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Review article

Hepatic MRI with SPIO: detection and characterization of focal liver lesions

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Abstract. A variety of parenterally administered iron oxides have been developed for contrast-enhanced MRI of the liver. Two different classes of iron oxides are currently clinically approved or in phase 3 trials: superparamagnetic iron oxides (SPIO) with a high R2/R1 relaxivity ratio and short blood half-life (AMI-25 and SH U 555 A), and ultrasmall paramagnetic iron oxides (USPIO) with a lower R2/R1 relaxivity ratio and longer blood half-life (AMI-227). All iron oxides significantly increase tumor-to-liver contrast and allow detection of more lesions than unenhanced MRI on T2-weighted images at a field strength of 0.2–1.5 T. Malignant lesions without phagocytic cells exhibit constant signal on T2-weighted accumulation phase images with all three iron oxides. All iron oxides cause a signal decrease of benign lesions with either phagocytic cells or a significant blood pool on T2-weighted accumulation phase images. The signal decrease of benign lesions is proportional to the Kupffer cell activity or tumor vascularity and is useful for lesion characterization. Another enhancement feature for the differentiation of benign from malignant lesions is ring enhancement of malignant lesions (metastases) on T1-weighted enhanced images either during the perfusion phase with SH U 555 A or during the accumulation phase with AMI-227, which is attributed to the blood pool effects of the compounds. Differentiation of lesions and vessels is easier on enhanced images with angiographic effects than on unenhanced images. Iron oxides improve the quality of two-dimensional MR angiography techniques of the portal venous system by decreasing background signal (liver tissue with all iron oxides) and increasing intravascular signal (AMI-227). The use of iron oxides for hepatic MRI provides an alternative to the existing multistep diagnosis with CT, CT portography, MRI and biopsy.

Key words: Iron oxides – Liver – SPIO – USPIO

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Perspective

Superparamagnetic iron oxides are the first clinically approved liver-specific contrast agents in Europe and the United States among a variety of cell-specific MR contrast agents [1]. The purpose of this review is to summarize current clinical experience with superparamagnetic iron oxides for the detection and characterization of focal liver lesions, and contrast-enhanced MR angiography of the portal venous system. The overall goal is to provide an alternative to the existing multistep diagnosis with CT, CT portography, MRI and biopsy.

Introduction

A variety of parenterally administered iron oxides have been developed for contrast-enhanced MRI of the liver [2]. Two classes of iron oxides are currently clinically approved or in phase 3 trials (Table 1): superparamagnetic iron oxides (SPIO) with a high R2/R1 relaxivity ratio and short blood half-life (< 10 min), and ultrasmall paramagnetic iron oxides (USPIO) with a lower R2/R1 relaxivity ratio and longer blood half-life (< 2 h) [3–5]. The higher the R2/R1 relaxivity ratio the higher the T2 effect and the signal decrease on T2-weighted images (Table 1).

SPIO agents [e.g., AMI-25 (Advanced Magnetics, Cambridge, Mass.), SH U 555 A (Schering, Berlin, Germany)] efficiently accumulate in liver (approximately 80 % of the injected dose) and spleen (5–10 % of the injected dose) within minutes of their administration [3, 5, 6]. Following sequestration by phagocytic cells, these agents significantly decrease the liver and spleen signal within several minutes. Malignant tumors are typically devoid of a substantial number of phagocytic cells so appearing as hyperintense/bright lesions contrasted against the hypointense/black liver on T2-weighted sequences. Tumors with a substantial number of phagocytic cells (e.g., focal nodular hyperplasia, hepatocellular adenoma, well-differentiated hepatocellular carcinoma) and/or a significant blood pool (hemangioma) may show

Table 1. Some properties of parenterally administered iron oxides for hepatic MRI

Agent	Generic name	Size (nm)	R2/R1 ($1\,mmol^{-1}\,s^{-1}$)	Coating	Blood half-life (min)	Status
SPIO						
AMI-25	Ferumoxide	80	160/40	Dextran	8	Approved
SH U 555 A		62	151/25	Carboxydextran	3.9–5.8	Phase 3
USPIO						
AMI-227	Ferumoxstran	17–20	53/24	Dextran	> 100	Phase 3

From [3, 5, 6]

sufficient uptake of SPIO to decrease in signal on T2-weighted sequences. The signal decrease is related to the Kupffer cell activity or tumor vascularity [2, 7].

