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REVIEW

MR Imaging in Patients with Suspected Liver Metastases: Value of Liver-specific Contrast Agent Gd-EOB-DTPA

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The appropriate staging of malignant tumors is increasingly important as new therapeutic strategies develop. Because metastatic involvement of the liver in extrahepatic malignant disease may significantly change therapeutic approach, it is important to rule out such involvement with high confidence. Moreover, the differentiation between incidental benign lesions, such as hemangioma, focal nodular hyperplasia (FNH), or adenoma, is of high interest. Magnetic resonance (MR) imaging has proved reliable for diagnostic work-up of the liver. Liver-specific contrast agents have been especially helpful in detecting and precisely characterizing focal liver lesions, but the use of these agents has been limited because it has not been possible to perform both proper vascular phase and liver-specific phase within a reasonable time frame and in a single examination after a single injection of contrast agent. However, the hepatobiliary contrast agent gadolinium-ethoxybenzyl (Gd-EOB)-DTPA now allows combined dynamic imaging and hepatocyte-specific imaging in one examination. Gd-EOB-DTPA can be injected as a bolus and shows the enhancement characteristics and vascularity of liver lesions. In the delayed phase, which is acquired most appropriately 20 min after injection, Gd-EOB-DTPA is taken up selectively by functioning hepatocytes. Thus, malignant liver lesions, e.g. metastases, are spared from contrast uptake of the surrounding liver parenchyma. These lesions are hypointense in contrast to the surrounding bright liver. We review the current literature and present a practical approach to Gd-EOB-enhanced MR imaging using imaging examples of patients with liver metastases.

Keywords: ***MR imaging, liver, hepatobiliary contrast agents, gadoxetic acid, metastases***

Introduction

Metastatic liver disease is a common cause for malignant liver lesions worldwide.[1] The choice of appropriate therapy requires the accurate and clinically appropriate staging of liver disease. Because metastatic involvement of the liver in extrahepatic malignant disease significantly affects therapeutic approach in many cases, such involvement must be ruled out with high confidence. In the case of present liver metastasis, the number, size, and location of metastases will stratify the patients for surgery, minimal-invasive imaging-guided therapy, or pharmaceutical treatment. In a considerable number of patients with extrahepatic malignant disease, focal liver lesions may be depicted that are benign and require no treatment. We present an overview of the diagnostic potential of Gd-EOB-DTPA-enhanced magnetic resonance (MR) imaging of the liver in patients with suspected liver metastasis.

Gd-EOB-DTPA: Mode of Action and MR Examination

Gadoxetic acid (Gadolinium-ethoxybenzyl [Gd-EOB]-DTPA, approved in most European countries as Primovist®, Bayer Schering Pharma, Berlin) is a paramagnetic, hydrophilic, ionic, highly water-soluble, and therefore bolus-injectable Gd-DTPA derivative for T_1-weighted MR imaging.[2,3] The T_1-relaxivity (r1) measured in water at 1.5T is 4.7 L mmol^{-1} s^{-1} and increases in human blood at 37° Celsius to values of 7.3 L mmol^{-1} s^{-1}.[4] Com-

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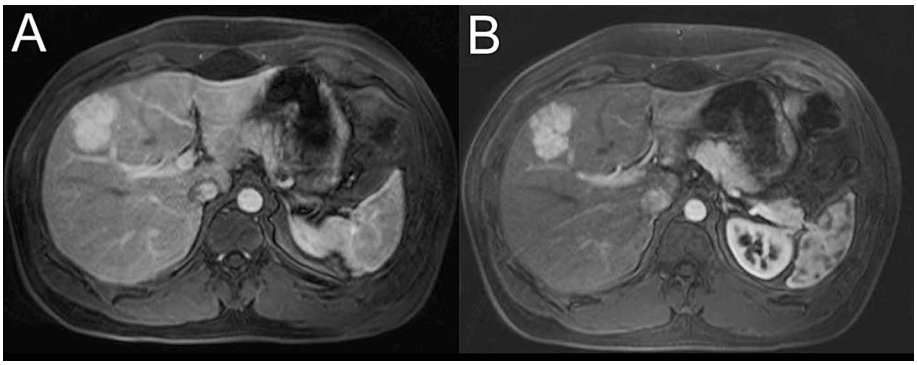

