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REVIEW

Contrast agents used in MR imaging of the liver

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ABSTRACT

Several categories of contrast agents with different biodistributions are currently available for magnetic resonance imaging of the liver. They improve lesion detection and characterization by increasing lesion-liver contrast. These agents include nonspecific extracellular gadolinium chelates, reticuloendothelial system-specific iron oxides, hepatocyte-selective agents, and combined perfusion and hepatocyte-selective agents. This article describes the currently used contrast agents in magnetic resonance imaging of the liver, summarizes their mechanisms of action, biodistributions, and safety profiles. Additionally, it reviews their main clinical indications, administration and imaging techniques, and the appearances of common hepatic lesions in contrast-enhanced studies.

Key words: • *contrast media* • *magnetic resonance imaging* • *liver neoplasms* • *gadolinium*

Intravenous administration of the contrast agents used for magnetic resonance (MR) imaging of the liver make the detection and characterization of diseases easier by increasing lesion-liver contrast. For this purpose, contrast agents have been used in the MR imaging examination of the liver since 1986. Following the clinical approval of gadopentate dimeglumine (Gd-DTPA) in 1988, the daily practical use of contrast agents became widespread and new agents were produced (1, 2). Despite the newly developed T1- and T2-weighted MR imaging sequences, the necessity of contrast agents did not diminish. Contrast-enhanced MR imaging is preferred to non-enhanced MR imaging and contrast-enhanced computed tomography (CT) in the detection and characterization of liver lesions (3-9). The ideal contrast agent for liver MR examinations must have a strong magnetic effect, little if any side effects and biodistribution differentiation (i. e., difference between enhancement in various tissues). Currently, clinically approved Phase III studies of contrast agents that were developed for liver MR imaging can be divided into three different groups as nonspecific extracellular gadolinium chelates, hepatocyte-selective contrast agents and reticuloendothelial system (RES)-specific contrast agents. In most cases, these are multi-centered studies, which are conducted with large groups of patients prior to clinical approval, and in which the efficiency of the contrast agent, side effects, and the advantage/disadvantage ratio are compared to other existing agents or methods. All contrast agents used in MR imaging of the liver display their effect by decreasing T1 and T2 relaxation times of liver parenchyma. Gadolinium and manganese containing contrast agents decrease T1 relaxation time significantly, so in T1-weighted sequences liver signal increases. Superparamagnetic iron oxides (SPFO) decrease T2 relaxation time and in T2-weighted sequences liver signal decreases. Ultrasmall superparamagnetic iron oxides (USPFO) decrease T1 and T2 relaxation times, so they can be evaluated in both sequences. The mechanisms of action and clinical characteristics of the contrast agents used in liver MR imaging examinations are shown in Table I. This article describes the pharmacological properties, mechanism of action, main clinical indications, and safety profiles of the contrast agents used in MR imaging of the liver.

Non-specific gadolinium chelates with extracellular distribution

These agents are frequently used in MR imaging examinations of the liver because they are inexpensive, safe, and they can also show other abdominal organ lesions in addition to liver lesions. Today, the gadolinium compounds that have 0.5 M concentration and are often used as extracellular space agents are gadopentate dimeglumine (Gd-DTPA) (Magnevist®, Schering, Germany), gadodiamide (Gd-DTPA-BMA) (Omniscan®, Amersham Health, UK), gadoterate meglumine (Gd-DOTA)

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Table 1. The mechanisms of effect and clinical properties of contrast agents used in liver MR imaging examination

	Non-specific agents	RES-specific agents		Hepatocyte-selective agents	
	Gadolinium chelates	Ferumoxide	Mn-DPDP	Gd-BOPTA	Gd-EOB-DTPA
Target tissue	Intravascular, extracellular space	RES cells	Hepatocyte	Hepatocyte	Hepatocyte
Transport	Blood	Phagocytosis	α_2 macroglobulin	Organic anion	Organic anion
Plasma half-life	10 min	10 min[a]	120 min	15 min	10 min
Elimination route	100% renal	100% iron metabolism	15-25% renal 45-55% biliary	2-4% biliary, 75-99% renal	50% renal 50% biliary
Side effects	Rare flushing	Back pain	Flush, nausea	Flush, nausea	Flush, nausea
Imaging properties	T1 enhancement, perfusion, dynamic examination	T2*, T2, and T1 enhancement	T1 enhancement, uptake unaffected by biliary obstruction	T1 enhancement, uptake decreases by biliary obstruction	T1 enhancement, uptake decreases by biliary obstruction
Indication	Routine, hypervascular lesion	Metastases	Metastases	Metastases	Metastases
Limitations	None	Patients with hemochromatosis	Low specificity, enhancement in hepatic tumors depends on degree of differentiation	Low specificity, enhancement in hepatic tumors depends on degree of differentiation	Low specificity, enhancement in hepatic tumors depends on degree of differentiation

[a] Organ half-life: 1-3 days

Table 2. Extracellular and hepatocyte-selective gadolinium chelates used in liver MR imaging examination

Generic name	Abbreviations	Trademark	Classification	Osmolality (mosmol kg^{-1} l^{-1})	Adult dose[b] (mmol/kg)
Gadopentate dimeglumine	Gd-DTPA	Magnevist®	Ionic-linear	1940	0.1 (bolus)
Gadodiamide	Gd-DTPA-BMA	Omniscan®	Non-ionic-linear	789	0.1-0.3 (bolus)
Gadoterate meglumine	Gd-DOTA	Dotarem®	Ionic-cyclic	1350	0.1 (bolus)
Gadoteridol	Gd-HP-DO3A	ProHance®	Non-ionic-cyclic	630	0.1-0.3 (bolus)
Gadobenate dimeglumine[a]	Gd-BOPTA	MultiHance®	Ionic-linear	1970	0.05 (bolus)
Gadoxetic acid disodium[a]	Gd-EOB-DTPA	Primovist® (Eovist)	Ionic-linear	890	0.025 (bolus)

