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An update on clinical applications of hepatospecific contrast media in magnetic resonance imaging of liver parenchyma

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Abstract. – Hepatobiliary-specific contrast agents are now widely used in magnetic resonance imaging (MRI) of liver parenchyma. As extracellular fluid agents, they provide informations regarding lesion vascularity and their use in the hepatobiliary or delayed phase (DPI), and give additional data regarding hepatocyte presence and function. The aim of this article is to review the recent literature about MRI using hepatobiliary-specific contrast agents and to discuss benefits and limits of their clinical applications.

Since November 2008, hepatobiliary contrast agents were routinely employed in our Institution for the characterization of equivocal liver lesions detected by other imaging modalities, and for the evaluation of hepatic nodules in liver cirrhosis.

The informations provided are particularly relevant for the detection of metastases, for the differentiation between focal nodular hyperplasia (FNH) and hepatocellular adenoma (HCA), and for the detection and differentiation between dysplastic nodules (DNs) and hepatocellular carcinoma (HCC) in the cirrhotic liver. The role in the cirrhosis grading and the quantification of liver function is still controversial. Finally, their biliary excretion allows evaluation of anatomy and function of the biliary tree.

According to the reported data, hepatobiliary contrast agents are able to improve liver lesions detection and characterization; their introduction in clinical practice has improved MRI diagnostic efficacy/accuracy, allowing to decrease the number of invasive diagnostic procedures.

Key Words:
Magnetic resonance imaging, Hepatobiliary-specific contrast agents, Gd-BOPTA, Gd-EOB-DTPA, Liver lesions.

Introduction

Magnetic resonance imaging (MRI) with multiphasic dynamic gadolinium-enhanced imaging provides a comprehensive work-up of focal and diffuse liver diseases and is widely used in clinical practice. Extracellular fluid agents, composed of gadolinium chelated to an organic compound, have been used for a long time in MRI of the liver, and are still widely used[1]. These contrast media distribute within and outside the vessels in the extracellular space and their dynamics is comparable to iodinated contrast media used in computed tomography (CT)[1,2]. Liver imaging with these agents mainly relies on differential blood flow between the normal parenchyma and focal lesions.

Hepatobiliary-specific contrast agents, currently used in clinical practice, distribute in the extracellular fluid compartment, as extracellular fluid agents do, and are subsequently taken up by the hepatocytes[3]. Hence, these agents offer the dual benefit of dynamic imaging capability as well as hepatobiliary delayed phase imaging (DPI)[3], providing morphologic and vascular informations as well as functional data related to the hepatocyte phase of enhancement[3,4].

Research has shown that hepatobiliary-specific agents improve detection and characterization of focal lesions and are particularly useful in determining whether a lesion is of hepatocellular origin or not[3-5]. In addition, the bile ducts can be depicted because of the biliary excretion of these agents[3].

In this article, we evaluated the current clinical applications of hepatobiliary-specific contrast agents in MRI of the liver.

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Hepatobiliary-Specific Contrast Agents Used for Liver MRI

The hepatobiliary-specific agents approved by the Food and Drug Administration (FDA) for clinical use are gadobenate dimeglumine (Gd-BOPTA), MultiHance, Bracco and gadoxetic acid (Gd-EOB-DTPA), Primovist in Europe – Eovist in the USA, Bayer Healtcare[1]. Both are considered as "combination agents" because of their dual capability for imaging in the dynamic and delayed hepatocyte-specific phases[1,3,5].

Although their doses and injection duration are different[3], they distribute into the vascular and extravascular spaces during the arterial, portal venous and late dynamic phases and are subsequently taken up by hepatocytes and then excreted into the biliary tree during the DPI[1].

Both agents are currently administered by means of an automatic infusion pump followed by a saline solution flush. Gadobenate dimeglumine (Multihance) is administered at the dosage of 0.1 mmol/kg (0.2 mL/kg), with flow injection rate of 2-2.5 mL/s and shows an excellent performance during dynamic phase imaging[6]. Gadoxetic acid (Primovist) is injected at the recommended dose of 0.025 mmol/kg (0.1 mL/kg), which correspond to one-quarter of gadobenate dimeglumine dosage, and has excellent performance during the hepatobiliary excretion[3,4,7]. The arterial phase acquisition time is critical and bolus tracking or bolus test techniques are used to obtain proper enhancement. The image quality of the arterial phase after gadoxetate dimeglumine injection has been shown to improve with a slower injection rate of 1 mL/s[8].