Fig. 1. Arterial phase imaging after manual bolus injection of 18 cc 0.5M gadolinium (Gd)-DTPA (**A**) and 9 cc 0.25M Gd-ethoxybenzyl [EOB]-DTPA (**B**) using a T_1-weighted 3D-gradient-echo (GRE) fs sequence (repetition time [TR] = 5.02 ms; echo time [TE] = 1.77 ms; flip angle [FA] = 15°; slice thickness = 4 mm, no gap). Both sequences were acquired 20 s after manual bolus injection. Morphology and enhancement pattern are identical in both images. The subjective quantitative enhancement of the lesion is also quite similar despite the lower dose of Gd-EOB-DTPA. Note that the timing of the injection by hand is slightly different.

pared to the relaxivity of standard gadolinium chelates in blood (around 4.5 L $mmol^{-1}$ s^{-1}), the relaxivity of Gd-EOB-DTPA is increased in human blood by the weak protein binding of Gd-EOB-DTPA.[4] The higher relaxivity of Gd-EOB-DTPA compensates in part for the lower gadolinium concentration, 0.25 mol/L, in its currently approved formulation (Primovist®, Bayer Schering Pharma, Berlin); in comparison, gadolinium concentration in other standard gadolinium chelates is 0.5 mol/L. The recommended dose, 0.025 mmol/kg body weight, is also lower than the dose of standard Gd chelates, 0.1 mmol/kg body weight. Nevertheless, early dynamic imaging with Gd-EOB-DTPA is feasible with sufficient quality,[5] although quantitatively, a lower signal in the vasculature of the liver and in hypervascular tumors can be expected (Fig. 1). However, the enhancement pattern and morphology exhibited using early dynamic Gd-EOB-DTPA-enhanced MR imaging has correlated strongly with those on reference examination performed using extracellular contrast agents.[5] Because the basic principle of early dynamic imaging with Gd-EOB-DTPA is the same as that with other standard gadolinium chelates, no special sequence recommendations are required for this examination phase. In our practice, the use of modern high-resolution 3D-gradient-echo (GRE) sequences with fat saturation is well established,[6] and this sequence type can be recommended as well for the early dynamic phase with Gd-EOB-DTPA. Because of the lower dosage, the bolus volume with Gd-EOB-DTPA will be only half the volume of extracellular agents (e.g., for a patient of 70 kg, 7 cc of Gd-EOB-DTPA compared to 14 cc of standard gadolinium chelate). This underlines the need for a more exact bolus timing, especially of the arterial phase.

Although the information obtained from the early dynamic-phase examination is of high importance for the interpretation of focal or diffuse liver disease, additional functional information regarding tissue structure that can be derived using the group of hepatobiliary contrast agents can be very helpful. This additional information from Gd-EOB-DTPA-enhanced MR is gathered during the hepatobiliary phase. The basic principle of this part of the examination are the hepatobiliary properties derived from the lipophilic EOB moiety, which is linked to the gadolinium complex. This moiety mediates the highly specific uptake of the agent into the hepatocytes through the organic anion-transporting polypedtide (OATP1). The high rate, almost 50%, of hepatobiliary uptake ensures that the hepatobiliary phase sequences can be started already at 20 min after injection.[2,3] The contrast agent's excretion via both renal and biliary pathways ensures its elimination in patients with impaired renal or liver function if one of the pathways is blocked.[7] T_1-weighted 2D GRE sequences with fat saturation imaging sequences were tested for the hepatobiliary phase in Phase III trials. Following increasing technical performance, modern T_1-weighted 3D GRE sequences as used for early dynamic imaging are also suitable for imaging the liver-specific phase. Our own experience confirms the high performance of these sequences in the hepatobiliary phase, especially for detecting

