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MAGNETIC RESONANCE

# Consensus report from the 7th International Forum for Liver Magnetic Resonance Imaging

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**Abstract**

*Objectives* Liver-specific MRI is a fast-growing field, with technological and protocol advancements providing more robust imaging and allowing a greater depth of information per examination. This article reports the evidence for, and expert thinking on, current challenges in liver-specific MRI, as discussed at the 7th International Forum for Liver MRI, which was held in Shanghai, China, in October 2013.

*Methods* Topics discussed included the role of gadoxetic acid-enhanced MRI in the differentiation of focal nodular hyperplasia from hepatocellular adenoma and small hepatocellular carcinoma (HCC) from small intrahepatic cholangiocarcinoma (in patients with chronic liver disease), the differentiation of low-grade dysplastic nodule (DN) from pre-malignant high-grade DN and early HCC, and treatment planning and assessment of treatment response for patients with HCC and colorectal liver metastasis. Optimization of the gadoxetic acid-enhanced MRI protocol to gain robust arterial and hepatobiliary phase images was also discussed.

*Results and conclusions* Gadoxetic acid-enhanced MRI demonstrates added value for the detection and characterization of focal liver lesions and shows promise in a number of new indications, including regional liver functional assessment and patient monitoring after therapy; however, more data are needed in some areas, and further developments are needed to translate cutting-edge techniques into clinical practice.

*Key Points*

- *Liver-specific MRI is a fast-growing field, with many technological and protocol advancements.*
- *Gadoxetic acid-enhanced MRI demonstrates value for detecting and characterizing focal liver lesions.*
- *Gadoxetic acid-enhanced MRI shows promise in regional functional assessment and patient monitoring.*
- *Further developments are needed to translate cutting-edge techniques into clinical practice.*

**Keywords** Gadoxetic acid · Hepatocellular carcinoma · Liver function tests · Liver neoplasms · Magnetic resonance imaging

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## Introduction

There is growing evidence for the benefits of gadoxetic-acid-enhanced magnetic resonance imaging (MRI) in a number of indications for liver imaging. Topics in this area were discussed by more than 70 international abdominal experts at the 7th International Forum for Liver MRI, held in Shanghai, China, in October 2013. Forum participants attended presentations by the authors of this article on the following related topics and discussed these data further in four workgroups:

1. Liver lesion characterization – challenging differential diagnoses
2. Differentiation of low-grade dysplastic nodule (DN) from pre-malignant high-grade DN and early hepatocellular carcinoma (HCC)
3. The role of Primovist® in treatment planning and assessment of treatment response
4. Tips and tricks session – how to improve imaging with Primovist® – differences versus traditional agents

Consensus statements on each topic were proposed based on available evidence and expert opinions of participants. The whole forum further discussed, amended, and voted on the statements, using an electronic voting system with the options 'agree', 'disagree' or 'abstain'. The final consensus statements and the voting results are presented in this article, with the intent to inform radiologists and assist them in their daily clinical practice.

## Challenging differential diagnoses in liver lesion characterization

### Focal nodular hyperplasia (FNH) and hepatocellular adenoma (HCA)

FNH and HCA are benign hepatocellular tumours; differentiating is important because FNHs are usually managed conservatively, while HCAs are managed according to risk of spontaneous bleeding and malignant transformation [1]. Distinguishing between FNH and HCA using dynamic contrast-enhanced (CE) computed tomography (CT) or MRI can be challenging when hallmark features (e.g. central scar) are absent, due to overlapping imaging features.

