

## Primovist, Eovist: What to expect?

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### Summary

Gadolinium ethoxybenzyl dimeglumine (Gd-EOB-DTPA, Primovist<sup>®</sup> in Europe and Eovist<sup>®</sup> in the USA) is a liver-specific magnetic resonance imaging contrast agent that has up to 50% hepatobiliary excretion in the normal liver. After intravenous injection, Gd-EOB-DTPA distributes into the vascular and extravascular spaces during the arterial, portal venous and late dynamic phases, and progressively into the hepatocytes and bile ducts during the hepatobiliary phase. The hepatocyte uptake of Gd-EOB-DTPA mainly occurs via the organic anion transporter polypeptides OATP1B1 and B3 located at the sinusoidal membrane and biliary excretion via the multidrug resistance-associated proteins MRP2 at the canalicular membrane. Because of these characteristics, Gd-EOB-DTPA behaves similarly to non-specific gadolinium chelates during the dynamic phases, and adds substantial information during the hepatobiliary phase, improving the detection and characterization of focal liver lesions and diffuse liver disease. This information is particularly relevant for the detection of metastases, and for the detection and characterization of nodular lesions in liver cirrhosis, including early hepatocellular carcinomas. Finally, Gd-EOB-DTPA-enhanced magnetic resonance imaging may provide quantitative assessment regarding liver perfusion and hepatocyte function in diffuse liver diseases. The full potential of Gd-EOB-DTPA-enhanced magnetic resonance imaging has to be established further. It is already clear that Gd-EOB-DTPA-enhanced magnetic resonance imaging provides anatomic and functional information in the setting of focal and diffuse liver disease that is unattainable with magnetic resonance imaging enhanced with non-specific contrast agents.

Keywords: Magnetic resonance imaging; Contrast media; Gadolinium ethoxybenzyl DTPA; Liver neoplasms; Liver cirrhosis; Liver function tests.

Received 29 June 2011; received in revised form 24 January 2012; accepted 27 January 2012

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Abbreviations: ABC, ATP-binding cassette; CCC, cholangiocarcinoma; CT, computed tomography; FNH, focal nodular hyperplasia; Gd-BOPTA, gadobenate dimeglumine; Gd-DO3A-butrol, gadobutrol; Gd-DOTA, gadoterate dimeglumine; Gd-EOB-DTPA, gadolinium ethoxybenzyl dimeglumine; Gd-DTPA, gadopentetate dimeglumine; HA, hepatocellular adenoma; HCC, hepatocellular carcinoma; ICG, indocyanin green; MELD, Mayo end-stage liver disease; MR, magnetic resonance; MRP, multidrug resistance protein; NTCP, sodium taurocholate-cotransporting polypeptide; OATP, organic anion transporter; SCTO, solute carrier transporter family of the OATPs; TIPS, transjugular intrahepatic portosystemic shunt.

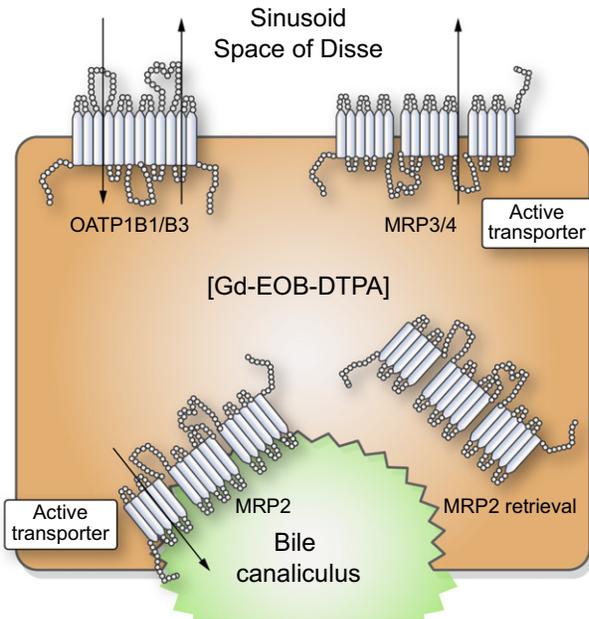
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### Introduction

Magnetic resonance (MR) imaging has an important role in the detection and characterization of focal and diffuse liver diseases. Contrast agents improve the detection of focal liver lesions by increasing the lesion-to-liver contrast. Depending on their pharmacokinetics, contrast agents also improve the characterization of focal and diffuse liver diseases by showing changes in the vascular, extracellular, or intracellular volumes, and by demonstrating modifications in the transfer rates between these compartments, including perfusion, endothelial permeability, extracellular diffusion, hepatocytic uptake and biliary excretion [1]. These volumes and transfer rates can be quantified at contrast-enhanced MR imaging, which has thus the potential to offer imaging biomarkers for the assessment of liver diseases [2].