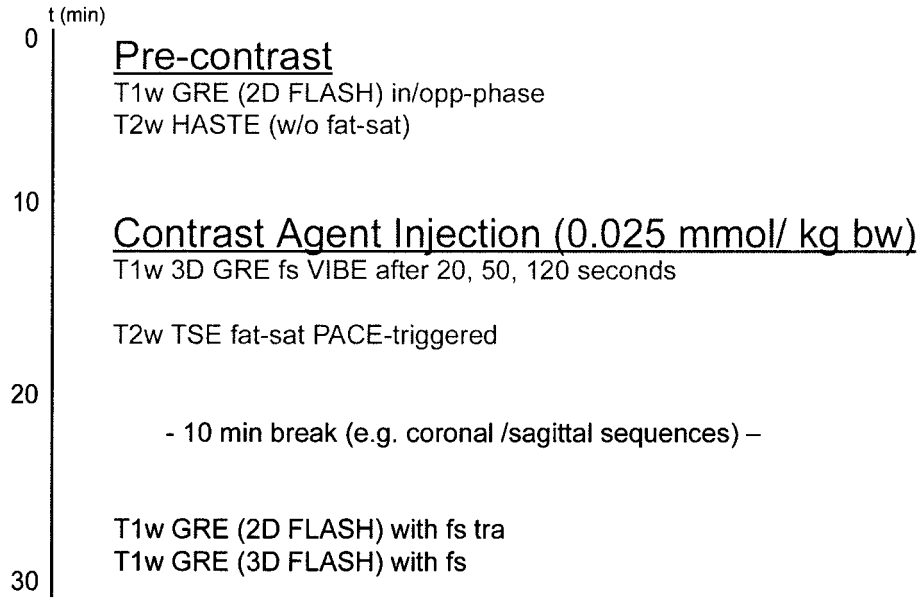

Fig. 2. Proposal for an examination protocol with gadolinium-ethoxybenzyl-DTPA (Gd-EOB-DTPA). The time-consuming respiratory-triggered T_2-weighted turbo spin-echo (TSE) sequence with fat saturation is performed after contrast agent injection, enabling overall examination time to remain at about 30 min despite the necessary delay of 20 min between injection of contrast agent and start of hepatobiliary phase.

very small metastases. The slice thickness in these sequences can be decreased to 3 to 4 mm for 1.5T systems and even 1.5- to 2 mm for 3T systems in a single breath-hold examination that covers the entire liver and still maintain an acceptable signal-to-noise ratio (SNR). At present, the complete omission of the 2D GRE sequences cannot be recommended, but a direct comparison between the sequences may change this situation.

Overall, MR examination using Gd-EOB-DTPA is the same as with any other gadolinium chelate apart from the additional liver-specific phase 20 min after contrast injection. Thus, for the pre-contrast MR examination, the same sequences can be recommended as those used for imaging utilizing standard gadolinium chelates. To shorten the complete examination to less than 30 min, the time-consuming high-resolution T_2-weighted imaging (T_2WI) may be performed after the contrast agent is injected. It has been shown that the signal intensities on T_2WI in the liver parenchyma and in focal liver lesions are not significantly modified within the expected concentration when the standard diagnostic dose of Gd-EOB-DTPA is used.[8] The gap of about 15 min from the end of the early dynamic phase to the onset of the liver-specific phase can be used for high-quality respiratory-triggered sequences, which are considered superior to T_2-weighted breath-hold sequences.[9] Nevertheless, one should be aware that a high concentration of Gd (as it may be encountered in the biliary system) can lead to signal decay in T_2WI sequences based on the increased T_2* effects.[10] A practical examination protocol for Gd-EOB-DTPA-enhanced MR imaging is suggested in Fig. 2.

With regard to safety, Gd-EOB-DTPA has the same favorable profile as other gadolinium chelates. Phase I through III trials have revealed no increase in rate of adverse events.[2,3,11–13]

Liver Metastasis

Liver metastases are classified according to their corresponding primary tumor, and morphological classifications are commonly used to describe different liver metastases in the daily practice. The most important classification is the differentiation between hyper- and hypovascular liver metastases with regard to contrast-agent enhancement in the early dynamic phase.

On unenhanced MR images, the vascularity of metastases cannot usually be visualized. On unenhanced T_1-weighted GRE images, the signal intensity of metastases is typically low, and on T_2-weighted sequences, it is moderately increased. The relatively high contrast between metastases and unaffected liver parenchyma in unenhanced T_1-weighted GRE images allows many metastases

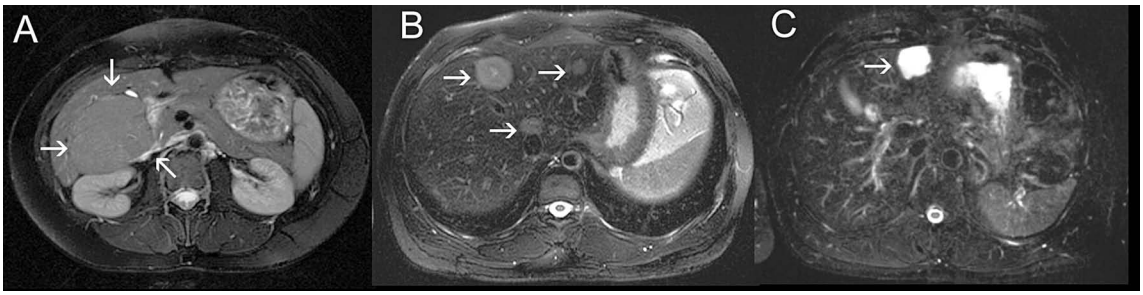

Fig. 3. Spectrum of signal intensities of different typical focal liver lesions (marked by small arrows) in a respiratory-triggered T_2-weighted turbo spin-echo (TSE) sequence with fat saturation: Isointense lesion compared to surrounding liver parenchyma arising from segment 5/6 of the liver (focal nodular hyperplasia [FNH]), 3 moderately hyperintense liver lesions in segments 2 and 4a (metastases), and a markedly hyperintense lesion in segment 2/3 (hemangioma). Despite the value of the contrast-enhanced imaging, the diagnostic information provided by pre-contrast T_2-weighted sequences is still considerable for the correct characterization of focal liver lesions.