USPIO agents [e.g., AMI-227 (Advanced Magnetics), also tested as BMS 180549] have a longer blood half-life and accumulate primarily in liver, spleen and lymph nodes. Since USPIO have a relevant R1 effect and long blood half-life, they can also be used as T1 (brightening) blood pool agents for MR angiography or hepatic lesion characterization. Well-perfused lesions increase in signal on T1-weighted images and decrease in signal on T2-weighted images. USPIO yield information on the vascular nature of liver lesions during accumulation phase images.

Clinical trials with AMI-25 have mainly emphasized lesion conspicuity [8–10]; however, the characterization of focal liver lesions is equally important in order to provide a complete clinical investigation [11]. Dynamic MRI with extracellular gadolinium chelates to characterize focal liver lesions is based on intravenous bolus injections and fast MRI techniques. Similar bolus injections with SPIO have not been feasible with prototype compounds such as AMI-25 or AMI-227 because of cardiovascular side effects and acute lumbar pain [2]. More recently, the new SPIO SH U 555 A did not show side effects following rapid intravenous injection [12]. The purpose of this review is to provide practical information on the clinical application of iron oxides for both detection and characterization of focal liver lesions. Strategies to characterize lesions based upon enhancement patterns due to tumor perfusion and/or the presence of phagocytic cells are presented.

Iron oxides

Clinical trials with intravenously administered AMI-25 (Table 1) were initiated as early as 1987 [13]. Early studies were performed with bolus injections of relatively high doses ($\leq$ 50 μmol Fe/kg body weight) of an initial formulation of AMI-25 that caused significant hypotension. Subsequently, the agent was reformulated to achieve iso-osmolarity and is currently administered by drip infusion over a period of 30 min, since side effects (facial flash, dyspnea, rash, lumbar pain) depend on the dose rate [2]. AMI-25 is a relatively safe drug if drip-infused in glucose or saline at a dose of 10–15 μmol Fe/kg body weight over 30 min with a flow rate of approximately 3 ml/min [9, 10, 14, 15].

SH U 555 A consists of superparamagnetic iron oxide microparticles coated with carboxydextran (Table 1). Its physical properties have been described in detail [3, 16]. A dose dependent (5–40 μmol Fe/kg body weight) increase in partial thromboplastin time was observed in phase 1 trials; however, the normal range was not exceeded. These minor changes in PTT were attributed to a transient decrease in factor XI activity. The transient decrease in clotting factor XI did not cause any clinical side effects in phase 2 and 3 trials. Previous studies assessing other SPIO or USPIO contrast agents did not report detailed information on clotting parameters. In phase 3, bolus injections (8–12 μmol Fe/kg body weight; 0.9–1.4 ml) were performed by preloading the contrast agent into a connecting intravenous line and flushing the line with 10 ml saline within 3 sec; no cardiovascular side effects were seen [17].

The first USPIO were prepared by fractionation of AMI-25. USPIO show a stronger biodistribution into bone marrow and lymph nodes than SPIO. Since USPIO exhibit a longer plasma circulation time and stronger T1 shortening characteristics than SPIO these compounds can also be used as blood pool agents with angiographic effects [18]. Newer USPIO such as AMI-227 (Advanced Magnetics, Cambridge, Mass.) have been prepared by direct synthesis and are currently in phase 3 clinical trials for contrast-enhanced MRI of liver, spleen and lymph nodes. Physical properties (Table 1) and phase 1 results have been described in detail [5, 19]. Plasma relaxation time measurements demonstrated a persistent, dose-dependent decrease in both T1 and T2 [5]. The USPIO particles have to be infused slowly over a period of 30 min to avoid hypotensive reactions or acute lumbar pain [5].