Both contrast agents are taken up from sinusoids and interstitium to hepatocytes via adenosine triphosphate-dependent organic anion transporter polypeptides (OATP1B1/B3), located at the sinusoidal pole which also carry bile acids, bilirubin, thyroid and steroid hormones across the hepatocyte basolateral membrane and whose expression increased from portal to pervious areas along sinusoids[9]. A fraction of hepatobiliary contrast agent is excreted by cMOAT (multispecific canalicular organic anion transporter) into the biliary canaliculi[10]. Lesions enhancement in the DPI depends on the expression and activity of such transporters, determining characteristic enhancement patterns related to the presence or absence of functioning hepatocytes[10].

As others Gd-based compound, these contrast media shorten T1 relaxation time, resulting in an increased signal intensity of the healthy liver parenchyma on T1-weighted images obtained in the DPI. Moreover, excretion into the biliary tree, causes hyperintensity of bile used for contrast-enhanced T1-weighted MR cholangiography.

DPI is performed either 15-20 min (Gd-EOB-DTPA)[1] or 60-120 min (Gd-BOPTA) after injection. In patients with normal liver and kidney function approximately 50% of the administered dose of Gd-EOB-DTPA is transported through the hepatocytes and excreted into the bile[1,3,5,11], a proportion much higher than that of Gd-BOPTA, which only has no more than 5% of hepatobiliary excretion, resulting in relatively weaker liver signal intensity and biliary tree enhancement[3,12]. However Gd-BOPTA yelds relatively greater enhancement of liver vessels than Gd-EOB-DTPA does and a better performance in the dynamic phase imaging.

The DPI should be considered technically adequate when the healthy liver is evenly enhanced and the blood vessels become hypointense compared to the liver parenchyma as the contrast medium is no longer in the vascular compartment (Figure 1); however, depending on poor hepatic function, these conditions cannot be achieved in some instances. Contrast uptake is also observed in lesions with functioning hepatocytes whereas any other focal mass either benign or malignant appears hypointense.

The percentage of the contrast agent that is not cleared by the hepatobiliary system is excreted by glomerular filtration in the kidneys.

Patients with hyperbilirubinemia may present less hepatobiliary contrast uptake due to the direct competition between bilirubin and hepatobiliary contrast agents for a single transporter in the hepatocytes. This represents a limiting factor in patients with total bilirubin levels > 3 mg/dL[10]. Patients with advanced cirrhosis and decompensated liver disease may also present less contrast uptake as a result of liver dysfunction[10].

Adverse effects and allergic reactions rarely occur and are similar to those reported for extracellular fluid agents[10]. The use should be avoided in pregnancy and in children and in patients with renal insufficiency with creatinine levels < 30 mL/min, because of the risk of nephrogenic fibrosis.

Indications of Liver-Specific Contrast AgentS

According to the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) panel of experts, MRI should be the preferred