to be detected with this sequence. On the other hand, T_2-weighted images (T_2WI) are valuable primarily for lesion characterization, not detection. Solid benign lesions tend to be almost isointense to the liver on unenhanced T_2WI, whereas cysts and hemangioma are markedly hyperintense (Fig. 3).

Primary tumors that are classically considered to be hypervascular and to have hypervascular liver metastases include mainly thyroid carcinomas, carcinoid tumors, neuro-endocrine tumors, and renal cell carcinomas.[14] However, metastases from pancreatic, breast, and colon carcinomas may also be hypervascular,[14] and the hypervascular type may occasionally be seen among liver metastases from cancers of unknown primary site (CUP). The hypervascular nature of these lesions can be best appreciated in the arterial-dominant phase of the liver. Because the strong vascularity leads to fast wash-out of contrast agents in later phases, a correctly timed arterial-dominant phase using computed tomography (CT) or MR imaging is indispensable in every dedicated liver study.

The hypovascular metastases appear hypointense in both arterial and portal-venous phases. Nevertheless, one should be aware that this classification reflects only the degree of enhancement of the lesion compared to the liver parenchyma on the arterial dominant and portal venous phases.[14] Hypovascular lesions can also be assumed to have considerable vascularization and show contrast uptake, but to a lesser degree than surrounding liver parenchyma.

The degree of vascularity of different hepatic lesions determines their individual enhancement pattern after administration of iodinated contrast agents and gadolinium chelates. The early dynamic phase of extracellular agents reflects the kinetics

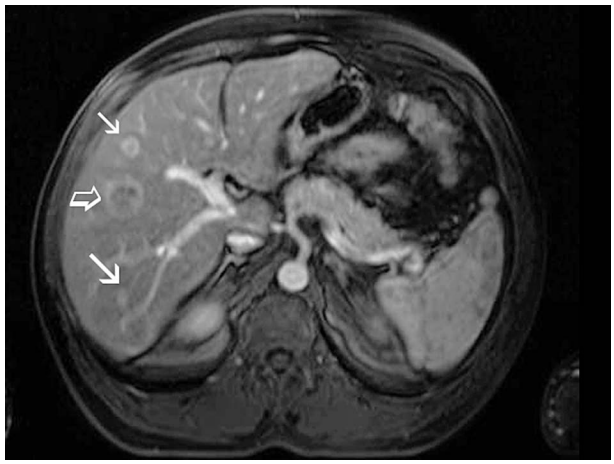

Fig. 4. Hypervascular liver metastasis in a 59-year-old male patient with melanoma. Note the peripheral enhancement in a metastasis with central necrosis (large arrow) compared to the homogenous enhancement of the smaller lesions (small arrows).

of tumor vascularization, such as perfusion and capillary diffusion into the extracellular space.[15] The differences in the degree of enhancement thus reflect differences in the number and permeability of vessels and size of the extracellular space. Enhancement patterns vary according to the presence of fibrous tissue or a high cellular density of the tumor.[15] and the enhancement pattern of hypervascular metastases depends mostly on their size. Because a homogenous high arterial supply is unlikely in large lesions, large hypervascular metastases often exhibit heterogeneous enhancement (Fig. 4), predominantly in the periphery.[1,14] This pattern has to be distinguished from perilesional enhancement (Fig. 5) in hypovascular metastases, which Semelka and colleagues have shown to correlate with histopathologic changes in

