Application of liver-specific contrast agents for evaluation of focal liver lesions – Expert recommendations from the Gastrointestinal and Abdominal Imaging Workgroup of the German Roentgen Society

Einsatz leberspezifischer Kontrastmittel in der MRT zur Beurteilung von Leberläsionen – Expertenempfehlungen der AG Gastrointestinal- und Abdominaldiagnostik der Deutschen Röntgengesellschaft

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ABSTRACT

Purpose Contrast-enhanced MRI is the imaging modality of choice for the detection and differential diagnosis of focal liver lesions. Liver-specific contrast agents (CAs) are now well established in addition to extracellular contrast agents. However, there is a lack of explicit recommendations reflecting the pros and cons of each specific contrast agent in the daily routine.

Materials and Methods Development of recommendations for the clinical application of liver-specific CAs by members of the Gastrointestinal and Abdominal Imaging Workgroup within the Germany Radiological Society, using methodology comparable to that of an S1 guideline with informal consensus. The diagnostic criteria for the evaluation of liver lesions are intentionally outside the scope of this article, as there are already plenty of excellent publications available.

Results and Conclusion The application of liver-specific CAs in the daily routine is associated with advantages and disadvantages due to the specific pharmacokinetic and pharmacodynamic properties and necessitates adjustment of the imaging technique as well consideration during image interpretation. Recommendations for the application of liver-specific CAs are presented based on different clinical scenarios, taking into account current evidence and guidelines.

Key points

- Both liver-specific and extracellular contrast agents are established
- Liver-specific contrast agents make it possible to draw conclusions about the hepatocellular function of a lesion
- Recommendations for the use of liver-specific contrast agents in the daily routine are presented

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ZUSAMMENFASSUNG

Hintergrund Die Kontrastmittel (KM)-verstärkte MRT ist die bildgebende Methode der Wahl für die Detektion und differenzialdiagnostische Abklärung fokaler Leberläsionen. Leberspezifische KM sind mittlerweile neben extrazellulären KM etabliert. Allerdings fehlen klare Handlungsempfehlungen, die das Für und Wider bezüglich der Wahl des geeigneten KM im radiologischen Alltag berücksichtigen.

Methoden Erarbeitung von Handlungsempfehlungen für den klinischen Einsatz leberspezifischer KM durch Mitglieder der AG Gastrointestinal- und Abdominaldiagnostik der Deutschen Röntgengesellschaft, vergleichbar der Methodik einer S1-Leitlinie mit informellem Konsens. Bewusst stehen hierbei nicht diagnostische Kriterien für die Läsionsbeurteilung an sich im Vordergrund, da es hierzu bereits mannigfaltige und hervorragende Publikationen gibt.

Ergebnisse und Schlussfolgerung Der Einsatz leberspezifischer KM im radiologischen Alltag ist aufgrund spezifischer pharmakokinetischer und pharmakodynamischer Eigenschaften mit Vor- und Nachteilen verbunden und erfordert Anpassungen an die Untersuchungsdurchführung sowie Berücksichtigung bei der Befundinterpretation. Handlungsempfehlungen für den Einsatz leberspezifischer KM werden basierend auf verschiedenen klinischen Szenarien unter Berücksichtigung aktueller Evidenz und Leitlinien präsentiert.

Kernaussagen

- Leberspezifische KM sind neben extrazellulären KM in der MRT etabliert.
- Leberspezifische KM ermöglichen Rückschlüsse auf die hepatozelluläre Funktion einer Läsion.
- Handlungsempfehlungen für die Verwendung leberspezifischer KM werden dargelegt.