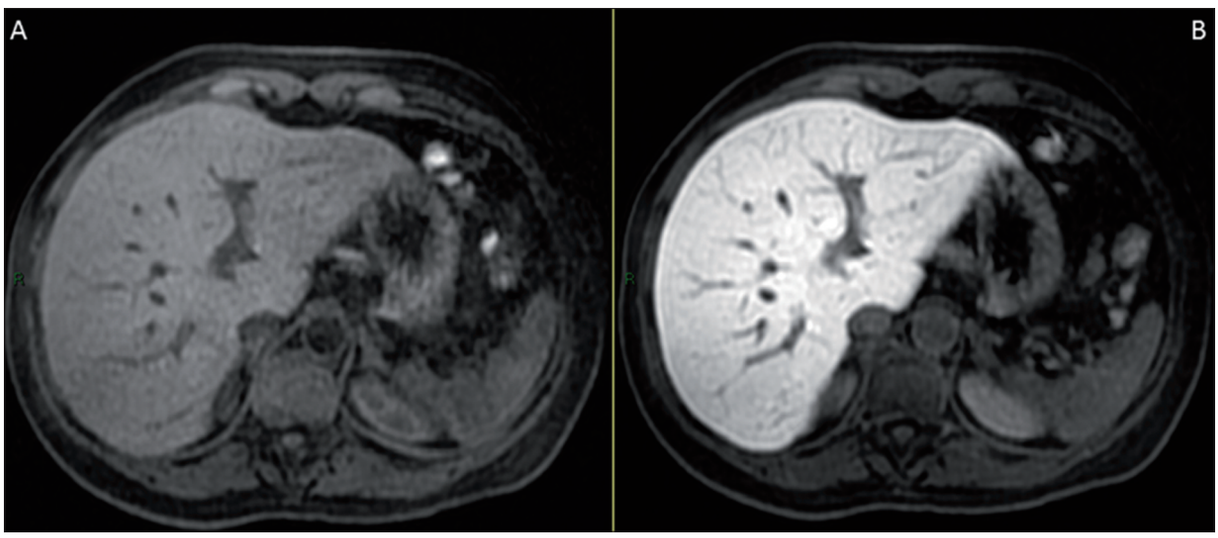

Figure 1. Normal liver. ***A,*** Axial T1-weighted fat-suppressed image, obtained before contrast infusion. ***B,*** Axial T1-weighted fat-suppressed image obtained in the hepatobiliary phase shows enhancement of the normal liver parenchyma and hypointensity of intrahepatic vessels.

imaging modality for the detection and characterization of equivocal liver lesions detected by other imaging modalities. In most cases, a definitive diagnosis can be achieved avoiding invasive procedures[2,10].

As a rule, in DPI all non-hepatocellular lesions appear hypointense whether benign (e.g. hemangiomas) or malignant (e.g. metastases). Malignant hepatocellular lesions without functioning hepatocytes such as nodules of hepatocellular carcinoma (HCC) appear hypointense. Lesions with normal hepatocytes such as focal nodular hyperplasia (FNH) or low-grade dysplastic nodules appear iso or hyperintense relative to normal parenchyma. Hepatic excretion results in enhancement of biliary ducts allowing evaluation of the biliary tract (Table I).

Benign Hepatocellular Liver Lesions

Liver-specific contrast agents are useful in the evaluation of benign hepatocellular liver lesions and particularly in the differential diagnosis between FNH and liver adenoma (HCA); differentiating these two entities can be difficult with conventional morphological and dynamic sequences alone, if typical features are not seen[3,4]. Grazioli et al[13,14], through a quantitative analysis of signal intensity, lesion-to-liver contrast, and enhancement ratio, demonstrated that gadoxetic acid-enhanced MRI enables the differential diagnosis between HCA and FNH, and that this was possible with Gd-BOPTA. The differential diagnosis is clinically relevant as a conservative management is recommended for FNH whereas HCA may require surgical treatment or close monitoring particularly in the case of lesions diagnosed in men or larger than 5 cm because of the known risk of spontaneous rupture, hemorrhage or malignant transformation[3,15].

Table I. Liver lesions.

Benign hepatocellular liver lesions	Focal nodular hyperplasia Adenoma
Focal lesions in liver cirrhosis	Rigenerative nodule Dysplastic nodule Hepatocellular carcinoma
Malignant lesions	Primitive Secondary

Focal Nodular Hyperplasia

FNH is the second most common benign liver tumor and is present in about 3-5% of the population. About 80% of the cases occur in women of child-bearing age[1]. FNH is defined as a frequently single, well circumscribed liver lesion, characterized by a fibrotic central scar, surrounded by hyper plastic hepatocyte agglomerates and small biliary duct, in a liver with normal histological appearance[4].

The typical FNH presents intermediate signal intensity on T1- and T2-weighted sequences, low lesion to organ contrast and arterial uptake, with

decay in the subsequent phases[6,10]. The presence of a central scar hyperintense on T2-weighted and hypointense on T1weighted sequences, with no contrast uptake in the arterial phase and late contrast uptake is typical[6,10]. FNH presents greater density of functioning hepatocytes than normal liver parenchyma, in association with abnormal bile ducts not communicating with greater bile ducts[1,3], and this results in a slower biliary excretion compared to the surrounding liver[1,10]. Therefore, FNH presents contrast uptake greater or equal compared to the adjacent liver parenchyma and central scar usually hypointense in the DPI[1,3,4,6,10,16] (Figure 2).