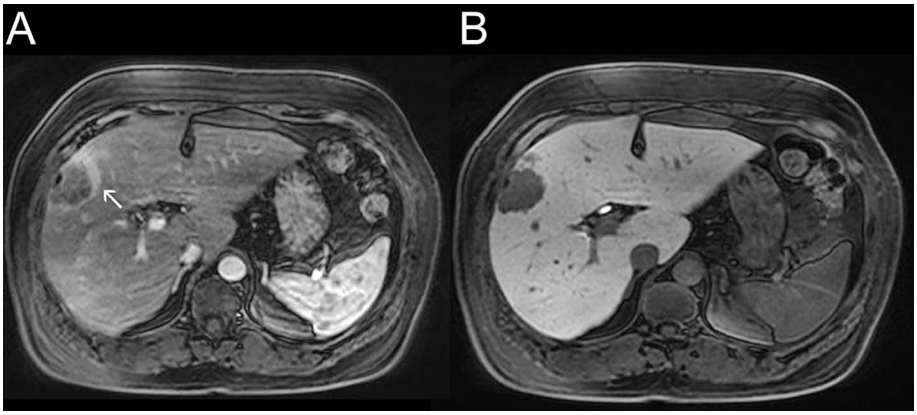

Fig. 5. Hypovascular liver metastasis of a sigmoid cancer in a 51-year-old female patient. Arterial phase (**A**) and hepatocyte phase (**B**) with a T_1-weighted 3D-gradient echo (GRE) sequence after bolus injection of gadolinium-ethoxy-benzyl-DTPA (Gd-EOB-DTPA). Note the perilesional enhancement in the arterial phase. In the hepatocyte phase (**B**), the margins of the lesion appear very clear and sharply delineated from increased contrast between the metastasis (no liver-specific uptake) and surrounding liver parenchyma (regular uptake).

the liver parenchyma that include peritumoral desmoplastic reaction, inflammatory cells, and vascular proliferation.[16] The typical extracellular enhancement phenomena seen using x-ray (iodinated) contrast agents are strong enhancement in the arterial-dominant phase and marked early wash-out. The most important advantages of MR imaging compared to ultrasonograhy and CT are the high reproducibility, high spatial resolution without compromising contrast, potential tissue characterization based on different weightings, absence of radiation exposure so that multiphasic examinations may be performed, and availability of tissue-specific contrast agents (Fig. 6).

The arterial-dominant phase is commonly used to characterize lesions by identifying signs of hypervascularity, but this phase is also crucial for detecting lesions, especially hypervascular metastases. Several publications note the high detection rate for hypervascular lesions with standard gadolinium chelates in this phase as compared to the delayed phase alone after administration of different liver-specific contrast agents.[17–19] In these trials, the combined reading of early dynamic-phase images (obtained with standard gadolinium chelates) and delayed-phase images obtained with liver-specific agents yielded information regarding agents offering the highest detection rates.[17,19] With Gd-EOB-DTPA, both early dynamic phase and liver-specific phase can be acquired in one examination after a single injection of contrast agent.

Hypervascular metastases show marked arterial enhancement in the early dynamic phase and typical wash-out in the portal-venous phase that results in an iso- or even hypointense signal. This wash-out has to be distinguished from the wash-out of benign lesions, such as FNH or adenoma, which is usually less pronounced.[20,21] Hypovascular metastases sometimes exhibit a slightly hypervascular rim. Because their contrast uptake is lower than in the surrounding liver parenchyma in the early dynamic phase, they appear as hypointense lesions with the best contrast and the best lesion conspicuity in the portal-venous phase. Based on the above-mentioned properties of extracellular contrast agents, Gd-EOB-DTPA enables the depiction of vascularity.[5,22,23]

In the hepatocyte phase using Gd-EOB-DTPA, both hyper- and hypovascular metastases are hypointense. In this phase, wash-out within the lesion on one hand and liver-specific enhancement in the surrounding liver parenchyma on the other improve conspicuity of the lesion by increased tumor-to-liver contrast (Fig. 7). This allows significantly higher detection with high confidence, especially for lesions smaller than 1 cm in diameter.[12] The detection rate of Gd-EOB-DTPA-enhanced MR imaging has been investigated with T_1-weighted 2D GRE sequences with fat saturation.[12,13] It can be assumed that the broad availability of 3D GRE sequences and their ultra-high-resolution capabilities will further improve the detection rate of Gd-EOB-DTPA-enhanced MR imaging (Fig. 8).

Hypervascular lesions of benign origin, e.g. hemangiomas or-even more challenging-solid le-

