

- Liver Specific Contrast Agents: An Update -

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Introduction

Ultrasound has traditionally been a modality for the primary screening of patients with abdominal pain but with the advent of contrast-enhanced ultrasound techniques it is now a highly capable methodology for both the characterization and improved detection of liver masses [1]. In the case of computed tomography (CT), this technique has generally been considered the imaging approach of choice for the detection of liver masses principally because of the ease of performing and interpreting large numbers of examinations, its widespread availability, and a generally acknowledged superior ability to evaluate the extra-hepatic abdomen [2]. With the recent developments in MDCT technology, particularly the emergence of 16- and 64-row scanners combined with highly concentrated iodinated contrast agents, the impact of CT for both the detection and, to a lesser extent, characterization of focal liver lesions has markedly improved. In particular, the substantially shorter acquisition times, the possibility to acquire thin sections on a routine basis within a single breath-hold, the opportunity to retrospectively calculate thinner or thicker sections from the same raw data, and improved 3D-postprocessing techniques now permit the acquisition of almost similar diagnostic information to that attainable on contrast-enhanced MR imaging with conventional extracellular gadolinium contrast agents in which information derives from differential blood flow between tumour and surrounding normal liver parenchyma [3, 4]. However, unlike the situation in MR

imaging there are as yet no hepatospecific contrast agents available for CT. Hence, additional information based on the functionality of liver lesions, which is attainable on MR imaging, is not yet attainable on MDCT. Moreover, concern over the nephrotoxicity of certain iodinated contrast agents and the requisite use of ionizing radiation in CT examinations are perennial factors to be considered when referring patients for diagnostic evaluation of the liver [5].

In contrast to the situation in CT, several different classes of contrast agent are available for routine clinical use in MR imaging of the liver [6, 7, 8]. These include non-specific materials that distribute extracellularly in a manner similar to that of the iodinated agents used in CT, materials that are taken up specifically by hepatocytes and excreted in part through the biliary system, and materials that are targeted specifically to the Kupffer cells of the reticuloendothelial system (RES) (Tables 1, 2). The differential use of these agents according to the clinical questions to be answered can maximize the diagnostic information available to the investigating radiologist. Properties and indications of each category of contrast agent for MR imaging of the liver will be discussed and examples of the behaviour of the agents in typical pathologies will be presented.

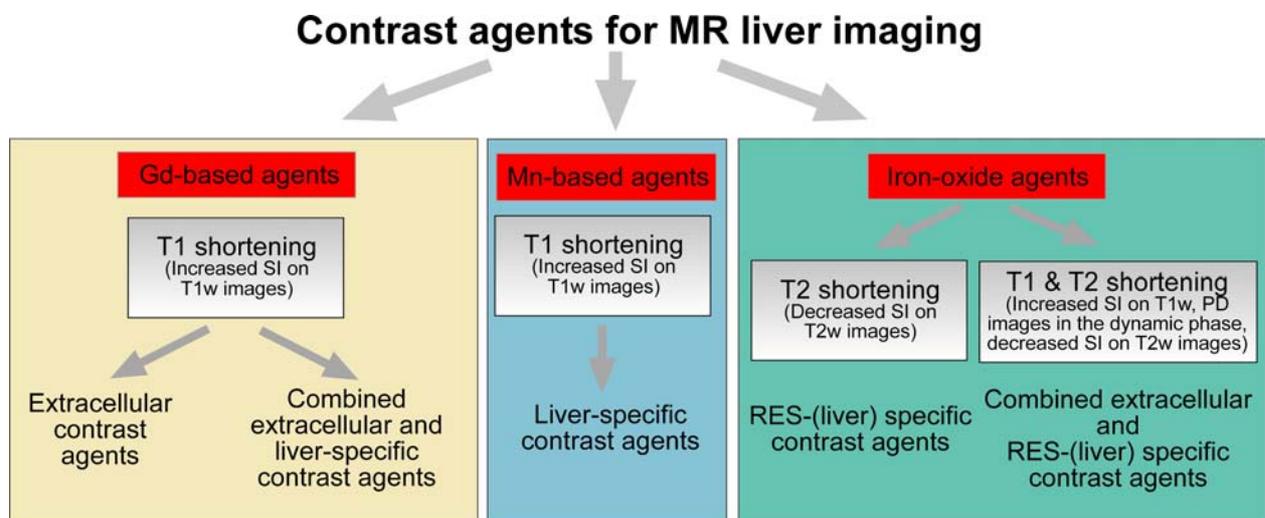


Table 1

Contrast Agents for liver imaging

MRI is an established diagnostic modality for the evaluation of focal liver lesions (FLL), although the accuracy of unenhanced MRI for lesion characterization is comparatively low [9]. In order to adequately detect and characterize FLLs on MRI it is necessary to utilize contrast media (CM) which are able to modify the signal

intensity of either the lesion or surrounding normal liver parenchyma. By providing information on the vascularization of FLLs, intravenously administered CM can contribute substantially to the accurate characterization of FLLs [10, 11].

The conventional approach to contrast enhanced MRI of the liver is to use extracellular gadolinium contrast agents that distribute exclusively to the extracellular space. With regard to the mechanism of FLL depiction, these agents permit the acquisition of images which are at least comparable to those from double helical CT after bolus injection of iodinated CM. They are able to provide information on the arterial and portal-venous vascular supply of the liver and important information on the vascularization of an FLL [12]. However, the recent availability of CM targeted to either hepatocytes or Kupffer cells has revolutionized the possibilities for liver MRI. These CM utilize the paramagnetic properties of gadolinium, manganese, or the superparamagnetic properties of iron [13-16].

In general contrast agents for liver imaging can be subdivided into three classes based on the primary distribution of the agent: agents with a purely extracellular distribution, agents with a purely hepatobiliary distribution and agents that are targeted specifically to the reticulo-endothelial system (RES) (Table 2).

