HEPATOBILIARY-PANCREAS

Accuracy of gadoxetic acid-enhanced magnetic resonance imaging for the diagnosis of sinusoidal obstruction syndrome in patients with chemotherapy-treated colorectal liver metastases

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Abstract

Objective To assess whether reticular hypointensity on hepatobiliary phase images of gadoxetic acid-enhanced magnetic resonance imaging (EOB-MRI) is a diagnostic finding of sinusoidal obstruction syndrome (SOS) in patients with hepatic metastases who have undergone chemotherapy.

Methods We retrospectively analysed EOB-MRI of 42 patients who had undergone chemotherapy before hepatic resection of colorectal hepatic metastases. Two radiologists, who were unaware of whether or not the patients had SOS, reviewed the hepatobiliary phase images to determine the presence of hypointense reticulation in the liver using a 5-point scale. The sensitivity, specificity and area under the receiver operating characteristics curve (A_z) were calculated for each reviewer.

Results The sensitivity, specificity and A_z for the diagnosis of SOS were 75%, 100% and 0.957 for reader 1 and 75%, 96.2% and 0.936 for reader 2, respectively. In one patient who received a false-positive diagnosis by one reader, there was sinusoidal fibrosis on histological examination, but not diagnostic for SOS. False-negative diagnosis occurred in four patients for both readers; histology of these patients showed minimal and localised sinusoidal congestion and fibrosis.

Conclusions Reticular hypointensity on hepatobiliary phase images of EOB-MRI is highly specific for the diagnosis of SOS in patients with treated colorectal hepatic metastases.

Key Points

• *Gadoxetic acid enhanced magnetic resonance imaging (EOB-MRI) can identify the sinusoidal obstruction syndrome (SOS)*

• *The diagnosis can be achieved with high specificity and good interobserver agreement.*

• *SOS typically demonstrates diffuse hypointensity on hepatobiliary phase images on EOB-MRI.*

• *EOB-MRI may be falsely negative in patients with minimal degree of SOS.*

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Introduction

Sinusoidal obstruction syndrome (SOS) is an adverse side-effect of systemic chemotherapy for colorectal cancer with a reported incidence between 42% and 51%. Particularly, incidence of SOS in patients treated with oxaliplatin showed higher incidence of SOS (51–79%) than that in patients treated with other drugs (21–30%) [1–3]. Histologically, it is characterised by obliteration of small hepatic venules with surrounding fibrosis and clogging of the sinusoids with debris from endothelial cell necrosis [4, 5]. Although SOS associated with chemotherapy for colorectal hepatic metastases is usually asymptomatic, it may increase morbidity and liver failure after surgical resection of hepatic

metastases [2, 6–10]. Therefore, identification of SOS on imaging is important for determining the timing of hepatic resection and for the planning of further chemotherapy [11].

Recently, Ward et al. [11] reported that superparamagnetic iron oxide (SPIO)-enhanced magnetic resonance imaging (MRI) can effectively detect SOS with a sensitivity of 87% and specificity of 89% by demonstrating diffuse or patchy reticulations that reflect locally impaired Kupffer cell functions. Unfortunately, however, SPIO is currently not widely used for liver imaging because of its limited dynamic imaging capability, and its high sensitivity was not reproduced in a recent study [12]. Gadoxetic acid disodium (Gd-EOB-DTPA, Primovist® or Eovist®, Bayer Schering Pharma AG, Berlin, Germany) is a newly available hepatobiliary contrast agent that has both dynamic and hepatobiliary phase imaging capabilities [13, 14]. Although there have been no reports addressing the utility of gadoxetic acid-enhanced MRI (EOB-MRI) for the diagnosis of SOS, we encountered reticular hypointensity in the liver on delayed hepatobiliary phase images on EOB-MRI in patients who underwent chemotherapy for the treatment of hepatic metastases. We hypothesised that this reticular hypointensity may represent the hepatic abnormalities associated with SOS that have been reported with SPIO-enhanced MRI [12, 15]. Therefore, the purpose of this study was to assess whether the reticular hypointensity seen on hepatobiliary phase images of EOB-MRI is a diagnostic finding of SOS in patients who have undergone chemotherapy for the treatment of colorectal hepatic metastases.