[a] both extracellular and hepatocyte-selective agents
[b] recommended dose in liver MR imaging examination

(Dotarem®, Guerbet, France), and gadoteridol (Gd-HP-DO3A) (ProHance®, Bracco, Italy). Gadobutrol (Gadovist®, Schering, Germany) in 1 M concentration has not been approved for use in liver parenchymal lesions. Gadobenate dimeglumine (MultiHance®, Bracco), 0.5 M concentration and gadoxetic acid disodium (Gd-EOB-DTPA [Primovist® (Eovist), Schering]), 0.25 M concentration both can show extracellular distribution and hepatocyte accumulation (3). These ionic or non-ionic agents have macrocyclic or linear biochemical structures (Table 2).

Gadolinium chelates work by damaging the high magnetic moment of the seven unpaired electrons in gadolinium (Gd^{+3}), breaking down the relaxation of nearby protons and decreasing both T1 and T2 times. Because they have greater effect in T1, they increase tissue signals in T1-weighted sequences. Their effect on images is most prominent with short TR and TE time spin echo, and short TR and high flip angle gradient echo sequences. The T1 relaxivity values of all present gadolinium chelates are similar to each other and vary from 3.7-4.9 mmol l^{-1} s^{-1}. Because free gadolinium is toxic, it must be in ligand-chelated form. Gadolinium chelates are removed from the kidney 550 times more than non-chelated gadolinium. Following intravenous injection, these agents first spread throughout the blood pool and then they go to extracellular cavities with rapid capillary filtration. Gadolinium contrast agents filtered from glomerules are excreted in urine without any change (more than 95% of the total in one day). In rats, residual gadolinium in macrocyclic agents is found in lower amounts in the body after 14 days (gadoteridol=gadoterate =gadopentate<<gadodiamide) (5). In 50% of tested animals, LD_{50} value is

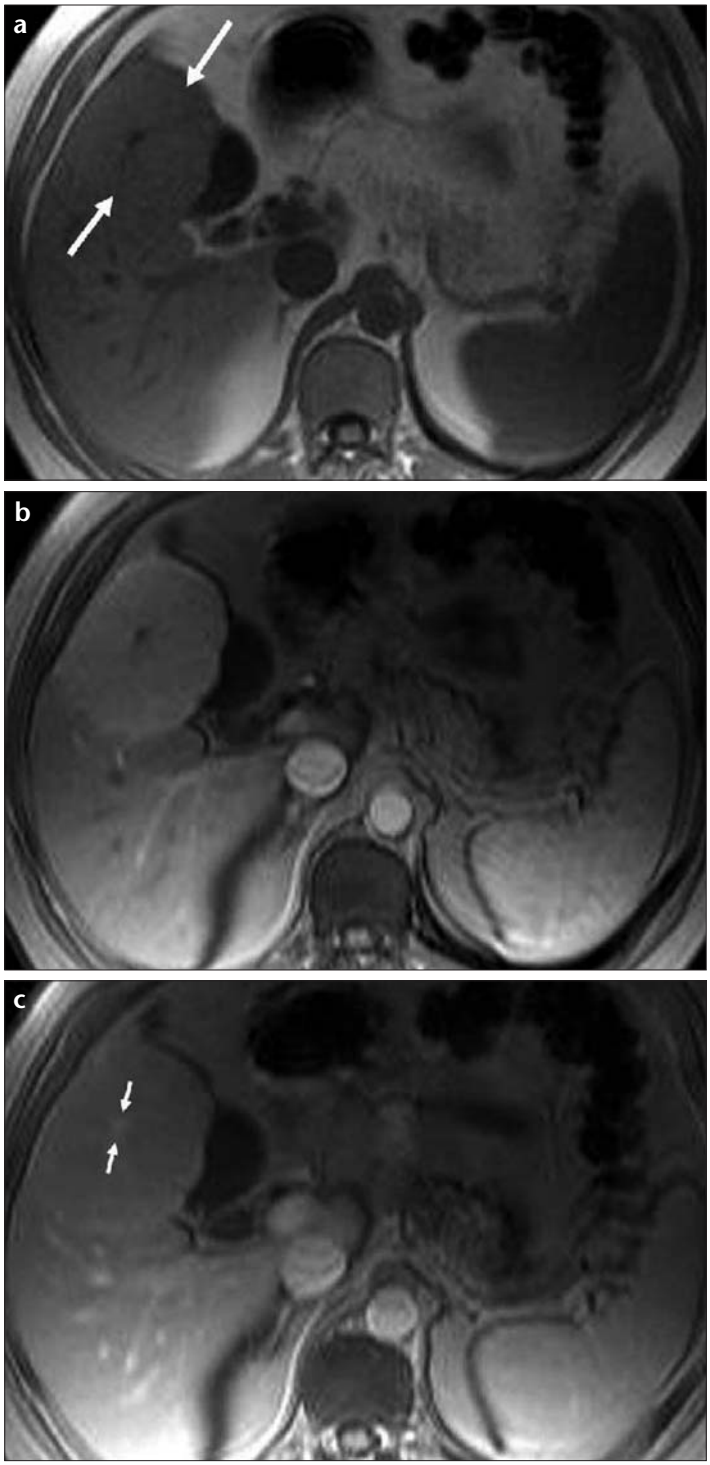

Figure 1. a-c. Focal nodular hyperplasia. **a.** Transverse non-enhanced T1-weighted MR image shows isointense lesion, which has a hyperintense area at the center with lobulated contours in segment V *(arrows)*. **b.** Image taken at 20 seconds after intravenous gadolinium chelate injection shows that the lesion displays homogenous enhancement except for the central scar area. **c.** On the delayed phase image (90 sec), the lesion shows wash-out, whereas the central scar shows enhancement *(arrows)*.