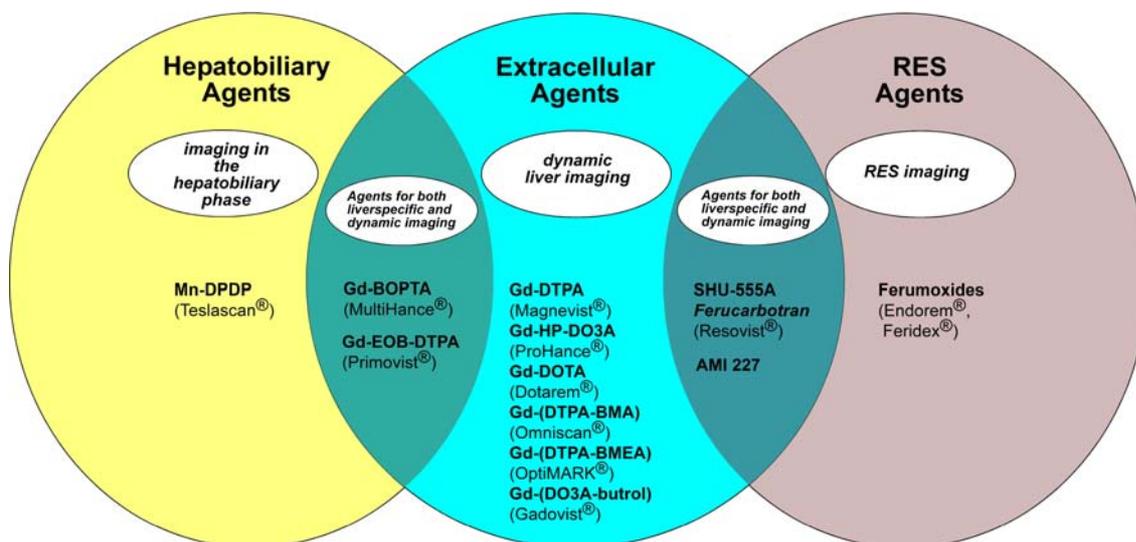


Table 2

More recent developments have seen the emergence of agents with dual distribution profiles that combine the properties of both an extracellular agent and a hepatobiliary-targeted agent, or an extracellular agent and a RES-targeted agent. Examples of the former class of agent are Gd-BOPTA and Gd-EOB-DTPA while

examples of the latter class of agent are SHU-555A and AMI 227. Each of these agents can be used in the initial dynamic phase after injection when enhancement is based solely on the extracellular distribution of the CM. Thereafter these agents are taken up by either functioning hepatocytes or the Kupffer cells of the RES.

Extracellular Gadolinium agents

Chelates of the paramagnetic gadolinium ion that distribute solely to the extracellular space (i.e., do not have any tissue specific biodistribution) have been commercially available since 1986. The four non-specific gadolinium chelates approved in the USA are gadopentetate dimeglumine (Magnevist[®], Gd-DTPA; Berlex Laboratories/Schering AG), gadoteridol (ProHance[®], Gd-HP-DO3A; Bracco Diagnostics), gadodiamide (Omniscan[®], Gd-DTPA-BMA; GE Healthcare), and gadoversetamide (Optimark[®], Gd-DTPA-BMEA; Mallinckrodt). Other non-specific gadolinium agents currently approved in Europe only include gadoterate meglumine (Dotarem[®], Gd-DOTA; Guerbet) and gadobutrol (Gadovist[®], Gd-BT-DO3A; Schering AG) (Table 2).

Extracellular agents are currently the most widely employed CM in liver imaging. These agents shorten the T1 relaxation time of tissues resulting in an increase in tissue signal intensity. However, they are applicable solely for the dynamic phase of contrast enhancement for the acquisition of images during the arterial phase, the portal-venous phase and the equilibrium phase of liver perfusion after the bolus injection of the contrast agent.

The extracellular contrast agents that are available today do not differ significantly in terms of their physico-chemical properties or their enhancement of the normal liver parenchyma after intravenous bolus injection. A relatively recent example of this type of agent (Gd-DO3A-butrol; Gadovist[®]) is a contrast agent with a chemical structure that is very similar to that of Gd-HP-DO3A (ProHance[®]). This agent is formulated to a two-fold higher concentration in solution and thus differs from the other agents in that the total volume of CM injected is half of that of the other agents. A possible advantage of this agent is the ability to administer a shorter bolus perhaps resulting in denser profiles of the arterial and portal-venous phases.

All of these extracellular agents permit satisfactory differentiation of FLLs into three classes:

- Lesions that are hypervascular in the arterial phase (Fig. 1),
- Lesions that are hypovascular in the arterial phase (Fig. 2), and
- Lesions which demonstrate delayed persistent enhancement (Fig. 3).

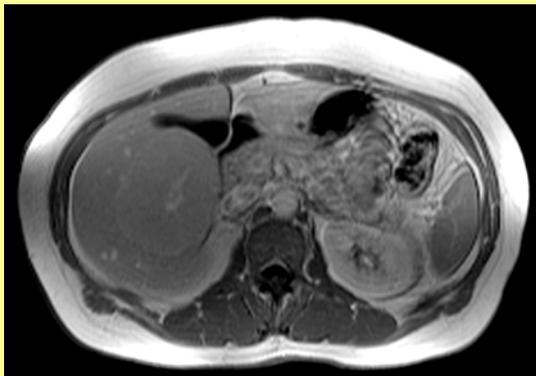
Fig. 1 a-e



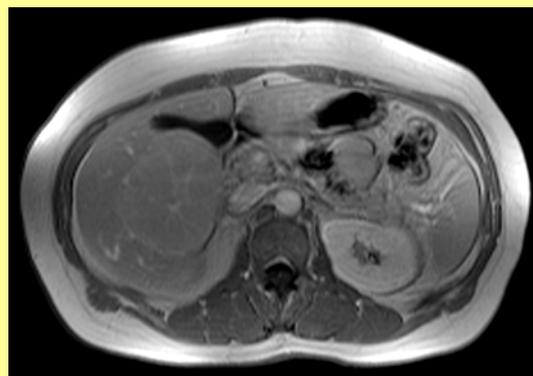
a)



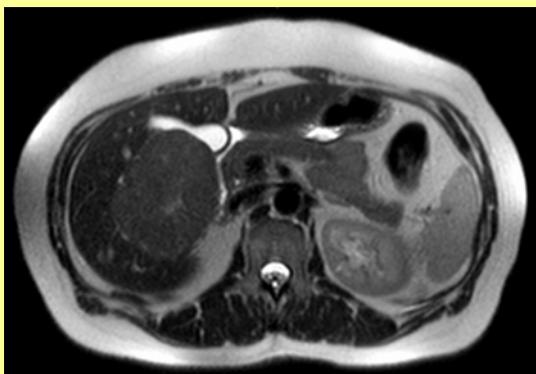
b)



c)



d)



e)

Typical hypervascular liver lesion (FNH) evaluated with an extracellular Gd-agent. On the unenhanced T1w-image (a) the lesion (arrow) is slightly hypointense and demonstrates strong arterial hypervascularization in the arterial phase after bolus CM

injection (b). Note the hypointense central scar in the arterial phase indicative of a focal nodular hyperplasia (FNH). In the portal-venous phase the lesion shows wash-out of CM and enhancement of the central scar (c). In the equilibrium phase (3-5 min post CM injection) the lesion is isointense to normal liver parenchyma (d). The corresponding T2w image shows a lesion that is slightly hyperintense to normal liver tissue with a hyperintense central scar (e). These features on unenhanced and contrast enhanced images allow for the accurate diagnosis of FNH.