**Consensus statement 1.1** The hepatobiliary phase (HBP) of gadoxetic acid-enhanced MRI can help in the differential diagnosis of FNH and HCA. Specifically, hyperintensity or isointensity relative to the liver, which may be diffuse or peripheral, favours FNH. Delineation of a hypointense central scar strongly favours FNH. Diffuse hypointensity relative to the liver strongly favours HCA. *[67/69 (97.1 %) agreement]*

The HBP imaging features of FNH on gadoxetic acid-enhanced MRI commonly include iso- or hyperenhancement in the HBP (largely strong homogeneous enhancement) [1–4], with hypoenhancement of any central scar relative to the rest of the lesion on T2-weighted images [1]. On the other hand, for HCA, hypointensity in the HBP, relative to the surrounding liver parenchyma, is common [2, 5, 6]. Recent evidence suggests that the HBP of gadoxetic acid-enhanced MRI has a sensitivity and positive predictive value (PPV) of 96 % for differentiation of FNH and HCA [7], and may increase correct lesion diagnosis and reader confidence versus unenhanced and dynamic images alone [8].

**Consensus statement 1.2** Further research is needed to determine the role of the HBP of gadoxetic acid-enhanced MRI in predicting HCA subtype. *[71/73 (97.3 %) agreement]*

Only a few studies [5, 9, 10] are currently available to assess the value of HBP images from gadoxetic-acid-enhanced MRI in differentiating HCA subtypes; however, uptake in the HBP appears to be useful additional information.

### Small intrahepatic cholangiocarcinoma (ICC) and HCC in patients with chronic liver disease

Patients with liver cirrhosis or chronic hepatitis are at risk of developing malignant liver lesions – most commonly HCC, but also ICC. Differential diagnosis is important, as prognoses and patient management differ [11, 12]. Using extracellular agents, portal venous and delayed-phase images help in the differentiation; progressive or sustained concentric enhancement favours ICC, whereas diffuse or nodular washout appearance favours HCC. Using gadoxetic acid, the differential diagnosis is more difficult as both lesions typically are hypointense in the hepatobiliary phase. Therefore, recent retrospective studies have attempted to identify discriminatory imaging features using gadoxetic acid.

**Consensus statement 1.3** In patients at increased risk for HCC with small nodules (<3 cm) that are suspicious for malignancy but lack hallmark imaging features of HCC, reliable differentiation between HCC and ICC may not be possible.

Gadoxetic acid-enhanced MRI features that favour ICC over HCC include:

- lobulated shape
- rim enhancement in the arterial phase
- target appearance on diffusion-weighted images
- target appearance in the HBP

Gadoxetic acid-enhanced MRI features that favour HCC over ICC include:

- intralesional fat
- diffuse hyperintensity on pre-contrast T1-weighted imaging
- nodule-in-nodule architecture
- diffuse hyperintensity relative to liver in the HBP

*[63/72 (87.5 %) agreement]*

**Consensus statement 1.4** Prospective studies in consecutive patients are needed to refine and validate gadoxetic acid-enhanced MRI features for differentiation of small ICC and HCC in patients at increased risk for HCC. *[62/72 (87.5 %) agreement]*

Univariate analyses of imaging features in gadoxetic-acid-enhanced MRI that were predictive of ICC over HCC revealed significance ($P \leq 0.005$) for lobulated shape, arterial phase rim enhancement, target appearance in the HBP (central hyperintensity with a peripheral hypointense rim on the 10- or 20-min images) and target diffusion-weighted imaging (DWI) appearance (central hypointensity and peripheral hyperintensity on b=800 s/mm$^2$ images) (Fig. 1); however, only target appearance on DWI remained significant in multivariate analyses [13]. Other studies reported lobulated shape, arterial phase rim enhancement and target HBP appearance in varying proportions of ICCs, thus these features are suggestive, but not conclusive, of ICC [14–19].

Although uncommon, imaging features on gadoxetic-acid-enhanced MRI that are suggestive of HCC in patients with chronic liver disease include diffuse hyperintensity in the HBP, diffuse hyperintensity on pre-contrast T1-weighted images, presence of intralesional fat and a nodule-in-nodule appearance [20, 21]. To our knowledge, these MRI features have not been described for ICC before. Furthermore, intralesional fat and nodule-in-nodule appearance are not included in the WHO's description of ICC pathology [22].

## Differentiation of low-grade DN from pre-malignant high-grade DN and early HCC

Detection of pre-malignant nodules and early HCCs in patients with chronic liver disease improves the chances of curative treatment as progression after radiofrequency ablation (RFA) is less frequent in hypovascular versus hypervascular small HCC [23, 24]. On CE-MRI, these pre-malignant nodules often lack the hallmark imaging features of HCC and pose a diagnostic challenge.