Materials and methods

Patients

The study was approved by the Institutional Review Board. Between February 2006 and March 2010, 96 consecutive patients underwent EOB-MRI for preoperative evaluation of hepatic metastases followed by surgical resection. Of these 96 patients, 54 were excluded from this study because the interval between MRI and surgical resection was longer than 2 months (n=19), the primary cancer was not colorectal cancer (n=9), chemotherapy was not conducted before MRI (n=24), or chemotherapy was conducted during the interval between MRI and surgery (n=2). We excluded the latter two patients because findings on MRI may have changed due to the subsequent chemotherapy. We excluded patients who did not receive chemotherapy because SOS is a disease associated with chemotherapy. Therefore, the remaining 42 patients (23 men, mean age, 59.9 years, range 42–72 years; 19 women, 50.1 years, 32–69 years) were included in this study. None of the patients had chronic liver diseases. Forty patients underwent

segmental resection or non-anatomical metastasectomy, and two patients underwent ultrasound-guided biopsy. In all patients, a sufficient area of surrounding liver was obtained to allow histological evaluation for the presence of SOS. The chemotherapy regimens of the 42 patients were as follows: fluorouracil (FU) and oxaliplatin (FOLFOX) (n=16); FU, irinotecan, and leucovorin (LV) (FOLFIRI) (n=5); capecitabine (n=5); FOLFIRI and bevacizumab (n=3); FOLFOX and cetuximab (n=2); FU (n=2); FOLFOX followed by FOLFIRI (n=2); FU and LV followed by FOLFIRI (n=1); FOLFIRI followed by capecitabine (n=1); FU and irinotecan (n=1); FU followed by irinotecan (n=1); FU followed by capecitabine (n=1); FU followed by doxifluridine (n=1); and FU, LV, and bevacizumab (n=1). The mean interval between surgery and imaging was 19.5 days (range, 1 to 46 days).

In all patients, alkaline phosphatase (ALP), alanine transaminase (ALT), total bilirubin, platelet count and the international normalised ratio (INR) were measured. The reference ranges for the blood sample parameters utilised by our institution were as follows: 60–300 IU/L for ALP, 5–46 IU/L for ALT, 0.2–1.2 mg/dL for total bilirubin, 150–$400\times10^3/\mu$L for the platelet count, and 0.91–1.16 for INR. Data for perioperative complication such as amount of intraoperative blood loss and transfusion, duration of hospital stay after operation, and 90-day mortality was also collected.

MR imaging

All patients were examined with a 3.0 T MR system (TrioTim, Siemens, Erlangen, Germany; or Intera Achieva, Philips Medical Systems, Beth, the Netherlands) except for one patient examined with a 1.5-T MR system (Intera, Philips Medical Systems, Beth, the Netherlands). All images were obtained in the axial plane using a single, dedicated body-phased array coil anteriorly and spine array coils posteriorly. Routine liver MR images were acquired before the administration of Gd-EOB-DTPA using the following sequence: two-dimensional dual-echo breath-hold T1-weighted spoiled gradient echo (GRE) sequence at opposed-phase (repetition time [TR]/effective echo time [TE], 150/1.23 ms) and in-phase (150/2.46) with a flip angle of 65°, one signal acquired, a matrix of 256×192, 7-mm slice thickness and a 0.7-mm gap; a navigator-triggered T2-weighted turbo spin-echo (TSE) sequence with TR range of 3,300–4,900 and TE 73–88 ms, echo train length of 14, one signal acquired, a matrix of 320×202, superior and inferior spatial presaturation and chemical fat saturation, a 4-mm slice thickness and a 1-mm gap; and a breath-hold, heavily T2-weighted half-Fourier acquisition turbo spin echo (HASTE) with a TE of 150 ms, a matrix of 320×179, 4-mm slice thickness, and a 1-mm gap.

For dynamic and delayed hepatobiliary phase MR imaging, a bolus of 0.025 mmol/kg body weight Gd-EOB-DTPA (Bayer Schering Pharma AG, Berlin, Germany) was injected as a rapid bolus, immediately followed by a 20-ml saline flush with a power injector at an injection rate of 2 mL/s. A three-dimensional (3D) spoiled GRE sequence with chemical selective fat suppression was performed before intravenous injection of the contrast agent. Four consecutive contrast-enhanced dynamic images were obtained with an 18–24 s duration for each acquisition. Imaging delay for the arterial phase was usually 20–30 s and was determined using a bolus-tracking technique or a test-bolus injection technique. Dynamic images were obtained at 60–70 s, 90–100 s, and 120–150 s after injection. Hepatobiliary phase images were obtained 15–20 min after contrast material injection. The MR parameters included TR/TE 2.54/0.92, a flip angle of 13°, a 256×192 matrix, one signal acquired, and 2-mm slice thickness using an interpolation technique.