Background

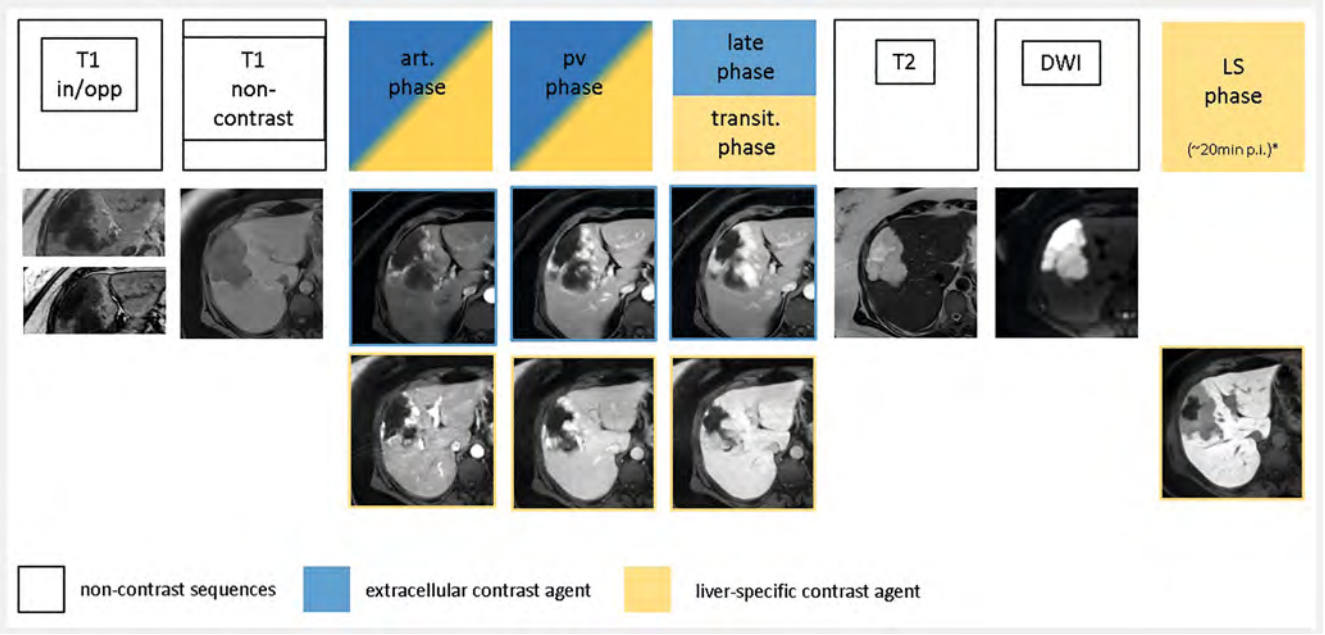
In addition to extracellular contrast media (CM), liver-specific contrast media, also known as hepatobiliary-specific CM, are well established for the detection and differential diagnosis of focal liver lesions in magnetic resonance imaging (MRI). However, there is a lack of clear application recommendations that take into account the pros and cons with regard to choosing the appropriate CM in everyday radiological practice. The German S3 guidelines on diagnostics and treatment/therapy of hepatocellular carcinoma and biliary carcinoma, which were last revised in July 2022, are the only guidelines that recommend the following in the background text: “in the case of pronounced cirrhosis and unclear findings, [we recommend] an MRI with a hepatobiliary-specific CM for the late-phase analysis” (“bei ausgeprägter Zirrhose und bei unklaren Befunden ein MRT mit hepatobiliärem KM zur Analyse der Spätphase”) [1]. However, this does not always reflect current clinical practice. Particularly in light of the respective advantages and disadvantages of liver-specific and extracellular CM (associated, among other things, with differences in pharmacokinetics and dynamics as well as costs), central questions arise regarding the choice of the “right” or “optimal” CM in routine clinical practice.

Method

The authors of this publication represent the Working Group (WG) of the German Gastrointestinal and Abdominal Diagnostics Radiological Society (“Gastrointestinal- und Abdominaldiagnostik der Deutschen Röntgengesellschaft”, DRG). The proposals presented here are the results of a national expert meeting focusing on developing MRI application recommendations for liver-specific CM. Based on the classification of the Working Group of Scientific Medical Societies (“Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften”, AWMF), the methodology is comparable to that of an S1 guideline, in the sense of an informal consensus [2]. The target groups are all radiologists who regularly or only occasionally perform liver MRI examinations in the context of diagnostic confirmation of focal liver lesions. The focus is intentionally not on the examination or diagnostic criteria for the assessment of the lesion per se, as there are already numerous, excellent publications on this topic, but rather on recommendations for the use of liver-specific CM based on concrete clinical scenarios. This will be achieved by taking into account current evidence from the literature as well as national and international guidelines.

CM-supported liver MRI

Most CM for magnetic resonance imaging are based on Gadolinium (Gd) and lead to a shortening, in particular, of the T1 relaxation time in the tissue through interactions with the local magnetic field. The structure of CM influences their distribution mechanisms in the body. Accordingly, a distinction can be made between extracellular and liver-specific (or hepatobiliary-specific) CM. Extracellular CM (e. g., gadobutrol, gadovist, Bayer Vital GmbH; gadoteric acid, Dotarem, Guerbet) have been well-estab-



▶ **Fig. 1** Example of an examination protocol for the workup of focal liver lesions on MRI in a 50-year-old patient with a hemangioma in the right liver lobe. art = arterial, pv = portal venous, transit. = transitory, DWI = diffusion-weighted imaging, LS = liver-specific.

lished for decades. They are well suited for the detection and characterization of focal liver lesions, with the enrichment behavior based on tumor vascularization and morphology, similar to the use of iodine-containing CM in computed tomography (CT). Elimination of extracellular CM occurs via the kidneys.

Liver-specific CM are characterized by partial hepatic cell uptake. The remaining extracellular portion is excreted competitively via the kidneys, and the hepatocellular portion is eliminated via the bile. Hepatic cell uptake is mediated by the binding of lipophilic side chains to the Gd ion. To date, two liver-specific CM have been approved in Germany, Gd-BOPTA (Multihance, Bracco) and Gd-EOB-DTPA (Primovist, Bayer Healthcare). Essentially, these two CM differ in the proportion of agent absorbed by hepatocytes and, consequently, eliminated via the bile. In patients with normal liver and renal function, approximately 50 % of Gd-EOB-DTPA is absorbed by hepatocytes; for Gd-BOPTA, this proportion is about 3–5 % [3, 4].