In the liver, contrast agents are categorized into non-specific agents that distribute into the vascular and extravascular extracellular spaces (such as the linear gadopentetate dimeglumine (Gd-DTPA), Magnevist<sup>®</sup>, Bayer HealthCare, Berlin, Germany; and the macrocyclic gadobutrol (Gd-DO3A-butrol), Gadovist<sup>®</sup>, Bayer HealthCare, and gadoterate dimeglumine (Gd-DOTA), Dotarem<sup>®</sup>, Guerbet, Aulnay-sous-Bois, France) and liver-specific agents taken up by liver cells. These liver-specific agents are either taken up by Kupffer cells (such as the superparamagnetic iron oxide particles ferumoxides, Endorem<sup>®</sup>, Guerbet; and ferucarbotran, Resovist<sup>®</sup>, Bayer HealthCare) or by hepatocytes (such as gadolinium ethoxybenzyl dimeglumine or gadoxetate dimeglumine (Gd-EOB-DTPA), Primovist<sup>®</sup> in Europe and Eovist<sup>®</sup> in the USA, Bayer HealthCare; and gadobenate dimeglumine (Gd-BOPTA), MultiHance<sup>®</sup>, Bracco, Milan, Italy). Gd-EOB-DTPA and Gd-BOPTA can be injected as an intravenous bolus and provide information regarding lesion vascularity in the early arterial and venous phases and regarding hepatocyte presence and function in the delayed hepatobiliary phase performed either 20 min (Gd-EOB-DTPA) or 60–120 min (Gd-BOPTA) after injection. With Gd-EOB-DTPA, approximately 50% of the administered dose in the normal human liver is transported through the hepatocytes and excreted into the bile, a proportion much higher than that of Gd-BOPTA, which only has up to 5% hepatobiliary excretion [3].





**Fig. 1. Cellular pharmacology of Gd-EOB-DTPA.** Following distribution in the hepatic sinusoids and Disse spaces, Gd-EOB-DTPA enters into hepatocytes through the organic anion transporting polypeptides OATP1B1 and OATP1B3. Gd-EOB-DTPA exits through the ATP-dependent canalicular membrane multidrug resistance protein MRP2. MRP3 and MRP4 are transporters located in the sinusoidal membrane that may allow the efflux of Gd-EOB-DTPA back to sinusoids. The OATP are bidirectional transporters ( $\rightleftharpoons$ ). Transport through MRP2 is unidirectional ( $\rightarrow$ ) and MRP2 is regulated by retrieval from the membrane (decreased bile efflux) and insertion (increased bile efflux) while the localization of OATP never changes. Gd-EOB-DTPA is not metabolized within hepatocytes and is excreted unchanged into bile.

The percentage of the contrast agent that is not cleared by the hepatobiliary system is excreted by glomerular filtration in the kidneys. The plasma half life of Gd-EOB-DTPA is approximately 56 min in subjects with normal hepatorenal function, which is shorter compared to extracellular contrast agents (e.g. Gd-DTPA 96 min) [4]. A study by Gschwend *et al.* assessing the pharmacokinetics and safety of Gd-EOB-DTPA in patients with renal failure, hepatic failure or both showed that in patients with mild-to-moderate hepatic impairment, renal excretion was increased to compensate for hepatic impairment, and hepatic elimination was increased in the case of renal impairment [5]. The pharmacokinetic parameters of Gd-EOB-DTPA were markedly altered in patients with end-stage renal disease requiring chronic hemodialysis only, and the MR imaging signal enhancement of the liver was decreased in the presence of Child C and bilirubin values  $>3$  g/dl.

### Characteristics of Gd-EOB-DTPA

Gd-EOB DTPA is an amphipathic derivative of Gd-DTPA (Gd-DTPA with a covalently bound lipophilic ethoxybenzyl moiety). It has a molecular weight of 726 daltons and higher protein binding capacity than Gd-DTPA (10% vs. 1.5%). This binding increases the T1 relaxivity of Gd-EOB DTPA and resultant signal enhancement in blood and liver compared to Gd-DTPA. It has been reported that the T1 relaxivity of Gd-EOB-DTPA in water, rat blood and rat liver at 20 MHz and 39 °C is 5.3 L/mmol s, 11.2 L/

mmol s and 16.6 L/mmol s respectively, compared to a relatively constant relaxivity of Gd-DTPA at 5 L/mmol s in the same conditions [6,7]. This high relaxivity explains the lower clinical recommended dose of Gd-EOB-DTPA, 0.025 mmol/kg vs. 0.1 mmol/kg for Gd-DTPA and other non-specific gadolinium-based contrast agents.