Adenoma

HCA are rare liver lesions especially occurring in women taking oral contraceptives, with a female-to-male ratio of 5:1[1]. HCA consist of well differentiated hepatocyte cords, with absence of biliary ducts or portal tracts[4], and can be subclassified into 4 types according to their genetic and phenotypic characteristics: hepatocyte nuclear factor (HNF) 1A mutated HCAs characterized by marked steatosis, inflammatory HCAs showing polymorphic inflammatory infiltrates and sinusoid dilatation, beta-catenin mutated HCAs and unclassified HCAs[15].

On MRI HCAs frequently show heterogeneous hyperintensity on T2-weighted images and heterogeneous hypointensity on T1-weighted images. More specifically HNF1A HCAs show diffuse signal dropout on T1-weighted chemical shift sequence due to the presence of fat whereas inflammatory HCAs show hyperintensity on T2-weighted sequences and persistent enhancement in portal venous phases due to the presence of dilated sinusoids[17]. A hypointense peripheral rim corresponding to a fibrous capsule can also be present. Then, the specific MRI appearance is that of a fat containing or hemorrhagic lesion with increased peripheral vascularity as HCAs are composed of hepatocytes containing glycogen and lipids surrounded by a capsule. Although containing functioning hepatocytes, there is a lack of biliary ducts resulting in a deficiency in bilirubin and hepatobiliary contrast excretion[1,4,6,10]. Additionally, HCAs present smaller expression of membrane transporters such as OATP1B1/B3[6]. Thus, in the DPI, most HCAs are hypointense in relation to the surrounding parenchyma[1,4,10]. This enhancement pattern in liver-specific phase is opposite to that observed in FNH and is one of the main features for differential diagnosis. The different behavior is related to the different structure and functional pattern of the lesions (Figure 3).

Malignant Non-Hepatocellular Liver Lesions-Metastases

The liver is the most common site for metastases; an accurate detection and localization of these lesions is crucial for the definition of the therapeutic approach, especially in colorectal cancer as surgical resection improves survival, compared to other treatment methods[1,3,4,6].

Metastases do not contain functioning hepatocytes or biliary ducts, and do not show contrast uptake during the DPI[1,10]. Therefore, they appear hypointense in DPI, regardless of the primary tu-

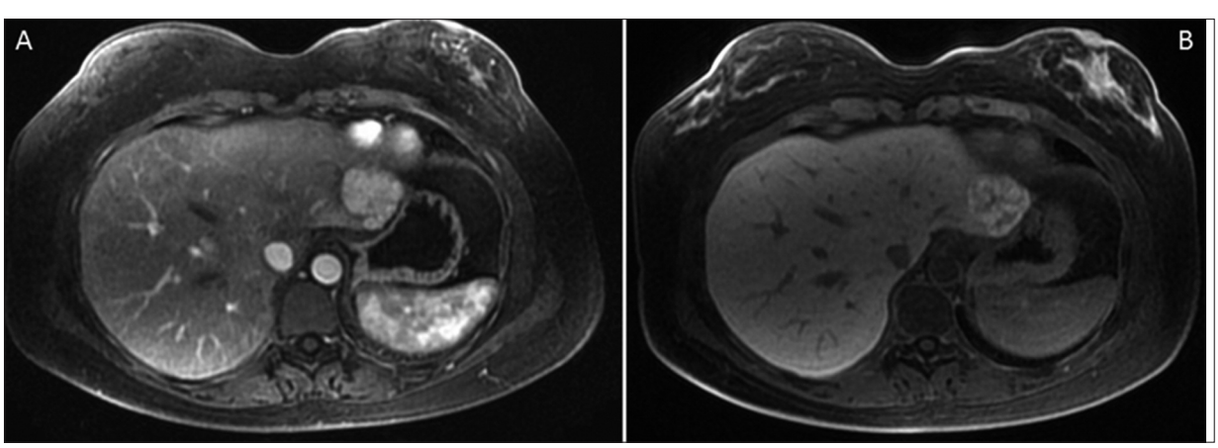

Figure 2. Focal nodular hyperplasia. ***A,*** Post contrast axial T1-weighted-fat suppressed acquisition in the arterial phase, shows a hypervascular lesion in the left liver lobe. ***B,*** In the hepatobiliary phase the lesion appears hyperintense compared with the background liver with a non-enhancing central scar.

