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Abstract

► Despite the excellent soft tissue contrast provided by plain MRI, the use of intravascular contrast agents is often performed in a variety of clinical settings being an instrumental component of many MR studies. Several compounds have been developed for contrast-enhanced MR imaging of the abdomen, with the purpose of increasing tumor detection and differentiation between normal and pathological tissues. MR contrast agents can be divided according to their magnetic properties into paramagnetic and superparamagnetic agents. They are also classified as interstitial, nonspecific, or liver-specific contrast media, with the latter subdivided according to their target-cell population: hepatocyte-selective or Kupffer cell contrast agents.

► A review of their main characteristics including physicochemical properties, pharmacokinetics, and safety profile is performed under the scope of this chapter. For each class of contrast media, suggested imaging protocols and current clinical indications are also provided for the typical setting of 1.5T magnets. Main imaging findings and diagnostic information obtained with these agents is provided for comparing accuracy with other imaging techniques or modalities. Pitfalls, limitations, and future directions are also addressed in order to keep the reader fully aware of their current clinical spectrum.

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2.1 Introduction

The differentiation between normal and diseased tissue by means of magnetic resonance (MR) imaging relies on their distinctive signal intensity (SI) which depends, among other factors, on intrinsic properties of tissue (T1 and T2 relaxation times). However, the relaxation times of normal and abnormal tissues frequently overlap. As a consequence, the ability of plain MR imaging to detect and to characterize abnormal tissue may be compromised. This shortcoming is, however, overcome by applying specialized pulse sequences, or instead by using MR contrast agents, substances which change the tissue relaxation times and can, therefore, be administered in order to manipulate their signal intensity. In clinical practice, contrast media with paramagnetic or superparamagnetic properties are used to shorten the T1 and T2 relaxation times. In abdominal MR imaging, several different classes of contrast agents are available for routine clinical use. These include non-specific media that distribute extracellularly in a manner similar to that of the iodinated agents used in computed tomography (CT), materials that are taken up specifically by hepatocytes and partly excreted into the biliary system, and agents that are targeted specifically to the Kupffer cells of the reticuloendothelial system (RES) in the liver or the macrophages in the lymph nodes. The differential use of these agents, depending on the clinical setting, can improve the diagnostic information available to the radiologist and help to solve several diagnostic dilemmas.

2.2 Paramagnetic Agents

2.2.1 History

Chelates of the paramagnetic ion gadolinium (Gd) that distribute solely to the extracellular space (i.e., do not have any tissue-specific biodistribution) have been commercially available since 1986 [1]. A variety of these compounds are produced with different binding complexes that behave similarly. The prototypical complex of this class of agents is gadopentetate dimeglumine (Magnevist®, Gd-DTPA; Schering AG), which was the first MR contrast agent introduced into the market [2]. Other Gd-chelates include gadoteridol (ProHance®, Gd-HP-DO3A; Bracco Diagnostics), gadodiamide

(Omniscan®, Gd-DTPA-BMA; GE Healthcare) gadoversetamide (Optimark®, Gd-DTPA-BMEA; Mallinckrodt), gadoterate meglumine (Dotarem®, Gd-DOTA; Guerbet), gadobutrol (Gadovist®, Gd-BT-DO3A; Schering AG), and gadofosveset (Vasovist®, Schering AG).

In 1998, a combined extracellular and hepatobiliary medium, gadobenate dimeglumine (MultiHance®, Gd-BOPTA; Bracco Diagnostics) has been approved in Europe for MRI of the liver. Another agent with combined extracellular and hepatobiliary properties, gadoxetic acid disodium, or gadolinium-ethoxybenzyl diethylenetriaminepentaacetic acid (Primovist®, Gd-EOB-DTPA; Schering AG), has been approved for use in Europe, albeit at a formulation of only 0.25 mol/L and at a dose of 0.025 mmol/kg body weight [3, 4].

A dedicated hepatocyte-selective contrast agent is mangafodipir trisodium (Teslascan®, Mn-DPDP; GE Healthcare), which was approved for clinical use in 1997 [5–7].

2.2.2 Physicochemical Properties

Paramagnetism arises in atoms that have unpaired electrons. Placed in an external magnetic field, these atoms show a significant net magnetization because of the preferential orientation of the paramagnetic dipole moments parallel to the applied magnetic field; its magnitude is proportional to the magnitude of the external magnetic field. The most important chemical subgroup of paramagnetic compounds are metal ions (e.g., Mn^{2+}) and lanthanide elements, such as Gd, one of the strongest paramagnetic substances known since it has seven unpaired electrons. Paramagnetic agents cause shortening of both the T1-relaxation time and – at higher tissue concentrations – the T2-relaxation time [2].

Because of its strong paramagnetic effect, Gd is the base for all available extracellular MR contrast agents. Due to the high toxicity of free Gd in vivo, it needs to be bound to ligands, resulting in highly hydrophilic Gd-chelate complexes.

Gd-BOPTA is an octadentate chelate of Gd. It possesses higher relaxivity than equimolar formulations of other extracellular contrast agents, because of its more lipophilic structure [8]. Its contrast-effective moiety interacts weakly and transiently with serum albumin. As a consequence, a T1 relaxivity in human

plasma that is approximately twice that of the conventional gadolinium agents is achieved [9]. This substance differs from the purely extracellular Gd agents as it combines the properties of a conventional non-specific Gd medium with those of an agent targeted specifically to the hepatocytes [6].

Gd-EOB-DTPA is a paramagnetic hepatobiliary contrast agent with hepatocellular uptake by the anionic-transporter protein [10]. It has higher T1-relaxivity in human plasma than Gd-BOPTA, a fact possibly explained by the greater degree of protein binding. Like Gd-BOPTA, Gd-EOB-DTPA has a higher T1 relaxivity compared to the conventional extracellular agents and distributes initially to the vascular and interstitial compartment after bolus injection [4].

Mn-DPDP is an anionic manganese chelate that dissociates rapidly following administration, yielding free Mn^{2+} ion [11].

Some physicochemical properties of the main paramagnetic contrast agents are summarized in Table 2.1.

2.2.3 Pharmacokinetics

While Gd is responsible for the paramagnetic effect of complexes, the ligand determines the pharmacokinetic behavior. Due to the high hydrophilicity and low molecular weight of the Gd-chelates, they diffuse rapidly into the interstitial space after intravenous injection. The protein binding is negligible. The elimination of the unmetabolized Gd complexes from the body occurs via renal excretion with a plasma half-life of about 90 min. The compounds are completely eliminated after a maximum of 24 h if the glomerular filtration rate is not diminished, but the half-life is prolonged in patients with impaired renal function [2].

Gd-BOPTA differs from other available Gd-chelates in that it distributes not only to the extracellular fluid space, but is selectively taken up by functioning hepatocytes and excreted into the bile by the canalicular multispecific organic anion transporter that is used to eliminate bilirubin [12, 13]. Unlike the conventional agents, approximately 3–5% of the injected dose of Gd-BOPTA is taken up by functioning hepatocytes and ultimately excreted via the biliary system. As a result, the normal liver parenchyma shows strong enhancement on delayed T1-weighted (T1-w) images that is maximal approximately 1 h after injection [13]. As with other Gd compounds, Gd-BOPTA is mainly eliminated by the kidneys.

Gd-EOB-DTPA provides a triphasic pharmacokinetic profile similar to that of Gd-BOPTA. The lipophilic side chain EOB produces a high affinity to the organic anion transporter system, which is also responsible for the uptake of Gd-BOPTA. After intravenous bolus injection, Gd-EOB-DTPA is rapidly cleared from the intravascular space to the extracellular space; from here the compound is both taken up by hepatocytes and eliminated by glomerular filtration [11].

Whereas only 3–5% of the injected dose of Gd-BOPTA is taken up by hepatocytes and eliminated in the bile, in the case of Gd-EOB-DTPA 50% of the injected dose is taken up and eliminated via the hepatobiliary pathway after approximately 60 min [3]. The maximum increase of SI of liver parenchyma is observed approximately 20 min after injection and lasts for approximately 2 h [3, 14]. In contrast to Gd-BOPTA, urinary filtration and fecal excretion by way of bile account for approximately equal portions of the administered dose. Although the degree of renal elimination augments with increasing doses, its hepatic clearance reveals a moderate saturation phenomenon in higher doses [11].

Regarding Mn-DPDP, after in vivo dissociation of the largest portion of the Mn-DPDP complex into free Mn^{2+} and DPDP, the free ion is taken up by hepatocytes, whereas a transmetallation with Zn^{2+} could be shown for DPDP. By another specific carrier mechanism, some of the remaining Mn-DPDP complex is also taken up by the hepatocytes and shows intracellular dissociation. Whereas DPDP and the still complete Mn-DPDP complex (15–20%) are renally eliminated within 24 h, free Mn^{2+} remains in the body for several days and accumulates not only in the liver but to a lesser extent in the pancreas, gastric mucosa, adrenal glands, and some intracerebral structures before it is eliminated by bile or urine. The half-life, therefore, is not clearly determined [2].

Table 2.1 Physicochemical properties of Gd-based contrast agents

	Osmolality (Osm/kg)	Viscosity (MPa/s)	Relaxivities at 1.5T (mM/s)	
			R1	R2
Gd-DTPA	1.96	2.9	3.9	5.3
Gd-BOPTA	1.97	5.3	6.3	8.7
Gd-EOB-DTPA	0.69	1.19	6.9	8.7
Mn-DPDP	0.30	0.8	3.6	7.1

2.2.4 Safety

Overall, this class of contrast media is the safest compared with other contrast agents, with an incidence of adverse reactions of 1–2%, mostly mild and transient. This incidence may be about two to three times higher in patients with a history of allergies or with asthma [2]. Most of the Gd-chelates result in minor changes in the serum iron and bilirubin levels and demonstrate passage across the placenta and excretion into the breast milk [15]. This occurs within 24 h of injection; therefore, the administration of Gd-chelates during pregnancy or breast-feeding is generally not recommended, but they can be used in selected cases according to clinical indication [11]. The most relevant adverse reaction which may occur after intravenous injection of Gd compounds is an anaphylactoid reaction. The incidence of anaphylactoid reactions is about six times lower than with non-ionic X-ray contrast agents. As far as it is known, there is no relationship between adverse reactions and doses of up to at least 0.3 mmol/kg of body weight [2].

Although the safety profiles of these agents are all extremely attractive, especially in comparison to iodinated x-ray contrast agents [16, 17], possible problems associated with the least stable of these agents (gadodiamide and gadoversetamide) have recently come to light [16]. Both, but none of the other approved Gd agents, have been shown to cause spurious hypocalcemia as a result of interference with laboratory tests for serum calcium [16, 18].

