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### ESGAR Consensus Statement on Liver MR Imaging



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## Clinical Use of Liver-Specific Contrast Agents

The European Society of Gastrointestinal and Abdominal Radiology (ESGAR) formed a multinational European panel of experts, selected on the basis of a literature review and their leadership in the field of liver magnetic resonance (MR) imaging, to develop a consensus and provide updated recommendations on liver MR imaging and the clinical use of liver-specific contrast agents.

The consensus provided updated recommendations on the methodology, and clinical indications, of MRI with liver specific contrast agents in the study of liver diseases.

### Methodology

A modified Delphi process was adopted to draft a list of statements. Descriptive and Cronbach's statistics were used to rate levels of agreement and internal reliability of the consensus. Three Delphi rounds were conducted and 76 statements composed on MR technique (n = 17), clinical application of liver-specific contrast agents in benign, focal liver lesions (n = 7), malignant liver lesions in noncirrhotic (n = 9) and in cirrhotic patients (n = 18), diffuse and vascular liver diseases (n = 12), and bile ducts (n = 13). The overall mean score of agreement was 4.84 (SD  $\pm 0.17$ ). Full consensus was reached in 22 percent of all statements in all working groups, with no full consensus reached on diffuse and vascular diseases.

### Background

The advantages of MR imaging in the investigation of the liver are well documented since this examination provides a comprehensive work-up of focal and diffuse liver diseases.

Recent state-of-the-art techniques including fast scanning acquisitions and new MR imaging contrast agents enable improvements in detection and characterisation of focal liver lesions. Therefore, together with appropriate clinical information, in most cases, a definitive diagnosis can be adequately achieved avoiding invasive procedures such as liver biopsy. This is based on the unique properties of MR imaging resulting in a high intrinsic soft tissue contrast between normal liver parenchyma and liver lesions, which can be further enhanced with intravenous administration of non-specific (extracellular) and liver-specific (hepatobiliary) gadolinium-based contrast agents.

Multiphasic dynamic gadolinium-enhanced imaging, which is considered essential in detection and characterization of liver lesions, is routinely

obtained by using non-specific intravenous contrast agents that distribute in the extracellular space, both within and outside the vessels, and have imaging dynamics comparable to the extracellular iodinated contrast media used in CT.

The so-called liver-specific (or hepatobiliary) contrast agents (gadobenate dimeglumine, Gd-BOPTA, and gadoxetic acid, Gd-EOB-DTPA), are characterised by a dual behaviour: by exhibiting elimination through both renal and hepatic excretion pathways and thereby possessing both early perfusion information (renal elimination pathway) and, later, hepatocyte-selective information (hepatic excretion pathway) mediated through protein transporters, located in the canalicular or sinusoidal pole of the hepatocytes.

The liver-specific contrast agents are Gd-based compounds and, therefore, shorten the T1 relaxation time that results in an increased signal intensity of the healthy liver parenchyma on T1-weighted images.

## Discussion

Along the entire consensus process, the panel of experts completed three rounds; the first served to elaborate the basic statements, whereas the second and third rounds contained the core of the discussion and were necessary to reach the maximum consensus, in order to create an optimised and homogeneous opinion for each statement.

Finally, the overall mean score of the panellists was 4.84 (SD  $\pm 0.17$ ), which should be considered an almost excellent result of agreement. A mean score of 4 was considered a good agreement between panellists and a score of 5 a complete agreement.

All panellists exhibited a high level of agreement for the MR technique with clear recommendations regarding the use of MR coils, type of contrast agent, and the specific MR sequences to be used in liver MR examinations. These data reflect a consolidated approach to liver MR examination with no significant difference among panel members despite their wide geographical spread.

As a basic rule of MR technique, all the panellists clearly addressed that the workup of solid focal liver lesions should include axial T2- and T1-weighted sequences, followed by T1-weighted gradient dual echo images, DWI (using low and high b-values) and dynamic contrast-enhanced T1-weighted fat-saturated. However, no full consensus was reached on statements that addressed similar results of MR imaging at 3 and 1.5 T. This incomplete agreement can be explained by the discrepancies of the comparative studies on the use of 1.5 vs. 3 T MRI.