highest (34 mmol/kg) in gadodiamide and is lowest (7 mmol/kg) in gadopentate. As it is 70-300 times the recommended dose, they have no practical importance (3, 4, 6, 7). The side effects of gadolinium chelates are minimal and rare, making them safe for use in children and adults. However, their safety for use during pregnancy has not been proven and they should not be given to pregnant patients. Gadolinium chelates minimally pass into breast milk; therefore, women who are breastfeeding should wait as a precaution 24 hours after injection to breastfeed (3).

Imaging of extracellular cavities is dependent upon enhancement, vascularity by contrast agents (hypo- or hypervascular), and the amount of interstitial space. Contrast agents work in three phases according to their biodistribution. These are arterial, blood pool, and extracellular phases. After rapid bolus injection, these agents quickly pass to the extracellular space; therefore, dynamic examination must be done with T1-weighted two-dimensional [(FLASH, turbo FLASH, Siemens), (SPGR, General Electrics), (TFE, FFE, Philips)] or three-dimensional [(VBE, Siemens), (FAME, General Electrics)] spoiled gradient echo sequences. After the contrast agent is injected, the liver is imaged in the hepatic artery (18-20 sec delayed), portal vein (45-60 sec), and interstitial (90 sec-5 min) phases, and it can be characterized by the enhancement patterns at these phases, the differences between the degree and duration of enhancement and wash-out. During the hepatic arterial dominant phase, cysts do not show enhancement, hemangiomas show nodular peripheral enhancement, adenomas (Figure 1) and focal nodular hyperplasia (FNH) show intense uniform enhancement (Figure 2), metastases show ring enhancement, and hepatocellular carcinomas (HCC) show diffuse heterogeneous enhancement. In the portal venous phase, liver signals are very high and hypovascular metastases can be observed clearly; also the status of liver veins can be evaluated. In the late interstitial phase, hemangiomas show centripedal enhancement, adenomas and FNH rapidly wash-out and appear isointense, and FNH scars are enhanced. During this phase, liver metastases show peripheral wash-out and hepatocellular carcinomas show heterogeneous wash-out and delayed capsular enhancement. Although fibrous tissues are hypovascular, they hold contrast well in the late phase because they have large interstitial gaps. Moreover, many metastases can be seen as hyperintense in the extracellular phase because of having large interstitial gaps.

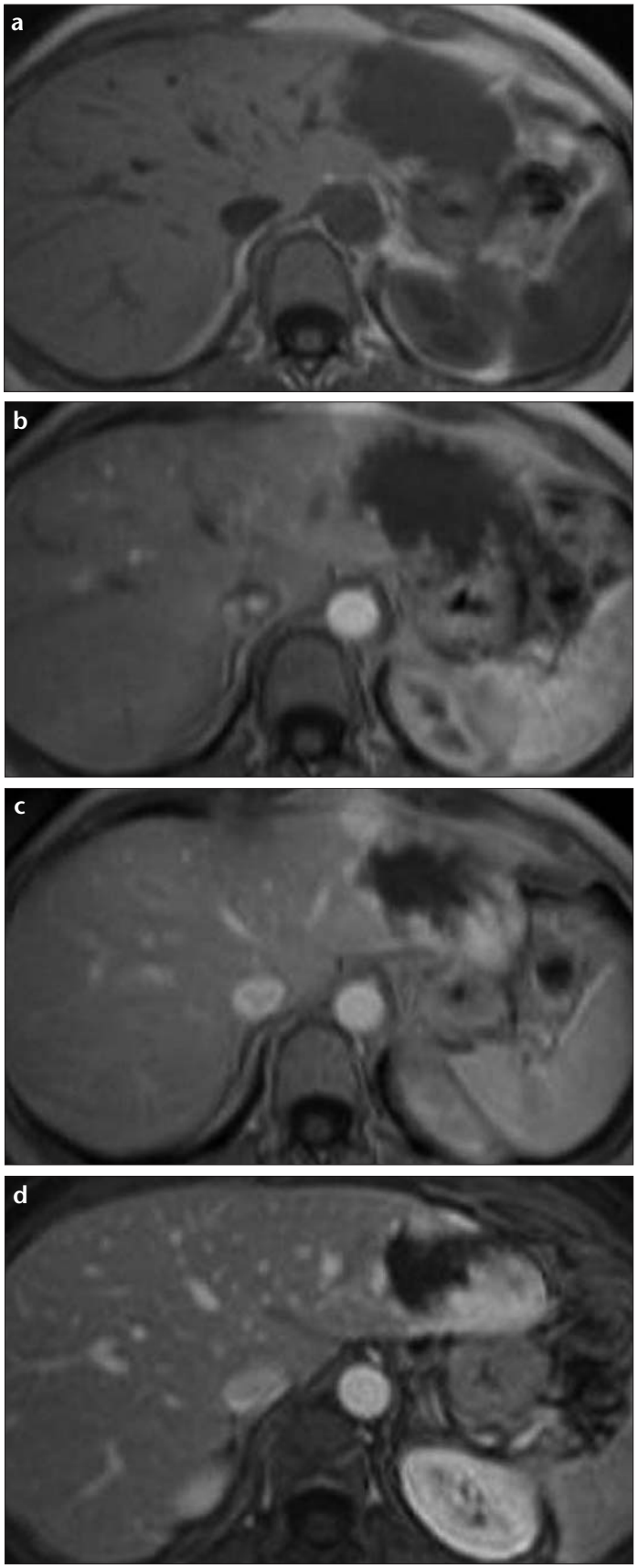

Figure 2. a-d. Cavernous hemangioma. **a.** Transverse non-enhanced T1-weighted MR image shows a hypointense lesion in hepatic segment II. **b.** Peripheral nodular enhancement in the arterial phase is seen after intravenous gadolinium chelate injection. Centripedal enhancement is seen on portal **(c)** and delayed **(d)** phase images.

