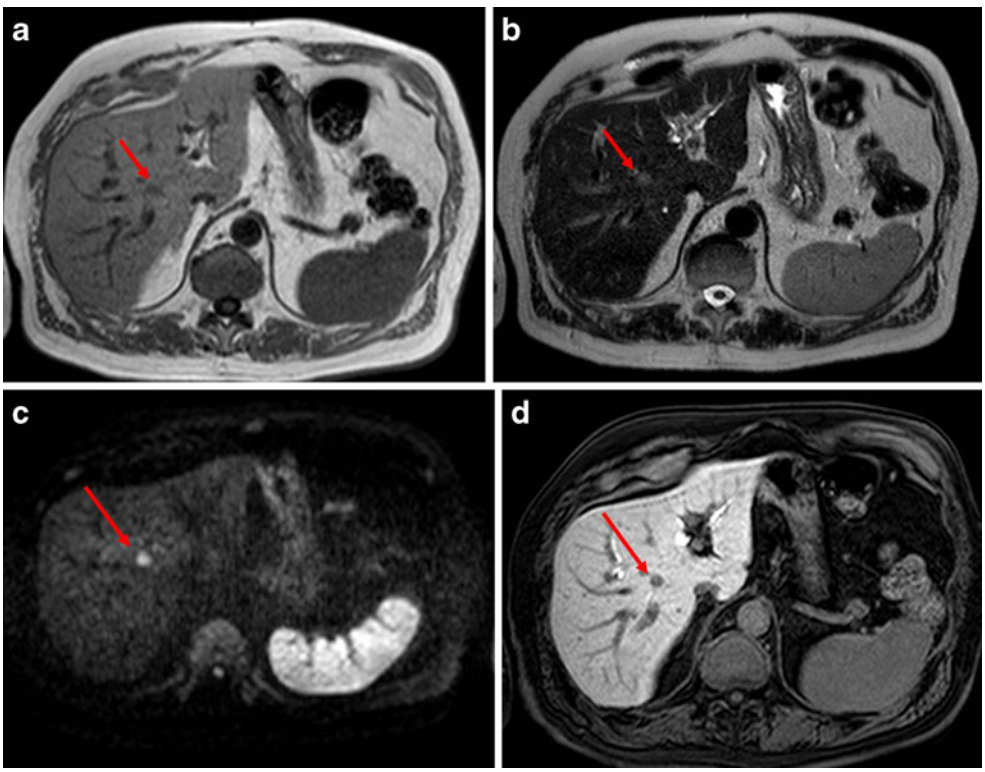

Fig. 3 Metastasis detected on imaging sets 1, 2 and 3. This lesion was indentified on T1-weighted (**a**), T2-weighted (**b**), DWI (**c**) and during hepatospecific phase imaging (**d**)