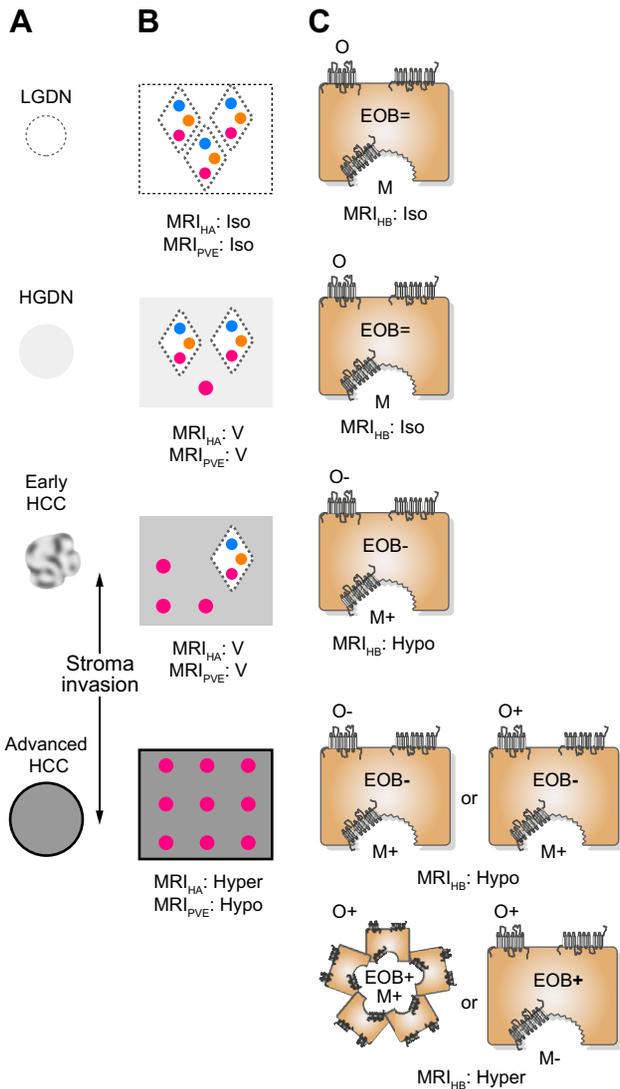
However, this low clinical dose of Gd-EOB-DTPA may lead to lower enhancement of the aorta, liver and portal vein during the arterial and venous phases as compared to non-specific gadolinium chelates at their recommended dose [8]. Moreover, the injection volume of Gd-EOB-DTPA is smaller than that of non-specific gadolinium agents. This small volume can result in acquisition timing error and truncation artifacts in the arterial phase if not properly timed. Using fluoroscopic triggering with a low injection rate of 1 ml/s to stretch the bolus or diluting the contrast with normal saline to 20 ml to enable a rapid injection rate at 2 ml/s are suggested solutions [9–11]. Doubling the dose of Gd-EOB-DTPA has also been suggested. In a study of patients with cirrhosis and hepatocellular carcinomas (HCC), it has been shown that doubling the dose improves the tumor-to-liver contrast during the arterial phase in all patients and during the hepatobiliary phase in Child B patients [12]. The clinical impact of this policy in terms of lesion detection remains unknown.

Gd-EOB-DTPA is well tolerated with adverse events similar to those reported with non-specific gadolinium chelates. Of 162 patients included in a phase III trial of Gd-EOB-DTPA injection, a total of 11 (6.8%) patients reported a total of 21 adverse events. These adverse events were assessed as: one definitely related, five probably, seven possibly, one unlikely and seven not related to the study drug. The most frequently reported adverse events of definite, possible or probable relationship to the contrast agent were nausea, vasodilatation, headache, taste perversion, and injection site pain [13].

Gd-EOB-DTPA is an open-chain (linear) gadolinium chelate that has a lower kinetic stability than macrocyclic gadolinium chelates [14]. To the best of our knowledge, no case of nephrogenic systemic fibrosis has been reported after the injection of Gd-EOB-DTPA. However, the clinical experience with Gd-EOB-DTPA is more limited than with non-specific gadolinium chelates. As the other gadolinium chelates, Gd-EOB-DTPA should be used cautiously in patients with renal insufficiency, especially in patients with a glomerular filtration rate  $<30$  ml/min/1.73m<sup>2</sup> [15].

Gd-EOB-DTPA transport in the hepatocytes is mediated by two different transport systems located at the sinusoidal and canalicular membranes of the cell [16]. The contrast agent enters the hepatocytes through the organic anion transporting polypeptides OATP1B1 and OATP1B3 which belong to the solute carrier transporter superfamily of the OATPs (SCTO). Following transport through the hepatocytes, it is excreted into the bile via the multidrug resistance protein 2 (MRP2), which belongs to the ATP-binding cassette C (ABCC) transporter subfamily [17–22].

Regarding the function of MRP2, the location of the transporter within the canalicular membrane or inside the hepatocytes is important. Thus, MRP2 function is regulated by transporter retrieval from the canalicular membrane or insertion into it. It has been reported that oxidative stress induces MRP2 retrieval from the canalicular membranes and causes cholestasis [23]. In contrast, tauroursodeoxycholic acid inserts MRP2 into the canalicular membranes and stimulates organic anion secretion into bile [24].