Hepatocyte-selective contrast agents

These agents are taken up by hepatocytes and eliminated through bile. Since these agents have a clear effect on T1 relaxation time, normal liver and focal liver lesions containing hepatocytes are seen as hyperintense on T1-weighted images, whereas hepatocyte-free lesions are seen as hypointense (4, 8, 9). The only hepatocyte-selective contrast agent that has been approved for clinical use is mangafodipir trisodium (Mn-DPDP), whereas Gd-DTPA and Gd-EOB-DTPA are contrast agents that are both hepatocyte-selective and show extracellular distribution. The R1 values of these agents in the liver are 21.7 mmol l^{-1} s^{-1} for Mn-DPDP, 30 mmol l^{-1} s^{-1} for Gd-BOPTA, and 16 mmol l^{-1} s^{-1} for Gd-EOB-DTPA (4).

Mangafodipir trisodium (Mn-DPDP)

Mn-DPDP is a chelate that is formed by binding to a ligand (fodipir, DPDP) in order to reduce the toxic effect of manganese ion (Mn^{+2})(Teslascan®, Amersham Health, UK). This chelate has a net electrical charge of -3 (Mn^{+2}, $DPDP^{-5}$) and this effect is balanced by three sodium ions having +1 charge. It is available as two different preparations: its USA form has a concentration of 0.05 mol/l and is injected in 1-2 minutes, while the 0.01 mol/l form, which is administered with a 10-15-minute infusion, is used in Europe. Due to its five unpaired electrons, manganese has a strong paramagnetic effect and it increases the tissue signals in T1-weighted images by shortening the T1 relaxation time of the hepatocytes. The R1 values in liquid solutions are similar to the other gadolinium chelates (2.8 mmol l^{-1} s^{-1}), whereas R1 values in the liver are higher (21.7 mmol l^{-1} s^{-1}) because it is taken up by hepatocytes. The recommended dose is 5 µmol/kg (0.1 mL/kg). Probably because of a similarity to vitamin B, it is thought that Mn-DPDP attaches to α_2 (macroglobulin) and is then taken up by liver cells (4, 9). Mn-DPDP is metabolized by losing its phosphorus (dephosphorilation) and by transmetalation with zinc. Between 15 minutes and 4 hours after its injection, manganese, which has a strong paramagnetic effect, accumulates in hepatocytes and causes an increase in signals on T1-weighted images of the liver. Furthermore, it also shows the difference between the liver and such lesions as non-enhancing hemangiomas,