Other adverse events after intravenous injection of Gd-chelates include nausea and vomiting, warmth and pain at the injection site, headache, paresthesia, dizziness, urticaria/allergy-like skin reaction, and focal convulsion [2].

Both Gd-BOPTA [12] and Gd-EOB-DTPA have a safety profile that is not dissimilar from those of the conventional extracellular Gd agents [3, 4]. The most frequently reported symptoms of adverse effects were nausea, vasodilatation, headache, taste perversion, and injection site pain [4].

All Gd-based agents increase the risk of nephrogenic systemic fibrosis (NSF) in patients with acute or chronic severe renal failure (glomerular filtration rate < 30 mL/min/1.73 m²) and in patients with acute renal insufficiency of any severity due to hepatorenal syndrome or in the perioperative liver transplantation period. Extensive literature on NSF has been published in the last years and may be consulted for in-depth information [19].

As with Gd-chelates, Mn-DPDP is considered to have an acceptable safety profile although injection-related minor adverse events such as flushing, nausea and dizziness are relatively common [6, 20]. However, these symptoms are transient and of mild intensity and affect the patient's well-being but do not raise a true safety concern. Some authors performed a fast injection while administering this agent, which potentially increases the incidence of adverse events. Moreover, this contrast dissociates rapidly following administration to yield free Mn²⁺ ions, which may be associated with increased neurological risk in patients with hepatic impairment [21]. Nevertheless, serious side effects have not been described with this substance [6].

2.2.5 Imaging Protocols

As paramagnetic compounds, Gd-chelates shorten T1 tissue relaxation times when injected intravenously. At recommended doses of 0.1–0.3 mmol/kg their main effect is to shorten the T1 relaxation time resulting in higher SI of tissue, which is best demonstrated on heavily T1-w images [22]. Due to rapid redistribution of Gd-chelates from the intravascular compartment to the extracellular space, these contrast agents must be administered as a rapid intravenous bolus at a dose of 0.1 mmol/kg (0.2 mL/kg) bodyweight and at a flow rate of 2–3 mL/s. Injection of the contrast agent should be followed by a saline flush of 20 mL at the same injection rate. Thereafter, imaging of the entire liver is performed in a single breath hold during the dynamic phase of contrast enhancement. This is most commonly undertaken with a 2D or 3D T1-w gradient-echo (GRE) sequence with serial imaging in the arterial dominant phase (25–30 s post-injection), the portal-venous phase (60–80 s post-injection), and the equilibrium phase (3–5 min post-injection). The 3D fat-saturated (FS) GRE sequence should be performed with parallel imaging resulting in lower acquisition times and breath hold times.

Imaging with contrast agents that have a combined extracellular and hepatocyte-specific distribution can be performed during the dynamic phase of contrast enhancement in a manner identical to that used with the non-specific Gd-chelates that have a purely extracellular distribution. For this purpose, these agents are injected as a bolus, typically at a dose of 0.05–0.1 mmol/kg BW (0.1–0.2 mL/kg bodyweight) for Gd-BOPTA and 0.025 mmol/kg BW (0.1 mL/kg bodyweight) for

Gd-EOB-DTPA, at a flow rate of 2–3 mL/s. The injection of the contrast agent should be followed by a saline flush of 20 mL at the same injection rate. Contrast-enhanced 2D or 3D GRE T1-w or T1-w FS imaging of the entire liver is typically performed in a single breath hold at 20–25 s post-injection (arterial phase imaging), 60–80 s post-injection (portal-venous phase imaging) and 3–5 min post-injection (equilibrium phase imaging).

Hepatobiliary imaging after injection of Gd-BOPTA is performed at 45 min to 3 h post-injection (enhancement is most prominent 60–120 min after intravenous injection). Conversely, with Gd-EOB-DTPA imaging in the hepatobiliary phase can usually be performed as soon as 20 min post-injection (highest liver-to-lesion contrast is observed 20–45 min after injection). The use of fat saturation improves contrast-to-noise ratio (CNR) on hepatobiliary phase images [23].

Mn-DPDP has to be administered as a drip infusion over a period of approximately 10 min at a dose of 5–10 $\mu\text{mol/kg}$ bodyweight (0.5 mL/kg; maximum dose, 50 mL), which precludes dynamic imaging. Moreover, because the 5–10 mmol/kg dose of mangafodipir is 10% or less than that of the Gd agents, imaging with this contrast during its distribution phase in the extracellular fluid compartment does not contribute to diagnosis [20]. This contrast causes increased SI in the liver on T1-w images [6]. GRE T1-w breath hold sequences are normally used for image acquisition. Fat saturation has been shown to improve contrast [24]. Imaging is usually performed at 15–20 min post-injection, but in some cases, later images at 4 h provide additional information for lesion characterization [2].

Figure 2.1 and Table 2.2 show suggested protocols for MR imaging using paramagnetic contrast agents.

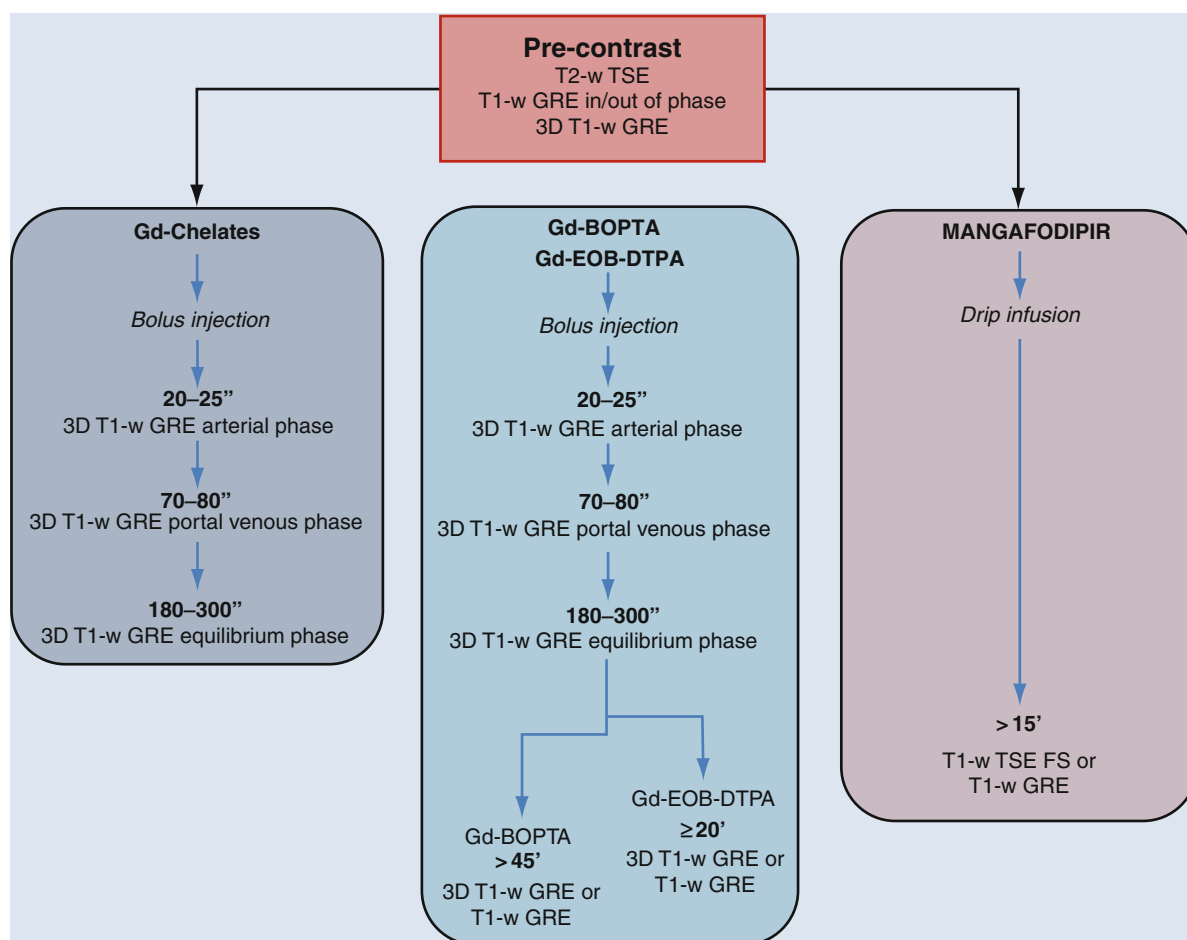


Fig. 2.1 Imaging protocols for paramagnetic contrast-enhanced MRI

Table 2.2 Suggested sequences used in MRI studies employing paramagnetic contrast agents

	TR (ms)	TE (ms)	Flip angle (°)	Matrix (mm)	FOV (mm)	Slice thickness (mm)	Intersection gap (mm)	Fat suppression	Respiratory triggering	Breath hold	Acquisition time
T2-w TSE	1,800	93	150	384 × 264	360 × 270	8	1.6	Yes	Yes	No	1'55"
T1-w TSE	692	10	70	384 × 264	360 × 330	8	1.6	Yes	Yes	No	2'19"
T1-w in/out phase	100	2.32/5.24	70	256 × 180	350 × 350	9	1.8	No	No	Yes	9" (×2)
3D T1-w GRE	3.64	1.44	8	256 × 256	400 × 400	3.5	0.7	Yes	No	Yes	14"

2.2.6 Current Clinical Indications

The extracellular contrast agents have a broad indication spectrum. In imaging of the liver, they provide important information for the detection of lesions and for characterization of focal and diffuse liver pathologies (in general using dynamic imaging). Regarding lesion characterization, characteristic enhancement patterns have been identified for several benign and malignant masses (Tables 2.3 and 2.4) of both hepatocellular and non-hepatocellular origin (Figs. 2.2–2.4) [25, 26].

For gadobutrol, it should be stressed that because it consists of a 1 M concentration instead of the 0.5 M concentration of all other Gd-chelates, (resulting in double the concentration and half the injection volume for the same dose), it is advantageous for first-pass imaging examinations, such as perfusion imaging and high-gradient 3D MR angiography [2]. The contrast

agent gadofosveset is also particularly employed for use in MR angiography.

In addition to the hepatic imaging capability of Gd-BOPTA, biliary excretion also facilitates its use for biliary tract imaging, while the increased relaxivity deriving from weak plasma protein interaction may be beneficial for hepatic MR angiography. Both of these features have proven advantageous for the preoperative evaluation of potential liver donors in transplant surgery [27]. Gd-EOB-DTPA is also a suitable agent for liver and biliary imaging [28]. Table 2.4 summarizes the expected behavior of various focal liver lesions on hepatobiliary phase of enhancement after injection of hepatocyte-specific contrast agents.

Although Mn-DPDP is primarily considered an agent for MRI of the liver, some studies demonstrated a potential usefulness for imaging of the pancreas as well [29]. Moreover, since the Mn^{2+} ion is partly excreted through the biliary system, this contrast may prove effective for biliary tract imaging [30].