**Fig. 2. Classification of nodules in liver cirrhosis.** (A) Pathological classification of nodules into low grade dysplastic nodules (LGDN), high grade dysplastic nodules (HGDN), early HCC, and progressed HCC. Early HCCs show a vaguely nodular appearance and are well differentiated. Progressed HCCs grow in an expansile fashion with formation of a fibrous capsule and are moderately differentiated. The differentiation between HGDN and early HCC may be difficult at histopathological examination. The presence of stromal invasion is a useful criterion of malignancy. (B) Vascularity of nodules in liver cirrhosis and contrast-enhanced MR imaging features during the dynamic phase. Unpaired arteries (red dots) appear in HGDN and more extensively in early HCC. The increase of unpaired arteries is paralleled by a decrease of portal tracts (diamonds containing portal venous branch in blue, arterial branch in red and bile duct in orange). Progressed HCCs only contain unpaired arteries. This evolution explains that progressed HCCs typically appear hyperintense (Hyper) relative to the liver parenchyma during the arterial phase at MR imaging ( $MRI_{HA}$ ) and hypointense (Hypo) during the portal venous and/or the late dynamic phase ( $MRI_{PVE}$ ). In contrast, LGDN appear iso-intense (Iso) and early HCC have a variable enhancement (V) depending on their arterial and portal venous supply. (C) Transporters in nodules of liver cirrhosis and MR imaging features during the hepatobiliary phase. In early and progressed HCC, OATP1B1/B3 expression is often decreased (or absent) relative to that of the liver parenchyma (O-), whereas MRP2 expression is often increased (M+). These HCC appear hypointense during the hepatobiliary phase ( $MRI_{HB}$ ). In some HCC, OATP expression is increased (O+). In these HCC, the signal intensity will depend on MRP2 expression. When MRP2 expression is high, the HCCs usually appear hypointense. Hyperintense (or isointense) HCCs during the hepatobiliary phase are HCCs having high expression

Organic acid efflux from hepatocytes may also occur through the sinusoidal membrane because the transport through OATP is bidirectional and because the sinusoidal membrane also contains multidrug resistance proteins (MRP3 and MRP4). These efflux pumps are normally expressed at low levels in normal hepatocytes but can be upregulated in pathologic conditions, such as cholestasis [25] (Fig. 1).

The uptake of hepatobiliary contrast agents into hepatocytes may compete with numerous endogenous compounds and drugs. OATP1B1 and OATP1B3 transport a broad number of compounds and competition for uptake may limit Gd-EOB-DTPA uptake by hepatocytes. When rifampicin is injected before Gd-EOB-DTPA in normal rats, the antibiotic significantly prevents the increase of liver signal intensity [26]. Such competition between the substrates Gd-EOB-DTPA, rifampicin, and bromosulphthalein was also found in human embryonic kidney 293 cells injected with the human OATP1B1/B3 transporters [18]. In humans, the first interaction to be investigated was that of erythromycin [27]. The co-administration of erythromycin had no effect on GD-EOB-DTPA-enhanced liver MR imaging.

**Liver tumor detection**

Liver-specific contrast agents such as Gd-EOB-DTPA were first developed to improve the contrast-to-noise ratio between metastases and liver parenchyma. Lesions with no hepatocytes, such as metastases, or with less functioning hepatocytes, such as most HCCs, do not accumulate Gd-EOB-DTPA and appear as low signal intensity foci against the enhancing high signal parenchyma in the hepatobiliary phase, thus improving tumor detection. Several studies have shown that GD-EOB-DTPA-enhanced MR imaging has a higher sensitivity compared to dynamic contrast-enhanced CT and MR imaging enhanced with non-specific contrast agents for the detection of liver metastases and HCC [13,28-33]. Recently, the detection of small liver metastases has also been improved by unenhanced diffusion-weighted MR imaging. This last imaging sequence tends to have lower spatial resolution than the hepatobiliary phase of Gd-EOB-DTPA, and a combination of the two imaging sequences has been recommended for improved diagnostic efficacy [34]. Regarding therapeutic efficacy, it has been shown in a large multicenter trial that GD-EOB-DTPA-enhanced MR imaging changed the surgical strategy in 19 of 131 patients (14.5%) [13]. It should be noted that the time-efficiency of GD-EOB-DTPA-enhanced MR imaging can be improved by performing T2-weighted and diffusion-weighted MR imaging during the time period of more than 15 min between the completion of the dynamic series and the acquisition of the hepatocyte phase images [34]. This policy is justified because it has been shown that the lesion-to-liver contrast was significantly higher on T2-weighted and diffusion-weighted MR images after Gd-EOB-DTPA and that the apparent diffusion coefficients of focal liver lesions did not change significantly [35,36].

of OATP and low expression of MRP2 (M-) or HCCs having high expression of OATP and MRP2 with Gd-EOB-DTPA excretion in pseudoglands. This figure illustrates the superiority of GD-EOB-DTPA-enhanced MR imaging relative to MR imaging enhanced with non-specific gadolinium chelates in the differentiation between dysplastic nodules and early HCC because early HCC appear hypointense during the hepatobiliary phase at GD-EOB-DTPA-enhanced MR imaging, whereas the enhancement of dysplastic nodules and early HCC does not differ at MR imaging enhanced with non-specific gadolinium chelates.