Detection of focal liver lesions

All iron oxides significantly increase tumor-to-liver contrast and allow detection of more lesions than unenhanced MRI (Fig. 1) on T2-weighted images at a field strength of 0.2–1.5 T [10, 15, 20]. Lesion-liver contrast and lesion conspicuity on T2-weighted images significantly increase only for malignant lesions, because only malignant lesions show no significant lesion enhancement.

A complete MRI examination with AMI-25 consists of separate unenhanced and enhanced studies requiring two different MRI time slots with contrast infusion out-

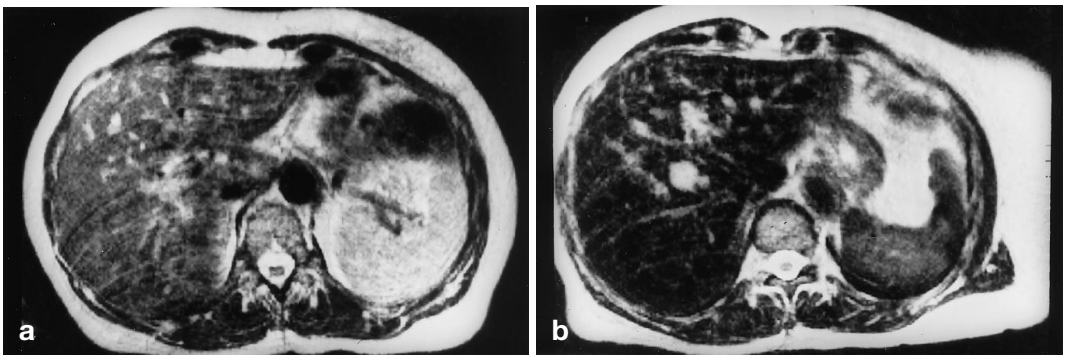

Fig. 1 a, b. Detection of malignant lesions with iron oxides: liver metastasis. Plain (**A**) and AMI-25-enhanced (**B**) T2-weighted TSE images (TR 4050 ms/TE 90 ms) of a patient with histopathologically proven liver metastases. The lesion in the center of the right liver lobe shows increased contrast and conspicuity on enhanced images

side the magnet under medical supervision [9, 10, 14, 21]. AMI-25-enhanced MRI proved to yield more specific results than portal CT at a similar sensitivity [22]. More recently, T1-weighted breathhold gradient echo imaging has been evaluated for tumor detection using the signal inversion of lesions on enhanced T1-weighted gradient echo images [23]. Lesions demonstrated contrast comparable to T2-weighted images, with bright lesions contrasted against a dark liver because of the sensitivity of gradient echo techniques to susceptibility effects. This technique yielded a lower sensitivity than spiral CTAP (95 % vs 84 %) but higher specificity (79 % vs 99 %) in a small number of 22 patients [24].

SH U 555 A was tested in phase 2 trials at doses of 4, 8 or 16 μmol Fe/kg (corresponding to 0.25, 0.5, and 1.0 mg Fe/kg) body weight. A significant increase in lesion-liver contrast and the number of visible liver lesions was observed at a dose of 8 and 16 μmol Fe/kg body weight. The dose of 8 μmol Fe/kg body weight was as effective as the highest dose of 16 μmol Fe/kg body weight. T2-weighted Turbo spin-echo (SE) images showed better lesion conspicuity than T2-weighted conventional SE sequences [12].

Phase 2 studies with doses between 0.8 and 1.7 mg Fe/kg body weight demonstrated that AMI-227 enhanced signal in normal liver and blood vessels on T1-weighted images and decreased signal in these tissues on T2-weighted images. Lesion-liver contrast significantly increased for solid tumors on both T1- and T2-weighted images. Differentiation between blood vessels and small lesions was easier on contrast-enhanced images due to the angiographic effects of the contrast agent [25].