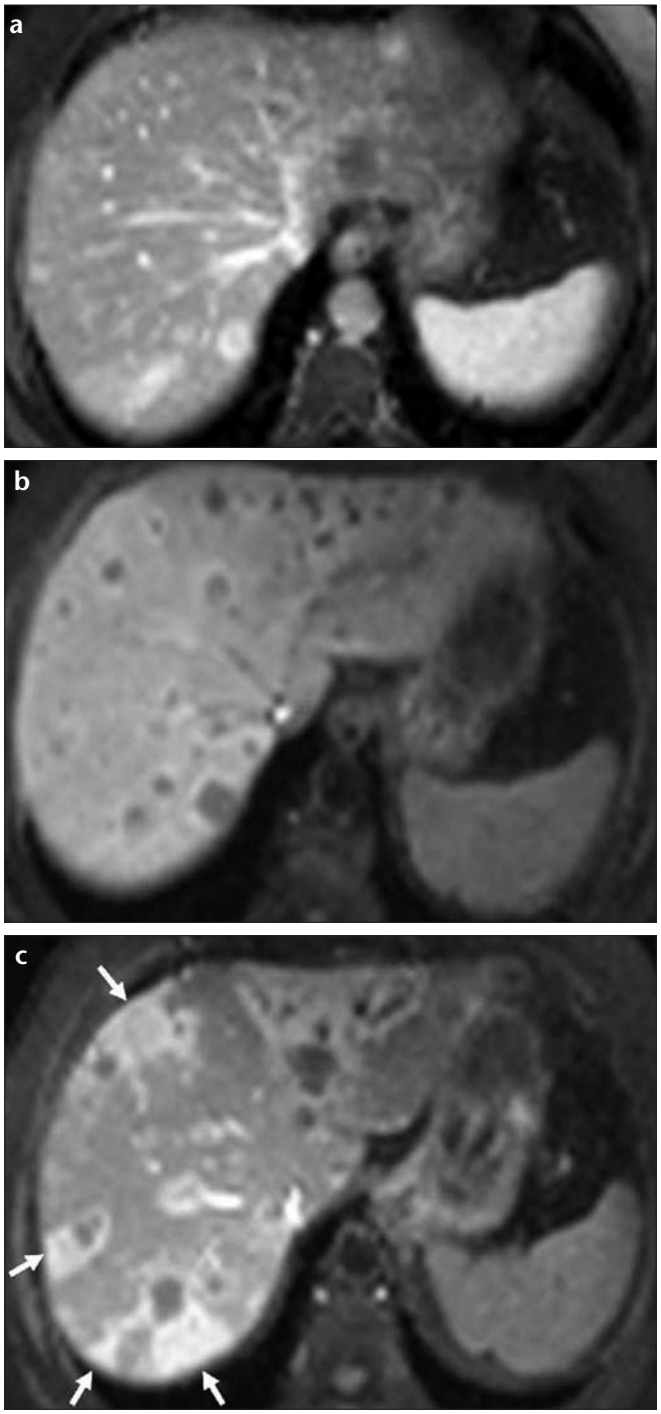

Figure 3. a-c. Liver metastases in pancreas carcinoma. **a.** Diffused hypervascular lesions in the liver on the delayed phase MR image taken after intravenous gadolinium chelate injection. **b.** The number of metastases, which were peripherally hyperintense and centrally hypointense, increase on the image taken from a similar level 20 minutes after intravenous mangafodipir trisodium injection. **c.** On the image taken 24 hours after contrast injection, peripheral, triangular areas *(arrows)* occured besides the hypointense metastases secondary to delayed wash-out of contrast from hepatocytes, which is probably due to functional biliary obstruction.

metastases, intrahepatic cholangiocarcinomas, and lymphomas. In metastases, especially on images taken after 24 hours, clearly observable ring-shaped peripheral enhancement is common (Figure 3). This enhancement is probably caused by its accumulation in the neighboring liver tissue or proliferation in the bile duct. Functional biliary blockage secondary to metastases also decreases the removal of contrast agent from hepatocytes and may lead to triangular-shaped enhancement (Figure 3). Because they contain hepatocytes, well-differentiated hepatocellular carcinomas, adenomas, FNH, and regeneration nodules take up Mn-DPDP (10, 11). Therefore, while Mn-DPDP is successful in imaging focal liver lesions, it has a limited ability to differentiate these lesions (11). The most important role of Mn-DPDP is to determine the number of colorectal metastases in patients who will have surgery to remove them (4, 8, 12). It can be used for showing the functions of hepatocytes and the entirety of the bile ducts (13). In cirrhotic livers, there is heterogenous opacification and decreased fibrous enhancement. In a meta-analysis, more lesions were determined in post-manganese MR images of livers both with (*n*=137) and without (*n*=480) cirrhosis than in pre-constant images (14). Mn-DPDP is not only specific to the liver and hepatocellular tumor imaging, it is also taken up by the pancreas, kidneys, adrenal glands, heart muscles, and liver metastases of endocrine-originated tumors (15). Differing from the use of non-specific extracellular gadolinium chelates, high Tesla power and breath holding are not necessary for MR examinations when Mn-DPDP is used. For obtaining high-resolution images with this agent, spoiled gradient echo sequences are very useful. This agent can be tolerated well and the more common side effects are headache, nausea, and itching (12, 16). In humans, approximately 12-25% of the administered Mn-DPDP is eliminated in urine, and 47-59% is eliminated in feces (4, 8).

Hepatobiliary gadolinium chelates (both extracellular and hepatocyte-selective contrast agents)

Differing from other extracellular contrast agents with gadolinium, which are eliminated with glomerular filtration, liver-selective gadolinium chelates can be eliminated in urine and bile because they have a chain that carries a benzene circle in their structure and this causes them to connect to anion-carrying proteins in hepatocytes. In this way, similar to other gadolinium chelates, it is useful for the evaluation of liver perfusion in the early phase and determining if lesions contain hepatocytes in the late phase. Paramagnetic hepa-

tobiliary agents made for this target are gadobenate dimeglumine (Gd-DTPA) (MultiHance®, Bracco, Italy) and gadoxetic acid disodium (Gd-EOB-DTPA, [Primovist® (Evoist), Schering, Germany]). By imaging the liver in different phases with dynamic examination in the early phase following bolus injection, lesions can be detected and characterized. For a relatively long time-period following injection (for Gd-DTPA, 40-120 min; for Gd-EOB-DTPA, 15-20 min), these chelates are held by normal functioning hepatocytes and cause prolonged opacification of the normal liver parenchyma (3, 8, 11). Thus, tumor cells in the liver without normal hepatocytes will not take up contrast and can be observed as hypointense.

In all European countries, the use of gadobenate dimeglumine (Gd-DTPA) in the liver and central nervous system has been approved and according to published research, it was shown that Gd-DTPA is useful for detecting and characterizing liver tumors (17). The liver takes up 2-4% of injected Gd-DTPA. This agent is also suitable for MR angiography because of its low and temporary capacity to bind to protein. In liver imaging, the recommended dose is 0.05 mmol/kg (0.1 mL/kg, 0.5 M solution); furthermore, the contrast agent must be given undiluted, and then physiological saline must be administered.

The use of gadoxetic acid disodium (Gd-EOB-DTPA) in the liver is approved in many countries. It is eliminated by the urinary and biliary systems (42-51% and 43-53% of the total, respectively), while 2-4% of it is eliminated through the enterohepatic system (18). Because of its high protein binding percentage (approximately 10%), its T1 relaxivity in plasma is more than that of Gd-DTPA (R1= 8.7 $mmol^{-1}$ s^{-1}). Moreover, it is excreted from the biliary system more efficiently than Gd-DTPA, so it is also possible to do contrast-enhanced MR cholangiography. In liver imaging, the recommended dose is 0.025 mmol/kg (0.1 ml/kg, 0.25 M solution).

The safety profile of gadobenate dimeglumin (Gd-DTPA) for adults is quite good, but its safety and efficiacy has not been proven for those younger than 18 years old; therefore, it is contraindicated for this age group. According to a multi-centered study of 162 patients, which examined gadoxetic acid disodium's (Gd-EOB-DTPA) safety profile in humans (18), minor side effects were reported in 7% of the patients and no serious side effects were detected.