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The improved diagnostic efficacy of Gd-EOB-DTPA relative to non-specific gadolinium chelates has to be balanced against its increased cost. The cost of gadolinium chelates varies among countries. In several European countries, the cost of Gd-EOB-DTPA is about three times higher than that of non-specific gadolinium chelates [37]. Very few health-economic studies about Gd-EOB-DTPA are available. In an economic evaluation in patients with metachronous colorectal liver metastasis, it was reported that a strategy starting with GD-EOB-DTPA-enhanced MR imaging was cost saving compared to non-specific gadolinium chelate MR imaging by improving pre-operative planning and decreasing intra-operative changes [37]. More cost-effectiveness studies based on clinical trial data rather than on expert opinion are needed in the future.

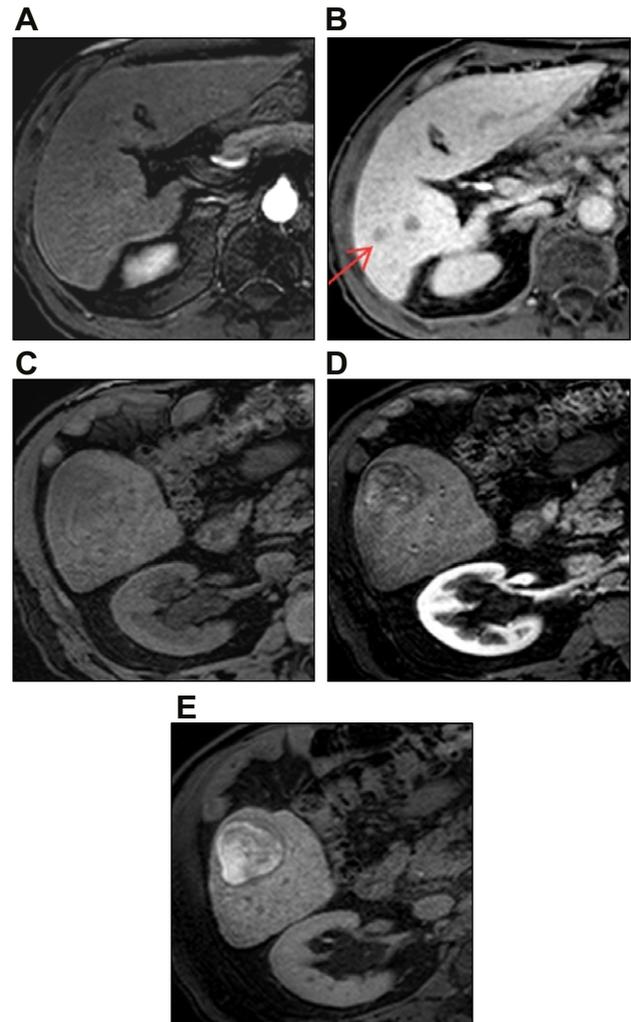
### Liver tumor characterization

At MR imaging, tumor characterization is a complex process based on the analysis of the morphology and signal intensity of the lesion on the various imaging sequences. Dynamic contrast-enhanced MR imaging during the arterial, portal venous, and equilibrium phases has an important role in this context by showing differences of contrast agent distribution between the vascular and extravascular spaces of tumors and liver parenchyma [1]. GD-EOB-DTPA provides similar information to that provided by non-specific gadolinium chelates during the arterial and venous phases, but enhancement in the equilibrium phase has contribution from hepatic cellular uptake and contrast in bile ducts, in addition to contrast in the intravascular and extracellular spaces. This phase is therefore better referred to as “late dynamic phase” [4]. Because of increased parenchymal enhancement in this phase, the delayed enhancement traditionally used to diagnose lesions such as hemangioma and cholangiocarcinoma (CCC) is altered and may no longer be discernable [38]. The high parenchymal enhancement at Gd-EOB-DTPA enhancement explains that hemangiomas may appear hypointense during the equilibrium and hepatobiliary phases [39].

#### Hepatocellular carcinomas

At dynamic, contrast-enhanced imaging with non-specific gadolinium contrast, hepatocellular carcinomas (HCC) are diagnosed when arterial hypervascularity and portal venous and/or late dynamic phase hypointensity or “washout” are demonstrated [40]. Arterial hypervascularity manifests as increased tumor enhancement relative to hepatic parenchyma during the arterial-dominant phase, and washout as hypointense tumor relative to hepatic parenchyma during the venous and/or late dynamic phases. These characteristic features are observed in most HCCs and are related to features such as the development of unpaired arteries, absence of portal vein supply and nodular growth. However, it has been reported that in nodules 20 mm or smaller, the sensitivity of MR imaging for the diagnosis of HCC based on these criteria is only 62% and it is even lower for contrast-enhanced ultrasound [41]. This low sensitivity is explained by the fact that early HCCs often lack the characteristic features of HCC. Indeed, early HCCs often are not hypervascular, have persistent portal venous blood supply and replacing growth [42].