Image analysis

Two radiologists (M.J.K., who has 18 years' experience in abdominal MR imaging, and N.Y.S., a radiology resident) independently reviewed only the hepatobiliary phase images from all of the MR sequences. They were aware that the patients underwent hepatic resection for colorectal metastases but were blinded to other clinical and histological data, such as the presence of SOS or detail of the chemotherapeutic regimen. Images were presented to the readers in a random sequence, and interobserver agreement of the independent analysis was assessed using kappa (κ) statistics.

Each observer recorded the confidence level of the presence of reticular hypointensity on hepatobiliary phase images using a 5-point scale: 1 = definitely not present; 2 = probably not present; 3 = equivocal; 4 = probably present; 5 = definitely present (Fig. 1). A confidence score of 4 or 5 was considered a positive diagnosis for SOS on MR imaging. One (N.Y.S) of the reviewers also measured the longest diameter of the spleen in both pretreatment CT, as a baseline, and post-treatment MR images in the transverse plane because a previous study showed that splenomegaly can be a useful indicator of the presence of SOS [16]. We calculated the change in spleen size by using the following formula: (long axis diameter on post-treatment MR imaging—long axis diameter on pretreatment CT)/long axis diameter on pretreatment CT x 100 (%).

Reference of standard

A pathologist (Y.N.P.) with more than 10 years' experience in gastrointestinal disease who was blinded to the results of the MR imaging reviewed non-tumourous liver tissue to define the presence of SOS. SOS was diagnosed when there

were histological features such as sinusoidal dilatation and congestion, sinusoidal fibrosis, atrophy or necrosis of pericentral hepatocytes, and narrowing and eventual fibrosis of the central veins.

Statistical analysis

Whether data were normally distributed or not was determined by using the Kolmogorov–Smirnov test. Accordingly, data that exhibited a normal distribution are presented as mean ± standard deviation, and quantitative variables were compared using an unpaired t-test. Otherwise, data are presented as median with the interquartile range (IQR), and the Mann–Whitney test was used for comparing quantitative values. Qualitative data were analysed using the Chi-squared test.

The sensitivity (SN), specificity (SP), positive predictive value (PPV) and negative predictive value (NPV) for detection of SOS were calculated with a 95% confidence interval (CI). The diagnostic performance of hepatobiliary phase images for predicting SOS was assessed by using receiver operating characteristic (ROC) curves. The area under the ROC curve (A_z) along with its 95% CI was calculated for each reviewer. The interobserver agreement for assessment of imaging findings was determined using the κ-statistic. The level of agreement was defined as follows: poor, κ-values of 0.20 or less; fair, κ-values of 0.21–0.40; moderate, κ-values of 0.41–0.60; good, κ-values of 0.61–0.80; and very good, κ-values of 0.81–1.00. All of the data management and statistical calculations were performed using MedCalc® software (MedCalc, Version 11.3.6.0, Mariakerke, Belgium).

Results

Of a total of 42 patients, SOS was diagnosed histologically in 16 patients (38%) (Table 1). The sensitivity was 75% for both observers and the specificity 100% and 96.2%, respectively (Tables 2 and 3). Interobserver agreement was 0.765. The presence of reticular hypointensity on hepatobiliary phase images yielded A_z values for the diagnosis of SOS of 0.957 and 0.936 for observers 1 and 2 respectively (Table 3).

In one patient for whom a false-positive diagnosis was made by one of the observers, areas of sinusoidal fibrosis were noted on histological examination, but the abnormality was not considered sufficient for the diagnosis of SOS (Fig. 2).

Five patients were given false-negative diagnoses (three by both observers, one by observer 1, and one by observer 2) and were graded with confidence scores of 2 or 3 on MRI. In these patients, the areas of histological abnormality were not distributed globally (Fig. 3).