**Consensus statement 2.1** Hypointensity in the HBP of gadoxetic acid-enhanced MRI provides high sensitivity for the detection of iso-/hypovascular pre-malignant (HGDN) and malignant (eHCC) hepatocellular lesions; however, differentiation of these lesions is not currently possible. *[67/73 (91.8 %) agreement]*

**Consensus statement 2.2** Gadoxetic acid-enhanced MRI, incorporating a combination of ancillary features (lesion size, lesion growth, T2 intensity, DWI, T1 intensity, HBP intensity and intralesional fat), improves risk stratification of patients with chronic liver disease and lesions without hallmark vascular features of HCC. *[51/57 (89.5 %) agreement]*

Progression of pre-malignant/early HCC has been linked to size (>1 cm) [25–30], and an increased risk of hypervascularization is associated with the presence of fat ($P<0.01$), enlargement during follow-up ($P=0.04$), T2 hyperintensity ($P=0.06$) [29, 31] and hyperintensity on DWI [31].

Hypointensity in the HBP of gadoxetic acid-enhanced MRI is suggestive of pre-malignancy or malignancy (irrespective of lesion vascularity) and can increase the sensitivity of diagnosis [32], with almost all HCC and some high-grade DNs being hypointense in this phase [33]. While some low-grade DNs and regenerative nodules (RNs) also show hypointensity in the HBP [34, 35], these nodules are usually <1 cm [36], while high-grade DN and early HCC tend to be >1 cm. Enhancement ratios for gadoxetic acid decreased with nodule differentiation, but are unable to distinguish between DN and hypovascular well differentiated HCC due to considerable overlap [35, 37].

## The role of gadoxetic acid-enhanced MRI in treatment planning and assessment of treatment response

### Pre-operative diagnosis and staging of liver lesions

Wider use of local treatments and more aggressive surgical options require more meticulous pre-operative planning, alongside volume-based functional analyses [38, 39]. Gadoxetic acid-enhanced MRI can provide comprehensive morphological and regional functional information in a single examination and is showing promise as a pre-operative assessment tool.

*Colorectal liver metastases (CRLM)*

Hepatic metastases occur in more than half of patients with primary colorectal cancer [40]. Around 20–25 % of patients with CRLM will present with resectable disease [40, 41]. Patient selection and therapy planning may be improved by

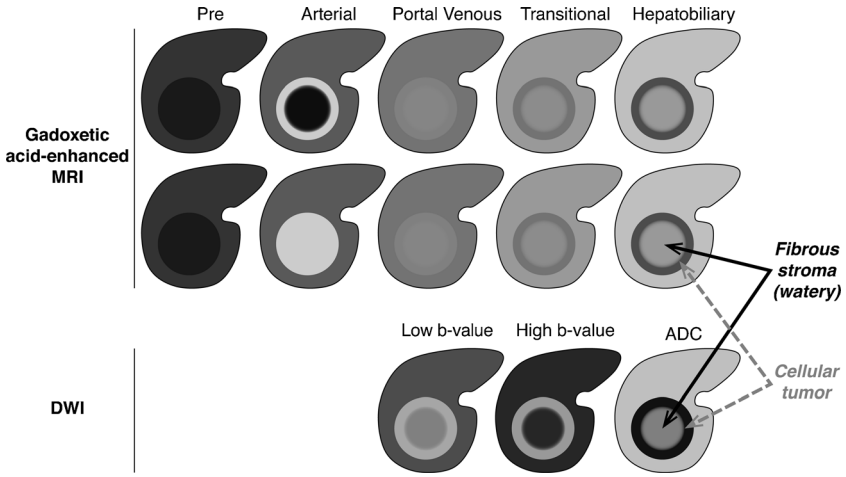


**Fig. 1** Target appearance of intrahepatic cholangiocarcinoma on gadoxetic acid-enhanced MRI and diffusion-weighted imaging. Images courtesy of Claude Sirlin

better estimation of liver remnant function, and by accurate detection and staging of tumours.