Fig. 2 a-e



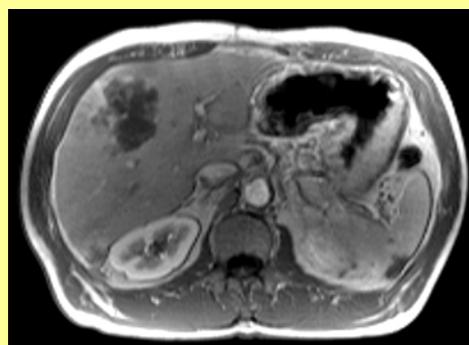
a)



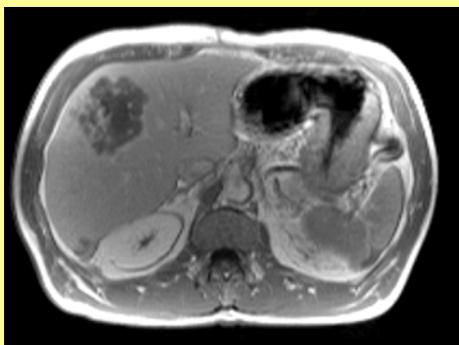
b)



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d)



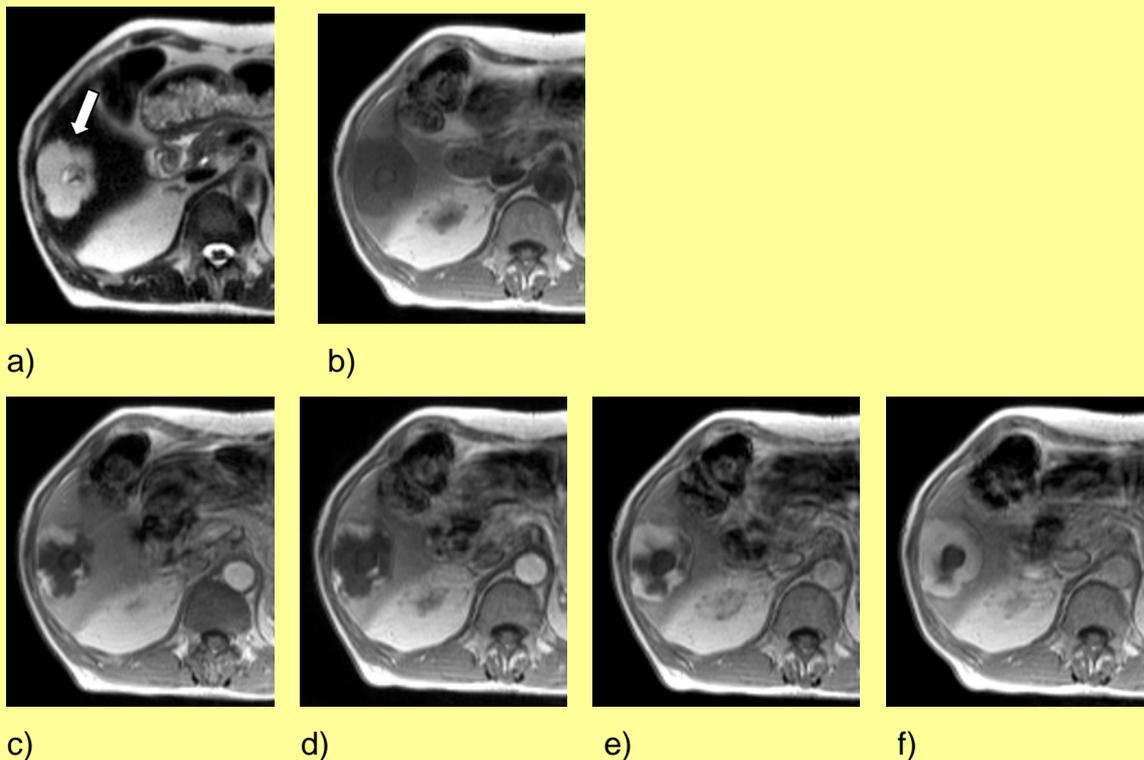
e)

Hypovascular liver metastases of colorectal carcinoma.

Unenhanced T2w (a) and T1w (b) images show two liver lesions with increased SI on the T2w image and decreased SI on the T1w image (arrows). Following the injection

of an extracellular Gd-agent both lesions show some peripheral enhancement in the arterial phase (c) whereas the central parts of the lesions remain hypovascular. In the portal-venous (d) and equilibrium (e) phases the lesions are still hypointense and can be clearly differentiated from surrounding liver tissue.

Fig. 3 a-f



Typical liver lesion with delayed persistent enhancement after injection of an extracellular Gd-agent. The unenhanced T2w (a) and unenhanced T1w (b) image show a hyperintense and hypointense liver lesion, respectively (arrow). The central areas of the lesion show myxoid changes on the T2w scan. Following bolus injection of an extracellular Gd-agent, the lesion demonstrates nodular peripheral enhancement in the arterial phase (c) that progresses centrally during the portal-venous (d) and equilibrium (e) phases. At 10 min after CM injection (f) the lesion shows homogeneous uptake of CM along with spared central areas of thrombosis and myxoid changes that are often seen in large hemangioma. The observed centripetal filling that starts with a nodular peripheral enhancement during the arterial phase is typical of hemangioma.

These types of enhancement behavior permit satisfactory differentiation of a large variety of lesions. In conjunction with typical imaging signs such as peripheral

washout of CM from liver metastases during the equilibrium phase, these agents are frequently sufficient for the highly accurate differentiation of benign from malignant lesions.

Unfortunately for some liver lesions, particularly hypervascular benign and malignant lesions, there is a large overlap in the enhancement behavior during dynamic phase imaging. In order to satisfactorily characterize these lesions additional information about the cellular architecture of the lesion is needed. The availability of liver specific agents has gone some towards making this additional information attainable.