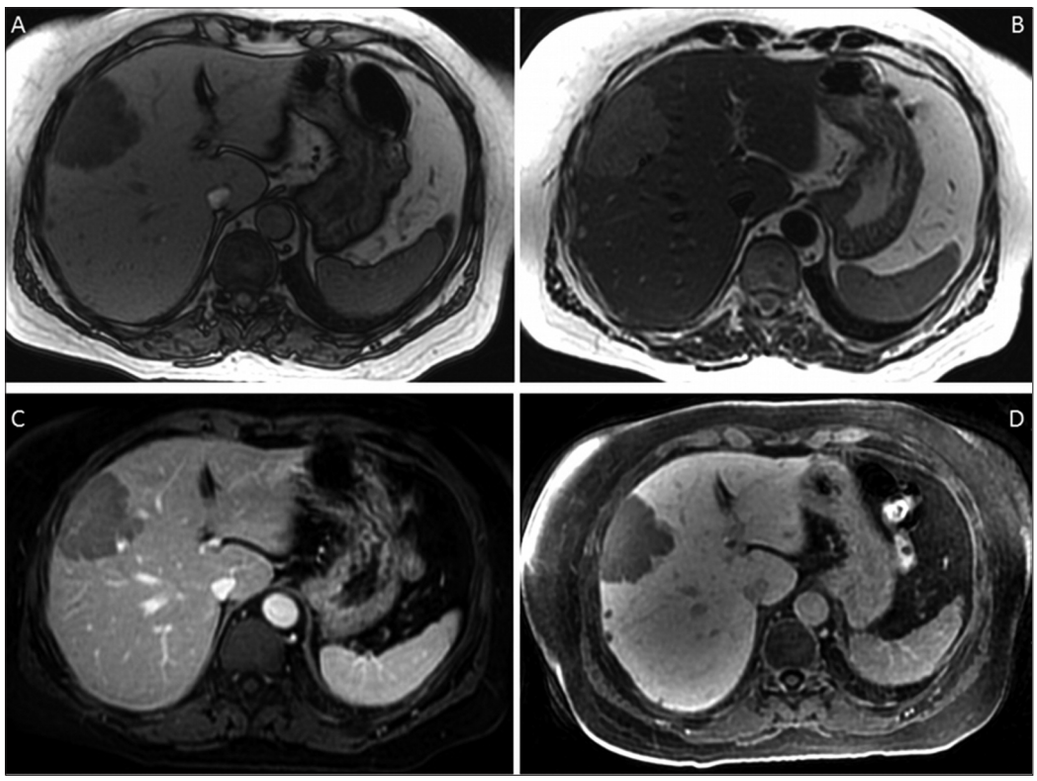

Figure 3. Hepatic adenoma. ***A,*** Axial T1-weighted-out of phase image shows in the right liver lobe a hypointense, fat containing lesion. ***B,*** Axial T2-weighted image shows slightly hyperintensity of the lesion. ***C,*** In the portal phase, after contrast media injection, the lesion appears hypointense. ***D,*** In the hepatobiliary phase, the lesion is definitely hypointense.

mor and whether hypo or hyper-vascular on dynamic images[1,3]. The results of several studies have shown that hepatobiliary-specific agents increase the sensitivity of MRI as the number of detected liver metastases is higher than that found on contrast-enhanced MRI with extracellular fluid agents[4,6,18] (Figure 4).