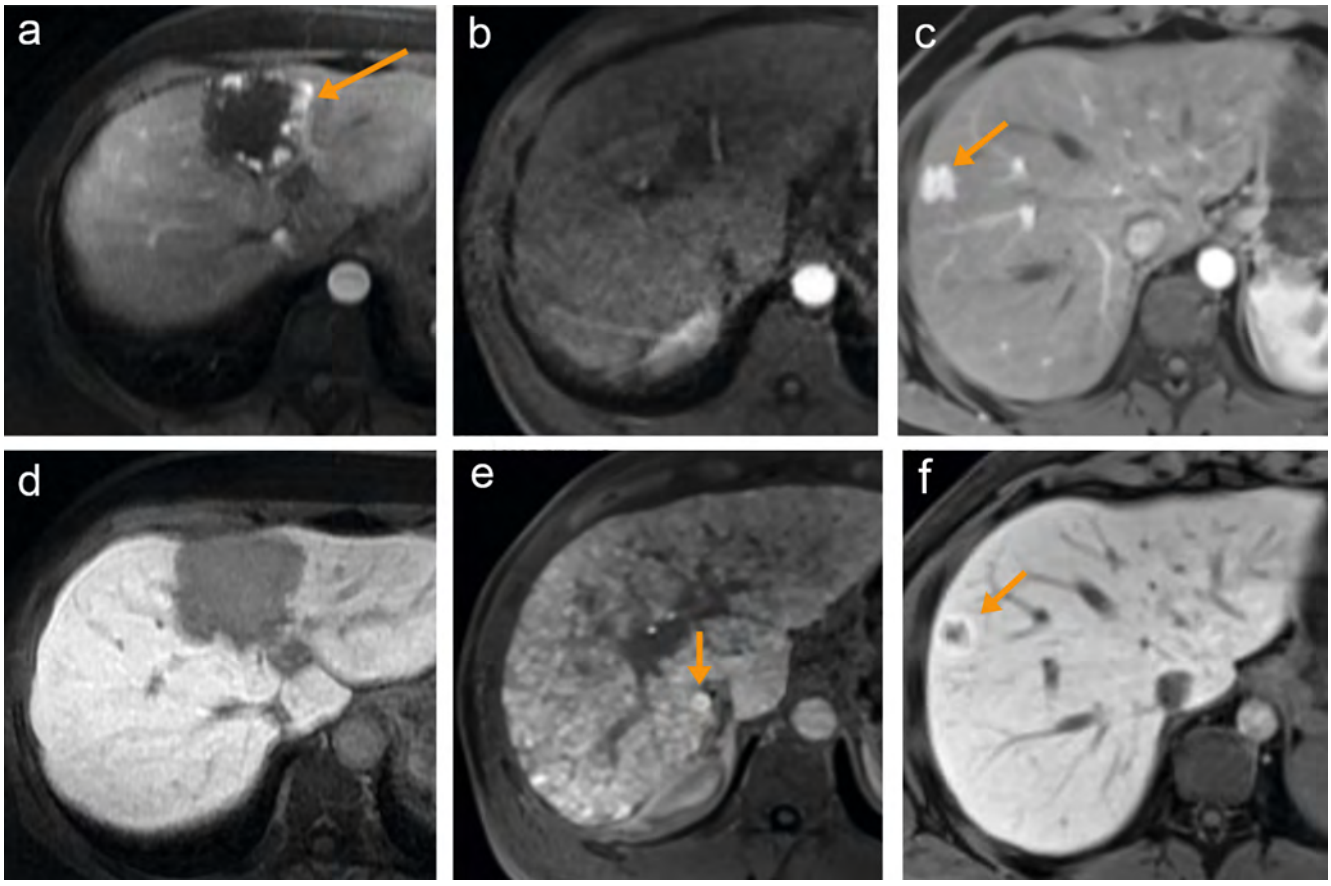
If liver-specific CM are used, the procedure is performed after an intravenous bolus injection to initially assess vascularization in the dynamic phase by capturing the primary extracellular distribution. Subsequently, acquisitions are performed in the liver-specific or hepatobiliary phase. The hepatobiliary phase is typically 15–20 minutes after injection of Gd-EOB-DTPA and 60–120 minutes after injection of Gd-BOPTA (▶ **Fig. 1**). An increase in the background liver signal in the liver-specific phase, as a result of hepatocellular-specific CM uptake, can increase the lesion's parenchymal contrast [5, 6]. In addition, the signal behavior of lesions in this phase also allows conclusions to be drawn about the hepatocellular function of changes.

Specifics of Gd-EOB-DTPA

When using liver-specific CM, the visual impression of lesions may differ from that obtained with extracellular CM, especially in the later CM-supported phases. For example, an increase in the background signal of the hepatic parenchyma can lead to a so-called pseudo-washout just minutes after the injection of Gd-EOB-DTPA. As a result, lesions that exhibit an absolute increase in signal behavior appear isointense or hypointense because the background signal also increases (▶ **Fig. 1**). For this reason, the classic "washout", i. e., contrast reversal, of hepatocellular carcinoma (HCC) when using Gd-EOB-DTPA should only be evaluated in the portal venous phase [7].