Hepatocyte-Targeted Contrast Agents

Hepatocyte-selective contrast agents undergo uptake by hepatocytes and are eliminated, at least in part, through the biliary system.

Mn-DPDP

A prototypical, dedicated hepatocyte-selective contrast agent is mangafodipir trisodium (Teslascan[®], Mn-DPDP; GE Healthcare) which was approved for clinical use in 1997. As with gadolinium chelates, mangafodipir trisodium is considered to have an acceptable safety profile although injection-related minor adverse events such as flushing, nausea and dizziness are relatively common. Moreover, Mn-DPDP dissociates rapidly following administration to yield free Mn⁺⁺ ion which, in patients with hepatic impairment, may be associated with increased neurological risk.

Mangafodipir trisodium is, like the gadolinium agents, a paramagnetic agent and primarily affects T1 relaxation times. The increased signal intensity generated in functioning hepatocytes improves the contrast against non-enhancing tissues on T1-weighted images. This agent is administered as a slow intravenous infusion over 1-2 minutes which unfortunately precludes the possibility to perform dynamic phase imaging in the manner performed with gadolinium-based agents. Moreover, because the 5 to 10 $\mu\text{mol/kg}$ dose of mangafodipir trisodium is 10% or less than that of the gadolinium agents, imaging with mangafodipir during its distribution phase in the extracellular fluid compartment does not contribute to diagnosis. Doses above 10 $\mu\text{mol/kg}$ do not contribute to additional enhancement either. Liver enhancement is maximal within 10 minutes of mangafodipir trisodium infusion and persists for several hours. Since dynamic images are not acquired with this agent, any T1-weighted

sequences can be used. Use of fat saturation has been shown to improve contrast. More importantly, higher spatial resolution imaging can be used effectively even if the entire liver cannot be covered in one data acquisition. On state of the art scanners a useful sequence would be a 2D or 3D spoiled GRE sequence with a matrix size of 512/256 x 512 [17].

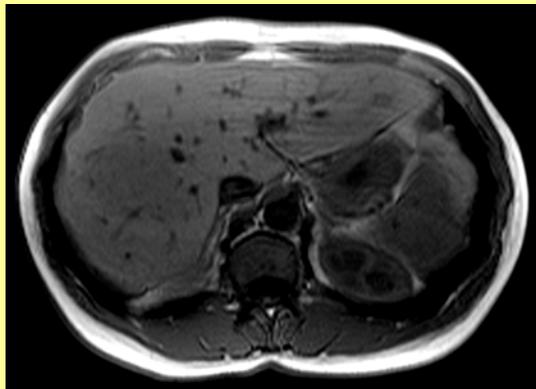
Because liver enhancement in patients with cirrhosis is limited with mangafodipir trisodium, liver lesion detection on mangafodipir-enhanced MR imaging is primarily effective in patients with normal liver parenchyma. In these patients non-hepatocellular focal lesions generally appear hypointense to the normal liver on post-contrast T1-weighted images.

Several studies have shown a benefit for liver lesion detection with mangafodipir-enhanced hepatic MR imaging as compared with unenhanced MR imaging. Moreover, since hepatocellular lesions such as FNH, hepatic adenoma and HCC generally enhance with mangafodipir, it is frequently possible to differentiate detected lesions of hepatocellular origin from lesions of non-hepatocellular origin (Fig. 4) [17].

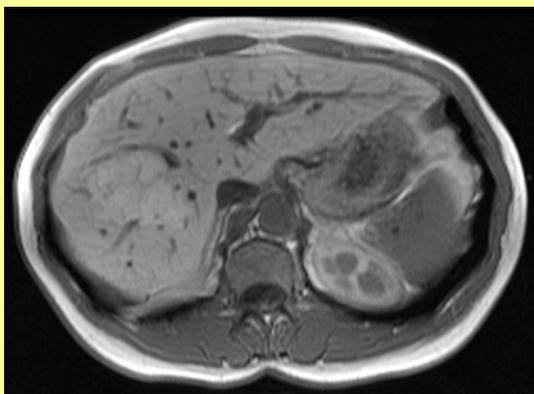
Fig. 4 a-d



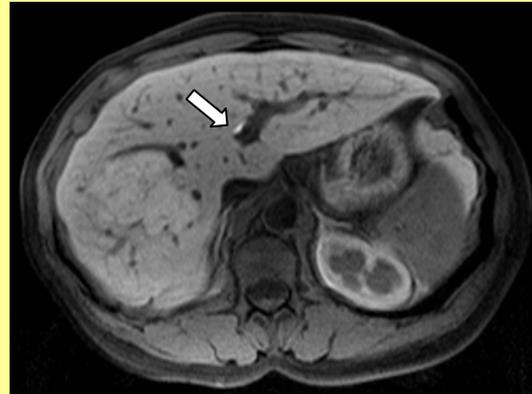
a)



b)



c)



d)

Mn-DPDP enhanced MRI of FNH.

The unenhanced T2w image (a) shows a slightly hyperintense lesion in the right liver lobe (arrow). On the corresponding unenhanced T1w image (b) the lesion appears slightly hypointense. Following the administration of Mn-DPDP the lesion appears hyperintense compared with surrounding liver tissue on the T1w image (c). This uptake is even more obvious on the T1w fat suppressed image (d) in which excretion of the CM into the bile duct is also visible (arrow in d). Uptake of the CM into the liver lesion indicates the presence of a hepatocellular lesion although it is not possible to reliably differentiate between FNH, hepatic adenoma and well differentiated HCC.

Unfortunately, because mangafodipir trisodium often causes the enhancement of both benign and malignant lesions of hepatocellular origin, it is not always possible to differentiate benign from malignant lesion-types. In a study of 77 patients with histologically-confirmed diagnoses, the sensitivity and specificity of mangafodipir-enhanced MR imaging for the differentiation of histologically-confirmed malignant vs benign lesions was 91% and 67%, respectively, while that for the differentiation of hepatocellular vs non-hepatocellular lesions was 91% and 85%, respectively. Enhancement of both benign and malignant hepatocellular neoplasms limits the usefulness of this agent for the accurate differentiation of hepatocellular lesions and this, combined with the frequent need for delayed imaging at 4-24 hrs post-contrast, represents a principal shortcoming of this agent [18].

Apart from the inability to adequately differentiate benign from malignant lesions of hepatocellular origin, a further potential limitation of mangafodipir trisodium - enhanced liver MR imaging appears to be inadequate characterization of non-hepatocellular lesions. Common benign tumours such as hemangiomas and cysts, as well as non-neoplastic masses such as focal fatty infiltration and focal fat sparing may mimic malignancy in patients with known or suspected cancer. In these settings gadolinium-enhanced dynamic multiphase MR imaging is invaluable for satisfactory lesion characterization.