Focal Lesions in Liver Cirrhosis

HCC is one of the most common malignancies worldwide and its incidence continues to increase, due to the burden of chronic liver diseases associated with hepatitis C or B virus (HCV/HBV) infections[19]. Hepatocarcinogenesis is a multistep process that evolves from regenera-

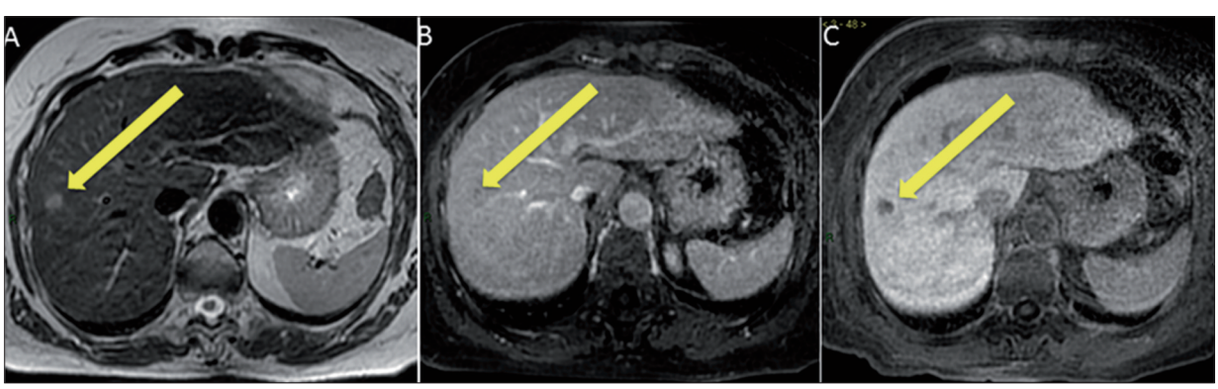

Figure 4. Liver metastasis. ***A,*** Axial T2-weighted image shows in the VIII hepatic segment a centimetric hyperintense lesion. ***B,*** In the portal phase after contrast injection, the lesion is barely visible. ***C,*** In the hepatobiliary phase, an hypointense nodule is clearly visible.

tive nodules (RNs) through dysplastic nodules (DNs) and well differentiated HCC, and eventually leads to advanced overt moderately-to-poorly differentiated HCC[19].

The ability to detect early HCC enables the access to surgical and ablative curative treatments and is crucial for decreasing mortality from this neoplasm; indeed, early diagnosis obtained through ultrasound monitoring and proper characterization by contrast-enhanced CT and MRI is of paramount importance. Because of the multistep process of hepatocarcinogenesis, dynamic imaging features of small nodules detected in the cirrhotic liver may overlap, and the differentiation of RNs or DNs from small HCCs is still a diagnostic challenge.

Diagnosis of malignancy is mainly related to the development of arterial neovascularity. Such vascular changes explain the typical behavior of HCC at the post contrast dynamic study. However, during the carcinogenetic pathway from dysplasia to full malignancy cytological changes occur as well and can precede the development of neoplastic nodule arterial supply. Indeed, the introduction of hepatobiliary MRI contrast agents with both an intravascular/interstitial distribution and a tissue-specific uptake enables the investigation not only of neoangiogenesis, but also of functional alterations of the hepatocytes, allowing the assessment of premalignant and malignant changes in the DPI[3].

It has been proven that the expression of OATP1B1/B3 decreases during hepatocarcinogenesis; expression levels are high in cirrhotic nodules and low-grade dysplastic nodules (LGDNs), and lower in many high-grade dysplastic nodules (HGDNs), early HCCs, and progressed HCCs[9,10,19,20,21] (Figures 5, 6, 7). Therefore, in patients with cirrhosis or other risk factors for HCC, a nodule that appears hypointense in DPI is likely to be a HGDN, early HCC, or overt HCC. Because of these properties hepato-