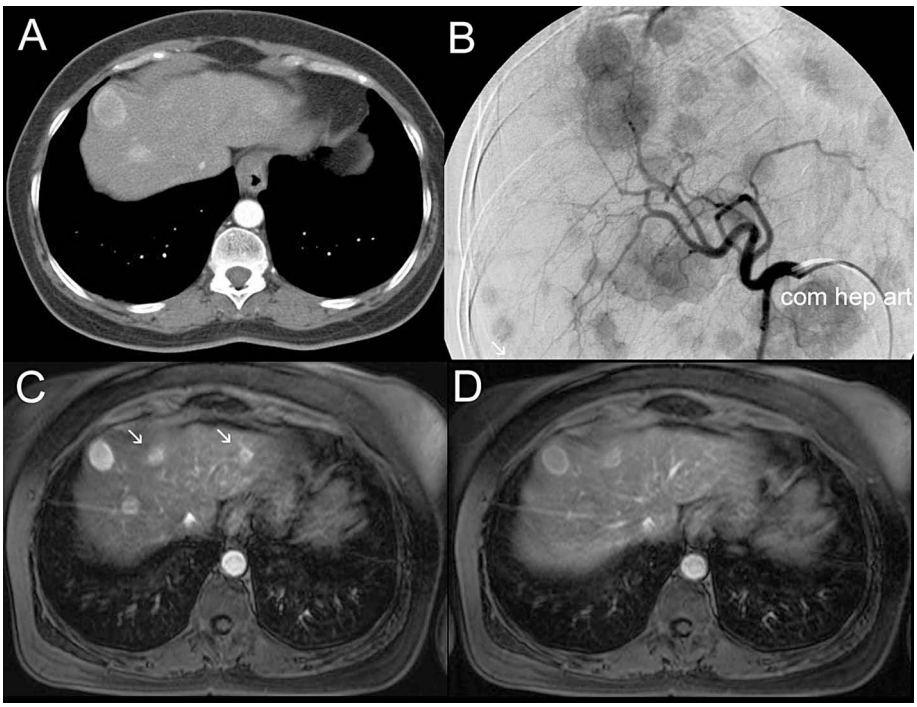

Fig. 6. Hypervascular liver metastases of a neuro-endocrine tumor of the stomach in a 54-year-old female patient. Strong vascular supply via the hepatic artery is seen in the angiography (**B**). Direct comparison of the arterial phase images of multidetector computed tomography (MDCT) (**A**) and gadolinium (Gd)-DTPA enhanced T_1-weighted 3D gradient-echo (GRE) fat saturated magnetic resonance (MR) imaging (**C**) shows the superiority of MR imaging to computed tomography (CT) with regard to the conspicuity of small lesions (arrows). Note the poor visualization of the smaller lesions in the portal-venous phase (**D**) caused by wash-out to nearly isointensity. This strengthens the need for an accurate arterial phase.

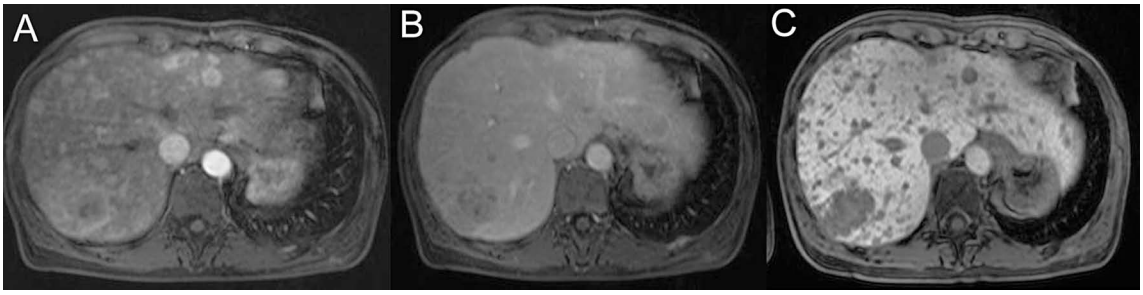

Fig. 7. Multiple hypervascular liver metastases of a neuro-endocrine tumor in a 44-year-old female patient. Gadolinium-ethoxybenzyl-DTPA (Gd-EOB-DTPA)-enhanced T_1-weighted 3D GRE fat-sat MR imaging in arterial (**A**), portal-venous (**B**), and hepatocyte phase (**C**). Note the difference in lesion conspicuity and liver-to-lesion contrast, which is excellent in the hepatocyte phase, good in the arterial phase, and insufficient in portal-venous. This example demonstrates the added value of images from the hepatocyte phase compared to early dynamic images alone.

sions, such as FNH or adenoma, have to be distinguished from hypervascular metastases. As mentioned, plain MR imaging can be helpful in characterizing lesions via the specific signal behavior of most benign lesions in T_2WI. Nevertheless, in many cases, distinguishing these lesions can still be very difficult, and the hepatocyte-phase images are then distinctly important (Fig. 9). The uptake of liver-specific contrast agents is not limited exclusively to normal liver parenchyma. It also occurs in lesions with functioning hepatocytes, such as FNH or adenoma,[5] which results in the iso- or even hyperintensity of these lesions on hepatocyte-phase images.[5,21] Overall, the rate of correctly character-