In the review of clinical records, 14 out of 16 patients (87.5%) with SOS and six out of 26 patients (23.1%) without
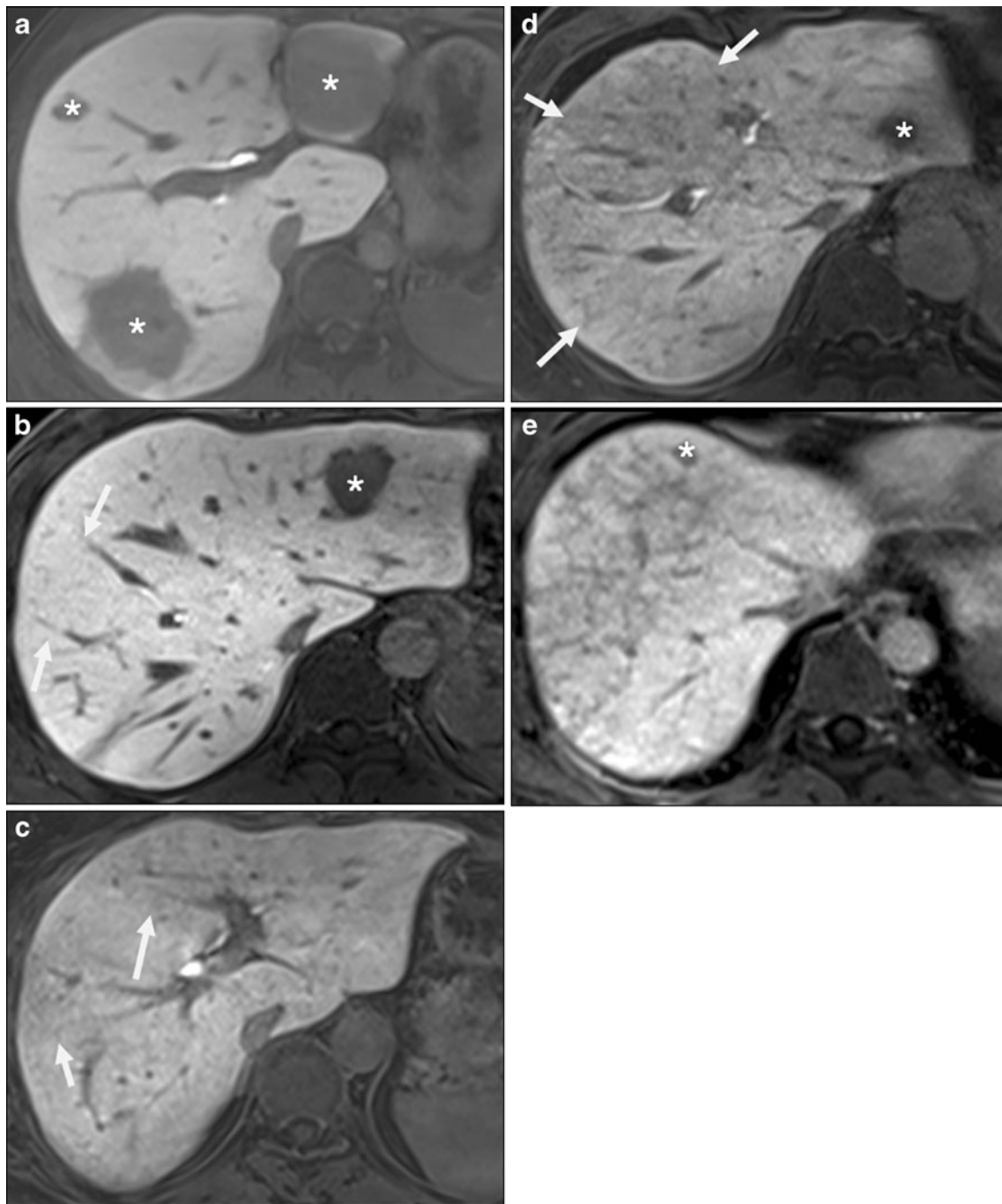
Fig. 1 Various degrees of sinusoidal obstruction syndrome on hepato-biliary phase images of EOB-MRI. **a** The liver shows homogeneous high signal intensity (confidence level = 1). **b** Subtle hypointense reticulations (*arrows*) in only a few sections, but not definite (confidence level = 2). **c** Fine hypointense reticulations in limited areas (*arrows*; confidence level = 3). **d** More prominent reticulations in all sections (*arrows*; confidence level = 4). **e** The liver parenchyma shows marked hypointense reticulations (confidence level = 5). Nodular lesions with hypointensity are metastatic lesions (*asterisks*)