Compared to other Gd chelates, Gd-EOB-DTPA has a higher T1 relaxivity, which allows this CM to be administered at a lower dose. However, the manufacturer's recommendation of 0.1 ml/kg (0.025 mmol/kg) is associated with a comparatively weaker contrast, especially in the arterial phase, which can be managed with more practice [8]. In order to achieve a more favorable bolus configuration and to compensate for the small volume, it is worth recommending reducing the CM injection speed to 1 ml/sec. In addition, the occurrence of respiratory artifacts in the arterial phase, which has been frequently described after administration of Gd-EOB-DTPA, may influence the assessment of the recordings [9–12]. In terms of costs, the comparatively higher consumption costs associated with the use of Gd-EOB-DTPA, some of which are country-specific, must be weighed up against the benefits and any additional examinations that may become unnecessary as a result [13].

All of these aspects described, with their advantages and disadvantages, must be taken into account when choosing the optimal CM for the diagnosis of focal liver lesions. Below we present expert recommendations based on typical clinical scenarios that



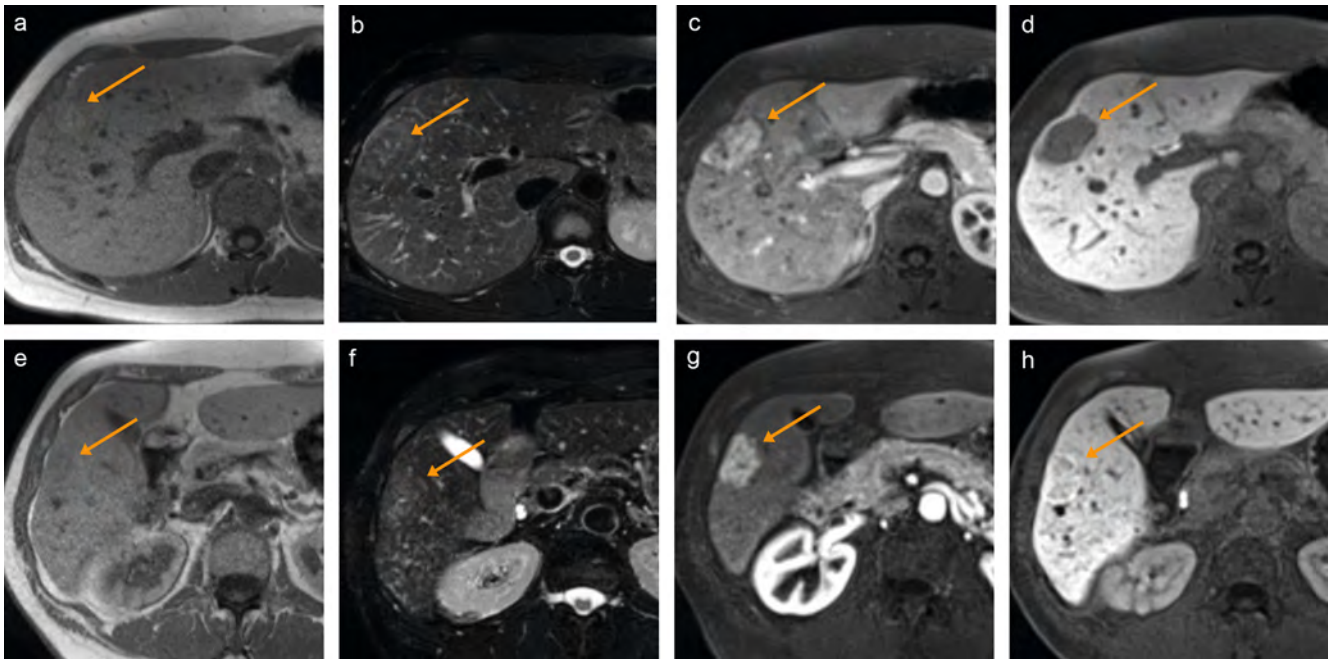
▶ **Fig. 2** MRI in the late arterial (**A**–**C**) and hepatocellular phases (**D**–**E**) after administration of a liver-specific contrast agent in three different patients with liver lesions. Cavernous hemangioma with late arterial contrast enhancement at the margins (arrow in **A**) and a lack of contrast enhancement in the hepatocellular phase (**D**). Non-hypervascularized regenerative nodules (**B**) with retention of the liver-specific contrast agent in the hepatocellular phase (arrow in **E**). FNH with late arterial vascularization (arrow in **C**) and retention of the contrast agent in the hepatocellular phase (arrow in **F**).

are intended to support the routine choice of CM. These recommendations represent the authors' consensus and literature-based expert recommendations and do not represent an interdisciplinary guideline.

Scenario 1: Which CM are recommended in patients without a known pre-existing liver disease for diagnostic confirmation of an incidental liver lesion?