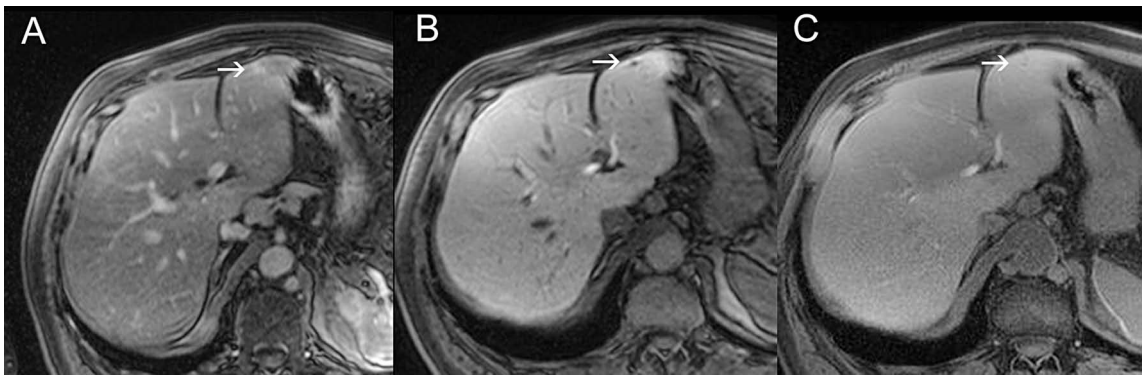

Fig. 8. Tiny metastasis (arrow) in a 58-year-old male patient suffering from a small bowel carcinoma. Arterial phase T_1-weighted 3D gradient-echo (GRE) sequence (**A**) as well as hepatocyte phase with a T_1-weighted 3D GRE sequence (**B**) and a T_1-weighted 2D GRE sequence (**C**) after bolus injection of gadolinium-ethoxybenzyl-DTPA (Gd-EOB-DTPA). The lesion is depicted well in the high resolution 3D GRE sequence with fat saturation in the arterial phase (**A**) as well as in the hepatocyte phase (**B**), whereas it cannot be properly identified in the 2D GRE sequence, most likely as a result of partial volume effects. This example emphasizes the importance of high spatial resolution. Note the superior lesion conspicuity in the hepatocyte phase as compared to the early dynamic phase.

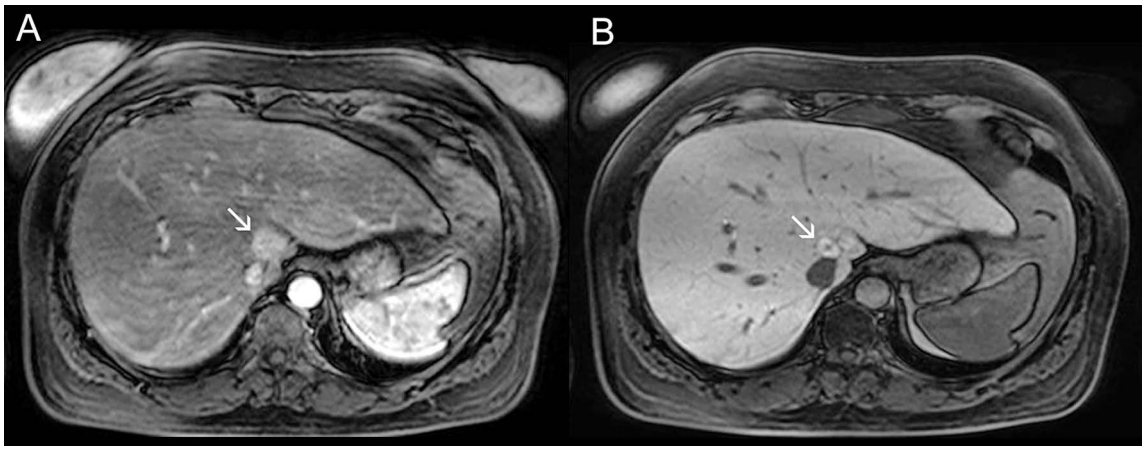

Fig. 9. T_1-weighted 3D gradient-echo (GRE) sequence with fat saturation in the arterial phase (**A**) and in the hepatocyte phase (**B**) after bolus injection of gadolinium-ethoxybenzyl-DTPA (Gd-EOB-DTPA) in a 51-year-old female patient suffering from a sigmoid carcinoma with known liver metastases (same patient as Fig. 5). An additional hypervascular lesion was detected near the IVC that exhibited homogenous uptake of ethoxybenzyl (EOB) and a hypointense central spot. The lesion was interpreted as a focal nodular hyperplasia (FNH) and not as a metastasis. Further follow-up also confirmed the benign nature of this lesion.