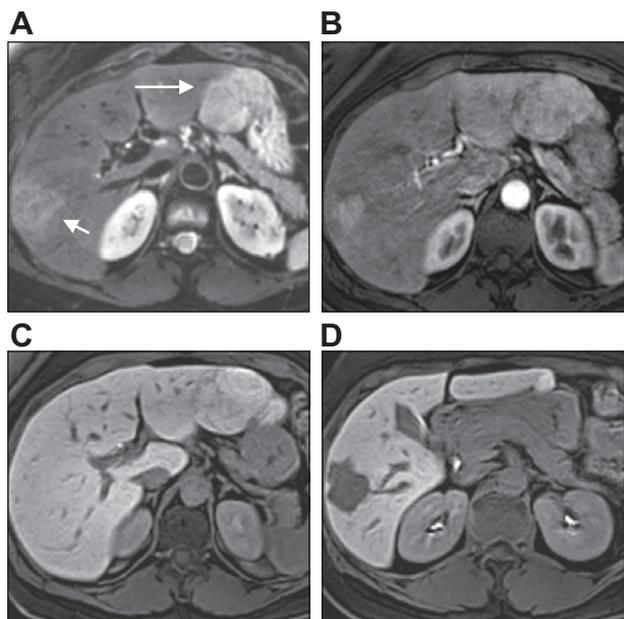
Interestingly, during the hepatobiliary phase at GD-EOB-DTPA-enhanced MR imaging, most HCCs, including hypovascular,



**Fig. 3. GD-EOB-DTPA-enhanced MR images of HCC in two patients.** (A) In the first patient, no lesion is seen during the arterial phase at Gd-EOB-DTPA MR imaging because of lack of hypervascularity in small HCC. (B) Two small HCCs (arrow) are seen as hypointense nodules in the right hepatic lobe during the hepatobiliary phase. (C) In another patient, a HCC of the right liver lobe is isointense relative to the liver on unenhanced T1-weighted MR image. (D) The progressed HCC is hypervascular during the arterial phase. (E) The tumor is hyperintense during the hepatobiliary phase at GD-EOB-DTPA-enhanced MR imaging.

early HCC, appear hypointense (Figs. 2 and 3) [43]. Thus, GD-EOB-DTPA-enhanced MR imaging appears useful for the characterization of small HCCs and for their differentiation from dysplastic nodules and vascular pseudolesions, which usually do not show this delayed hypointensity [44–47]. In a recent imaging study including 12 dysplastic nodules, 30 early HCCs and 66 progressed HCCs, Sano *et al.* showed that low signal intensity at hepatobiliary phase GD-EOB-DTPA-enhanced MR imaging had an area under the receiver operating characteristic curve of 0.98 for the diagnosis of HCC. This area was significantly larger than that of contrast-enhanced CT and combined CT during arterial portography and CT during hepatic arteriography [46].

Because of its high sensitivity in the diagnosis of HCC, GD-EOB-DTPA-enhanced MR imaging has been recommended in a recent consensus conference as a method for characterizing



**Fig. 4. GD-EOB-DTPA-enhanced MR images in a patient with FNH and HA.** (A) On diffusion-weighted MR image, both HA (short arrow) in the right lobe and FNH (long arrow) in the left lobe are slightly hyperintense. (B) The two lesions are hypervascular during the arterial phase after Gd-EOB-DTPA injection and cannot be differentiated. (C and D) Two MR images obtained during the hepatobiliary phase show that the FNH is isointense (C), whereas the HA is hypointense (D, slightly lower section).

a nodule that has been detected in the cirrhotic liver using ultrasonography [47]. However, more data should be obtained about the specificity of the hepatobiliary hypointensity sign in prospective studies that should include patients with other nodules than HCC and dysplastic nodules. Meanwhile, a hypointense nodule in the hepatobiliary phase of Gd-EOB-DTPA that is non-hypervascular in the arterial phase should be regarded as intermediate risk, whereas one that is hypervascular in the arterial phase is high risk [47].

The enhancement pattern during the hepatobiliary phase at GD-EOB-DTPA-enhanced MR imaging has been explained by OATP and MRP expression. Most HCCs appear hypointense during that phase because the expression of OATP1B1/B3 is decreased. When OATP1B1/B3 expression is maintained, the intensity of HCC depends on the expression of MRP2. In most HCCs, the expression of MRP2 is high and located on the canalicular membrane of hepatocytes. These HCCs are hypointense. In contrast, 5 – 10% of HCCs are iso- or hyperintense relative to the liver. This has been related to low MRP2 expression or high MRP2 expression at the luminal membrane of pseudoglands [48,49] (Figs. 2 and 3).