Reticuloendothelial system-specific contrast agents

RES-specific contrast agents are those that contain iron oxide particles, and they affect RES cells, receptors in cell walls or blood pool. Superparamagnetic iron oxide (SPFO) particles are taken up by macrophage-monocytic system cells in the liver, spleen, and bone marrow, leading to signal loss in T2*- and T2-weighted sequences (8, 11, 19-21). Following intravenous injection, the largest portion (approximately 80% of the injected dose) of SPFO particles is taken up by the liver, whereas 5-10% is taken up by the spleen (19, 22).

There are two groups of iron oxide particles that have clinical approval whose Phase III studies are continuing. These agents are studied in two groups: superparamagnetic iron oxides (SPFO), which have particle diameters larger than 50 nm, and ultrasmall superparamagnetic iron oxides (USPFO), which have particle diameters smaller than 50 nm (11, 19). SPFO agents have manifest T2 relaxivity (R2/R1 high) and a short blood half-life. In this group there are two different iron oxide (SPFO) preparations: ferumoxide (AMI-25) (Endorem®, Guerbet, France; Feridex®, Berlex, Canada) and ferucarbotran (SHU 555A) (Resovist®, Schering, Germany). USPFO agents have both T1- and T2-relaxivities (R2/R1 low) and their plasma half-life is long. Ferumoxtran, which is also in this group, is in ongoing Phase III studies. It can be used in imaging of lymph nodes and MR angiography.

Ferumoxide is a clinically approved SPFO and its preparation concentration in Europe is 22.4 mg iron/ml. SPFO particles, which encase the 3-5 nm diameter iron oxide nuclei, are made up of the low-weight molecule dextran [Ferumoxide (AMI-25)] or carboxydextran [ferucarbotran (SHU 555A)]. The particle size, material surrounding the nucleus, and electrical charge at the surface affect the pharmacodynamic and clinical characteristics of the agents. Small pieces can remain in plasma for a long time and accumulate in macrophages at RES, whereas bigger particles have a short blood half-life and accumulate more often in the liver (19, 22). Ferumoxide (AMI-25) has an 80-150 nm diameter and its plasma half-life is 8 minutes. Ferucarbotran (SHU 555A) has a smaller diameter (62 nm) and it has a similar blood half-life. The relaxivity values and recommended doses of these agents are summarized in Table 3. Ferumoxide is administered with slow infusion lasting at least 30 minutes diluted in 100 ml of 5% isotonic glucose solution. It

Table 3. Superparamagnetic iron oxides used in liver MR examination and RES-specific contrast agents

Contrast agents	Classification	Generic name	Trademark	Effect mechanism	R_2/R_1 $mmol\ l^{-1}s^{-1}$	Length (nm)	Dose	Current state
AMI-25	SPFO	Ferumoxide	Feridex® Endorem®	T2* and T2 ↓ low T1 ↓	98/24	80-150	15 µmolFe/kg, Infusion[a]	Approved
SHU 555A	SPFO	Ferucarbotran	Resovist®	T2* and T2 ↓ medium T1 ↓	151/25	62	8 µmolFe/kg, Bolus	Phase III completed
AMI-227	USPFO	Ferumoxtran	Sinerem® Combidex®	T2* and T2 ↓ T1 ↓	44/21	11	14-45 µmolFe/kg, Slow infusion	During Phase III

[a]100ml in 5% glucose with 30 min infusion

R_1: T1 relaxivity, R_2: T2 relaxivity
SPFO: Superparamagnetic iron oxide
RES: reticuloendothelial system
USPFO: Ultra small superparamagnetic iron oxide