Characterization of focal liver lesions

Benign liver lesions

All iron oxides cause a signal decrease of benign lesions with either phagocytic cells or a significant blood pool on T2-weighted accumulation phase images (Fig. 2, 3). The signal decrease of benign lesions is related to the Kupffer cell activity or tumor vascularity [2, 7, 26]. Focal nodular hyperplasia (FNH), regenerating nodules, adenomas and adenomatous hyperplasia may show variable uptake because the degree to which tumors contain Kupffer cells is variable [27]. Hemangiomas demonstrate increased signal on T1-weighted accumulation phase images with all iron oxides [23, 25, 28]. Cysts show no signal change.

Additional information for lesion characterization may be obtained by dynamic imaging with bolus-injectable SH U 555 A (Fig. 4). In one particular study both dynamic T1-weighted FLASH and T2*-weighted FLASH MRI were evaluated [28]. On dynamic T1-

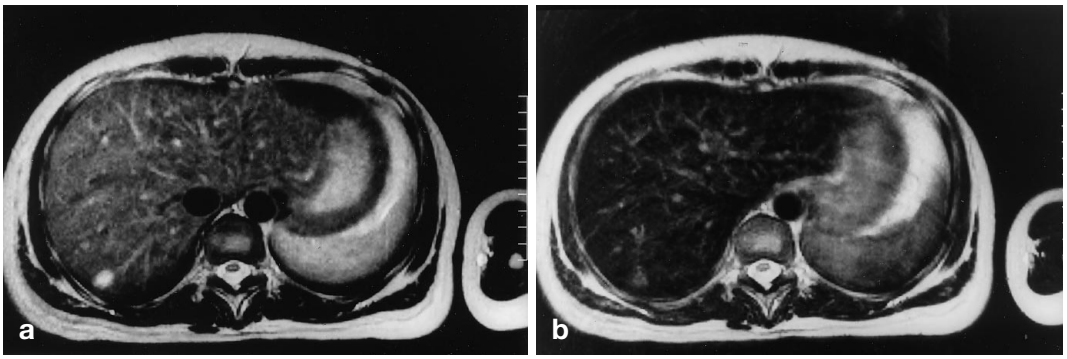

Fig. 2 a, b. Enhancement of benign lesions: adenoma. Plain (**A**) and SH U 555 A-enhanced (**B**) T2-weighted TSE images (TR 4050 ms/TE 90 ms) of a patient with histopathologically proven liver adenoma. The lesion in the right liver lobe shows decreased contrast and conspicuity on enhanced images because of a decrease in signal intensity within the lesion due to uptake of contrast material