SOS received oxaliplatin as a neoadjuvant chemotherapeutic agent ($P=0.0001$) (Table 1). The median number of chemotherapy cycles in patients with SOS (10 cycles; range, 4–16 cycles) was significantly greater than that in patients without SOS (8 cycles; range, 2–26 cycles) ($P=0.0279$). The mean difference in spleen longitudinal diameter between pre-treatment and post-treatment CT or MR axial images was also significant. Patients with SOS showed a slight increase in spleen size (mean ± standard deviation [SD], 7.3%±10.7) while patients without SOS showed no remarkable change in

Table 1 Demographic characteristics and laboratory findings in patients with and without sinusoidal obstruction syndrome (SOS)

	All patients (n=42)	Without SOS (n=26)	With SOS (n=16)	P value[c]
Sex (M / F)[b]	23 / 19	15 / 11	8 / 8	NS
Age (years)[a]	55.5±11.0	54.7±10.8	56.6±11.6	NS
ALP (IU/L)	73.5 (44.0–174.0)	70.0 (46.0–166.0)	89.5 (44.0–174.0)	NS
ALT (IU/L)	18.0 (7.0–66.0)	17.5 (10.0–66.0)	18.0 (7.0–50.0)	NS
T. bil (mg/dL)	0.60 (0.20–1.90)	0.60 (0.30–1.90)	0.60 (0.20–1.30)	NS
INR	0.95 (0.85–2.29)	0.95 (0.88–1.08)	0.96 (0.85–2.29)	NS
Platelet (x 10^3/μL)[a]	215.5±71.0	208.5±76.4	227.0±62.0	NS
Difference of spleen size (%)[a]	2.8±11.3	0.1±11.0	7.3±10.7	0.0462
Median CTx-surgery interval	67.5 (16–1,089)	86 (16–913)	50.5 (24–1,089)	NS
Median No. of CTx cycle	9.0 (2.0–26.0)	8.0 (2.0–26.0)	10 (4.0–16.0)	0.0279
Use of oxaliplatin[b]	20 (47.6%)	6 (23.1%)	14 (87.5%)	0.0001
Use of bevacizumab[b]	4 (7.1%)	3 (11.5%)	1 (6.3%)	NS
Use of cetuximab[b]	2 (4.8%)	1 (3.8%)	1 (6.3%)	NS

ALP alkaline phosphatase; *ALT* alanine transaminase; *CTx* chemotherapy; *INR* international normalised ratio; *NS* not significant; *SOS* sinusoidal obstruction syndrome; *T. bil* total bilirubin

Unless otherwise indicated, data are presented as the median with the range in parentheses

[a] Data are presented as mean ± standard deviation

[b] Data are presented as number of patients

[c] P values for comparing patients who had SOS with patients who did not have SOS

spleen size (0.1%±11.0) (P=0.0462). The diagnostic performance of the difference in the longest diameter of the spleen was fair (0.706), and the best cut-off value was > 0.4% with a sensitivity of 56.3% and specificity of 80.8% (Fig. 4). No other clinical and laboratory data including perioperative complication, even though a patient with SOS who was given a confidence score 5 by both observers suffered from nonhepatic complications such as acute respiratory distress syndrome, disseminated intravascular coagulation, multiple brain hemorrhage, and sepsis, showed significant differences between patients with and without SOS. Multiple logistic regression showed that the use of oxaliplatin was the only significant predictor of the presence of SOS (b_i=4.35, P= 0.001), and the corresponding odds ratio was 77.67 (95% CI, 6.21–970.97).

Discussion

Our results showed that the presence of reticular hypo-intensity on hepatobiliary phase images of EOB-MRI is highly specific (100% for observer 1 and 96.2% for observer 2) for the diagnosis of SOS in patients who are candidates for hepatic resection of colorectal hepatic metastases after chemotherapy.

In our study, a false-positive diagnosis was made in only one patient by one observer. The one patient for whom a false-positive diagnosis occurred actually showed a minor degree of histological change that was considered to be the resolving features of previous SOS. The patient underwent

Table 2 Histological correlation of MRI findings

Histology	Observer 1		Observer 2	
	MRI (No. of patients)		MRI (No. of patients)	
	Positive	Negative	Positive	Negative
Positive	12	4	12	4
Negative	0	26	1[a]	25

MRI magnetic resonance imaging; *No* number

[a] Histology showed some but not all features of SOS

Table 3 A_z, sensitivity, specificity, and positive and negative predictive values for each observer