**Consensus statement 3.1** Evidence and experience suggest that gadoxetic acid-enhanced MRI combined with DWI is the most accurate imaging modality for preoperative diagnosis of CRLM. *[54/66 (81.8 %) agreement]*

Estimation of segmental liver function using MRI, based on hepatic uptake of gadoxetic-acid, has shown good correlation with conventional measures of function, and with disease severity scoring systems [27, 42–44]. Gadoxetic-acid-enhanced MRI has shown a high sensitivity and PPV (96 % and 0.91, respectively) for the pre-operative work-up of patients with CRLM (superior to both MDCT and positron emission tomography [PET]/CT) [45], and was more sensitive than MDCT for the detection of histopathologically proven CRLM, especially those <1 cm [46]. Combining gadoxetic-acid-enhanced MRI with DWI appears to further improve the detection of CRLM compared with the individual imaging techniques [47, 48], especially for small metastases [49], including patients who have undergone pre-operative chemotherapy [50].

*Hepatocellular carcinoma (HCC)*

International guidelines on HCC management recommend stratification of treatment into potentially curative and palliative therapies according to the severity of underlying liver disease and the number, size and invasiveness of hepatic nodules [51, 52].

**Consensus statement 3.2** Increasing evidence suggests that gadoxetic acid-enhanced MRI combined with T2-weighted imaging and DWI is an accurate method for the diagnosis and staging of HCC. *[63/68 (92.6 %) agreement]*

According to the current guidelines, multiphasic MDCT and MRI with extracellular contrast agents are the first-line imaging modalities to characterize lesions in patients at risk for development of HCC. However, features like hyperintensity in DWI and hypointensity in HBP images are considered as valuable contributions to the vascular assessment of such lesions.

Gadoxetic-acid-enhanced MRI has high sensitivity for the diagnosis of HCC, especially those ≤2 cm [34, 53–57], and is more sensitive than MDCT for detecting HCC ≤1 cm [58]. Pre-operative detection of additional very small liver lesions (potentially leading to recurrence) may change the proposed therapy and increase the chance of curative treatment [59].

DWI increases the detection rate of focal liver lesions compared with breath-hold T2-weighted MRI alone [60]. One recent study showed that on MDCT 64/102 (63 %) small (≤2 cm) HCCs showed a target appearance, while 13 (13 %) were not detected [61]. In contrast, 84 (82 %) HCCs demonstrated target arterial hyperintensity, HBP hypointensity and DWI hyperintensity on gadoxetic acid-enhanced MRI, and a further eight hypovascular HCCs could be identified as hyperintense lesions on DWI [61].

## Assessment of the liver following non-surgical treatment of liver malignancies

Locoregional therapies are recommended when surgical resection or transplantation are not options for malignant liver lesions [51, 62, 63]. Subsequent assessment of the liver involves evaluation of therapeutic success, liver injury as a result of the treatment, and detection of recurrence.

**Consensus statement 3.3** Gadoxetic acid-enhanced MRI shows promise for assessment of radiation-induced liver injury. *[61/67 (91.0 %) agreement]*

Reduced gadoxetic-acid uptake (diffuse hypointensity on HBP images) following interstitial brachytherapy correlates with radiation dose-related

hepatocyte dysfunction [64], and subsequent repair of the parenchyma post-therapy is evident as a reduced area of hypointensity [65]. Thus, gadoxetic-acid-enhanced MRI can be used to detect parenchymal damage and assess the value of protective therapies [66]. In addition, the dose range of proton therapy can be similarly assessed [67].

**Consensus statement 3.4** Gadoxetic acid-enhanced MRI is useful for follow-up after local and locoregional therapy of HCC with respect to the assessment of new lesions, but the value of the HBP is questionable for the assessment of local control after thermal ablation in early follow-up. *[55/67 (82.1 %) agreement]*

Evaluation of sensitivity, specificity and accuracy of unenhanced T1-weighted, T2-weighted and dynamic gadoxetic acid-enhanced MRI to detect HCC recurrence following radiofrequency ablation of the liver showed similar results; addition of HBP images did not improve these results [68]. In many cases, HBP hypointensity due to reactive therapeutic responses around the treated lesion could not be distinguished from tumour recurrence.