Table 2.3 Magnetic properties of focal liver lesions on CE-dynamic MR

	FNH	HCA	Hemangioma	HCC	Cholangiocarcinoma	Metastases
Arterial	Homogeneous strong enhancement (except for hypointense central scar)	Heterogeneous enhancement	Peripheral globular enhancement	Heterogeneous strong enhancement	Heterogeneously hypointense	Variable, usually hypointense with rim enhancement
Portal	Isointense (hypointense scar)	Iso to hypointense, heterogeneous	Progressive centripetal enhancement	Iso to hypointense, heterogeneous	Hypointense, heterogeneous	Hypointense
Equilibrium	Isointense (enhanced hyperintense scar)	Iso to hypointense, heterogeneous	Progressive centripetal filling	Hypointense, heterogeneous, peripheral capsule	Heterogeneous late enhancement	Hypointense, peripheral washout

Table 2.4 Behavior of different hepatic focal lesions on hepatobiliary phase after administration of hepatocyte-specific contrast media

	FNH	HCA	Hemangioma	HCC	Cholangiocarcinoma	Metastases
T1-w hepato-biliary phase	Iso- to hyperintense; hypointense central scar	Heterogeneous, variable SI (usually hypointense)	Hypointense	Hypointense (iso- to hyperintense if well-differentiated tumors)	Hypointense	Hypointense (occasional enhancement)

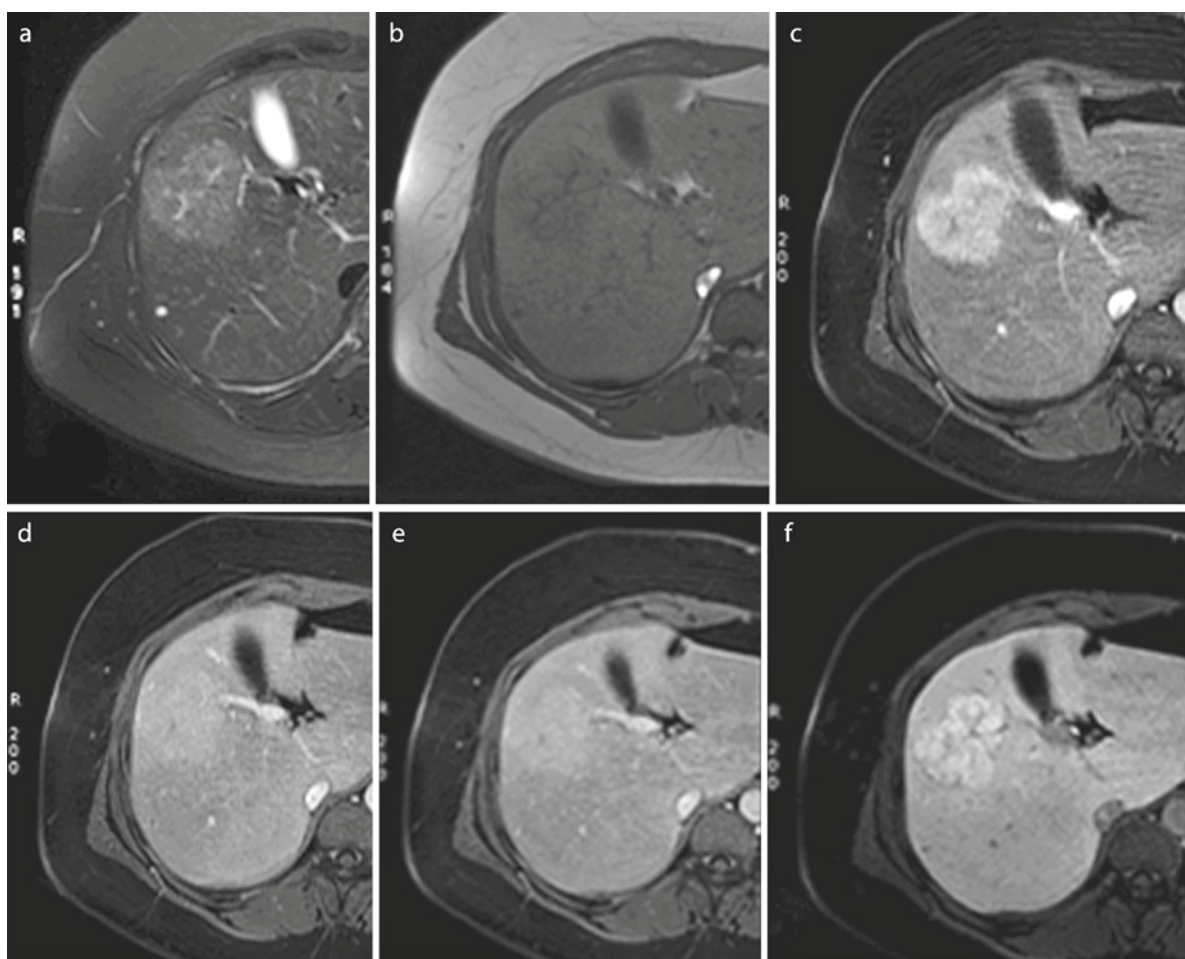


Fig. 2.2 FNH: the lesion is slightly hyperintense on T2-w (a) and hypointense on T1-w (b) images; after Gd-EOB-DTPA, there is strong enhancement on the arterial phase (c) and washout

on the portal venous and equilibrium phases (d, e); the nodule is hyperintense to liver on the hepatobiliary phase (f)

Key Points: Paramagnetic Agents

- Paramagnetic contrast agents shorten the T1 relaxation time of tissues.
- The most important subgroups of paramagnetic compounds are metal ions and lanthanide elements, such as Gd, that has seven unpaired electrons.
- Regular Gd-based compounds show a rapid vascular passage followed by interstitial diffusion (non-specific agents).
- Hepato-biliary compounds are dual agents, initially with extracellular distribution, and over a time frame taken up by hepatocytes and excreted into the bile.
- The transport mechanism is competitive with bilirubin uptake and excretion. Serum

bilirubin values >3 mg/L interfere with the amount of biliary excretion.

- Nonspecific Gd compounds should be administered as a rapid intravenous bolus injection at a dose of 0.1 mmol/kg body weight and at a flow rate of 2–3 mL/s.
- Typical hepatocyte-specific phase used for liver imaging ranges from 20 min for Gd-EOB-DTPA to 60 min for Gd-BOPTA. The use of fat saturation improves contrast-to-noise ratio (CNR) on hepatobiliary phase images.
- All Gd-based agents increase the risk of nephrogenic systemic fibrosis (NSF) in patients with acute or chronic severe renal failure.

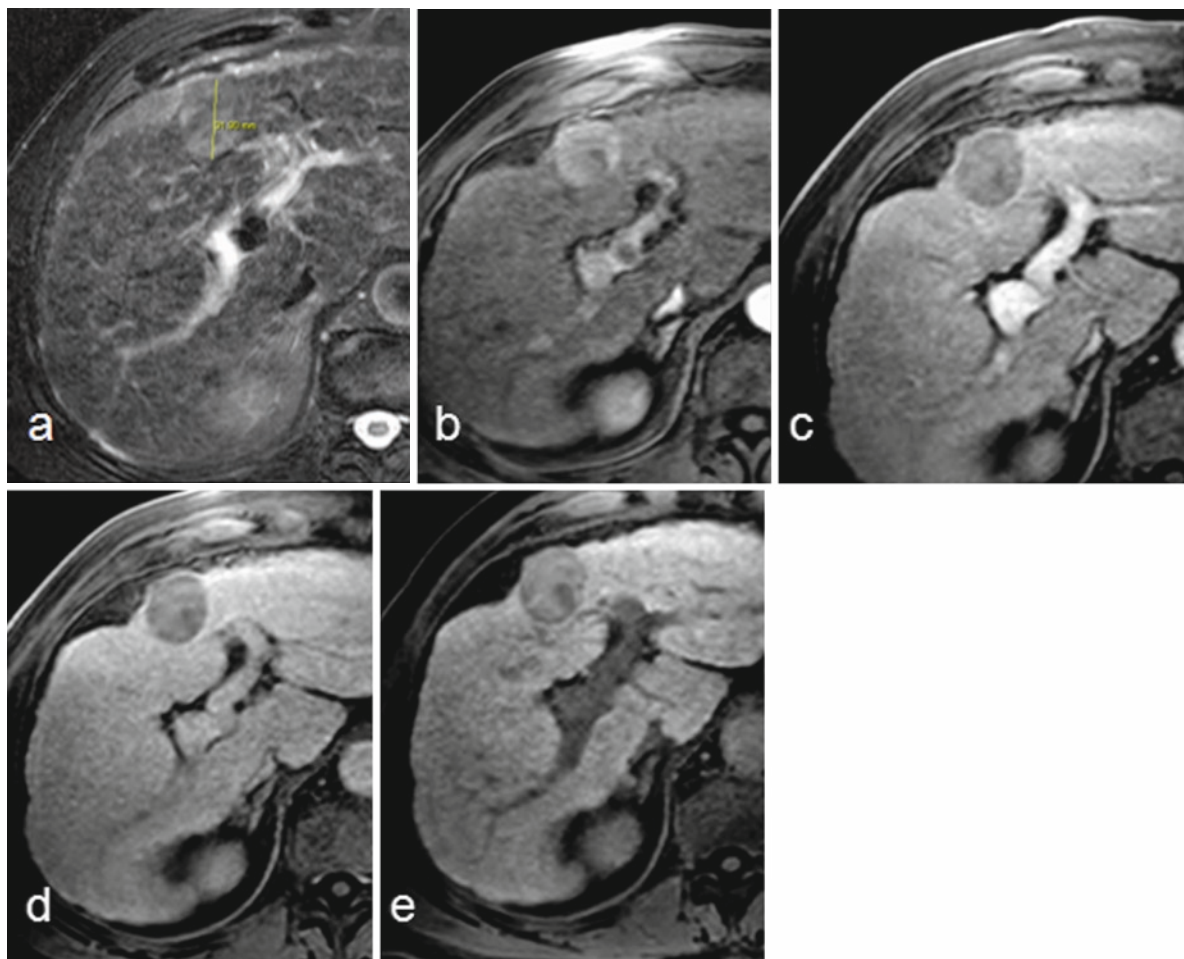


Fig. 2.3 HCC: the tumor is hyperintense on T2-w images (a); imaging after injection of Gd-EOB-DTPA demonstrates hypervascular features (b, c, d) and is hypointense to surrounding liver on the hepatobiliary phase (e)

2.3 Superparamagnetic Agents

2.3.1 History

Iron oxide particles of different sizes have been developed for clinical applications on MR imaging. They are referred to as superparamagnetic iron oxides (SPIO, mean size > 50 nm) and ultrasmall superparamagnetic iron oxides (USPIO, mean particle size < 50 nm) [11].