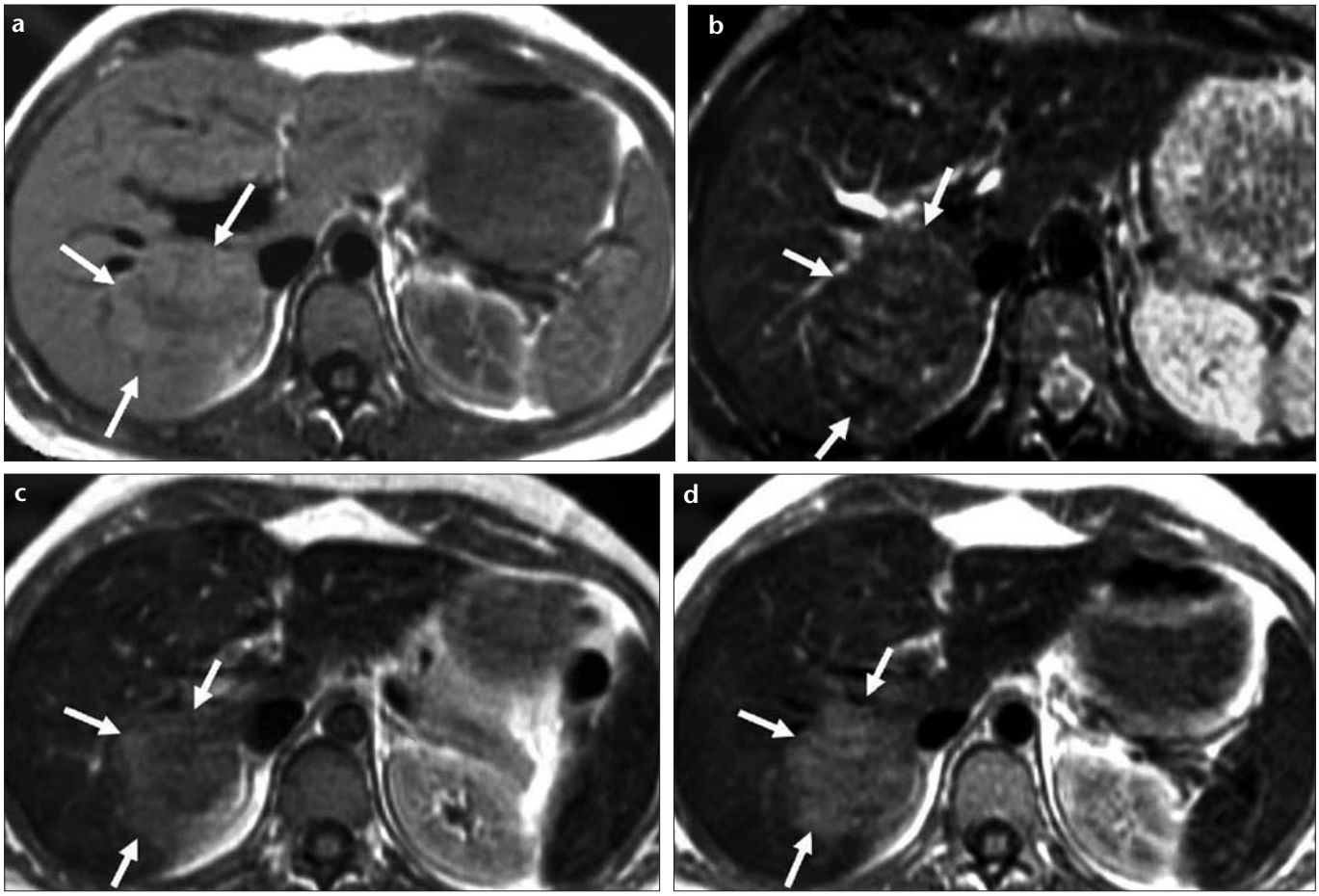

Figure 4. a-d. Hepatic adenoma. **a.** Transverse non-enhanced T1-weighted MR image shows a lesion, which is minimally hyperintense compared to the liver with barely recognizable borders in the right lobe posterior segment of the liver *(arrows)*. **b.** Transverse T2-weighted MR image reveals the hyperintense nature of the lesion compared to the liver *(arrows)*. At images taken 6 hours **(c)** and 24 hours **(d)** after superparamagnetic iron oxide injection, it is shown that liver and spleen signals decreased significantly, lesion-tissue contrast increased, and borders of the lesion became more recognizable *(arrows)*.

has a long imaging time and T2*- and T2-weighted sequences can be taken 30 min-6 hours after the infusion (liver concentration is highest at the second hour) (23). The contraindication of ferumoxide (AMI-25) is dextran allergy and it must be used carefully in patients who have hemosiderosis or hemochromatosis. Most frequent side effects are low back pain (4%), flushing (2%), and dyspnea. In these patients it is suggested that the infusion rate be decreased, or stopped and restarted after the low back pain subsides (8, 19, 22). Ferucarbotran (SHU 555A) does not have side effects like low back pain and it can be given as a bolus injection. It can be used in dynamic T1-weighted MR imaging examinations and MR angiography because it has small particle size, strong T1 relaxivity and it can be administered as a bolus injection.

Particles that are taken up by normal RES Kuppfer cells and normal liver parenchyma are seen as hypointense in T2*- and T2-weighted sequences. In addition to pathologic conditions (metastases), a high percent of hepatocytes without healthy RES cells are seen as hyperintense because they maintain the signals (Figure 4). FNH, adenoma, and rarely, well-differentiated hepatocellular carcinoma may demonstrate SPFO uptake (24). Although hemangiomas do not contain Kuppfer cells, hemangiomas can take up iron oxide between distribution phase and retention phase images. Dynamic studies with gadolinium can be done following SPFO (Figure 5). Because of its T1 effect, lesion characterization (hypervascular lesions, hyperintense) can be done with bolus injection of ferucarbotran (SHU 555A) by dynamic examination, similar to gadolinium chelates (25). In the retention phase, liver vessels are prominently seen as hyperintense so their patency can be evaluated. It was shown that in the detection of liver lesions, MR images following SPFO are superior to non-enhanced T1- and T2-weighted images and enhanced helical CT (26). Furthermore, experimental studies have shown that MR images taken after SPFO might be useful in assessing hepatic function via observation of the degree of phagocytosis of SPFO in the liver (27). Additionally, it was shown that the uptake of SPFO decreases in acute rejection of transplanted livers and in liver injury caused by irradiation (27, 28).

The half-life of iron is 3 days in the liver and 4 days in the spleen. SPFO particles change into the non-super paramagnetic form of iron by being metabolized and are added to the body iron pool (ferritin, hemosiderin, and hemoglobin) within a few days. The total iron amount for a single dose is not more than the 2% of total body iron.