### Evaluation of liver dysfunction after liver transplant

Dysfunction in transplanted livers following orthotropic liver transplantation (OLT) may involve structural complications (vascular or biliary complications, HCC recurrence, lymphoproliferative disorder) or more diffuse conditions (acute and chronic rejection, cold ischaemia, recurrent viral hepatitis, autoimmune hepatitis, fibrosis, cirrhosis) [69, 70]. These conditions are commonly assessed using a combination of serum liver function tests and imaging [70].

**Consensus statement 3.5** Preliminary data show a correlation between parenchymal dysfunction and gadoxetic acid uptake and excretion in post-liver transplantation patients. This could play a future role in monitoring OLT dysfunction, and further investigation is warranted. *[59/68 (86.8 %) agreement]*

Gadoxetic acid-enhanced MRI is a promising tool for regional liver function assessment [27, 42, 43] and may be a useful, non-invasive, prognostic biomarker for chronic liver graft rejection and patient outcome [71]. Liver transplant recipients with impaired hepatobiliary excretion of gadoxetic-acid showed significantly higher median serum bilirubin levels (4.9 vs. 1.2 mg/dL, $P<0.001$), aspartate aminotransferase (89 vs. 41 IU/L, $P=0.003$) and alkaline phosphatase (322 vs. 143 IU/L, $P=0.007$), and within 1 year, 11/20 patients died or required re-transplantation, while all 31 patients with normal gadoxetic acid excretion survived without re-transplantation ($P<0.001$) [71].

In a recent study [72], a significant correlation was found between relative liver enhancement (RLE) at 20 min and liver failure in retrospective univariate and multivariate analyses in 73 patients who underwent gadoxetic-acid-enhanced MRI prior to resection of three or more liver segments. Pre-operative RLE was inversely related to the probability of post-operative liver failure [72]. The probability of liver failure was close to zero for a RLE >100 %, suggesting that an RLE of 100 % may be a cut-off to predict patients at risk for liver failure. However, determination of cut-off values must be viewed cautiously and more data is needed to validate these values.

## Tips and tricks to optimize imaging with gadoxetic acid-enhanced MRI

### Arterial phase imaging

Gadoxetic acid differs from extracellular MR-contrast media in that it has higher T1 relaxivity [73], and is formulated at half of the gadolinium concentration with a recommended quarter standard dose (0.025 mol/kg body weight) in half the standard injected volume. Working with a compact bolus can be challenging, but strategies to ensure robust arterial phase imaging are available.

**Consensus statement 4.1** Artefacts observed in gadoxetic acid-enhanced MRI in the arterial phase can be reduced by using multiphase pulse sequences with short acquisition times. *[58/64 (90.6 %) agreement]*

**Consensus statement 4.2** Ancillary strategies for reducing arterial phase artefacts include stretching the contrast bolus, sequential k-space filling and patient-tailored timing of the hepatic arterial phase acquisition. *[62/64 (96.9 %) agreement]*

Artefacts seen in the arterial phase of CE-MRI include breathing or motion artefacts, truncation artefacts and phase ghosting (due to rapid change of gadolinium concentration during k-space acquisition) [74]. Breathing artefacts can be reduced by good patient instructions. Both breathing and truncation artefacts can be addressed by shortening the acquisition time, for example by acquiring multiple short arterial phase sequences rather than a single longer one. In this way, at least one phase will likely coincide with optimal arterial enhancement, and transient artefacts (e.g. due to motion) may contaminate only one of the acquired phases [75]. Truncation or phase-ghosting artefacts can also be reduced by stretching the contrast bolus [76–80]. Furthermore, timing of the contrast bolus can be improved with semiautomated, bolus-triggered techniques.