One superparamagnetic contrast medium is ferumoxides, which has been on the market in Europe since 1996, under the trademark Endorem® (AMI 25, Laboratoires Guerbet). Another contrast agent, ferucarbotran (Resovist®, SH U 555 A, Schering AG) is available in most European countries since 2002. Both these agents belong to the so-called SPIO's category.

Whereas the bigger iron oxide particles are mainly taken up in the liver, spleen, and bone marrow, USPIO agents are able to penetrate the vascular endothelium. From the interstitial space, they reach the lymphatic system and suffer phagocytosis by macrophages in lymph nodes. One such compound, ferumoxtran-10, (Sinerem®, AMI 227, Laboratoires Guerbet), is currently under development [2].

2.3.2 Physicochemical Properties

Iron oxide nanoparticles composed of maghemite and magnetite (Fe_2O_3 , Fe_3O_4) and stabilized by various coating agents are characterized by a large magnetic

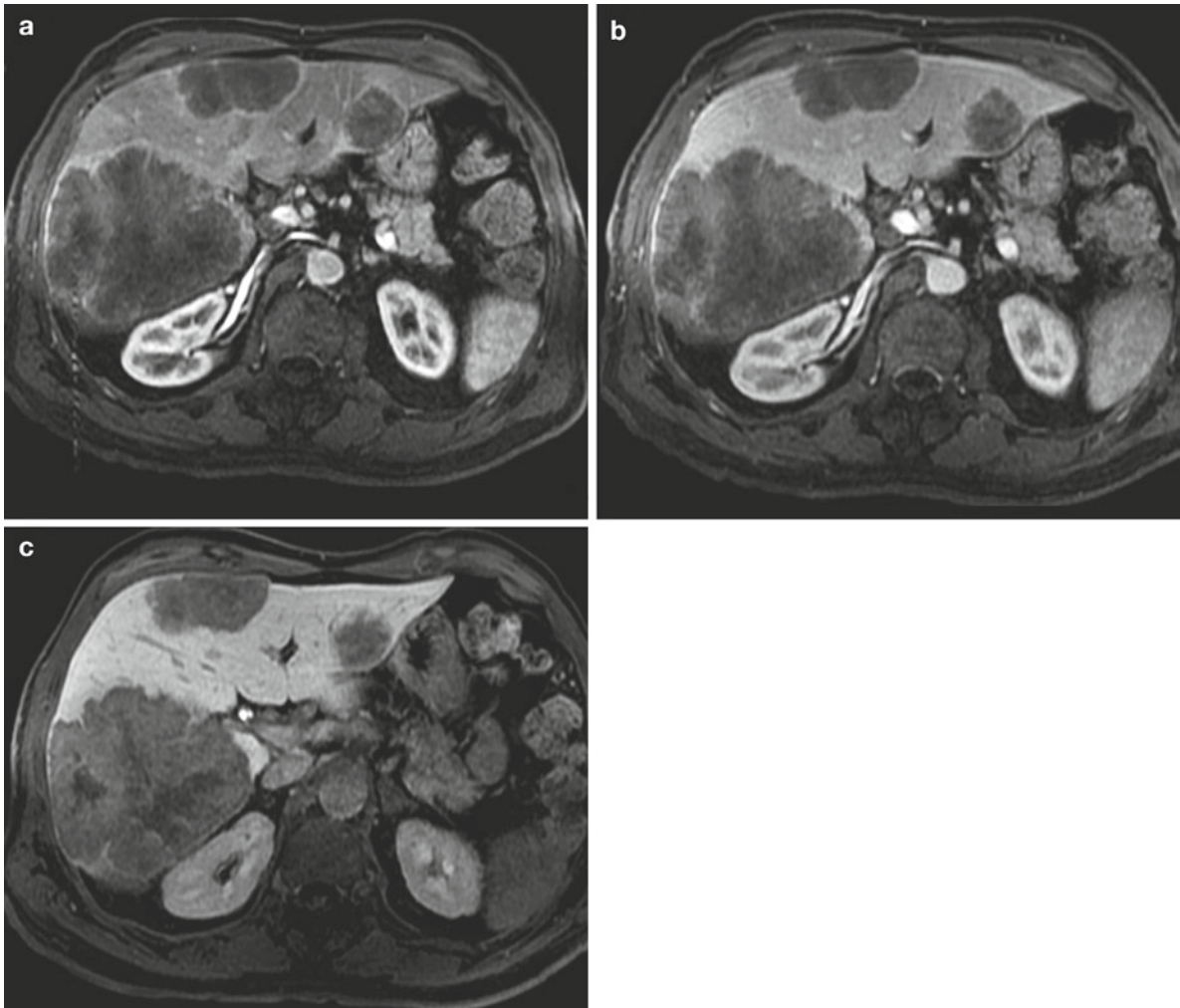


Fig. 2.4 Colorectal metastases: multiple liver nodules demonstrate peripheral rim of enhancement on the arterial phase (a); there is no enhancement on the portal phase (b) nor on the hepatobiliary phase (c)

moment in the presence of a static external magnetic field, making them suitable contrast agents for MRI.

Formed by small ferromagnetic clusters, they can randomly flip direction. As a result, they are magnetized except under an externally applied magnetic field. Normally, coupling forces in ferromagnetic materials cause the magnetic moments of neighboring atoms to align, resulting in very large internal magnetic fields.

Superparamagnetism occurs when the material is composed of very small crystals. In this case even the energy does not overcome the coupling forces between neighboring atoms, but it is sufficient to change the direction of magnetization of the entire crystal. Thus,

the magnetic moment of the entire crystal tends to align with the magnetic field.

As a consequence, superparamagnetic crystals are characterized by a large magnetic moment in the presence of an external magnetic field, but no remnant magnetic moment when the field is zero, contrarily to ferromagnetic substances, which have a remnant magnetic moment at zero field once magnetized (magnetic memory).

The colloids of magnetic iron oxide are composed of a crystalline core measuring 4–6 nm. Once submitted to an external magnetic field, they align and create high local magnetic field gradients inducing water proton spin dephasing and reduction of T1 and T2 relaxation times of the surrounding water molecules.

Table 2.5 Physicochemical properties of particulate iron oxides (PS – photocorrelation spectroscopy)

	Hydrodynamic diameter (PS) (nm)	Crystal core size (nm)	Coating	Relaxivities in water at 37°C (1.42T) (mM/s)	
				R1	R2
Ferumoxides	120–180	5	Dextran T10 kDa	10.1	120
Ferucarbotran	65	4	Carboxydextran T1.8 kDa	9.7	189
Ferumoxtran-10	15–30	6	Dextran T10 kDa, T1 kDa	9.9	65

In most situations, it is the decrease of the so-called T2* relaxivity that is explored by MRI, also known as susceptibility effect. It consists of differences in magnetization between different voxels on the imaging plane with inhomogeneous distribution of superparamagnetic particles, originating local field gradients that accelerate loss of spin phase coherence. Like many other agents, to avoid in vivo clustering of the particles and to increase tolerance, iron oxide particles had to be coated with low molecular weight dextran, also becoming more hydrophilic [2].

The physicochemical properties of the iron oxide contrast agents are summarized in Table 2.5.

2.3.3 Pharmacokinetics

Nanoparticles are usually taken up by Kupffer cells in the liver, spleen, and bone marrow and, to a lesser extent, lymph nodes.

SPIO shows higher cellular uptake than USPIO when comparing agents with identical compositions. It seems that the larger particle size of SPIO is responsible for the higher rate of macrophage extraction from the bloodstream. Also to take into account is the fact that ionic nanoparticles such as ferucarbotran show a higher uptake than nonionic nanoparticles (ferumoxides and ferumoxtran-10). Slower rates of uptake of the smaller particles lead to a longer blood half-life, allowing it to reach other targets such as the lymph nodes. The blood half-lives of the various iron oxide nanoparticles administered in patients vary from 1 to 36 h (Table 2.6).

Blood half-life is dose dependent for the iron oxide nanoparticles. This is related to a progressive saturation of macrophage uptake in the liver or other macrophage-rich organs.

Dextran-coated iron oxide nanoparticles are biodegradable, and therefore do not have long-term toxicity: the dextran coating undergoes progressive degradation

Table 2.6 Pharmacokinetic profile of superparamagnetic iron oxides

	Human half-life (h)	Degree of macrophage uptake
Ferumoxides	1–2	High
Ferucarbotran	2.4–3.6	High
Ferumoxtran-10	24–36	Low

by intracellular dextranase after uptake by macrophages and is almost exclusively eliminated in the urine (89% in 56 days) due to its low molecular weight, while the remaining dextran is excreted in the feces. The degradation of iron oxide has been described to occur in the lysosomes of macrophages. The iron oxide is solubilized into iron ions, which are progressively incorporated into the body's iron pool and then into hemoglobin. Like endogenous iron, it is eliminated very slowly, as only 16–21% of the injected iron is eliminated after 84 days in the feces being the urinary excretion negligible (<1%).

2.3.4 Safety

Safety data from more than 800 patients were reported from phase-III clinical trials with ferumoxides. The reported incidents of adverse events range between 10.3% in Europe and 15% in the USA. One of the most frequently reported adverse effects is lumbar back pain which was observed in more than 3–4% of the patients [2]. The nature of this symptom is unknown but it appears to be a side effect of particulate agents in general; it is not specific to ferumoxides and is limited to the injection period and slightly beyond. Back pain develops in patients in whom the contrast agent is administered too rapidly (i.e., faster than the recommended slow intravenous drip infusion) and is more

likely to occur in patients with liver dysfunction, such as cirrhotic patients [7]. The incidence and severity of adverse events (such as back pain, thoracic pain, or hypotension) correlates with the speed of infusion. Therefore, the drip infusion should be stopped until the symptoms disappear and resumed at a slower rate under medical supervision. If reactions such as nausea, urticaria, or other allergic skin reactions occur, the administration should be stopped and not resumed [23].

Ferucarbotran has been administered to more than 1,200 patients during clinical phase-II and phase-III trials worldwide. The overall incidence of adverse events is about 9%. Back pain was reported in less than 0.5% of cases and is of mild intensity. Other secondary effects include paresthesia, headache, nausea, anxiety, vomiting, and pain at the injection site. With regard to laboratory parameters, a transient decrease within the normal range of the activity of clotting factor XI has been observed. This does not result in any changes in the overall bleeding time or coagulation tests such as PTT and Quick [2]. No changes in urinary chemistry or blood creatinine have been reported. Similarly, no impairment of liver function was found in previous studies.

The adverse reactions associated with the use of ferumoxtran-10 are similar to the ones reported for the other iron oxide agents. The most common adverse event from the previously performed studies was mild lumbar back pain in fewer than 4% of patients [31].