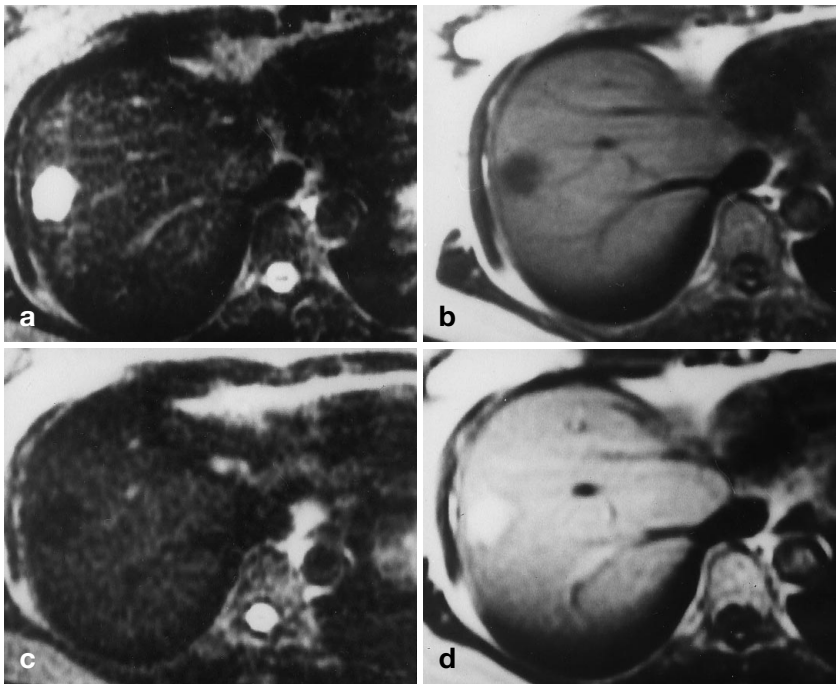

Fig. 3 a–d. Enhancement of benign lesions: hemangioma. T1- and T2-weighted SE images of a hemangioma in the right liver lobe before and after infusion of AMI-227 (1.7 mg Fe/kg). On T2-weighted images (**a, b** pre-contrast; **c, d** post-contrast) signal is reduced in liver, hemangioma and intrahepatic vessels after AMI-227. In comparison, on T1-weighted images there is uniform enhancement of the hemangioma. (Images courtesy of Sanjay Saini, M. D.)

weighted FLASH, hemangiomas showed a signal increase during the first 2 min with stable signal up to 10 min following injection of contrast agent. FNH as a hypervascular lesion exhibited an initial signal increase that was significantly lower than for hemangiomas. On dynamic T2*-weighted FLASH, hemangiomas and FNH demonstrated a decrease in signal over time. Hemangiomas demonstrated peripheral signal changes on dynamic scans with filling-in patterns visible only on T1-weighted images [28].

AMI-227 also offers additional features for lesion characterization because of unique enhancement patterns on T1-weighted or on T2-weighted images [25]. Cysts showed no enhancement and were best characterized on contrast-enhanced images. Hemangiomas (Fig. 3) enhanced on T1-weighted images, becoming hyperintense relative to liver, and showed a signal decrease on T2-weighted images, becoming isointense to liver only at the highest dose injected [29].

Malignant liver lesions

Malignant lesions (Fig. 1) without phagocytic cells exhibit constant signal on T2-weighted accumulation phase images with all three iron oxides [2, 30]. However, the presence of phagocytic cells within early stages of hepatocellular carcinoma may cause enhancement comparable with adenomatous hyperplasia [31].

Dynamic imaging of the perfusion phase with SH U 555 A can be used to study tumor vascularity and shows no significant changes in metastases and cholangiocarcinomas while hepatocellular carcinomas, as hypervascular lesions, may demonstrate an initial signal increase (Fig. 5, 6). These effects are best demonstrated on T1-weighted images such as FLASH. Dynamic T1-weighted FLASH showed ring enhancement of liver metastases significantly more frequently (80 %) than T2*-weighted FLASH (36 %). The intravenous bolus injection of SH U 555 A significantly improved the differentiation of benign and malignant focal liver lesions from 73 % on plain MRI to 84 % on delayed MRI, 86 % on dynamic FLASH, and 91 % for the complete MRI study [32].

The clinical evaluation of SH U 555 A-enhanced MR angiography of the portal venous system demonstrated no significant changes in vessel signal on accumulation phase images 20–30 min following contrast injection. Therefore, vessel contrast significantly increased because of decreased liver signal and the visibility of higher-order branches of the portal venous system increased (Fig. 7). Results assessing the surgical relevance for the evaluation of lesion resectability showed significant difference between plain and SH U 555 A-enhanced MR angiography studies in cases where plain MRI was not diagnostic. The diagnostic information provided by SH U 555 A-enhanced MR angiography was always rated as equal to or better than the diagnostic information provided by plain MR angiography [17].