	Observer 1	Observer 2	Weighted kappa
A_z	0.957 (0.845–0.995)	0.936 (0.816–0.988)	0.765
Sensitivity (%)	75 (47.6–92.7)	75 (47.6–92.7)	
Specificity (%)	100 (86.8–100)	96.2 (80.4–99.9)	
PPV (%)	100 (73.5–100)	92.3 (64.0–99.8)	
NPV (%)	86.7 (69.3–96.2)	86.2 (68.3–96.1)	

A_z area under the receiver operating characteristic curve; *PPV* positive predictive value; *NPV* negative predictive value

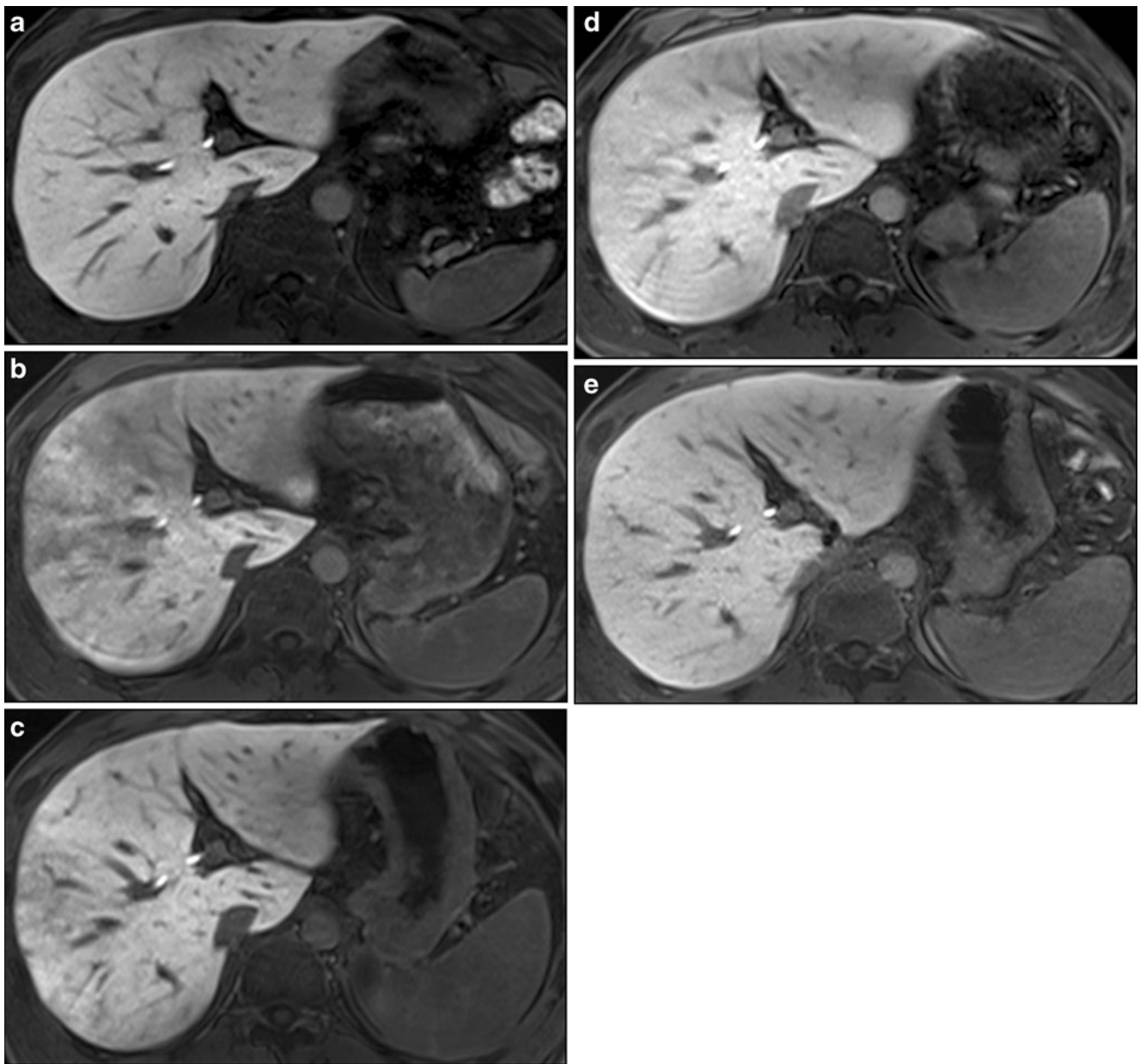Numbers in parentheses are 95% confidence intervals