As with all other contrast media, allergic or anaphylactic reactions can, in principle, occur with each of these contrast agents [2]. The iron moiety of this contrast media might cause a transient change in serum iron, ferritin, and iron-binding capacity, but there is no risk of iron overload.

2.3.5 Imaging Protocols

Imaging protocols may be variable but typically pre-contrast T1-, T2-, and T2*-w sequences are acquired when SPIO is used for liver imaging.

T2-w images should be obtained with fat suppression in order to reduce artefacts and increase lesion-to-liver contrast. T1-w sequences must include in- and out-of-phase images to provide information about the liver parenchyma and to detect or exclude diffuse liver diseases such as fatty infiltration [32].

The recommended dose range for ferumoxides in Europe is 10–15 $\mu\text{mol Fe/kg}$ of body weight (0.075 mL/kg). This contrast medium has to be prepared from

the stock solution immediately before administration by dilution in 100 mL of a 5% glucose solution and slowly infused as a drip infusion over a period of 20–30 min. The optimal time point for imaging in the accumulation phase after ferumoxides administration is between 30 min and 6 h after injection of the complete dose of contrast medium. Imaging protocols typically include T2-w turbo-spin-echo (TSE) sequences with FS, T2*-w GRE sequences, and, in selected cases, T1-w sequences [23]. SPIO-enhanced T2*-w GRE sequences are more sensitive and specific than T2-w TSE since a more intense SI loss of the enhancing tissue is expected related to their sensitivity to magnetic susceptibility effects, as they are devoid of the 180° refocusing radiofrequency pulses (Fig. 2.5).

Unlike ferumoxides, ferucarbotran is a ready-to-use suspension, which can be injected intravenously as a fast bolus, allowing dynamic imaging to be performed. The dose for patients with a body weight of less than 60 kg is 0.9 mL (total iron dose 0.45 mmol), while individuals with a body weight of more than 60 kg receive a dose of 1.4 mL (total iron dose 0.7 mmol). The contrast agent is administered as a bolus through a 5 μm -filter followed by a saline flush (0.9% saline solution) of approximately 20 mL. After bolus injection, dynamic contrast-enhanced T1-w imaging of the entire liver can be performed. This dynamic imaging is possible due to an intravascular and interstitial T1 effect occurring before phagocytosis by Kupffer cells, which only occurs later on, about 10 min after injection [11].

As a result, the time-point for imaging in the accumulation phase after ferucarbotran injection ranges from 10 min to 8 h after administration of the contrast agent.

At this time T2-w TSE FS images or, preferably, T2*-w GRE images should be obtained.

Ferumoxtran-10, which is primarily taken up by lymph node macrophages, is reconstituted using 10 mL of a 0.9% saline solution. The administered dose ranges from 1.7 to 2.6 mg of iron/kg of body weight and the corresponding volume of the contrast agent solution is diluted in 100 mL of a 0.9% saline solution. The final volume is injected intravenously, by drip infusion through a filter (pore size: 0.22 μm), at a rate of 4 mL/min, with an average infusion time of approximately 30 min. Imaging is performed 24–36 h after the intravenous injection of the contrast medium.

Achieving an accurate nodal characterization implies that the optimal sequence for MR lymphography should have a good CNR. T2-w images possess a

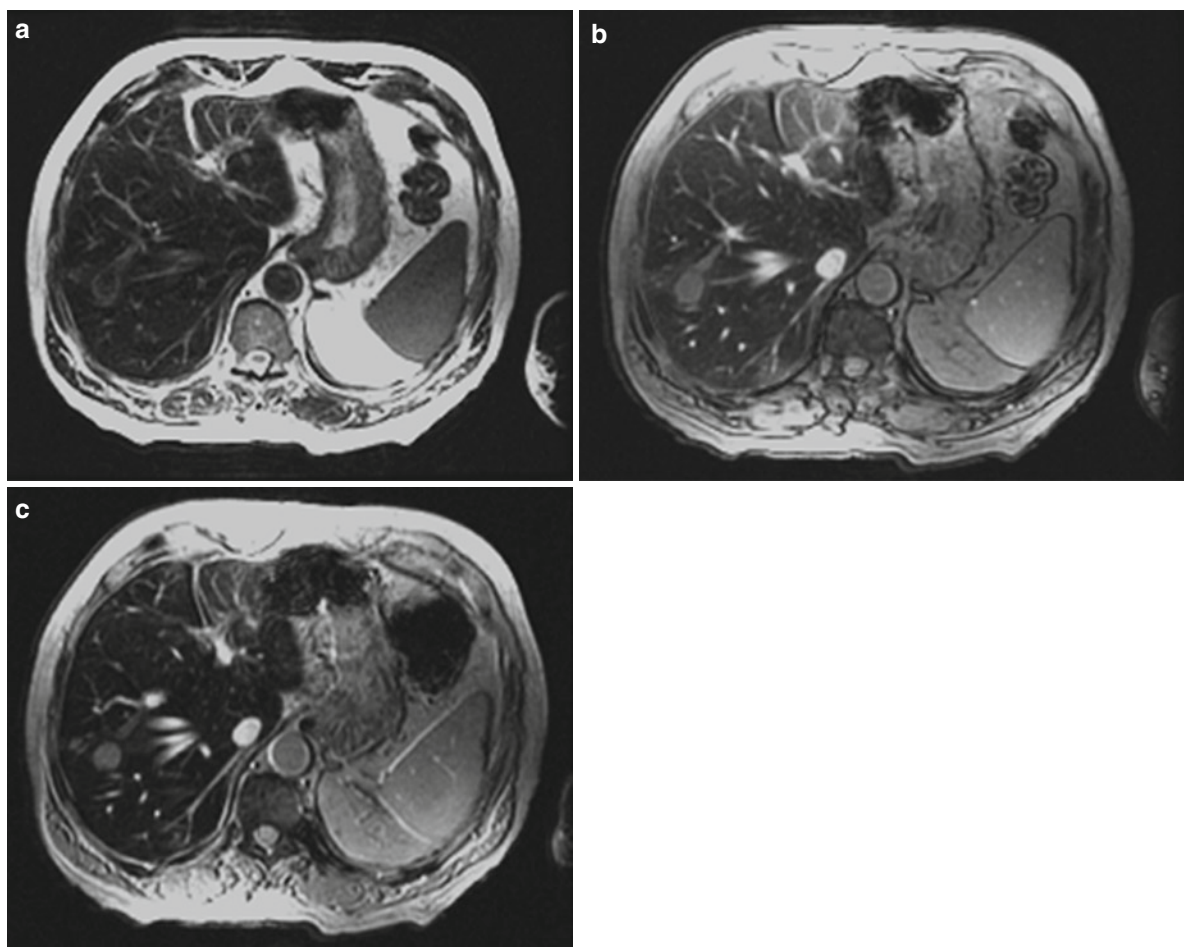


Fig. 2.5 Metastasis: SPIO-enhanced T2*-w GRE sequences (b, c) exhibit a more pronounced SI loss of the enhancing tissue than T2*-w TSE ones (a); as a consequence, detection of hypovascular lesions is better on T2*-GRE because there is an increased

contrast between the black (enhancing) liver and the metastatic nodule. Please also take into account the darker appearance of the enhancing liver with longer TE (c, TE 15 ms) than with shorter TE (b, TE 10 ms)

good signal-to-noise ratio (SNR) but are not very sensitive to the changes in intranodal susceptibility caused by intracellular ferumoxtran-10. Contrarily, the T2*-w sequences are exquisitely sensitive to susceptibility effects induced by the intranodal iron in normal nodes. T2*-weighted images have good CNR but lower SNR [33]. Thus, the imaging parameters for this sequence should be selected with caution. By selecting a sufficiently long echo time and a small flip angle, the T2* effect can be enhanced, allowing demonstration of satisfactory signal intensity decrease within an enhancing node [34]. However, by increasing the echo time, one must take a lower SNR into account [33].

Figure 2.6 and Table 2.7 provide suggested protocols for MR imaging with particulate iron oxides.

2.3.6 Current Clinical Indications

The major clinical indication of SPIO-enhanced studies is liver imaging. The rationale behind this is the fact that, because of the unique physiologic properties of the liver, opsonized iron oxide particles are sequestered by phagocytic Kupffer cells of normal RES. In this way, liver lesions that contain negligible or few RES cells remain largely non-enhanced, while the normal liver enhances (becomes hypointense on T2-w images), resulting in an improvement of the CNR ratio between enhanced (low SI) liver and non-enhanced (high SI) liver lesions on SPIO-enhanced T2-w images. Liver metastases constitute the type of lesion for which an increased detection rate with these contrast agents is more clinically relevant. Patients with potentially