AMI-227 also offers additional features for lesion characterization and MR angiography compared with AMI-25, because of persistent T1 effects and angiographic effects (Fig. 3) during the accumulation phase [25]. Solid lesions appear hypointense on postcontrast T1-weighted images, with improved contrast against enhancing normal liver and blood vessels facilitating the differentiation between lesions and vessels seen on cross-sections [29]. On T2-weighted images, AMI-227 decreases signal in normal liver and vessels and thus solid lesions become more conspicuous. Differentiation of lesions and vessels is easier on AMI-227-enhanced images than on unenhanced images. Another enhancement feature for the differentiation between benign and ma-

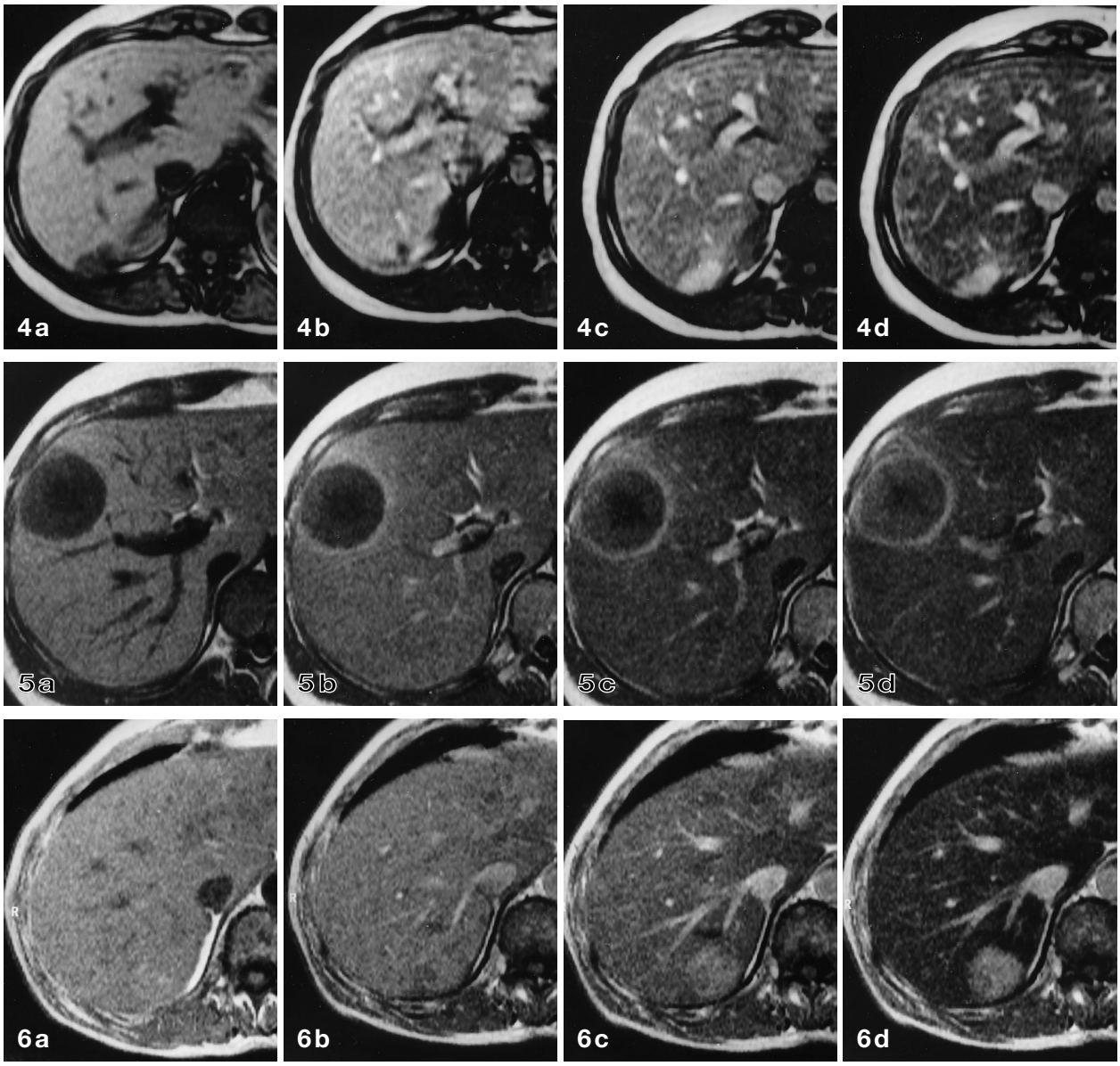

Fig. 4a–d. Dynamic signal changes of benign lesions: hemangioma. Dynamic SH U 555 A-enhanced T1-weighted images (**a** pre-contrast; **b** 60 s; **c** 240 s; **d** 400 s) of a patient with a liver hemangioma in the right liver lobe. Dynamic changes in tumor signal with early peripheral signal enhancement and subsequent filling-in of the hemangioma are demonstrated

Fig. 5a–d. Ring enhancement of metastasis. Dynamic SH U 555 A-enhanced T1-weighted FLASH-images (**a** pre-contrast; **b** 30 s; **c** 60 s; **d** 240 s) of a patient with surgically proven metastasis from colorectal cancer. The lesion shows ring enhancement during the perfusion phase outside the lesion

Fig. 6a–d. Dynamic enhancement of hypervascular lesion: hepatocellular carcinoma. Dynamic SH U 555 A-enhanced T1-weighted FLASH images (**a** pre-contrast; **b** 30 s; **c** 60 s; **d** 240 s) of a patient with surgically proven hepatocellular carcinoma. Dynamic changes in tumor and liver enhancement are demonstrated due to a shortened T1-relaxation time during the perfusion phase