Although mangafodipir trisodium is primarily considered an agent for MR imaging of the liver, a number of early studies demonstrated a potential usefulness for imaging of the pancreas as well. Moreover, since the Mn^{++} ion is excreted in part through the biliary system, mangafodipir trisodium may prove effective for biliary tract imaging [19].

Combined extracellular and hepatobiliary agents

Gd-BOPTA, Gd-EOB-DTPA

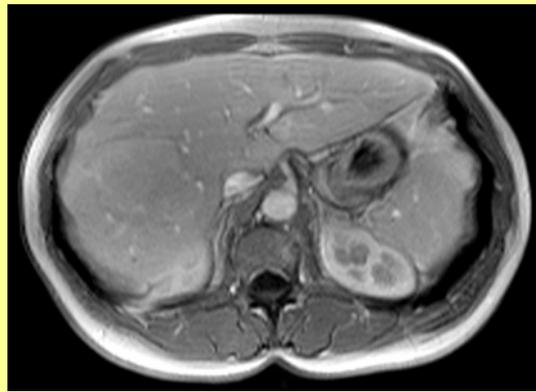
The possibility to obtain both dynamic and hepatobiliary phase images of the liver in a single examination is afforded by the availability of gadolinium-based contrast agents with combined extracellular and hepatobiliary properties. Two agents that show hepatocyte-selective uptake are Gd-BOPTA (MultiHance[®], Gd-BOPTA; Bracco Imaging SpA, Italy) and Gd-EOB-DTPA (Primovist[®], Gd-EOB-DTPA, Schering AG, Germany). Of these only Gd-BOPTA is approved by the U.S. Food and Drug Administration for use in the United States, however no specific approval for liver imaging is available in the US. Unlike Mn-DPDP, these agents can be administered as a bolus in an analogous manner to conventional, purely extracellular gadolinium agents. They distribute to the extracellular compartment in the first minutes after injection and can be utilized in standard protocols for the acquisition of dynamic phase images to obtain specific information on FLL vascularity.

The unique feature of Gd-BOPTA and Gd-EOB-DTPA, which distinguishes these agents from conventional gadolinium agents, is that following the initial extracellular distribution a fraction of the injected dose is then taken up by functioning hepatocytes and eliminated via the hepatobiliary pathway (Fig. 5). This uptake into functioning hepatocytes causes an increase of the signal intensity of normal liver parenchyma in a manner comparable to that obtained after injection of mangafodipir trisodium. In the case of Gd-BOPTA approximately 3-5% of the injected dose is taken up by functioning hepatocytes and ultimately excreted via the biliary system. As with mangafodipir trisodium, a result of the hepatocytic uptake is that the normal liver parenchyma shows strong enhancement on delayed T1-weighted images that is maximal beginning approximately 1 hr after administration. Advantages of a 1 to 3 hour time interval between the acquisition of dynamic and delayed, hepatobiliary phase images with Gd-BOPTA are firstly that the patient is not required to remain in the magnet for an extended period (he/she can re-enter the magnet for a brief period at a time convenient to both the patient and the investigating radiologist) and secondly, that the radiologist has an opportunity to review the dynamic series of acquisitions in order to decide whether a scan during the hepatobiliary phase is necessary or not – in many cases (e.g. hemangioma) the information available on dynamic phase images alone is sufficient for diagnosis.

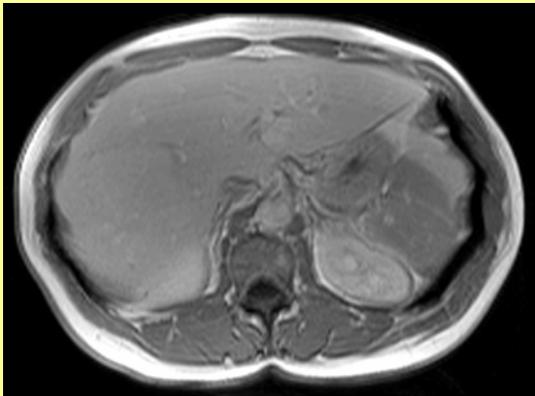
Fig. 5 a-e



a)



b)



c)



d)



e)

Gd-BOPTA enhanced MRI of FNH. (Same patient as demonstrated in Fig. 4)

After the bolus injection of Gd-BOPTA the lesion shows strong hypervascularization in the arterial phase (a) followed by a rapid wash-out in the portal-venous phase (b).

In the equilibrium phase (c) the lesion is isointense compared with normal liver tissue.

Since no central scar is visible, possible differential diagnoses for this lesion are atypical FNH without central scar and hepatocellular adenoma. However, in the

hepatocyte specific phase 1 hour after the injection of Gd-BOPTA the lesion shows

marked CM uptake on the T1w image (d, arrow), which is even more obvious on the T1w fat suppressed image (e). This uptake of Gd-BOPTA indicates an atypical FNH since hepatocellular adenoma appear hypointense in the hepatocyte-specific phase after Gd-BOPTA.