MRP3 is usually decreased in HCC [50]. It has been observed that the expression of MRP3 is increased rather than decreased in hyperintense vs. hypointense HCC [51]. This suggests that MRP3 expression has little influence on HCC signal intensity at GD-EOB-DTPA-enhanced MR imaging.

It has been recently reported that the OATP1B1/B3 expression is progressively lost in HCCs that gain a biliary phenotype with worse prognosis [52]. Moreover, it has been shown that MR imaging hypointensity during the hepatobiliary phase increases with increasing HCC grade [53]. However, the correlation between Gd-EOB-DTPA enhancement and tumor grade remains

controversial [54]. Further studies are needed to correlate the enhancement pattern in HCC to the expression of hepatic transporters in the various subtypes of HCC, according to molecular classification [55].

Finally, it has been reported that sorafenib, in contrast to sunitinib, is a substrate for MRP2 [56]. The relationship between the signal intensity of HCC at GD-EOB-DTPA-enhanced MR imaging and resistance to sorafenib is currently unknown.

#### Benign hepatocellular tumors

The expression of OATP1B1/B3 and MRP2, MRP3 has also been investigated in focal nodular hyperplasia (FNH) and hepatocellular adenomas (HA) [57]. Typical FNH is associated with chronic cholestasis, ductular reaction, and fibrosis. Bile canaliculi are not connected to bile ducts and bile compounds accumulate within the lesion. In FNH, OATP1B1/B3 expression is increased, MRP2 expression is similar to that in the normal liver, while MRP3 has a low expression. In HA, the OATP1B1/B3 expression is typically low, MRP2 expression is similar to that in the normal liver, while MRP3 has a diffuse and high expression.

In clinical studies, FNHs show enhancement during the hepatobiliary phase either similar to or more than liver parenchyma with low signal intensity of the central scar (Fig. 4) [58]. A case of FNH-like nodule in liver cirrhosis with lesion hypointensity during the hepatobiliary phase has been recently reported [59]. This lesion also showed arterial hyperintensity and was misdiagnosed as HCC.

The enhancement of HA is variable [60–62]. Most HA are hypointense during the hepatobiliary phase (Fig. 4). However, some HA may also take up the contrast agent and appear hyperintense. As for HCC, further studies are needed to correlate the enhancement pattern in HA to the expression of hepatic transporters in the various subtypes [63]. Currently, the added value of GD-EOB-DTPA-enhanced MR imaging relative to dynamic contrast-enhanced MR imaging with a non-specific gadolinium chelate in the differentiation of benign hepatocellular tumors remains to be proven. The enhancement characteristics of the most frequent liver tumors are shown in Table 1.

#### Bile duct diseases

GD-EOB-DTPA-enhanced cholangiography can be performed during the hepatobiliary phase. While the intrahepatic and extrahepatic ducts are well seen at 20 min [64], a delay of 30 min after the injection of Gd-EOB-DTPA is suggested by some authors to ensure sufficient enhancement of the bile ducts and demonstrate gallbladder enhancement [65,66]. Biliary enhancement is affected by hepatic function and has been shown to be weaker and delayed in the cirrhotic liver [67].

T1-weighted GD-EOB-DTPA-enhanced cholangiography may add functional information to unenhanced T2-weighted MR cholangiography. This may potentially be useful for the detection of bile duct leaks, the grading of bile duct obstruction, the differentiation between Caroli disease and peribiliary cysts, and the differentiation between parenchymal and small bile duct diseases [65]. However, the visualization of the bile ducts may be poor or even absent at GD-EOB-DTPA-enhanced cholangiography in patients with advanced diffuse parenchymal disease or bile duct obstruction [68]. T2-weighted MR cholangiography should be

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performed before Gd-EOB-DTPA administration due to the T2 shortening effect of enhanced bile which renders the biliary system invisible [69].

### Assessment of liver function

Assessment of liver function is important to determine the prognosis of patients with chronic liver diseases, and is particularly required in patients with cirrhosis to determine the optimal timing for transplantation or transjugular intrahepatic portosystemic shunt (TIPS) insertion [70]. Evaluation of total and regional liver function is also important before major liver resection to minimize the risk of post-operative liver failure, especially in patients with cirrhosis or even less advanced diseases such as steatosis, cholestasis, or chemotherapy toxicity [71,72]. Indocyanin green (ICG) clearance and hepatic scintigraphy with technetium-99m mebrofenin ( $^{99m}\text{Tc}$ -mebrofenin) have been proposed for assessing liver function. The organic anion  $^{99m}\text{Tc}$ -mebrofenin is a substrate of OATP1B1/B3, whereas ICG is a substrate of OATP1B3 and sodium taurocholate-cotransporting polypeptide (NTCP). Both ICG and mebrofenin are excreted in the bile by MRP2 without undergoing biotransformation [73,74].