Fig. 2 A 42-year-old male patient with rectal cancer with hepatic metastases. Hepatobiliary phase images of EOB-MRI of the patient with positive MR and negative histology. **a** Before chemotherapy, the liver shows homogeneous hyperintense parenchyma. **b** After 5 cycles of FOLFOX, the liver demonstrates diffuse hypointense reticulations on all sections with densely coalescent areas on multiple sections, suggesting definite presence of SOS. **c** 1 month after completion of FOLFOX, the abnormality was less marked. **d** After 4 cycles of FOLFIRI, the reticulation is further improved and graded 3 and 4 by observers 1 and 2, respectively, and histology showed some features of SOS which were not sufficient for definite diagnosis. **e** After operation, the liver parenchyma shows homogeneous hyperintensity, suggesting the absence of SOS. The longitudinal diameter of the spleen on post-chemotherapy MRI is larger than pre-treatment MRI, and is largest in (**c**)

serial follow-up with MRI during multiple cycles of chemotherapy using oxaliplatin. On the earlier MR images, which were not included in this study, diffuse reticular hypointensity was prominently noted but subsided during the subsequent follow-up examinations. If both observers made a consensus to determine the presence or absence of reticular hypointensity, this finding would have had 100% specificity for the diagnosis of SOS as the false-positive diagnosis was given by only one observer.

Our results showed modest sensitivity of EOB-MRI for the diagnosis of SOS that was confirmed histologically. This may indicate that the presence of reticular hypointensity may not be well appreciated in mild cases of SOS. In all five of the false-negative patients, the histological
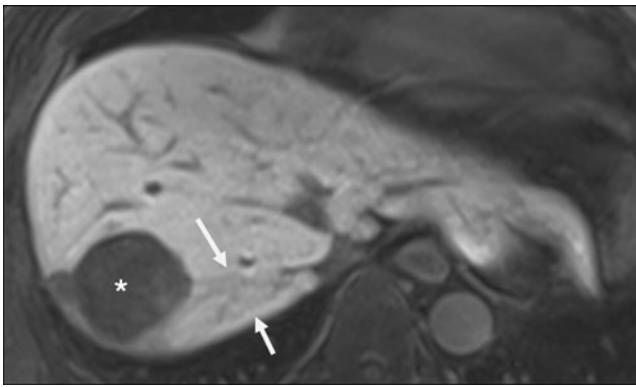
Fig. 3 A 51-year-old male patient with transverse colon cancer with hepatic metastases after 16 cycles of FOLFIRI with bevacizumab. Hepatobiliary phase images of EOB-MRI of the patient with negative MR and positive histology. There is subtle hypointense reticulations (*arrows*; confidence level = 2 by both observers) medial to metastatic lesion (*asterisk*). This finding is limited to a small area of liver dome and can easily be considered as peritumoral change or partial-volume average

abnormality was seen in limited areas of the surgical specimen without affecting the tissue globally. On retrospective review, subtle reticular hypointensity was seen in limited areas of the liver but was not as prominent as in the unequivocal cases. However, as the mild form of SOS may not affect the postsurgical outcome and may regress spontaneously, this relatively lower sensitivity may be regarded as clinically acceptable.

In our study, the interobserver agreement was good overall, and disagreement was noted mainly in those patients for whom false-negative diagnoses were made and the degree of histological change was relatively mild. Our results indicated that the clinically significant, modest, or severe form of SOS can be easily diagnosed with excellent interobserver agreement.

Except for the change in spleen size, no clinical and laboratory data correlated with presence of SOS on both MRI and histology in our study.

Although severe hepatic failure associated with SOS has rarely been reported [9, 10], SOS is usually asymptomatic and causes only mild liver dysfunction such as mild elevation of liver enzymes without statistic significance [11]. In our study, mild elevation of ALP and/or ALT was more often seen in patients with SOS than in patients without SOS on both MRI (41.7%/13.8%) and histology (25%/19.2%) without statistical significance, which were compatible with previous report.

There were some reports that showed association between SOS and perioperative complication [3, 6, 7]. In our study, although one patient who received confidence score 5 by both observers suffered from postoperative complication, there was no correlation between presence of SOS on both MRI and histology and increased morbidity such as amount of intraoperative blood loss and transfusion and duration of hospital stay after operation.