lignant lesions is ring enhancement on T1-weighted AMI-227-enhanced images, which is attributed to the blood pool effects of the compound. This feature was visible in 62 % (18/29) of malignant lesions and 14 % (2/14) of benign lesions [33]. The imaging window is different from that of SH U 555 A where ring enhancement has been observed up to 10 min following initiation of contrast agent injection while AMI-227-enhanced images are obtained as early as 30 min following initiation of contrast agent infusion. Recently, ring enhancement was observed also on T1-weighted images 45 min following infusion of AMI-25 in 5 of 23 metastases [23].

Significant vascular enhancement of upper abdominal vessels was noted with an increase in signal-to-noise ratio, such as in the portal vein from 19 ± 12 to 62 ± 20 [34]. Quality of angiographic images of the abdominal vasculature obtained at the equilibrium phase demonstrated a dose dependency, with a significant decrease in blood T1 relaxation time from 1210 ms precontrast to 280 ms at a dose of 1.1 mg Fe/kg, 222 ms at a dose of

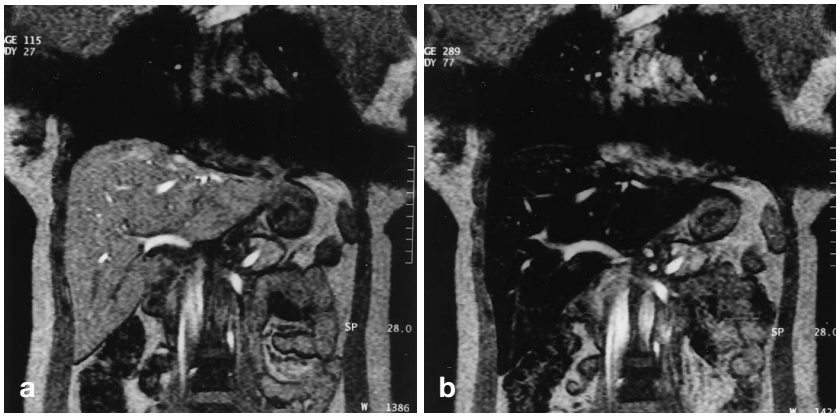

Fig. 7 a, b. Iron-oxide-enhanced MR angiography. Plain (**a**) and SH U 555 A-enhanced (**b**) two-dimensional time-of-flight images demonstrate increased visibility of portal venous vessels because of increased vessel-liver contrast

1.7 mg Fe/kg, and 159 ms at a dose of 2.6 mg Fe/kg [35]. Imaging during the equilibrium phase produces arterial and venous enhancement (Fig. 3) due to the shortened blood T1, independent of time-of-flight effects. Signal of background tissue does not significantly increase during the equilibrium phase with a blood half-life of 35 h [5]. The persisting high signal allows high-resolution techniques with signal averaging to obtain a high intravascular signal-to-noise ratio [35].