MRI is the method of choice for diagnostic confirmation of focal liver lesions, due to the high intrinsic soft tissue contrast and because it does not expose the patient to radiation, among other reasons. The patient's medical history can already provide valuable initial differential diagnostic information regarding the origin of a lesion and the subsequent examination strategy. In patients without a history of malignancy or known pre-existing liver disease, most incidental liver lesions are benign; these are primarily cysts, hemangiomas, and focal nodular hyperplasia (FNH). With a corresponding history of malignancy, the probability that an incidental liver lesion is a benign finding is reduced to about 30 % [14]. To date, there are no national guidelines for diagnostic confirmation of incidental liver lesions in Germany [15]. Appropriate recommendations of the American College of Radiology (ACR) for the diagnostic confirmation of incidental findings can be helpful as an initial guide [16], as can the recommendations of the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) [17]. The proposed ACR algorithm for diagnostic confirmation of incidental lesions detected by CT is essentially based on the size of a lesion and the risk profile of the patient, but also provides no further details on the choice of CM in MRI for additional diagnostic confirmation.

Further diagnostic confirmation of an incidental liver lesion, for example detected on ultrasound or CT, is a common question. In everyday clinical practice, it is not uncommon for patients to have incomplete clinical information at the time of the requested MRI, or there are still diagnostic uncertainties, so that MRI should be performed to provide as much information as possible. This may be an argument for the primary use of liver-specific CM. In addition to the perfusion of the lesion, conclusions can be drawn about the hepatocellular function of the change from the signal behavior in the liver-specific phase. In this respect, it is necessary to differentiate whether the putative CM uptake of a lesion is due



▶ **Fig. 3** MRI of a 23-year-old patient with a hepatocellular adenoma (**A**–**D**) and of a 25-year-old patient with focal nodular hyperplasia (FNH; **E**–**H**), both in the right liver lobe (arrows in **A**–**H**). Both lesions are weakly hypointense on the non-contrast-enhanced T1w images (**A**, **E**) and weakly hyperintense on the T2w images (**B**, **F**), while strong enhancement is seen in the late arterial phase (**C**, **G**). Differentiation between the two entities can only be achieved in the hepatocellular phase (**D**, **H**) in which the hepatocellular adenoma is hypointense and the FNH is characterized by retention of the liver-specific contrast agent.

to increased perfusion in the late arterial phase (e. g., in a hemangioma), due to preserved hepatocellular function in the liver-specific phase (e. g., in a pseudolobule), or due to the presence of both mechanisms described above (e. g., in classic focal nodular hyperplasia, FNH) (▶ **Fig. 2**).

In the case of cavernous hemangioma, classic centripetal enhancement may be more difficult to detect on MRI with liver-specific CM. In the late arterial phase, marginal CM uptake is initially comparable to extracellular CM. However, in the late dynamic phase, hemangiomas appear isointense or hypointense due to the simultaneous increase in background liver signal. This so-called "pseudo-washout" can make it difficult to differentiate from other lesions, especially hypervascularized metastases [18, 19].

Both FNH and hepatocellular adenoma (HCA) represent common incidental findings on ultrasound in young patients without known pre-existing diseases or a history of malignancy. Differentiating between these two types of tumors is important in light of the risk of malignant transformation and hemorrhage in the case of HCA. This is also crucial with regard to the further clinical procedure, especially since it is possible to subtype HCAs with liver-specific contrast media [20]. Both tumor entities are often difficult to distinguish from background liver parenchyma in the native T1 and T2 mapping, as a possible indication of a hepatocyte origin. In addition, both tumors can be characterized by often strong CM uptake in the late arterial phase (▶ **Fig. 3**). Based on the different signal behavior in the hepatocellular phase, differentiation of FNH from HCA on MRI is improved after administration of liver-specific CM, especially if the classic central scar of FNH cannot be delineated on imaging [21, 22]. However, it must be taken into account that there may be large overlaps for some HCA subtypes.

RECOMMENDATION 1.1 – GENERAL:

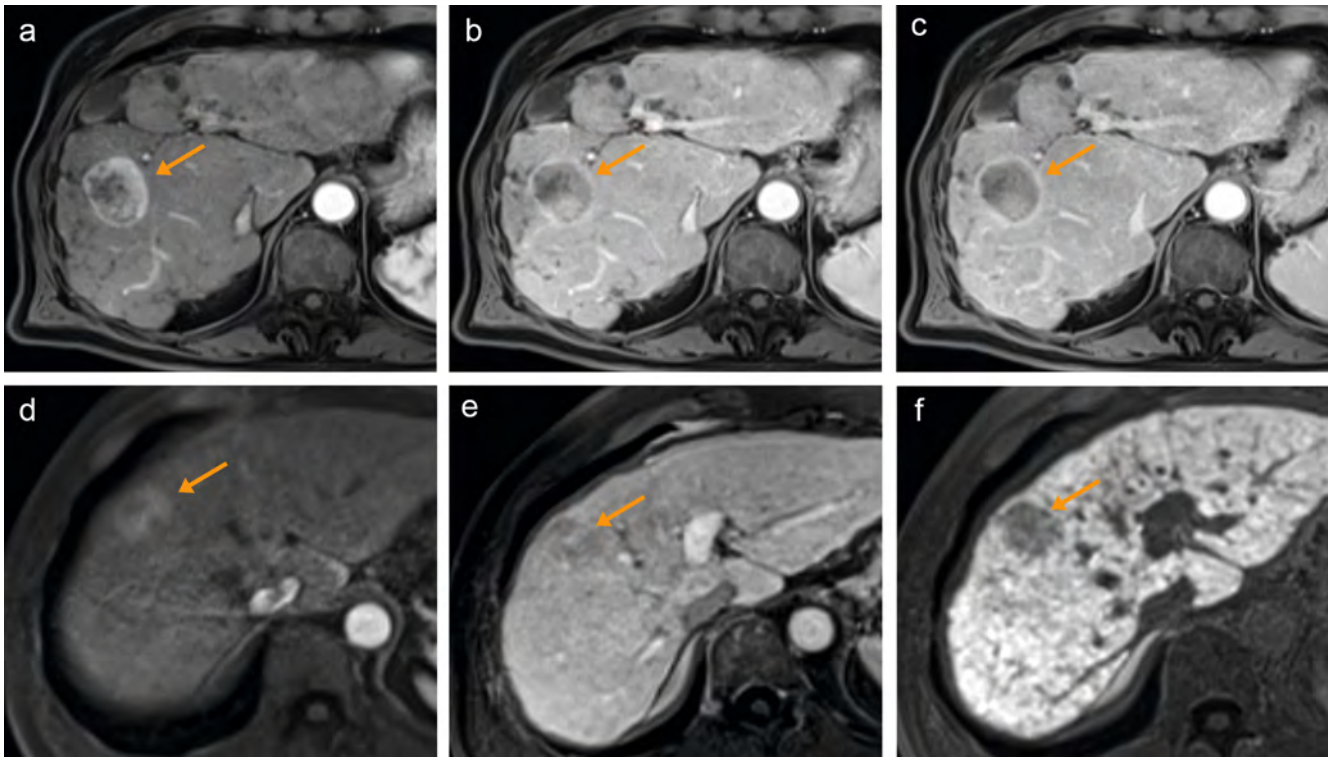
For diagnostic confirmation of an unclear incidental liver lesion > 0.5 cm, the primary use of a liver-specific CM can be recommended which allows MRI to provide a maximum amount of information, in addition to perfusion, to draw conclusions about hepatic cell function.

RECOMMENDATION 1.2 – SUSPECTED DIAGNOSIS OF HEMANGIOMA:

For suspected hemangioma, the use of extracellular CM may be beneficial to better visualize a classic centripetal enhancement.

RECOMMENDATION 1.3 – DIFFERENTIATION BETWEEN FNH AND ADENOMA:

To differentiate focal nodular hyperplasia (FNH) from hepatocellular adenoma (HCA), the primary use of liver-specific CM in MRI is recommended.



▶ **Fig. 4** MRI with extracellular contrast agent in a patient with HCC (arrows **A**–**C**) and MRI with liver-specific contrast agent in another patient with HCC (arrows in **D**–**F**). In the arterial (**A**, **D**) and portal venous phases (**B**, **E**), the signal behavior in both cases is similar, with the arterial contrast possibly being weaker in the case of a liver-specific contrast agent. When using extracellular contrast agent, the washout of a lesion in the late venous phase (**C**) can be additionally evaluated. When using a liver-specific contrast agent, hypointensity of the lesion in the hepatocellular phase (**F**) suggests malignancy.

Scenario 2: Which CM are recommended in patients with cirrhosis for diagnostic confirmation of HCC?

Over 80 % of hepatocellular carcinomas (HCC) progress from cirrhosis. The highest risk of HCC is observed in patients with chronic hepatitis C cirrhosis (lifetime risk: approx. 60 %), followed by patients with chronic hepatitis B (approx. 50 %), hemochromatosis (approx. 40 %), and alcohol-induced cirrhosis (approx. 30 %) [23]. In the cirrhotic liver, HCC is diagnosed based on its typical CM behavior on imaging, in the sense of arterial hypervascularization followed by contrast inversion, so-called washout, in the portal or late venous phase. According to the current S3 guidelines, contrast-enhanced MRI should be used for this purpose, initially without specifications for the particular CM [1]. This means that both extracellular or liver-specific CM may be appropriate. However, in patients with previously diagnosed hemochromatosis, no additional information is expected to be gained in the hepatocellular phase when liver-specific CM are used, since the high iron content of the liver parenchyma reduces the signal.

The CM behavior of HCC, with extracellular and liver-specific CM, is comparable in the late arterial and portal venous phases, although arterial enhancement may be slightly dimmer when liver-specific CM are used (▶ **Fig. 4**). However, due to the previously mentioned increase in background liver signal a few minutes after the CM injection, there is no late venous phase when liver-specific CM are used. This means that the washout in these cases can only be assessed in the portal venous phase. The absence of a true late venous phase may therefore present a limitation when using liver-specific CM in terms of detecting the washout. The signal behavior of the lesion may nevertheless provide valuable information in the additional hepatocellular phase that is now available, especially if the CM behavior of a lesion in the early CM dynamics is not typical of HCC. Studies have shown that in these cases, hypo-intensity of the lesion in the hepatocellular phase is indicative of (pre-)malignancy [24–26].