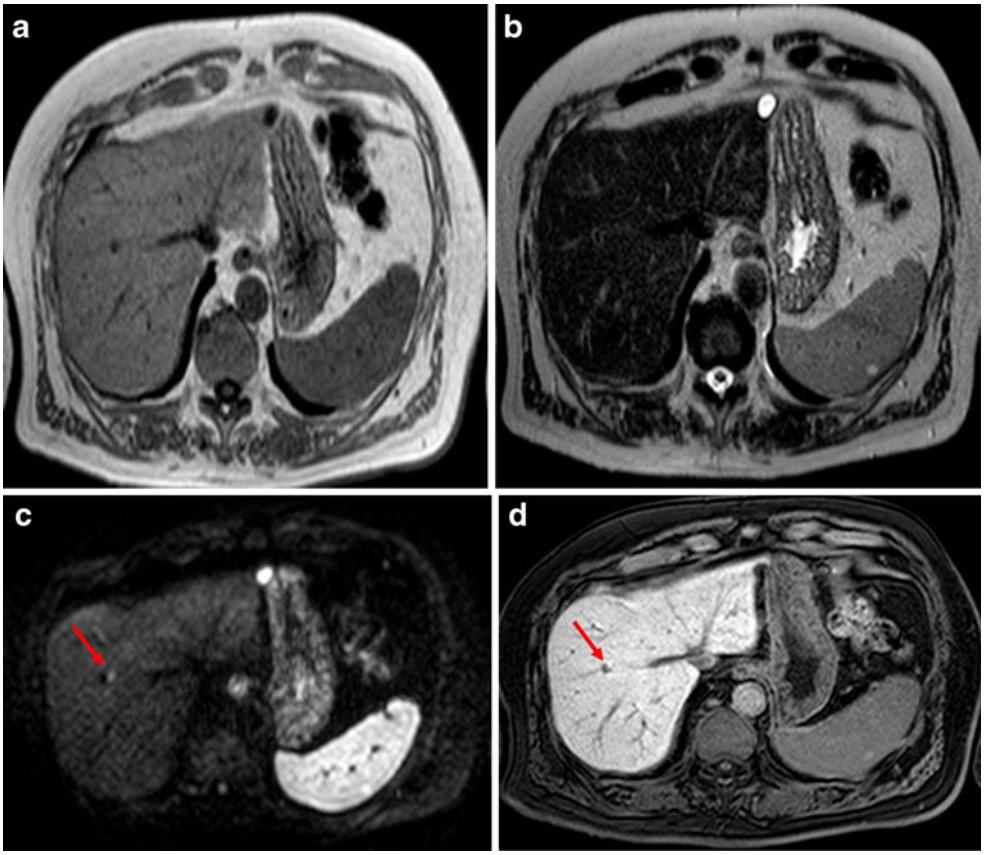

Fig. 4 This is an example of how DWI with unenhanced images can be difficult to interpret. In this image DWI identifies an hyperintense area (**c**) not detected on T1-weighted and T2-weighted images. During the hepatospecific phase (**d**), it is clear that this area corresponds to a biliary structure

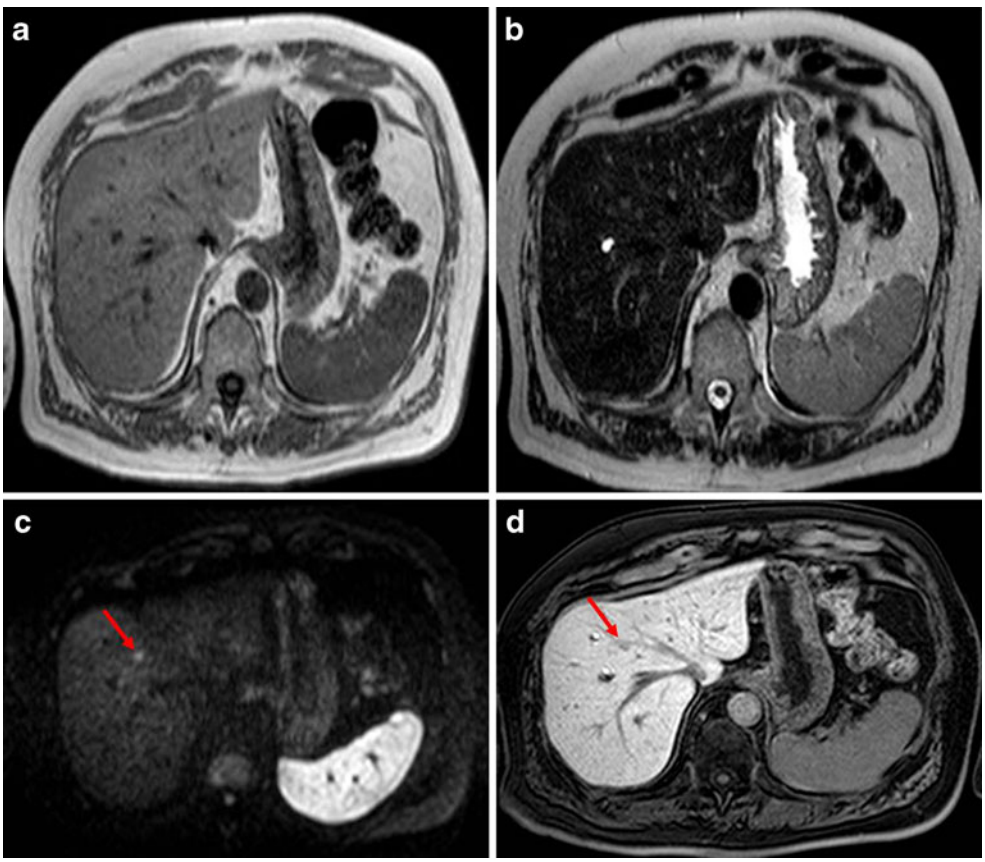

Fig. 5 This figure demonstrates how combined assessment of DWI and Gd-EOB-DTPA imaging (**c**, **d**) is useful in detecting a small metastasis not identified on T1-weighted and T2-weighted imaging (**a**, **b**)

Table 2 Diagnostic capability of the three image sets

	DWI-MRI	Contrast-enhanced MRI	Contrast-enhanced MRI + DWI
Diagnostic accuracy	65.1 % (57.3–72.3)	76.5 % (69.3–82.7)	89.2 % (83.4–93.4)
Sensitivity			
Overall	*60.4 % (51.9–68.5)*	*73.6 % (65.6–80.6 %)*	*91.0 % (85.1–95.1)*
Size <10 mm	*33.3 % (22.9–45.2)*	*52.0 % (40.2–63.7)*	*81.3 % (70.7–89.4)*
Size 10–20 mm	*81.1 % (64.8–92.0)*	*94.6 % (81.8–99.3)*	*100 % (90.5–100)*
Size ≥20 mm	*100 % (89.1–100)*	*100 % (89.1–100)*	*100 % (89.1–100)*
Specificity	95.4 % (77.2–99.9 %)	95.4 % (77.2–99.9)	77.3 % (54.6–92.2)
PPV	*98.9 % (93.8–100 %)*	*99.1 % (94.9–100)*	*96.3 % (91.6–98.8)*
NPV	26.9 % (17.5–38.2 %)	35.6 % (23.6–49.1)	56.7 % (37.4–74.5)