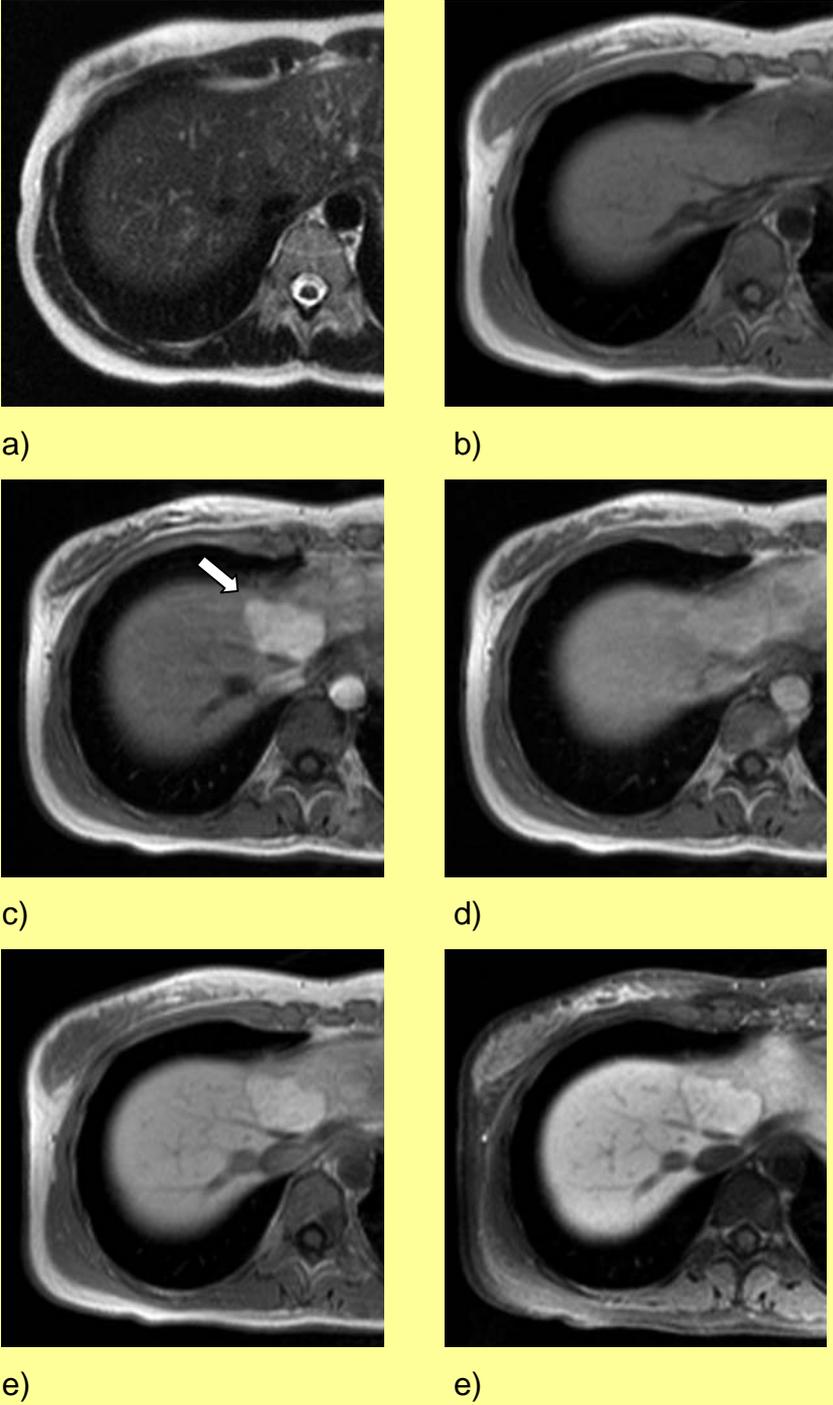
The uptake of both Gd-BOPTA and Gd-EOB-DTPA by functioning hepatocytes occurs by a more specific mechanism than that for Mn-DPDP. Specifically, an ATP-dependent canalicular multispecific organic anion transporter peptide (OATP) shared with bilirubin has been implicated in the transfer of Gd-BOPTA across the sinusoidal membrane of hepatocytes into the bile. The benefits of this specific uptake and elimination mechanism for differential diagnosis are that precise information on the cellular content and functionality of a lesion can be obtained which is additional to the purely vascular information available on dynamic phase images alone. In the case of Gd-BOPTA, the information available on delayed hepatobiliary phase images has been shown to be invaluable for the precise identification of atypical FNH [20] in cases in which dynamic images alone give equivocal results (see Fig. 5), for the accurate differentiation of FNH from HA [21], for the precise characterization of hypervascular HCC [22], and in certain cases for the accurate differentiation of benign regenerative nodules and well differentiated HCC. However, even with these agents some overlap of enhancement behavior may be seen. For example, certain well differentiated HCC may retain some primitive bile ducts resulting in uptake of CM and a hyperintense appearance on delayed images.

Whereas Gd-BOPTA was first introduced onto the European market in 1998, Gd-EOB-DTPA has just recently been approved and little information is as yet available beyond that deriving from Phase II and III clinical trials. It is likely that this agent utilizes the same hepatocellular carrier as Gd-BOPTA and behaves in a similar manner during the hepatocellular phase.

Like Gd-BOPTA, this agent has a higher T1 relaxivity compared to the conventional extracellular agents and distributes initially to the vascular and interstitial compartment after bolus injection. However, whereas only 3-5% of the injected dose of Gd-BOPTA is thereafter taken up by hepatocytes and eliminated in the bile, in the case of Gd-EOB-DTPA some 50% of the injected dose is taken up and eliminated via the hepatobiliary pathway after approximately 60 min. The maximum increase of liver parenchyma signal intensity is observed approximately 20 min after

injection and lasts for approximately 2 hours. As with Gd-BOPTA, the dynamic enhancement patterns seen during the perfusion phase after injection of Gd-EOB-DTPA are similar to those seen with Gd-DTPA (Fig. 6).

Fig. 6 a-e



The unenhanced T2w (a) and T1w (b) images do not reveal the presence of a liver lesion. In the arterial phase after the injection of Gd-EOB-DTPA (c) a hypervascular liver lesion is demonstrated (arrow). This lesion shows rapid wash-out and again appears isointense to normal liver in the portal-venous phase (d). In the hepatocyte-

specific phase 20 min after injection of Gd-EOB-DTPA the T1w image (e) reveals strong CM uptake by the liver lesion indicating a lesion of hepatocellular origin. The CM uptake is even more obvious on the T1w fat suppressed image (e). Whether this uptake is unique for FNH and is not observed in hepatocellular adenoma is still unclear for Gd-EOB-DTPA and further studies are needed to clarify this issue.

During the hepatobiliary phase, Gd-EOB-DTPA-enhanced images have been shown to improve significantly the detection rate of metastases, HCC, and hemangiomas compared with unenhanced and Gd-DTPA-enhanced images. Moreover, Gd-EOB-DTPA may also be a suitable agent for biliary imaging. Like Gd-BOPTA, Gd-EOB-DTPA is indicated to have a safety profile that is not dissimilar from those of the conventional extracellular gadolinium agents.

RES-targeted Contrast Agents

Another approach to imaging of the liver involves the use of superparamagnetic iron oxide (SPIO) particles targeted to the Kupffer cells of the RES in the liver parenchyma. A number of SPIO-based agents have either been approved in one or more countries of the world or are in the developmental phase. Although these agents differ from each other in terms of size of the SPIO particles and coating (i.e., starch or polydextran), their mechanism of action is similar. Iron oxide particles with a mean size of >50 nm are referred to as superparamagnetic iron oxides (SPIO) while those with a mean particle size of <50 nm are referred to as ultrasmall superparamagnetic iron oxides (USPIO). Of the various formulations, two have so far been developed clinically for MR imaging: ferumoxides (Feridex[®], Berlex Laboratories and Endorem[®], Laboratoire Guerbet) which has a particle size ranging between 50 and 180 nm and SH U 555 A (Resovist[®], Schering AG) which has a particle size ranging between 45 and 60 nm. The safety profiles of these agents are less attractive than those of the paramagnetic contrast agents: although serious adverse events are rare, with Endorem[®] approximately 3% of patients will experience severe back pain while the contrast agent is being administered [23].