Future directions

All the iron oxides described here increase lesion-liver contrast and improve the detection of focal liver lesions compared with unenhanced MRI (Fig. 1). Current data indicate that specific enhancement features allow for a more precise characterization of focal liver lesions than unenhanced MRI, CT portography and CT. Further studies are required to analyze the cost-benefit ratio for iron oxides and to compare iron-oxide-enhanced MRI with other modalities. These studies have to clarify whether the use of iron oxides leads to a change in patient treatment and whether these decisions are reliable. The realistic chance of a one-step diagnosis (detection and characterization) is an attractive alternative to the existing multimodality approach.

Both AMI-227 and SH U 555 A offer additional features for lesion characterization by means of T1-shortening effect (Fig. 3–6). AMI-227 enhances signal in normal liver and blood vessels on T1-weighted images and decreases signal in these tissues on T2/T2*-weighted images; however, due to safety reasons contrast administration has to be performed by drip infusion [25]. Dynamic T1-weighted MRI following bolus injection of SH U 555 A mimics signal changes established for gadolinium chelates and signal changes are better visualized on T1-weighted images than on T2/T2*-weighted images. Another potential benefit of dynamic T1-weighted MRI techniques is that the relationship between vessels and metastases is reversed on contrast-enhanced images. Hence, current difficulties in distinguishing vessels seen in cross-section from small focal lesions may not be present. This benefit has also been described by Saini et al. [25] for a blood-pool-based USPIO (AMI-227) and increased confidence in excluding hepatic metastases in uninvolved liver. The ideal iron oxide may facilitate a bolus injection for T1-weighted MRI of the perfusion/distribution phase and exhibit a long blood half-life for accumulation phase T1- and T2-weighted imaging with angiographic effects.

Contrast-enhanced MR angiography of the liver and portal venous system with iron oxides has been performed during the accumulation phase with increased vascular signal by a suppression of background signal by decreasing liver signal (Fig. 7). This approach differs from studies using gadolinium chelates where intravascular signal is increased due to the shortening of T1-relaxation time [36]. This contrast mechanism of iron oxides is likely to be valid for a large time window following extraction of particles from the intravascular space into the Reticuloendothelial system (RES). Contrast-enhanced MR angiography scans during or immediately following intravenous injection of iron oxides with a low R2/R1 ratio using rapid 2D- or 3D-techniques may rather demonstrate similar intravascular signal changes as gadolinium chelates [37]. Alternatively, iron oxide particles with a longer blood half-life such as USPIO or monocrystalline iron oxide nanopolymers (MION) may be combined with breathhold MR angiography techniques [38]. Blood pool agents such as the USPIO agent AMI-227 (Fig. 3) may make injection timing less critical and may even be injected before the patient reaches the scanner [34].

Summary

SPIO contrast agents have been shown to improve the detection of focal liver lesions compared with non-enhanced MRI and contrast-enhanced CT [8, 9, 13, 14, 25]. Recently, SPIO-enhanced MRI proved to yield more specific results than portal CT at a similar sensitivity [22]. SPIO-enhanced MRI strategies with AMI-25 have focused on T2-weighted imaging techniques following slow infusion of the contrast agent; however, SPIO enable a far more versatile approach by means of dynamic imaging with bolus-injectable compounds such as SH U 555 A and T1-weighted accumulation phase imaging by means of blood pool effects of smaller particles such as AMI-227. A combination of T1-weight-

ed and T2/T2*-weighted imaging appears to provide clinically more useful enhancement patterns than T2-weighted imaging alone. Heavily T2-weighted postcontrast imaging also provides useful clinical information by tumor enhancement of frequent benign tumors such as hemangiomas and RES-containing tumors.

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