Assessment of liver function at GD-EOB-DTPA-enhanced MR imaging may be an alternative to ICG clearance and hepatic scintigraphy with  $^{99m}\text{Tc}$ -mebrofenin. Hepatic extraction fraction of Gd-EOB-DTPA has been shown to correlate with ICG clearance in rabbits and liver-spleen contrast to noise ratio at GD-EOB-DTPA-enhanced MR imaging has been shown to correlate with ICG clearance in patients [75,76]. The advantages of GD-EOB-DTPA-enhanced MR imaging include absence of radiation, combined anatomical and functional assessment, and the ability to quantitatively assess hepatic perfusion and function [77]. A preliminary study in rats to evaluate liver fibrosis showed a good correlation between advanced fibrosis and the signal-intensity time course of GD-EOB-DTPA-enhanced MR imaging [78]. Decreased enhancement and increased enhancement time are attributed to slower hepatocyte uptake due to lower OATP1 activity, and rapid elimination due to increased MRP2 activity which is upregulated in the cirrhotic liver [79].

Several issues need to be taken into account when performing pharmacokinetic analysis of liver enhancement at GD-EOB-DTPA-enhanced MR imaging. These include the lack of linear relationship between signal intensity of liver and contrast agent concentration, and the differing relaxivity of Gd-EOB-DTPA in water, blood and liver [80]; the need to incorporate all factors that influence hepatic clearance of contrast agents such as blood flow, transmembrane barriers and the presence of other drugs metabolized in the liver [81,82]; and lastly the complexity of transporter regulation in hepatocytes including the inter-individual variability of transporter expression and the saturation of the transport systems at high concentrations of the contrast agents [83–85].

### Conclusions

Despite the difficulties in quantification of liver function, GD-EOB-DTPA-enhanced MR imaging offers a unique opportunity to combine qualitative and quantitative morphological and

functional information that may improve the assessment of focal liver lesions and diffuse liver diseases and probe liver function.

### Key Points

- Gd-EOB-DTPA is a liver-specific MR contrast agent that has 50% hepatocytic uptake and biliary excretion in the normal liver
- The transport of Gd-EOB-DTPA in the hepatocyte mainly occurs through OATP1B1/B3 transporters at the sinusoidal membrane and MRP2 at the canalicular membrane
- For liver imaging, Gd-EOB-DTPA behaves similarly to a non-specific extracellular gadolinium chelate during the arterial, portal venous and late dynamic phases, because both contrast agents are mainly located in the vascular and extravascular spaces during these phases, but Gd-EOB-DTPA adds information during the hepatobiliary phase (20 min after injection) because it is mainly located within hepatocytes and bile ducts at that time
- During the hepatobiliary phase, the high contrast between the hepatic parenchyma that contains Gd-EOB-DTPA and liver metastases that do not contain the contrast agent improves the detection of these tumors
- Hepatocellular tumors take up variable amounts of Gd-EOB-DTPA, which are related to their expression of OATP1B1/B3 and MRP2
- The detection and characterization of HCC, especially early HCC, is improved at Gd-EOB-DTPA-enhanced MR imaging because most of these lesions are hypointense during the hepatobiliary phase even if they do not show the characteristic features of arterial hypervascularity and washout during the portal venous and/or late dynamic phase
- The HCC hypointensity during the hepatobiliary phase is explained by decreased expression of OATP with high expression of MRP2. In contrast, some HCC are iso or hyperintense during that phase because of high OATP expression with decreased MRP2 expression or high OATP expression with high expression of MRP2 in luminal membranes of pseudoglands
- FNH is iso or hyperintense during the hepatobiliary phase, whereas HA have variable signal, most of them being hypointense
- The enhancement of the liver at Gd-EOB-DTPA enhanced MR imaging depends mainly on liver perfusion, vascular permeability, extracellular diffusion and hepatocyte transporter expression. These functions being modified during diffuse liver disease, Gd-EOB-DTPA-enhanced MR imaging has the potential to provide quantitative information about liver perfusion and function
- Combined anatomical and functional information on focal and diffuse liver diseases can be obtained at Gd-EOB-DTPA-enhanced MR imaging

**Table 1. Enhancement characteristics of the most frequent liver tumors.**

	Arterial phase	Portal venous phase	Equilibrium phase	Hepatobiliary phase
Hemangioma	Iso-hypo (peripheral nodular enhancement)	Iso-hypo (peripheral nodular enhancement)	Iso-hypo	Hypo
FNH	Hyper	Iso	Iso	Iso-hyper
Adenoma	Variable	Variable	Variable	Hypo or hyper
Metastasis	Hypo (ring enhancement) or hyper	Hypo (ring enhancement)	Hypo	Hypo
HCC	Hyper or iso, hypo	Hypo	Hypo	Hypo or hyper
CCC	Hypo or hyper	Variable, mostly hypo	Variable, mostly hypo	Hypo

**Conflict of interest**

Pr. Hero Hussain has served as occasional consultant for Bayer in 2010 and 2011. The other authors have no conflict of interest to disclose.

**Acknowledgements**

The authors thank Pr. Celso Matos from the Department of Radiology, Erasme Hospital, Free University of Brussels, Belgium for providing Figs. 3 and 4.

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