In each case these coated particles produce an alteration of the externally applied magnetic field in MRI which leads to magnetic field heterogeneities. These induced heterogeneities promote spin dephasing and hence, as a result of the

reduced T2 relaxation time, lead to signal loss or a decrease of signal intensity on T2-weighted images [24].

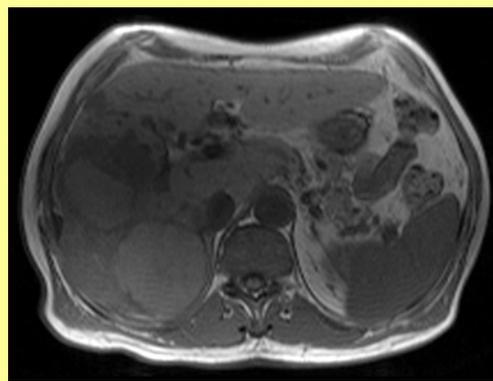
Purely RES specific agents

The principal superparamagnetic effect of the larger SPIO particles is mainly on T2 relaxation and thus MR imaging is usually performed using T2-weighted sequences in which the tissue signal loss is due to the susceptibility effects of iron. Enhancement on T1-weighted images can also be seen although this tends to be greater for the smaller SPIO and especially for the USPIO formulations. Since there is an overall decrease in liver signal intensity, T2-weighted imaging with SPIO requires excellent imaging techniques that are free of motion artefacts. Typically, moderate T2-weighting (TE of approximately 60-80 msec) is adequate for optimizing lesion-liver contrast. Since the larger SPIO agents need to be administered by slow infusion to reduce side effects, for these agents imaging is generally performed some 20 - 30 min after administration [25]. Thus, scanning speed is not important and both fast breath-hold and conventional SE imaging can be employed. Pulse sequences that are sensitive to magnetic field heterogeneity tend to be sensitive to the presence of iron oxide. T2*-weighted gradient echo images are very sensitive to SPIO. T2-weighted spin echo sequences are more sensitive than T2-weighted fast (turbo) spin echo sequences, because the multiple rephasing pulses used in the latter tend to obscure signal losses arising from local variations in the magnetic environment. Administration protocols vary but typically precontrast T1- and T2-weighted imaging is followed by post-contrast T2-weighted imaging (Fig. 7) [26].

Fig. 7 a-c



a)



b)



c)

SPIO enhanced MRI of HCC. The unenhanced T2w (a) and T1w (b) images show multiple lesions in the right liver lobe, although the borders of the lesion towards the left lobe are not clearly defined. Following the administration of SPIO (c) a decrease of the signal intensity both of the liver and the spleen is visible due to the uptake of SPIO particles by the cells of the RES. In addition much better delineation of the HCC against the unaffected liver parenchyma is visible (arrow). This helps in patient management decisions, i.e., in deciding whether the patient is a candidate for liver surgery or not.

Since SPIO particles are removed by the RES, the application of these agents is similar to the use of Tc-sulfur colloid in nuclear scintigraphy. Lesions that contain negligible or no Kupffer cells remain largely unchanged, while the signal intensity of the normal liver is reduced on T2-weighted images. As a result the contrast-to-noise ratio between the normal liver parenchyma and focal liver lesion is increased [25, 26].

Many well-controlled studies using surgical pathology or intraoperative ultrasound (IOUS) as gold standard have supported the efficacy of SPIO-enhanced MR imaging [25-28]. For example, an early multi-center Phase III study showed more lesions in

27% of cases compared to unenhanced MR and in 40% of cases compared to CT [25]. On the other hand, other early studies were not able to demonstrate a significant benefit over unenhanced imaging for the depiction of hepatic tumours. More recent studies, however, have shown that SPIO-enhanced MR imaging has significantly greater detection capability for liver malignancies as compared with spiral CT [29, 30]. Although comparisons of SPIO-enhanced MR imaging with other gadolinium-enhanced MR techniques have been somewhat limited until recently, the general conclusion is that gadolinium-enhanced imaging is the more valuable approach for the detection of hepatocellular lesions such as HCC and FNH [31].

Limitations of SPIO-enhanced MR imaging include an increased incidence of false positive lesions due to the possibility of vessels mimicking lesions against a background of black liver, and a longer imaging protocol that requires pre and post contrast imaging over a period of 30 minutes or more. Furthermore, the use of SPIO in patients with cirrhosis is also challenging due to the diminished uptake and heterogeneous signal arising from fibrosis. However, in this regard a recent study has suggested a lower dose of SPIO agent might be useful in patients with cirrhotic liver [32].

Combined dynamic and RES specific agents

In an attempt to overcome the problems inherent to pure RES imaging (i.e., the inability to obtain information on the vascular status of an FLL), agents with properties that permit their use for both dynamic and delayed phase imaging have been developed. The availability of SH U 555 A may go some way towards overcoming these problems in that this agent can be administered as a fast bolus in order to observe the early perfusion characteristics of the liver using T1- or T2*-weighted sequences. These sequences, combined with the enhancement patterns observed on delayed T1w and T2w images, may prove clinically useful for both the detection and characterization of lesions [33, 34].

SH U 555 A was introduced into several European countries in 2001. This agent differs from ferumoxides in that the coating substance is carboxydextran rather than dextran and that the overall particle size is in the range from 45 – 60 nm. This much smaller hydrodynamic diameter confers very different properties on ferucarbotran compared with ferumoxides. First, the smaller particle size allows for bolus injection of the contrast agent without the typical side effects associated with ferumoxides.

Second, the smaller particle size results in more rapid uptake of the CM by RES cells. This faster uptake means that acquisition of RES-specific images can be made as early as 10 min post injection. Moreover, the faster uptake also influences relaxivity related effects which means a higher R2-relaxivity for these particles. Finally, the possibility to use only a very small dose (roughly one tenth of the standard dose of a conventional extracellular gadolinium agent like Gd-DTPA) means that a valuable although less pronounced T1 effect can be observed. Combined with the possibility to perform bolus injection, this means that T1-weighted dynamic imaging can be performed in a similar manner to that performed with gadolinium agents.