Our study showed that the change in spleen size, as determined by the long-axis diameter, was significantly greater in patients with SOS. However, there was a large overlap between the two patient groups. Overman et al. [16] reported a 50% increase in spleen volume after oxaliplatin-based chemotherapy as a predictor of hepatic sinusoidal injury. In their study, the spleen size was measured by the summation of the section volume determined by tracing the spleen on the workstation. We speculated that the measurement of spleen volume using this method would not be practical in routine work; therefore, we measured the longest diameter of the spleen in the transverse plane before and after chemotherapy. We could not trace the change in spleen size using the same
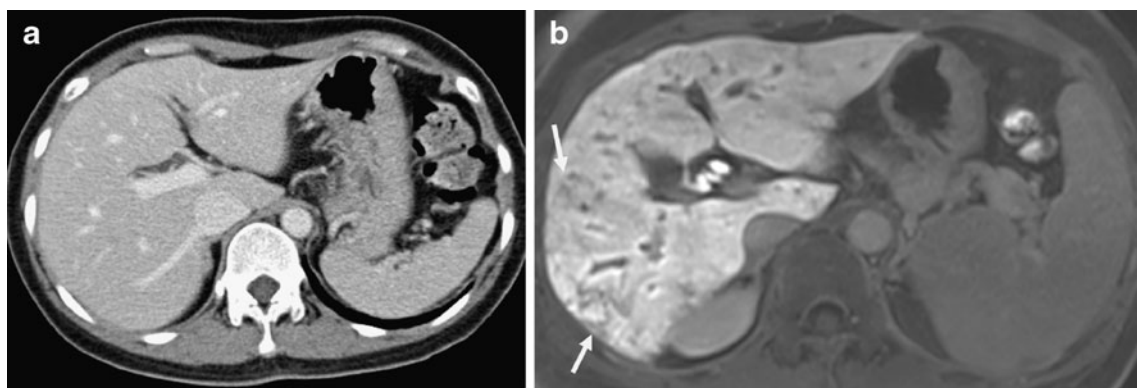

Fig. 4 A 52-year-old female patient with sigmoid colon cancer with hepatic metastases. **a** In CT obtained before chemotherapy, the longest diameter of the spleen is 9.1 cm. **b** After 15 cycles of FOLFOX, the hepatobiliary phase image of EOB-MRI shows a 35.2% increase in

the size of the spleen (12.3 cm in the longest diameter) compared with the baseline. The liver shows definite hypointense reticulations (*white arrows*; confidence level = 5 by both observers). SOS is confirmed by histology

imaging technique because, in most patients, pretreatment MR images were not available.

According to the previous studies, SOS was improved or resolved in 3 to 7 months [1, 11]. In our study, a patient whom a false-positive diagnosis was made by one observer showed improvement and better resolution of the abnormality on follow-up MRI performed 3 and 6 months after cessation of oxaliplatin-based chemotherapy, respectively. Because some surgical data show increased perioperative morbidity in patients with SOS [2, 3, 6, 7, 11], preoperative diagnosis of SOS could help determine the timing of hepatic resection and to plan chemotherapy. However, further study is needed to establish when physicians should postpone the operation or chemotherapy and when follow-up MRI is required.

One of the limitations of our study was that we could not correlate the histological change in the liver with the MR images because only a limited area of the liver with hepatic metastases that was removed during surgery was available in our study. The second limitation was that grade and extent of sinusoidal injury was not scored histologically as previously described [1, 11, 16]. Because we just reviewed histology of false-positive and false-negative cases retrospectively to establish the cause of discordance between MRI finding and histology, we could not evaluate whether confidence level of SOS on MRI significantly correlated with histological grade or extent of SOS. Although it would have been desirable to assess whether imaging findings have clinical significance, our study population showed no remarkable deterioration of liver function and there was no objective clinical or pathological criteria to determine the grade of the disease severity. Finally, we did not compare the imaging findings of hepatobiliary phase images with other imaging sequences, such as precontrast T1- or T2-weighted images or dynamic images. However, we considered it unnecessary because we had noted in our clinical practice that reticular hypointensity was barely visible in such sequences. Therefore, we attempted to determine whether the reticular hypointensity depicted on hepatobiliary phase images is an indicative finding for the diagnosis of SOS.

In conclusion, our study showed that the presence of reticular hypointensity on hepatobiliary phase images of EOB-MRI is highly specific for the diagnosis of SOS in patients who are candidates for hepatic resection of colorectal hepatic metastases after chemotherapy. Therefore, reticular hypointensity seen on hepatobiliary phase images of EOB-MRI obtained in patients with a recent history of chemotherapy should be considered a finding indicative of SOS.

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