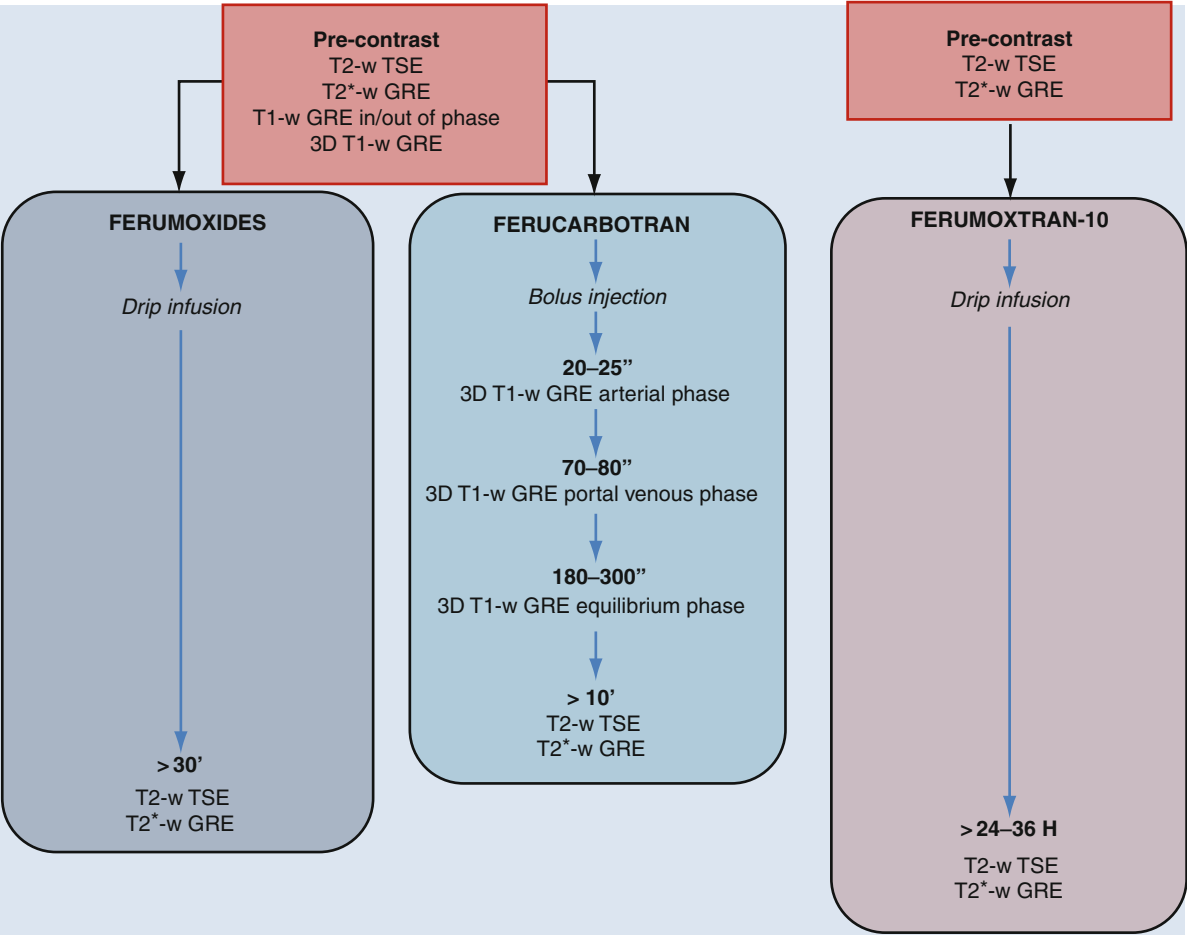


Fig. 2.6 Imaging protocols for SPIO- and USPIO-enhanced MRI

resectable liver metastases on the basis of limited involvement correspond to the patient group in which the role for SPIO agents may be most applicable (Fig. 2.7) [7].

Apart from the detection of focal liver lesions, SPIO agents may also play an important role for characterization. The increased uptake of iron oxides by focal nodular hyperplasia (FNH), due to its high content of functional RES cells, is a well-known example (Fig. 2.8).

Some overlap may occur with liver nodules potentially containing RES cells as hepatocellular adenoma (HCA), regenerative nodules, dysplastic nodules and well-differentiated hepatocellular carcinoma [11]. It should also be mentioned that lesions possessing a large blood pool, such as hemangioma, may also show a signal intensity drop-out on T2-w SPIO-enhanced sequences.

The following table summarizes the expected behavior of various focal liver lesions on SPIO-enhanced MRI (Table 2.8).

Smaller SPIO agents, such as ferucarbotran, possess a more prolonged intravascular half-life than do the larger particulate agents, exhibiting T1 effects that emulate the vascular phase effects of T1 agents. Therefore, they can provide additional information about the characterization of focal liver lesions, similarly to a Gd-based extracellular compound. Also, due to its vascular enhancement they were used for MR angiography [7], despite their weak T1-effect.

The main clinical application of USPIO agents is the characterization of lymph nodes through MR lymphography. After intravenous administration the iron particles are slowly extravasated from the vessels into the interstitial space, from where they are conducted to the lymph nodes. Entrance into lymph nodes is via

Table 2.7 Suggested pulse sequences for MRI studies employing particulate iron oxides

	TR (ms)	TE (ms)	Flip angle (°)	Matrix (mm)	FOV (mm)	Slice thickness (mm)	Intersection gap (mm)	Fat suppression	Respiratory triggering	Breath hold	Acquisition time
T2-w TSE	1,800	93	150	384 × 268	360 × 270	8	1.6	Yes	Yes	No	1'55"
T2*-w GRE	130	14	30	256 × 180	420 × 394	7	1.4	No	No	Yes	38" (three acquisitions)
T1-w in/out phase	100	2.32/5.24	70	256 × 180	350 × 350	9	1.8	No	No	Yes	9" (×2)
3D T1-w GRE	3.64	1.44	8	256 × 256	400 × 400	3.5	0.7	Yes	No	Yes	14"

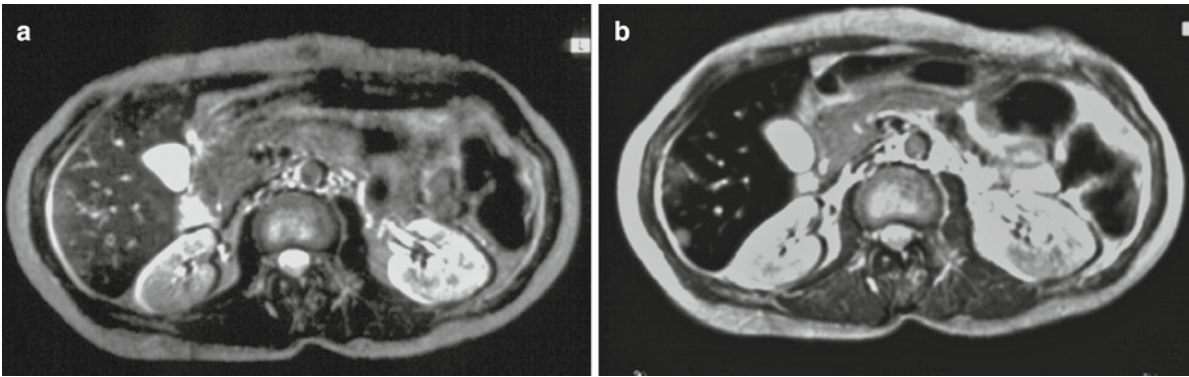


Fig. 2.7 Metastases: lesions on the right liver lobe are hardly recognizable on non-enhanced T2-w images (a), whereas on SPIO-enhanced T2-w sequences (b) even tiny nodules become readily apparent

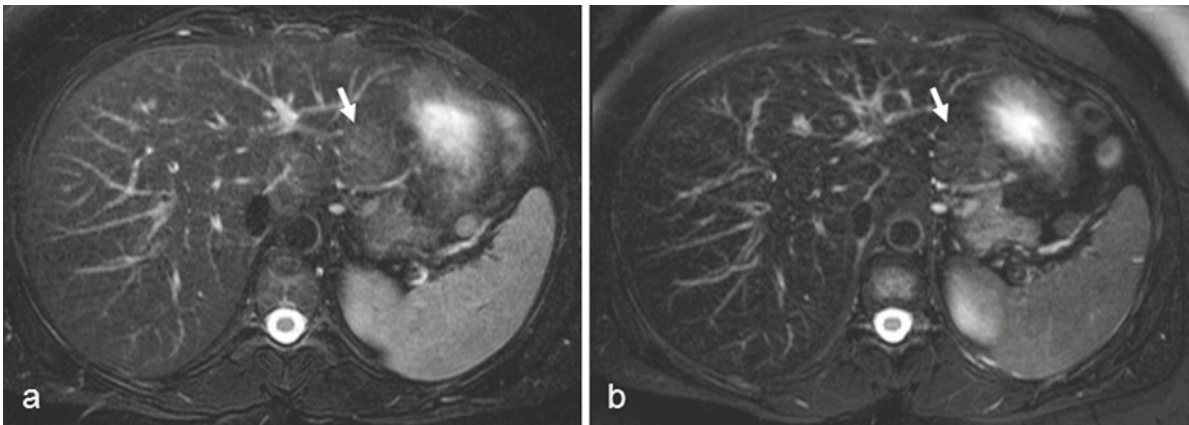


Fig. 2.8 FNH: Rounded lesion of the left liver lobe (white arrow), slightly hyperintense on FS T2-w images (a), demonstrating homogeneous SI loss on the same sequence after the administration of SPIO (b)

Table 2.8 Behavior of different hepatic focal lesions pre- and post-SPIO injection

	FNH	HCA	Hemangioma	HCC	Cholangiocarcinoma	Metastases
T2-w pre-contrast	Iso- to mildly hyperintense; hyperintense central scar	Heterogeneous, variable SI	Markedly hyperintense	Heterogeneous, hyper- to isointense	Hyperintense, heterogeneous	Variable, usually mildly hyperintense
T2-w enhanced	Homogeneous signal decay; hyperintense scar	Slight signal loss, mildly hyperintense	Variable signal decay	No SI decay (except well-differentiated HCC)	No signal dropout	No signal decay

two mechanisms, a direct transcapillary passage from venules into nodal medullary sinuses and nonselective endothelial transcytosis into the interstitial space [35]. The macrophages that are present in normal benign nodes take up the contrast agent, causing a signal intensity dropout. Benign nodes show

homogeneous USPIO uptake and consequently signal intensity loss on contrast-enhanced T2-w TSE and T2*-w GRE images, whereas a lymph node replaced by malignant cells remains bright after USPIO administration since it is deprived of macrophages (Figs. 2.9 and 2.10) [33].

Key Points: Superparamagnetic Agents

- Superparamagnetic contrast agents shorten the T2 relaxation time of tissues.
- Iron oxide particles create high local magnetic field gradients causing proton dephasing and reduction of the T2 relaxation times of tissues.
- Iron-oxide particles are primarily directed to the liver, bone marrow and spleen (SPIO, mean size > 50 nm), or lymph nodes (USPIO, mean particle size < 50 nm).
- Imaging with SPIO should be performed from a time frame of >10 min after bolus injection (ferucarbotran) to >30 min after slow venous infusion (ferumoxides).
- Imaging with USPIO should be performed 24–36 h after the slow infusion (ferumoxtran-10).
- T2*-w sequences are exquisitely sensitive to susceptibility effects and thus to the presence of intracellular iron.
- One of the most frequently reported adverse effects is lumbar back pain reported in about than 3–4% of the patients.

2.4 Imaging Findings and Intermodality Comparison

Contrast-enhanced imaging with the use of nonspecific extracellular agents has high accuracy in detecting and characterizing focal liver lesions [11].

The basic idea of the hepatobiliary-specific contrast media is that they can only be taken up by normal liver tissue. In lesions of hepatic origin, the uptake depends on the number and the functional integrity of the hepatocytes. The variation between several lesion types and the resulting differential uptake of contrast media provides useful information for lesion characterization [2]. With hepatobiliary agents, dynamic contrast-enhanced images exploit the differences in blood supply between lesions and normal liver parenchyma. The results are comparable with other conventional extracellular contrast agents. At the hepatocyte-retention phase there is an improvement in the detection of hypovascular lesions [6, 11] due to selective uptake by functioning hepatocytes in normal liver, contrarily to the tumors of non-hepatocytic origin, such as metastases or cholangiocellular

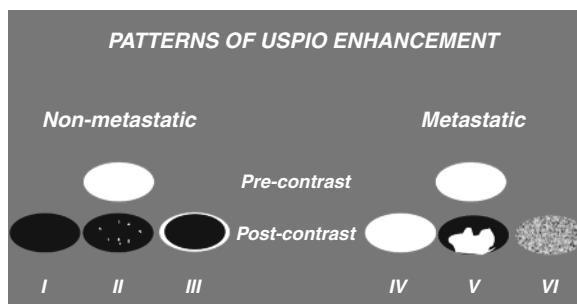


Fig. 2.9 Drawing for assessment of nodal signal intensity before and after USPIO administration, establishing enhancement criteria used to differentiate benign from metastatic nodes. The nodes showing a homogeneous signal decrease (I) on enhanced T2-w images or minute hyperintense foci (II) or a hyperintense peripheral rim (III), are considered nonmetastatic. Nodes that do not show signal intensity decrease (IV), that contain obvious foci of high SI (V) or are heterogeneous (VI) on T2-w images are considered metastatic

carcinoma. For instance, differentiation between HCA and FNH is possible during the hepatobiliary phase since FNH contains hyperplastic bile ducts resulting in contrast accumulation during the hepatobiliary phase contrarily to HCA (Fig. 2.11) [11].