ized FNH in a mixed study population is up to 88%.[21] Hemangiomas may be diagnosed primarily on the basis of their typical pattern of enhancement in dynamic phase because these lesions will not take up hepatobiliary contrast agents, and at the time of liver-specific imaging, extracellular pooling has often vanished. Atypical small hemangiomas may be difficult to differentiate from metastases because of only intermediate signal intensity in the T_2WI. Unfortunately, in this case, the liver-specific phase of hepatobiliary agents is not helpful because neither a metastasis nor hemangioma should exhibit specific uptake of the contrast agent; therefore these small hemangiomas will appear as hypointense lesions against the surrounding liver.

Comparison to the literature and other liver-specific agents

Several publications have shown that metastases can be reliably detected with the highest accuracy using liver-specific contrast agents, whether superparamagnetic iron oxide (SPIO) or hepatobiliary agents. All liver-specific agents have proven to be

Table. Detection rates for the different hepatobiliary contrast agents: examples from selected publications

	Number of Lesions	Detection Rate		Correct Characterization	
Gd-EOB-DTPA[1]					
Huppertz et al. 2004[12]	302 lesions	MRI plain:	80.8%	MRI plain:	51.2%
		MRI EOB:	87.4%	MRI EOB:	62.8%
Bluemke et al. 2005[13]	316 lesions	Biphasic CT:	65.9%	Biphasic CT:	68.4%
		MRI plain:	62.7%	MRI plain:	63.8%
		MRI EOB:	70.9%	MRI EOB:	70.7%
Mn-DPDP[2]					
Bartolozzi et al. 2004[26]	128 metastases	Biphasic CT:	71%	No characterization data	
		MRI plain:	72%		
		MRI Mn-DPDP:	90%		
Kim et al. 2006[33]	53 metastases	MRI Mn-DPDP:	82%	No characterization data	
		MRI SPIO:	90%		
Sahani et al. 2005[34]	79 metastases	MRI Mn-DPDP:	81.4%	No characterization data	
		PET-CT:	67.0%		
Gd-BOPTA[3]					
del Frate et al. 2002[29]	37 metastases	MRI Gd-BOPTA:	81%	No characterization data	
		MRI SPIO:	97%		
Pirovano et al. 2000[35]	107/149 lesions	MRI plain:	76.5%	MRI plain:	48.6%
		MRI Gd-BOPTA:	91.9%	MRI Gd-BOPTA:	74.5%

[1]Gd-EOB-DTPA (Primovist®, Bayer-Schering Pharma); [2]Mn-DPDP (Teslascan®, GE Healthcare);
[3]Gd-BOPTA (MultiHance®, Bracco)
Abbreviations:
CT (Computed Tomography)
MRI (Magnetic Resonance Imaging)
PET (Positron Emissions Tomography)

more effective than plain MR imaging or spiral CT in identifying liver metastases, with a very high diagnostic reliability and superiority.[12,24–32] Although valid data are rare to compare extracellular MR imaging and the group of hepatobiliary contrast agents directly, a diagnostic add-on can be assumed. The detection rates for the different hepatobiliary contrast agents range between 80 and 90%, and examples from selected publications are summarized in Table. Direct comparison of the different contrast agents and techniques is only possible with limitations as a result of the diversity in technical approaches, statistical evaluation, and standards of reference employed in these studies. Yet, the additional diagnostic impact of hepato-specific contrast agents on the detection and characterization of focal hepatic lesions can be considered common sense.

Conclusion

Gd-EOB-DTPA is a bolus-injectable, liver-specific Gd-DTPA derivate for T_1-weighted MR imaging. Its dual mode of action allows imaging in the early dynamic phase (as with standard gadolinium chelates) as well as in the hepatocyte phase within a single MR examination and with one contrast agent application only. The evaluation of vascularity and hepatocyte-specific uptake enables accurate detection and characterization of focal liver lesions. Based on our experience and the existing literature, imaging using this contrast agent can be expected to be superior to that using standard gadolinium chelates or to spiral CT, especially for the detection of small (< 1 cm) metastases and for the differential diagnosis of hypervascular lesions. Thus, Gd-EOB-DTPA-enhanced MR imaging is a suitable modality for the diagnostic work-up of focal liver lesions and in the staging of malignant disease prior to surgery or image-guided percutaneous interventional therapies.

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