In parentheses: 95 % confidence intervals

Discussion

The current study demonstrates that, in patients who have undergone chemotherapy for colorectal liver metastases, assessment of diffusion-weighted sequences increases the diagnostic accuracy and sensitivity of Gd-EOB-DTPA-enhanced MRI sequences (Fig. 6).

Despite advances in medical treatments and ablative therapies, liver resection remains the mainstay of treatment of colorectal liver metastases. Thus, accurate detection and precise localisation of all metastatic deposits within the liver are essential to determine resectability and the overall surgical strategy (i.e. one- or two-stage hepatectomy). In recent years, however, the efficacy of the newer cytotoxic agents has expanded the use of systemic chemotherapy in the preoperative setting before liver resection in both unresectable and resectable patients [14–16]. As a consequence, post-chemotherapy evaluation has become a routine challenge. In particular, while assessment of the tumour response using dimensional criteria [17] is relatively easy, a precise preoperative mapping might be problematic, especially in patients with multiple small lesions. Yet, this likely represents the key factor for improving patient selection and true radical resections. Difficulties in restaging the liver disease after chemotherapy derive from various aspects. Firstly, treated lesions often exhibit reduced contrast in respect to the liver parenchyma and ill-defined borders [9] as a consequence of a decrease in tumour size to sub-centimetre diameters or of a drug-induced steatosis [10], which modifies the imaging aspect of the liver parenchyma. Secondly, patients often commence chemotherapy without high-quality pre-treatment imaging used for comparison. Therefore, tiny lesions might be missed. In such cases, one might judge a patient for whom a radical resection might not otherwise be feasible to be resectable. To avoid unnecessary laparotomy, strategies to improve the preoperative detection rate have been investigated. We previously demonstrated that the accuracy and sensitivity of mangafodipir-trisodium MRI are significantly higher than those of spiral CT, with the largest difference observed in the detection of metastatic lesions of less than 1 cm [12]; nevertheless, in such patients the sensitivity was still low (67.7 %).

Therefore, since 2006 we have routinely favoured MRI in the assessment of liver disease. Use of the liver-specific MRI contrast agent Gd-EOB-DTPA has further increased the detection rate [13] and thus our diagnostic accuracy. In the present study we focussed on DWI. In particular, we investigated whether the diagnostic accuracy and sensitivity, which inversely

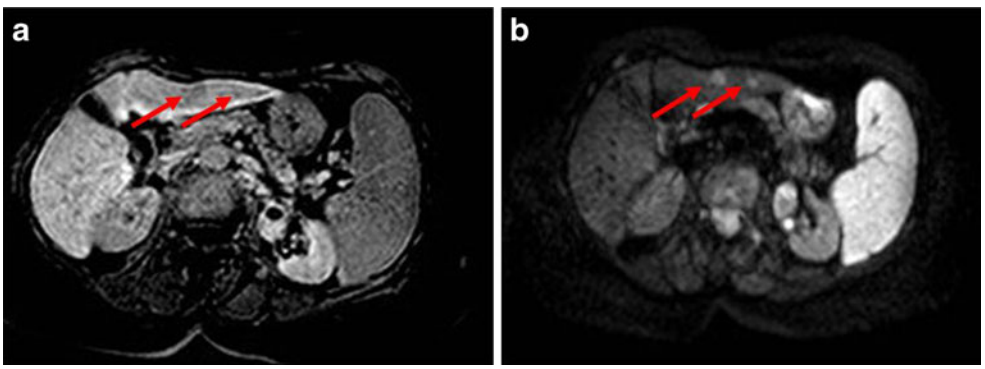

Fig. 6 Combined assessment of Gd-EOB-DTPA imaging (**a**) and DWI (**b**) has greater sensitivity in identifying lesions