### Hepatobiliary phase imaging

*Technique optimization*

The signal-to-noise ratio (SNR) of hepatobiliary contrast enhancement is related to the concentration of CM in the target tissue and the strength of T1 weighting.

**Consensus statement 4.3** For gadoxetic acid-enhanced HBP liver MRI, optimized pulse sequences using high flip angles can improve liver lesion conspicuity and detection. *[60/66 (90.1 %) agreement]*

Higher flip angles in HBP sequences can increase liver parenchymal contrast enhancement and improve the conspicuity of lesions [81]. At higher flip angles, sensitivity for lesion detection was significantly improved (89.0 % vs. 79.5 % for small flip angles, $P$=0.0003), particularly for small (3–10 mm) lesions (81.4 % vs. 65.7 %, $P$=0.0002) and the liver-to-lesion contrast was significantly greater in most large (≥10 mm) lesions (378 vs. 150, $P$<0.05) [82]. The optimal flip angle for imaging in the HBP has been suggested to be around 40° [83].

*Timing of the hepatobiliary phase*

Deciding when to acquire HBP imaging sequences on gadoxetic-acid-enhanced MRI is generally a compromise between shorter and longer delays (patient comfort vs. improved visualization of biliary excretion).

**Consensus statement 4.4** The post-injection delay for hepatobiliary imaging with gadoxetic acid is patient and indication specific. While a 20-min delay is acceptable in most cases, a shorter delay may be feasible for parenchymal imaging in some patients. Longer delays may be helpful for biliary imaging. *[61/62 (98.4 %) agreement]*

**Consensus statement 4.5** The post-injection delay for hepatocyte phase imaging with gadoxetic acid is patient and indication specific. Longer delays may be helpful for patients with impaired liver uptake. *[53/63 (84.1 %) agreement]*

The optimal delay before acquiring HBP images following gadoxetic acid administration was suggested to be 20 min [84]. Nonetheless, in a variety of patients, adequate HBP images can be obtained well before 20 min [85–88]. However, HBP enhancement occurs later and more weakly in patients with chronic liver disease, suggesting that a longer delay after injection of gadoxetic acid may be optimal in such patients [85].

For biliary imaging, the signal intensity of gadoxetic acid enhancement in the common bile duct reaches a peak at 30-min post-injection in patients with and without chronic liver disease (lower signal intensity in patients with liver disease) [89]. In addition, since gadoxetic acid and bilirubin are taken up by the same family of organic anion transport proteins (OATPs), the presence of an elevated serum bilirubin level is associated with reduced hepatic gadoxetic-acid uptake and poor enhancement in the hepatobiliary phase [54]. For this reason, an elevated bilirubin level is a relative contraindication in some centres for gadoxetic acid, with threshold bilirubin levels from 2.0–5.0 mg/dL [54, 90].

## Summary

Gadoxetic acid-enhanced MRI, including HBP imaging, provides high sensitivity for differentiating FNH and HCA; however, the role of the HBP to aid prediction of HCA subtype requires further research. Specific features of HCC and ICC demonstrated on gadoxetic acid-enhanced MRI can aiding differential diagnosis. Hypointensity in the HBP of gadoxetic acid-enhanced MRI provides high sensitivity for the detection of pre-malignant hepatocellular lesions, although it is currently not possible to differentiate those. Incorporating a combination of ancillary MRI findings can assist in patient risk stratification. Gadoxetic acid-enhanced MRI combined with DWI may be the most accurate imaging modality for the pre-operative diagnosis of CRLM. Gadoxetic acid-enhanced MRI also shows promise for evaluating radiation-induced liver injury and the occurrence of new lesions after locoregional therapy, and could play a role in assessing liver dysfunction after transplantation. Various techniques can increase the robustness of gadoxetic acid-enhanced MRI, reduce artefacts and improve lesion conspicuity in HBP images. Post-injection delays for hepatobiliary imaging with gadoxetic acid are patient- and indication-specific.

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M.R.B. is a member of the Liver Advisory Board for Bayer HealthCare, and is Principal Investigator, Investigator-Initiated Study, Bayer HealthCare.

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