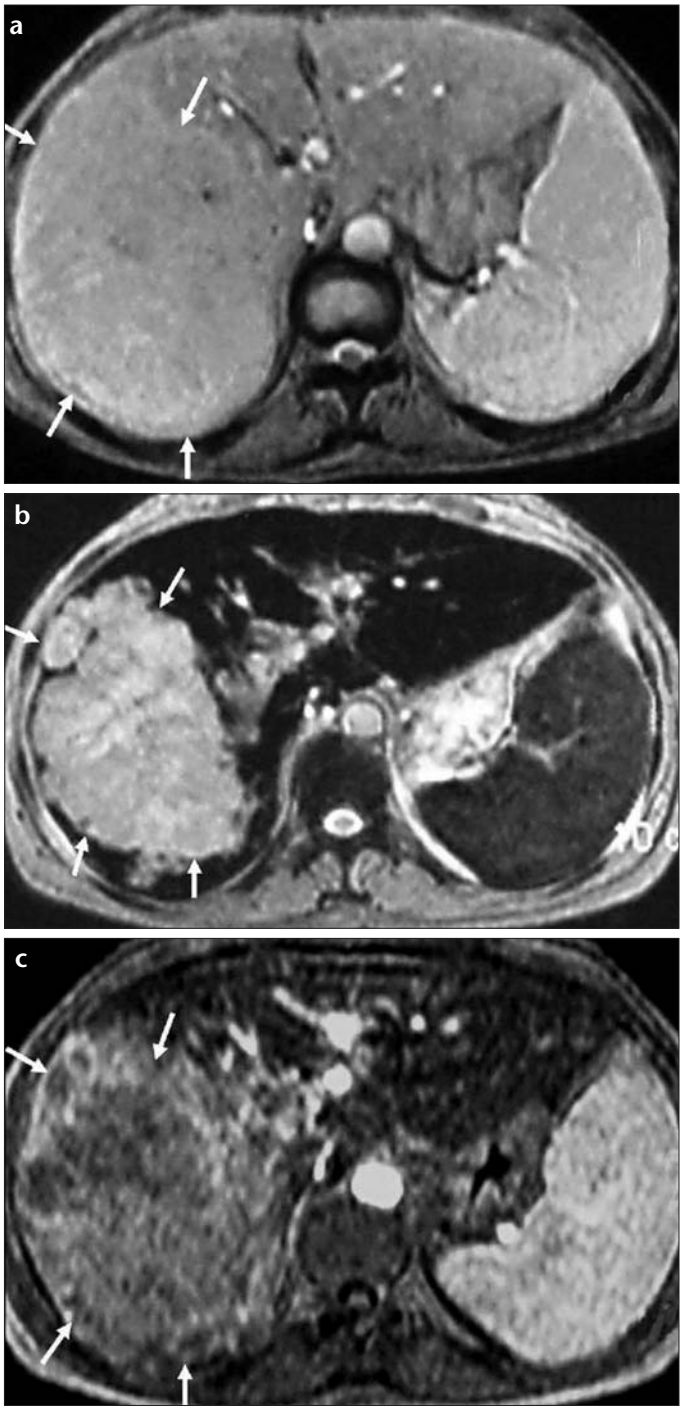

Figure 5. a-c. Hepatocellular carcinoma. **a.** Transverse T2-weighted MR image shows a slightly hyperintense lesion in the right lobe with barely recognizable borders *(arrows)*. **b.** After superparamagnetic iron oxide injection, the boundaries of the lesion become more recognizable *(arrows)* due to an increase in lesion-tissue contrast. **c.** On T1-weighted gradient echo image in the delayed arterial phase taken after gadolinium injection, which was administered nearly 40 minutes after superparamagnetic iron oxide injection, a decrease in the liver signal and diffused enhancement in the lesion at the right lobe *(arrows)* are shown *(courtesy of Devrim Akıncı, MD)*.

When should each contrast agent be used?

It is reported that enhanced MR imaging is superior to non-enhanced MR imaging and enhanced helical CT in the detection and characterization (i. e., benign or malign) of liver lesions (3-9, 17, 18, 26). The non-specific extracellular gadolinium chelates must be the first choice of contrast agent in routine MR examination of the liver because they are inexpensive, provide information about abdominal organ disease other than the liver, and they have virtually no side effects. These agents are more effective than cell-specific agents in the detection and characterization of hypervascular lesions like HCC. However, these lesions are supplied by the hepatic artery so that during dynamic gadolinium examinations they are hyperintense, with rapid enhancement in the hepatic arterial phase, and they show washout and are hypointense or isointense, with respect to liver parenchyma, in the portal phase. On the other hand, in patients with cirrhosis, normal hepatocytes and Kuppfer cells activities decrease so that contrast agent uptake by the liver decreases and the detection of hepatic lesions may become more difficult (26). As the hepatocyte-selective and RES-specific contrast agents are more effective in the detection of hypovascular lesions, these agents should be preferred for the determination of the number of metastases when planning surgical resection (26, 29). According to a study in which the effectiveness of Mn-DPDP and SPFO in the detection and characterization of liver lesions were compared, it was shown that SPFO was superior in the detection of small lesions and Mn-DPDP was superior in differentiating lesions that were hepatocellular in origin (30). No significant difference was found between these two contrast agents in the detection of lesions having diameters greater than 15 mm and in the differentiation of benign versus malign lesions. After the liver is studied with SPFO, dynamic examination (double contrast MR examination) can be done with gadolinium (31, 32). When double contrast MR imaging is performed for the detection of HCC in patients with cirrhosis, the sensitivity of MR investigation for all lesions is 78% and 92% for lesions larger than 11 mm if hypovascular lesions and/or lesions that do not uptake iron oxide are considered as HCCs (32). Hepatocyte-selective gadolinium chelates are useful in the detection and characterization of lesions because dynamic investigation in the early phase and hepatocyte-specific investigation at the delayed phase are both possible (33). In another study, the same au-

thors compared the effectiveness of Gd-DTPA and SPFO in the detection of liver lesions. It was shown that the sensitivity of metastasis detection and the diagonal confidence in the delayed phase images taken after Gd-DTPA and SPFO injection were similar, whereas Gd-DTPA was more successful in the detection of HCC (33-35). Consequently, characterization of liver lesions in the early (dynamic) phase and their detection in the delayed phase can be done by hepatocyte-selective gadolinium chelates. In another similar study done by another group of authors, it was shown that the sensitivity of MR imaging with iron oxide in the demonstration of liver metastases confirmed by intraoperative ultrasonography was 97%, whereas the sensitivity of MR imaging with Gd-DTPA was 54% in the dynamic phase and 81% in the delayed phase.

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