correlate with the number and size of liver metastases, can be further improved by the combination of DWI and Gd-EOB-DTPA-enhanced MRI sequences. The most important finding of our study is that the combined assessment has greater diagnostic accuracy and sensitivity (89.2 % and 91 %, respectively) compared to those of each individual method. The observation that assessment of DWI was particularly important in identifying small lesions, which may be missed or misinterpreted as peripheral vasculo-biliary structures or artifacts in contrast-enhanced sequences (Fig. 7), was noteworthy. Previous studies have suggested that the combination of DWI with hepatospecific contrast-enhanced sequences may improve our ability to detect colorectal liver metastases [13–18]. However, these data were obtained in small, heterogenous series. Our data are more robust since we analysed an almost two-fold larger series of colorectal liver metastases in an homogeneous population of patients. In addition, our study is the first to report results in the most challenging group of patients, i.e. those treated with preoperative chemotherapy [19–22]. By focussing only on this group of patients we selected individuals with more complex liver disease such as those with multiple small bilateral liver metastases. This underscores the importance of our findings and explains why we reported an overall sensitivity value of 73.6 %, which is slightly inferior to that reported in the literature (81–91 % [23]). Rather, our sensitivity of 73.6 % should be regarded as remarkable when considering that more than 50 % of the hepatic lesions were smaller than 1 cm and that all patients had a preoperative course of systemic chemotherapy, which may cause liver injuries. Image set 2 had low sensitivity in the detection of colorectal liver metastases. DWI with unenhanced images can be difficult to interpret because of the inherent problems in distinguishing vascular and biliary structures from small metastases and because this sequence has a low spatial resolution. Although in designing our study we felt it necessary to include this image set, we are aware that in clinical practice this set of images is not used. One of the limitations of this study is the absence of pathological characterisation of all suspected benign lesions. Nevertheless, intraoperative ultrasound is so accurate in identifying benign lesions, specifically cysts or haemangiomas, that we can assume that none of the lesions considered non-malignant were otherwise. In support of this, after a median follow-up of 13 months, none of the benign lesions proved to be metastatic at follow-up imaging.

Therefore, we believe that DWI should be routinely combined with contrast-enhanced MRI sequences, especially in patients with multiple small lesions treated with preoperative chemotherapy. The future challenge will be to further increase the detection rate with a parallel increase in specificity.

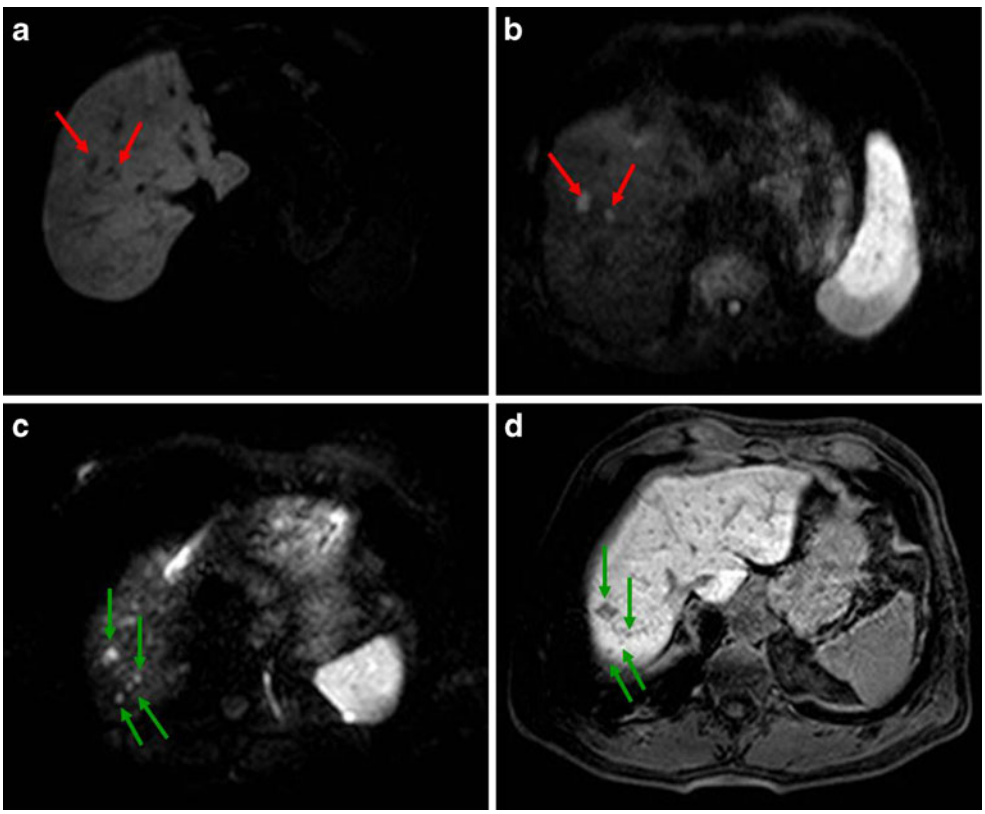

Fig. 7 These images show how DWI is especially useful in identifying small lesions (**a** and **b**, **c** and **d**)

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