A previous study [36] examined 249 patients with a variety of primary and secondary hypervascular tumors on both dynamic and delayed imaging after Gd-BOPTA. Delayed imaging provided additional information for lesion characterization with high accuracy in distinguishing benign lesions like FNH and regenerative hyperplasia from other lesions (sensitivity 79.7%, specificity 96.1%). Other authors [37] studied a subset of patients with FNH comparing Gd-BOPTA with ferumoxides. They noted that 57 of 60 lesions displayed typical enhancement characteristics after Gd-BOPTA and 100% were identified correctly, whereas after ferumoxides only 71.6% were correctly identified as FNH.

The diagnostic performance of Gd-EOB-DTPA-enhanced MR imaging for detection of liver lesions was evaluated in a large prospective study with the use of 25 mmol/kg dose [38]. More small lesions were detected on post-contrast than on pre-contrast images. Per patient sensitivity for characterization was significantly higher on post-contrast images alone. One prospective study also contained comparative data with biphasic (arterial and portal-venous phase) helical CT [38]. Gd-EOB-DTPA-enhanced MR imaging was superior to CT in the overall analysis for the pre-therapeutic approach in liver imaging regarding lesion detection, localization, classification, and

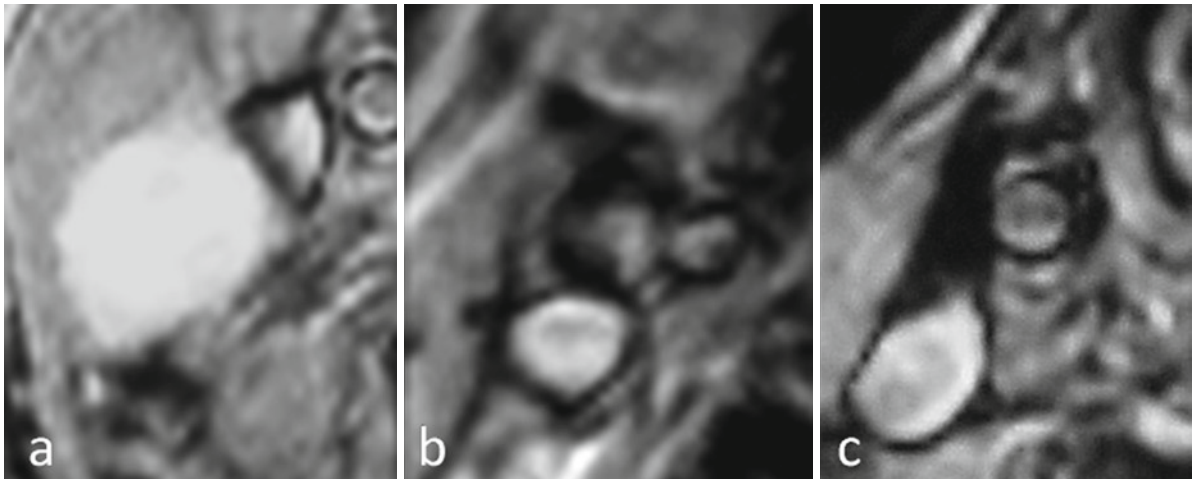


Fig. 2.10 After USPIO administration, the node that does not show signal intensity decrease (**a**) is totally replaced by metastases; the node that contains obvious foci of high SI (**b**) is par-

tially metastatic; the node that experiences a homogeneous signal decrease (**c**) on enhanced T2-w images is a nonmetastatic node

characterization. The frequency of correctly detected lesions by Gd-EOB-DTPA-enhanced MR imaging was 87.4% compared with 77.1% for CT (lesion-based analysis), being superior for the detection of lesions under 1 cm. Classification of detected lesions (benign versus malignant) was also superior for Gd-EOB-DTPA-enhanced MR imaging (82.1%) compared with CT (71%).

Using Mn-DPDP, tumors of hepatocellular origin, such as FNH, HCA, and well-differentiated HCC, have been shown to accumulate the contrast, providing additional information for characterization and ability to discriminate hepatocellular from non-hepatocellular tumors. Although Mn-DPDP can differentiate between hepatocyte- and non-hepatocyte-containing lesions, other lesions such as regenerative nodules, well-differentiated HCC, and metastases from endocrine tumors may also show contrast uptake and increased enhancement [39]. It should be stressed that lesion enhancement may be seen up to 24 h after administration [40, 41] providing a very large temporal window for imaging. In a study of 77 patients with histologically confirmed diagnoses, the sensitivity and specificity of Mn-DPDP-enhanced MRI for the differentiation of malignant versus benign lesions was 91% and 67%, respectively, while that for the differentiation of hepatocellular versus non-hepatocellular lesions was 91% and 85%, respectively [42].

Previous studies have shown a benefit for liver lesion detection with Mn-DPDP-enhanced hepatic MR imaging compared with unenhanced MRI [20, 43].

Regarding detection of liver metastases, well-controlled studies using surgical pathology or intraoperative ultrasound (IOUS) as gold-standard have supported the efficacy of SPIO-enhanced MRI. For example, an early multicenter phase III study showed more lesions in 27% of cases than unenhanced MR and in 40% of cases compared to CT [11]. Several other studies have compared the sensitivity of lesion detection regarding helical CT versus SPIO-enhanced MRI. For helical CT, sensitivity and specificity ranged from 60% to 85% and from 44% to 89%, respectively. The corresponding values for SPIO-enhanced MRI were 68–87% and 82–100%. SPIO-enhanced MRI has also proved by various authors to be as sensitive as but more specific than CT during arterial portography (CTAP) for the detection of liver metastases. There is also an advantage of SPIO-enhanced MRI over non-enhanced MRI in terms of sensitivity (95% versus 81%), but not specificity (89% versus 88%) for detecting liver metastatic lesions [44]. Thus, combined analysis of non-enhanced and SPIO-enhanced images is more accurate for characterization of focal liver lesions than the review of SPIO-enhanced images alone [45].

For detection of hypervascular HCC, it has been documented that SPIO-enhanced MRI is more sensitive than dual-phase spiral CT. A previous study showed that the mean sensitivity of SPIO-enhanced MRI was significantly higher (70.6%) than that of dual-phase spiral CT (58.1%). Other authors compared SPIO-enhanced MRI with triple-phase multidetector CT (MDCT) for preoperative detection of HCC [45]. Mean sensitivities

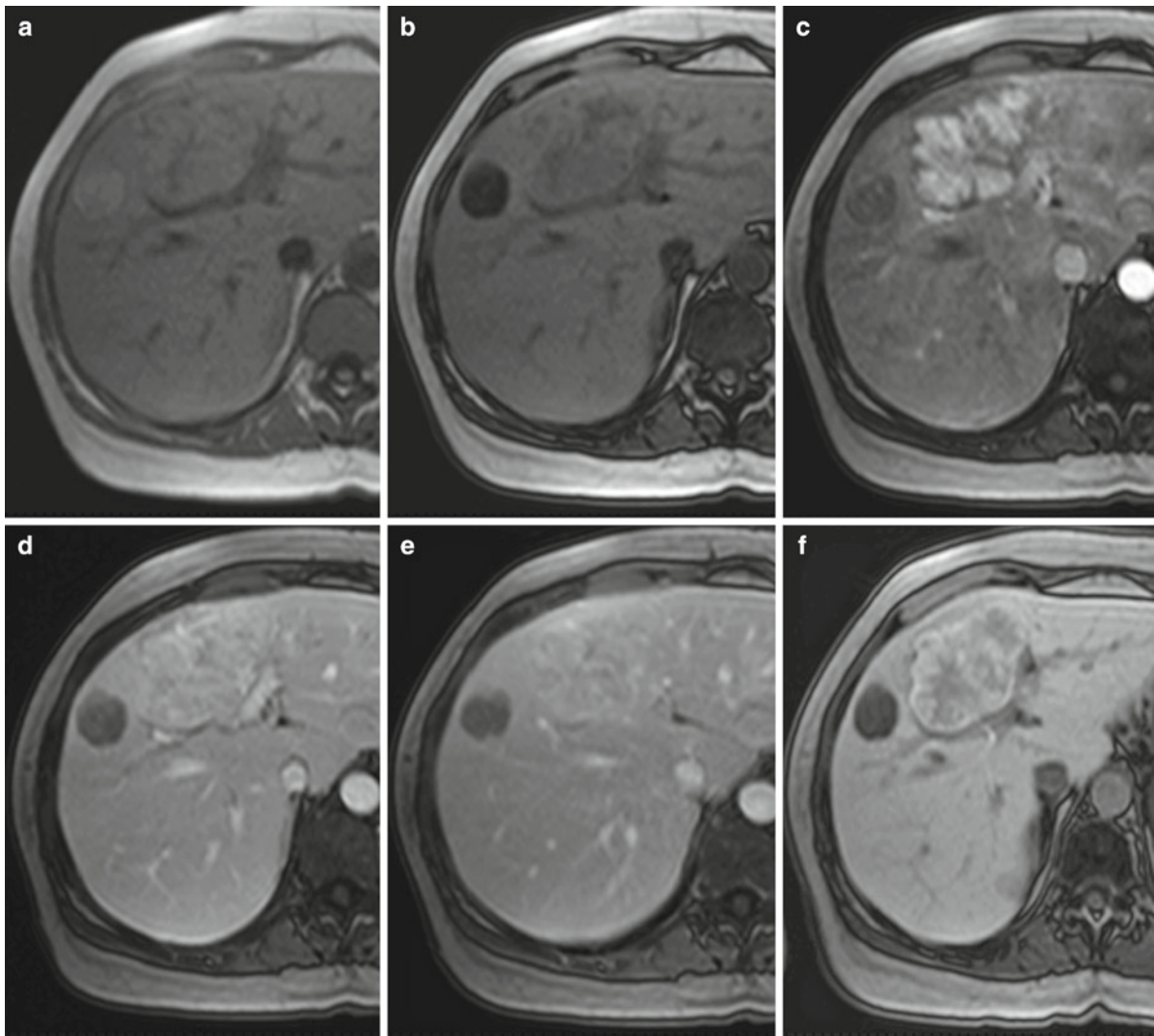


Fig. 2.11 On T1-w in-phase image (a) a hyperintense liver lesion is seen, which experiences SI dropout on T1-w out-of-phase image (b), indicating the presence of intralesional fat. Next to it there is a larger nodule which is isointense on T1-w in-phase image and slightly hypointense on T1-w out-of-phase sequence. After administration of Gd-BOPTA, the larger nodule shows hypervascular characteristics with enhancement on the

arterial phase, whereas the smaller one enhances only discretely (c). Both, particularly the larger one, show washout throughout the other phases of enhancement (d, e). On delayed hepatobiliary phase (f) the larger lesion appears brighter than the adjacent liver, corresponding to a FNH, and the smaller nodule, hypointense to the adjacent parenchyma, represents lipid-rich HCA (steatotic adenoma)

of MRI and triple-phase MDCT were 90.2% and 91.3%, and specificities 97.0% and 95.3%, respectively. They concluded that SPIO-enhanced MRI was as accurate as triple-phase MDCT for the preoperative detection of HCC but increased the diagnostic confidence for exclusion of pseudo-lesions [45].