This can increase the detection sensitivity of HCC, but at the expense of specificity, as premalignant lesions can also be identified. This circumstance is also discussed in more detail in the background text of the S3 guidelines on HCC, with the corresponding comment that “in the case of pronounced cirrhosis and unclear findings, an MRI with a hepatobiliary-specific CM [is recommended] in the late-phase analysis” [1]. From this, the implementation of MRI primarily with liver-specific CM may be advantageous, especially when it comes to individual therapeutic stratification [27]. However, this recommendation should be assessed critically, since in patients with advanced cirrhosis and specifically with elevated bilirubin levels, hepatocellular CM uptake is significantly reduced and thus the benefit of imaging in the liver-specific phase is very limited.

Currently, the situation is somewhat more complicated when it comes to selecting HCC patients for the liver transplantation list.

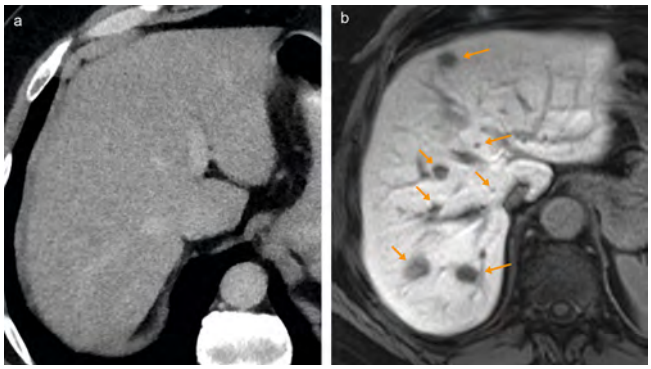
In the guidelines of the German Medical Association (Bundesärztekammer, BÄK) on organ transplantation, see Section 16 of the Transplantation Act, which first came into effect on 20 June 2017, an MRI specification calls for an "extracellular contrast medium that does not have dominant biliary excretion" ("extrazelluläres Kontrastmittel, das keine dominante biliäre Exkretion aufweist"), in the appendix under the heading "Minimum technical requirements for liver diagnostics" ("Minimale technische Anforderungen für die Leberdiagnostik") [28]. This requirement appears to have been translated from the English or taken from the US recommendations of the OPTN (Organ Procurement and Transplantation Network) [29], and creates uncertainty, especially in radiology. It remains unclear whether the wording really implies that liver-specific CM, which are only excreted to a maximum of 50 % via bile, and therefore, strictly speaking, do not exhibit a "dominant" biliary excretion mechanism, should therefore not be used for inclusion of patients on the liver transplantation list. If this is indeed the case, the authors of this publication are unfortunately not fully aware of the rationale for this. No justification or literature reference exists in the German Guideline for Liver Transplantation regarding this. A possible justification for this claim could be the weaker arterial contrast when liver-specific CM are used, or the lower specificity (despite a higher sensitivity), but this would be at the cost of an increased risk of including patients with a premalignant lesion (e. g., highly dysplastic lump) on the liver transplantation list. In light of the changing scientific standards, a certain degree of congruence with existing guidelines would certainly make sense in the future, this would also avoid any unnecessary repeat or complementary examinations in patients with HCC. Ideally, a corresponding update of the BÄK guidelines would also involve representatives of the radiological professional societies.

RECOMMENDATION 2.1. – GENERAL:

In patients with cirrhosis, implementation of MRI is recommended primarily with liver-specific CM to achieve high sensitivity for the detection of HCC.

RECOMMENDATION 2.2. – BEFORE LIVER TRANSPLANTATION:

In the context of including patients on the liver transplant list and with the aim of achieving the highest possible specificity for the diagnosis of HCC, the implementation of MRI, with extracellular CM, is recommended.