The remaining statements regarding MRI technique, even with less than “full” consensus, definitively addressed the modalities of contrast medium administration (flow-rate of 1–2 mL/s followed by a 20-mL saline flush at 1–2 mL/s using a bolus triggering technique) and timing of T2-weighted and DWI sequences (after the acquisition of the contrast-enhanced late dynamic phase).

With regards to the recommendations on the use of Gd-BOPTA and Gd-EOB-DTPA that are currently available on the market, the panel was aware there are no data indicating diagnostic superiority of one agent over the other.

All panellists fully agreed that all non-blood pool gadolinium chelate-based contrast agents are suitable for dynamic liver MRI, but the use of liver-specific contrast agents is mandatory to obtain the hepatobiliary phase in addition to the dynamic phase.

A mean good level of agreement was reached between the panellists regarding the application of liver-specific contrast agents in benign hepatocellular liver lesions, and addressed MRI as the preferred imaging modality for the characterization of equivocal focal lesions detected by other imaging modalities. Grazioli et al, through a quantitative analysis of signal intensity, lesion-to-liver contrast, and enhancement ratio, demonstrated that Gadoxetic acid-enhanced MR imaging facilitates the differential diagnosis of hepatocellular adenoma (HCA) and focal nodular hyperplasia (FNH). The same author showed in a previous article that this was possible with Gd-BOPTA.

A mean good level of agreement was also reached on the cluster of statements about malignant liver lesions in noncirrhotic patients, where the use of liver-specific contrast agents has been recommended to improve the differential diagnosis between a solid benign hepatocellular lesion and metastasis, and delineation of primary liver tumours (including intrahepatic or mass-forming cholangiocarcinoma).

With regard to mass-forming cholangiocarcinoma, the panel clearly stated that concerning the delayed phase enhancement obtained with non-specific extracellular agents, Gd-EOB provides a relative hypointense MRI pattern of the lesion both in the transitional and hepatobiliary phases that improves tumour conspicuity. The panel suggested also the use of DWI and perfusions techniques, and recently, Park et al demonstrated that the target appearance seen on the DWI was the most reliable imaging feature for distinguishing small mass-forming peripheral cholangiocarcinoma from small hepatocellular carcinoma (HCC).

The best agreement among the panellists was reached for focal liver lesions in cirrhotic patients. The panel stated with full agreement that a

confident diagnosis of HCC by using a complete dynamic study with pre-contrast and multiphase sequences can be optimally reached with a late hepatic arterial phase over early arterial phase, and the hepatobiliary phase may be delayed depending on a reduced liver function.

Of note, the panellists addressed that the use of liverspecific contrast agents has particular usefulness in improving the detection of HCC.

In summary, the panel suggests that in cirrhotic patients, the hepatic arterial phase and portal venous phase might not be sufficient to establish a confident diagnosis of HCC and should be integrated by the hepatobiliary phase.

No statement reached full agreement for diffuse and vascular liver diseases, and it was acknowledged that a correct estimate of the degree of steatosis and iron overload needs multiparametric MRI , even if the administration of contrast agents may alter the quantification of fat and iron liver content.

The final cluster of statements indicates that the evaluation of the biliary tract should be an integrant part of the liver study, and MR CP should be performed on pre-contrast series with heavily 2D and/or 3D T2-weighted sequences.

In the absence of liver function impairment/biliary obstruction, contrast-enhanced MR cholangiography (MR C) can be optimally obtained with Gd-EOB -DTPA at 20 min after injection. Hepatic excretion of liver-specific contrast agents results in enhancement of biliary structures, and it is likely to have a great impact on better visualisation of biliary system.

On the basis of these characteristics, it may potentially increase reliability of the MR examination or decrease the occurrence of a non-diagnostic or equivocal interpretation. This emerging diagnostic tool, especially when using Gd-EOB -DTPA , is particularly helpful for delineating the anatomy of the biliary tract and detecting post-operative complications such as anastomotic and non-anastomotic strictures and biliary leaks. In addition, it can provide functional information that is extremely promising in the grading of biliary obstruction. The drawbacks of contrast-enhanced MR C include its high cost (it is also a time-consuming technique) and limitations in depicting the biliary system in patients with hepatobiliary dysfunction.

#### **Key Points**

- Liver-specific contrast agents are recommended in MRI of the liver.
- The hepatobiliary phase improves the detection and characterisation of hepatocellular lesions.
- Liver-specific contrast agents can improve the detection of HCC.

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