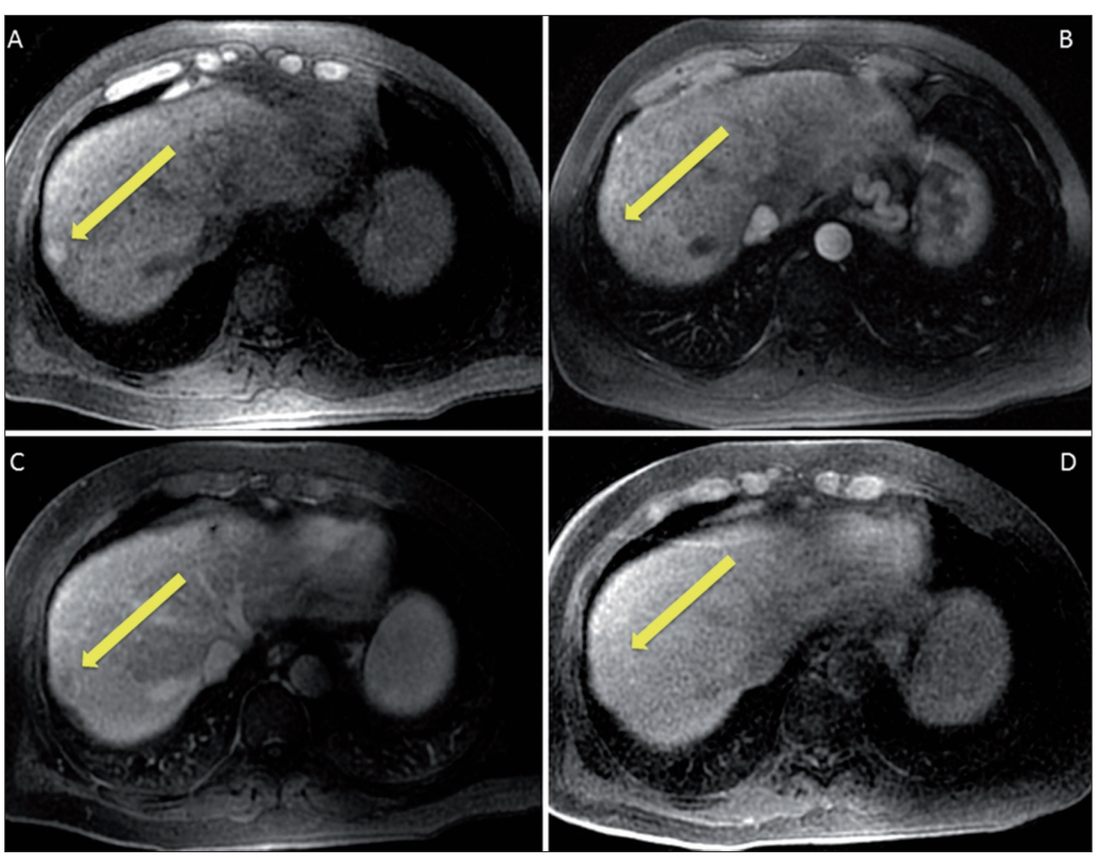

Figure 5. Low-grade dysplastic nodule (LGDN). ***A,*** T1-weighted axial image shows an hyperintense nodule on the lateral margin of the VIII hepatic segment. ***B,*** At dynamic imaging, in the arterial phase, no hypervascularity is shown. ***C,*** The nodule is slightly hypointense in the venous phase. ***D,*** In delayed phase imaging, the nodule is isointense relative to surrounding liver parenchyma.