Unfortunately, the enhancement observed on SH U 555 A – enhanced dynamic images is relatively weak due to the small dose that is injected (1 ml) from the pre-filled syringes. Comparisons from clinical routine of image quality between SH U 555 A and standard Gd-DTPA indicate that important diagnostic information may be missed with SH U 555 A on dynamic imaging due to the less pronounced T1 effect. Nevertheless, during the early equilibrium phase the T1 effect of SH U 555 A appears sufficient to differentiate between vessels and small liver lesions as well as to determine adequate differential diagnosis between hemangiomas, cysts and solid lesions (Fig. 8). Thus, it remains to be seen whether this agent will have widespread clinical impact for liver MRI.

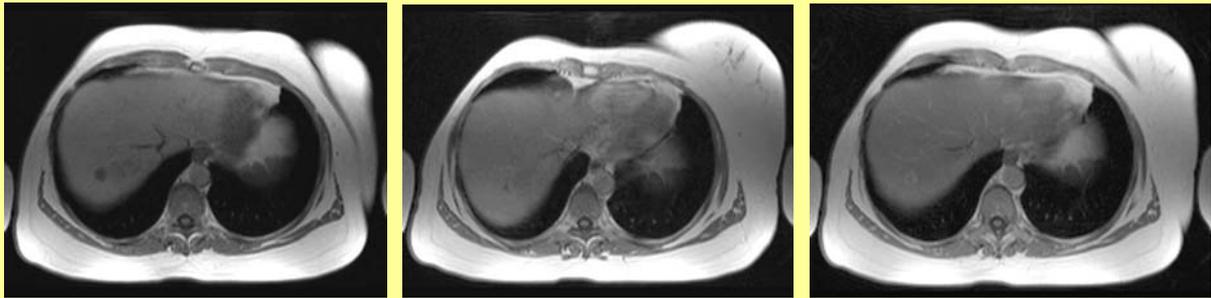
Fig. 8 a-g



a)



b)



c)

d)

e)



f)



g)

USPIO-enhanced MRI of FNH and Hemangioma. The unenhanced T2w (a) and T1w (b) images show a well defined lesion with high signal intensity on T2 and low signal intensity on T1 (arrow) in the right liver lobe. In addition a slightly hyperintense lesion adjacent to the well defined lesion is visible on the T2w image. This lesion appears slightly hypointense on the corresponding T1w image (arrowhead). Following the bolus injection of USPIO (SHU 555 A) the T1w images in the arterial (c), portal-venous (d) and equilibrium (e) phases demonstrate a delayed persistent enhancement of the first lesion indicating a hemangioma. However the hypervascular nature of the second lesion, which represents an FNH, is not clearly visible. Nevertheless the T2w image 15 min after USPIO injection (f) shows a decrease of SI of the second lesion indicating a normal Kupffer-cell content of the tissue characterizing the lesion as a benign tumour and most likely an FNH. Note that a decrease of signal intensity of the hemangioma is also visible on the T2w image and that the hemangioma still shows high signal intensity on a T1w image at 15 min after CM injection (g) due to the T1w effect of USPIOs.

In addition to possessing both T1 and T2 effects, the newer ultrasmall formulations currently under development have a longer intravascular residence time compared to the larger SPIO agents. One of the ultrasmall iron oxide-based agents under development is AMI 227 (Advanced Magnetics, Cambridge, MA). This agent has a very much smaller average particle size (approx. 5 nm diameter) and an iron

oxide core that is coated with low molecular weight dextran to give a final particle diameter of 17 – 20 nm. The smaller particle size results in a long intravascular half-life of over 200 min meaning that AMI 227 may find utility as a blood-pool agent. Although AMI 227 may be utilized in a similar way to SH U 555 A, this agent is not necessarily useful for imaging of the liver since the uptake of AMI 227 by the RES system is later than that of the SPIO agents and more prominent in the bone marrow and lymph nodes. Compared with the enhancement obtained with SPIO agents, T1-weighted acquisitions after injection of USPIO agents are likely to demonstrate signal enhancement not only of liver tissue, but also of blood and hemangiomas [35].

As with the larger SPIO particles, the Kupffer cells of the RES take up and eventually clear these USPIO particles over a period of about 24 hours. The prolonged imaging window, however, allows for more favourable image resolution and signal-to-noise ratio because the acquisition parameters are less constrained by time. For liver imaging the blood pool effect and combined T1 and T2 effects have shown promise for the detection and characterization of lesions. A specific advantage is that vessels and lesions show opposite enhancement. On T1-weighted images vessels are bright while lesions are dark whereas on T2-weighted images the reverse is true. An additional advantage is that MR Angiography may also be performed with these agents. An early study to evaluate the abdominal vasculature on delayed (45 min) images acquired following the infusion of AMI-227 revealed significant enhancement of all vessels. Similarly, TOF MR angiography prior to and following AMI-227 administration demonstrated that the depicted renal artery lengths increased significantly following contrast administration. Unfortunately, the use of blood pool agents is flawed, at the present time, by increased background signal and the superimposition of venous structures.

Summary

Various categories of MR contrast agents are available for clinical use, all of which permit the demonstration of more liver lesions than can be depicted on unenhanced imaging alone. The biggest impediment to the more widespread use of contrast agents for liver imaging in the USA in particular is that reimbursement schemes have not yet been established. Thus, these products have so far received

only a cautious welcome in the market place. In addition the added cost of the extended imaging time needed for the tissue specific (RES and hepatocyte) agents makes their use even less attractive at the current time. On the other hand, it is possible the added value and cost-effectiveness of some of the newer agents will become apparent from clinical use.

Until recently the absence in the USA of an approved contrast agent with combined extracellular and hepatobiliary distribution led various authors to propose sequential same-session imaging with both a tissue-specific agent and an extracellular gadolinium agent to improve liver lesion detection and characterization. The downside of this approach, however, is the need for two injections of two different contrast agents and the associated additional costs involved. The development of contrast agents such as gadobenate dimeglumine, which has the characteristics of both extracellular and hepatobiliary agents, allows functional information to be gained on hepatobiliary phase imaging in addition to that gained on standard dynamic phase imaging. In this regard, the use of agents with combined extracellular/hepatobiliary properties would appear to offer advantages not only in comparison to other MR contrast agents, but also in comparison to other imaging modalities such as MDCT.

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