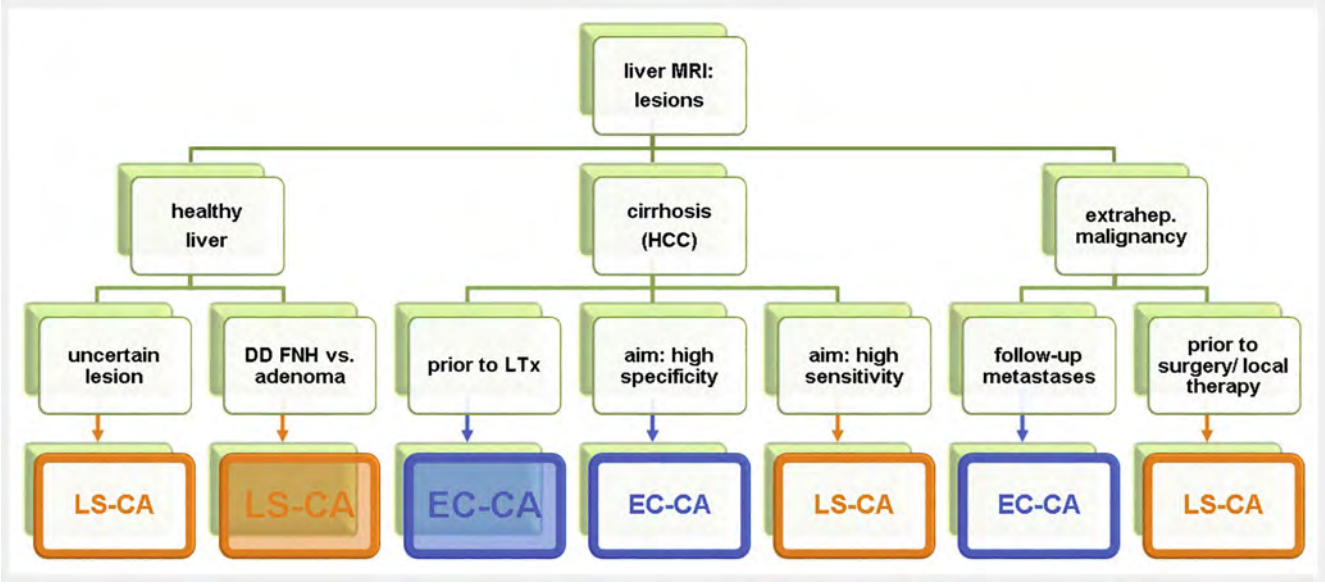


▶ **Fig. 5** 56-year-old patient with initial diagnosis of colorectal cancer. CT in the portal venous phase (**A**) and MRI in the hepatocellular phase (**B**) after administration of a liver-specific contrast agent with detection of multiple metastases (arrows).

Scenario 3: Which CM are recommended in patients with a known extrahepatic malignancy to exclude or detect liver metastases?

By far the most common malignant liver lesions are metastases, predominantly from primary gastrointestinal tract carcinomas (mainly colorectal, pancreatic, and gastric) [30]. The risk of malignancy is significantly higher in cirrhosis patients compared to patients without a known liver disease per se, although metastases are less common [14]. In most cases, MRI, with extracellular CM, is sufficient to detect or exclude metastases. It is very easy to differentiate between hypo- and hyper-vascularized metastases, but necrotic metastases can also be diagnosed, particularly with the aid of T2-weighted or diffusion imaging. Extracellular CM are thus sufficient for the primary diagnostic confirmation of liver metastases and also for follow-up imaging. The current national oncology guidelines do not provide more details on the technical aspects of CM for MRI imaging in terms of the diagnostic confirmation of liver metastases. In lieu of this, the S3 guidelines on colorectal carcinoma should be cited here, in which MRI is only mentioned in the background text, in that it is best suited to detect liver metastasis [31]. Similarly, the S3 guidelines on pancreatic carcinoma recommend preoperative liver MRI with diffusion weighting, without elaborating on the type of CM [32].

However, the exact number or localization of metastases can decisively influence the therapeutic procedure. Especially in patients starting treatment with curative intent or prior to surgery or localized treatment, it is important to exclude or detect metastases with the highest diagnostic certainty. The high parenchymal-lesion contrast in the hepatocellular phase can decisively improve the detection of metastases, especially very small metastases, in MRI with liver-specific CM and can change the therapeutic procedure [33]. Accordingly, in this particular situation, MRI with a liver-specific CM may be beneficial (▶ **Fig. 5**).



▶ **Fig. 6** Algorithm for using extracellular and liver-specific contrast agent in MRI in the workup of liver lesions. Recommendations of the Gastrointestinal and Abdominal Imaging Workgroup within the Germany Radiological Society. HCC = hepatocellular carcinoma, FNH = focal nodular hyperplasia, LTx = liver transplantation, LSKM = liver-specific contrast agent, EZ-KM = extracellular contrast agent

RECOMMENDATION 3.1. – GENERAL:
In most situations, MRI with extracellular CM including diffusion-weighted sequences is sufficient for the assessment of hepatic metastasis in patients with extrahepatic malignancies.

RECOMMENDATION 3.2 – FOLLOW-UP ASSESSMENT:
For purely follow-up imaging in patients with extrahepatic malignancies, MRI, with extracellular CM, is recommended or sufficient to assess hepatic metastases.

RECOMMENDATION 3.3 – BEFORE LOCAL TREATMENT/ THERAPY:
Prior to local or surgical treatment/therapy and treatment with curative intent, implementation of MRI, with liver-specific CM, is recommended for patients with extrahepatic malignancies.

Summary

MRI is the imaging method of choice for diagnostic confirmation of focal liver lesions. Extracellular and liver-specific CM are equally well-established and used to the same extent. The current recommendations presented by the working group of the German Gastrointestinal and Abdominal Diagnostics Radiological Society, in terms of CM selection, are situation-specific (▶ **Fig. 6**) and are intended to support the work carried out in routine clinical practice. The recommendations are based on a national expert consensus with a literature search and are not interdisciplinary guidelines.

Conflict of Interest

Kristina I. Ringe: Fees from Bayer Vital GmbH and Varian
Frank Fischbach: Fees from Bayer Vital GmbH
Lars Grenacher: none
Markus Juchems: Fees from Bayer Vital GmbH
Guido Kukuk: Fees from Bayer Vital GmbH
Thomas Lauenstein: Fees from Bayer Vital GmbH, Voyageur Pharmaceuticals
Johannes Wessling: Fees from Bayer Vital GmbH, Canon, Janssen Medical
Andreas G. Schreyer: Fees from Bayer Vital GmbH, Siemens Healthineers

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