Several studies have shown that Gd-based dynamic MRI is slightly better than SPIO-enhanced MRI for the detection of small (<2 cm) HCC, showing better conspicuity. However, SPIO-enhanced MRI may provide

additional information when imaging findings on dynamic MRI are doubtful due to the presence of intrahepatic arterio-portal (AP) shunts and/or post-therapeutic liver damage.

Previous works reported the usefulness of double-contrast MRI, that is, the concomitant use of SPIO- and Gd-dynamic MRI, for HCC diagnosis, showing a higher accuracy when compared to plain or SPIO-enhanced MRI alone (0,84, 0,64, 0,76, respectively). Both HCC and dysplastic nodules were correctly

characterized with all three techniques, although observer confidence was greatest for the double-contrast approach [45].

There are some reports regarding comparison of efficacy between SPIO and paramagnetic hepatobiliary agents in the diagnosis of HCC. A comparative study between SPIO and Gd-BOPTA reported a mean sensitivity and positive predictive value of SPIO-enhanced imaging of 81.0% and 85.0%, respectively, where those of Gd-BOPTA-enhanced MRI were 91.4% and 88.1%, respectively. The authors concluded that Gd-BOPTA-enhanced dynamic imaging exhibited a better diagnostic performance than SPIO-enhanced imaging for the detection of HCC [45].

SPIO-enhanced MRI has a diagnostic efficacy equivalent to that of CTAP plus CTHA as a preoperative test for HCC [44]. The SPIO-enhanced technique is recommended for the preoperative work-up of candidates for surgical resection of malignant hepatic tumors. Because CTAP plus CTHA is approximately three times more expensive than SPIO-enhanced MRI, use of SPIO is also economically favorable.

Regarding MR lymphography, several published studies in humans have shown the improved diagnostic efficacy of this technique in differentiating benign from metastatic nodes in comparison to other cross-sectional imaging modalities. The sensitivity and specificity values for this technique reported in the different clinical trials varied from 33% to 100% and from 37.5% to 100%, respectively. Nevertheless, a direct comparison of results obtained in different studies is difficult due to heterogeneities in study design, MRI technique, and anatomical area under appreciation. For instance, results obtained in the pelvic region may not be applicable to the mediastinum, where image degradation due to motion artefacts can decrease the sensitivity to further extent [34].

Several studies have been published in patients with head and neck cancer, with sensitivities ranging from 86% to 95% and specificities from 77% to 100%. Another trial evaluating nodal staging in patients with prostate cancer showed a significantly increased sensitivity for detection of metastatic lymph nodes, ranging from 35.4% for plain MRI to 90.5% for USPIO-enhanced MRI. Specificity was also increased, from 90.4% to 97.8%.

It is now accepted that ferumoxtran-10-enhanced MRI has a high sensitivity and specificity for the characterization of lymph nodes in the abdomen and pelvis, with the highest sensitivity and specificity being found in two studies reporting data for prostate cancer only [31].

Key Points: Detection/Characterization

- Several studies have shown that Gd-based dynamic MRI is slightly better than SPIO-enhanced MRI for the detection of small (<2 cm) HCC.
- The frequency of correctly detected lesions by Gd-EOB-DTPA-enhanced MR imaging was 87.4% compared with 77.1% for CT (lesion-based analysis), and Gd-EOB-DTPA-enhanced MR imaging was superior in the detection of lesions under 1 cm.
- HCA and FNH can be distinguished by the enhancement pattern as seen on the hepatocyte-specific phase.
- SPIO agents increase the accuracy of MRI for detection and characterization of focal liver lesions helping to reduce false-positives.
- The main clinical application of USPIO agents is for characterization of lymph nodes.
- Double-contrast MRI using SPIO and nonspecific Gd agents is feasible, and can increase HCC detection when compared to plain or SPIO-enhanced MRI alone.
- MR lymphography improves the diagnostic efficacy for differentiation of benign from metastatic nodes when compared to other imaging modalities.
- To date, the best clinical benefit for the use of USPIO agents concerns metastatic lymph node involvement in patients with prostate cancer.

2.5 Pitfalls and Limitations

For Gd-BOPTA, the long waiting time to explore the hepatobiliary phase is a disadvantage in daily practice. As for Gd-EOB-DTPA, the main current limitation is related to a lack of large-scale studies, since most of the data available derive from phase-II and III trials.

A problem for both agents, and also for Mn-DPDP, is the possible overlap of enhancement patterns between benignancy and malignancy on the hepatocyte-specific phase. For example, FNH, HCA and well-differentiated HCC may be difficult to differentiate from each other [32, 42]. It is also important to stress that delayed phase imaging per se is frequently

insufficient to provide accurate characterization since benign lesions (e.g., hemangiomas, cysts) behave similarly to malignancy, especially metastatic disease. So, it is necessary to evaluate all imaging sets from non-contrast to enhanced dynamic multiphase MRI when using BOPTA or EOB-DTPA [23]. Another shortcoming of these agents relates to reduced liver enhancement in the presence of jaundice. Serum bilirubin values $>3\text{mg/L}$ may impair diagnostic usefulness and biliary excretion may lack.

MRI with iron oxides requires a longer imaging protocol that generally implies pre- and post-contrast imaging over a period of 30 min or more in the case of SPIO, or more than 24 h when using USPIO for MR lymphography.

Limitations of SPIO-enhanced MRI of the liver include the possibility of false positives due to the increased signal of vessels seen end-on on cross-sectional axial slices against a background of black liver [23]. Furthermore, use of SPIO in patients with cirrhosis is challenging due to the diminished uptake and heterogeneous signal intensity due to Kupffer cell impairment, inflammation and fibrosis that may ultimately mimic or conceal HCC [23, 45]. As with hepatocyte-specific Gd-chelates, lesion characterization may encounter difficulties for differentiation between benign hepatocellular lesions and well-differentiated HCC due to the possible remnance of functional Kupffer cells [11].

Regarding ferumoxtran-10, preliminary results are promising; however, it has also been reported minimal or no uptake by inflammatory lymph nodes, which may reduce specificity of the technique [2]. Other false-positives are possibly related to the administration of lower doses of USPIO agents, the presence of lymph node necrosis or fatty metaplasia, a feature observed in about 5% of nonmetastatic nodes.

False negatives may also be generated due to the so called “blooming effect” resulting from the strong magnetic susceptibility artifact seen on T2*-w GRE sequences, obscuring nodal structure and hampering the detection of micrometastases. This may be, however, overcome by reducing the echo time in order to obtain the best image quality for the clinical purpose. Finally, it must be stressed that detection of intranodal micrometastases is still a problem owing to insufficient spatial resolution. This may be minimized by the use of state-of-art equipments with multi-element coils and stronger magnetic fields.

Summary

- › The use of intravascular contrast agents in MR examinations became widespread in a variety of clinical scenarios. They may play a pivotal role in several abdominal conditions, both by improving detection as well as characterization of lesions. MR contrast agents can be divided according to their magnetic properties into paramagnetic and superparamagnetic agents. They are also classified as interstitial, nonspecific, or liver-specific contrast media, with the latter subdivided according to their target-cell population: hepatocyte-selective or Kupffer cell contrast agents.
- › Paramagnetic contrast agents shorten the T1 relaxation time of tissues. They are Gd-based and may show a rapid vascular passage followed by interstitial diffusion (nonspecific agents) or experience an initial extracellular distribution followed by uptake from hepatocytes and biliary excretion (hepato-biliary agents). Superparamagnetic contrast media shorten the T2 relaxation time. They are composed of iron oxide particles which are primarily taken up, according to their size, by the liver, spleen and bone marrow (SPIO, mean size $> 50\text{ nm}$), or lymph nodes (USPIO, mean size $< 50\text{ nm}$).
- › Previous studies have shown that Gd-based dynamic MRI may be slightly better than SPIO-enhanced MRI for the detection and characterization of some lesions (such as small HCC), but SPIO agents increase the accuracy of MRI for detection and characterization of focal liver lesions helping to improve accuracy; this is especially true in the case of metastases. The main clinical application of USPIO agents is for characterization of lymph nodes and, at present, the best clinical benefit for the use of USPIO agents concerns metastatic lymph node involvement in patients with prostate cancer.
- › The prospects for new applications of particulate iron oxides in cellular imaging are very promising. Research is still ongoing to demonstrate the ability of nanoparticles to target inflammatory lesions via macrophage labeling. This opens up major and very exciting prospects for the characterization of numerous inflammatory and degenerative diseases. USPIO-

enhanced MRI may also play a role for detection of inflammatory atheroma plaques. Thus far, evidence suggests that macrophage uptake of USPIO at sites of atherosclerosis could indicate disease sites prior to luminal narrowing, leading to earlier diagnosis and treatment [46]. USPIO may also allow better display of the fibrous cap suggesting that this contrast agent could be used not only to detect inflammation within vulnerable lesions but also identify “safer” plaques with a significant fibrous component [47].

- ▶ Other field of research of SPIO is the active targeting of cells undergoing apoptosis. Apoptosis plays a role in the pathology of cancer, neurodegeneration, acute myocardial infarction, and chronic inflammation. SPIO targeting apoptotic cells could also allow for the real-time monitoring of drug efficacy [46].
- ▶ Finally, these contrast agents could be used to label hematopoietic cells allowing direct depiction of cellular traffic, homing in the bone marrow, differentiation of immature cells, and transplant rejection in vivo. By the addition of targeted ligands, these agents can potentially become disease specific products [48].

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