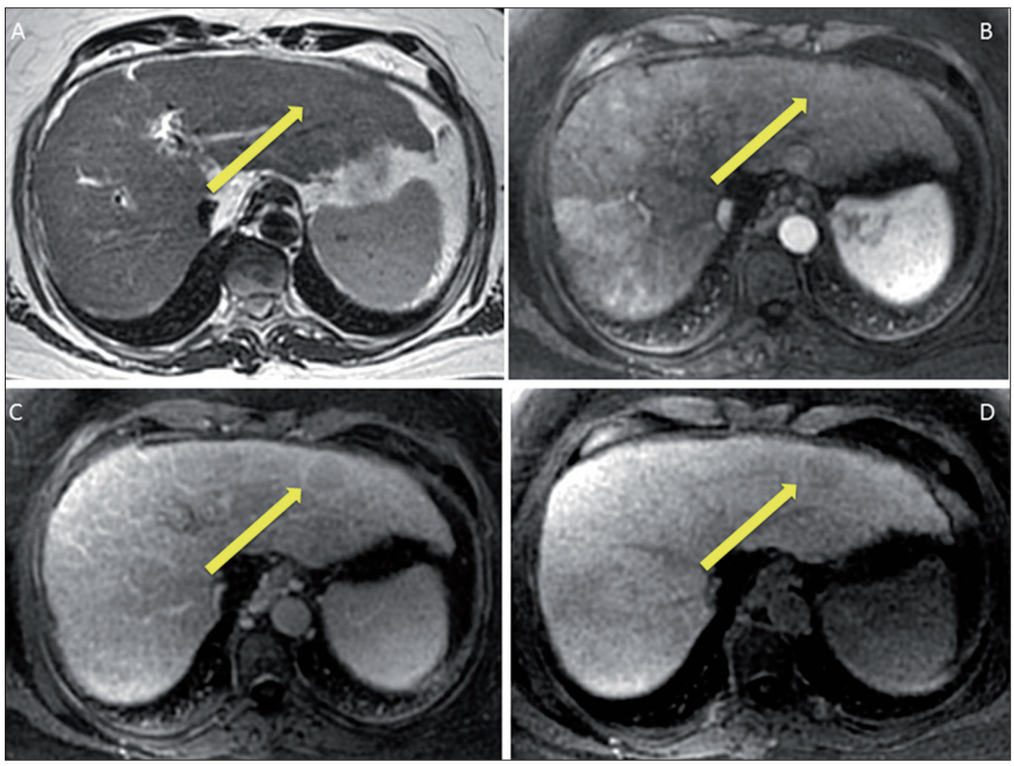

Figure 6. High-grade dysplastic nodule (HGDN). ***A,*** On the T2-weighted axial image, the nodule is not visible and isointense. ***B,*** At dynamic imaging, in the arterial phase, no hypervascularity is shown. ***C,*** The nodule is slightly hypointense in the venous phase. ***D,*** In delayed phase imaging, the nodule is hypointense relative to surrounding liver parenchyma.

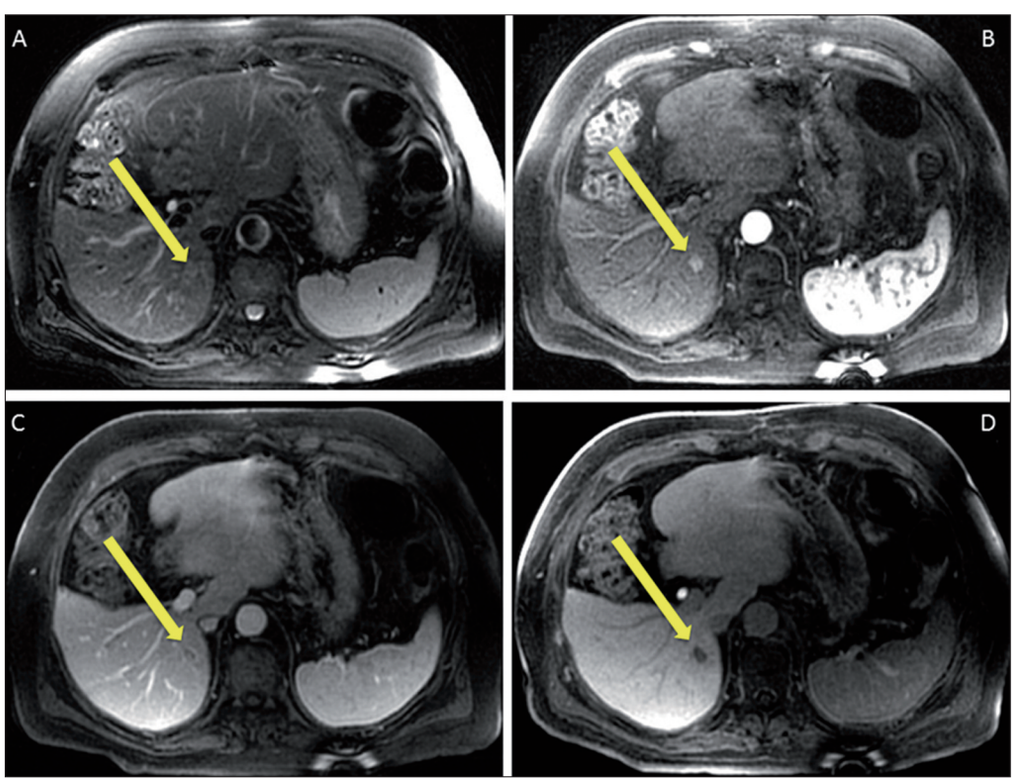

Figure 7. Well-differentiated HCC. ***A,*** On T2-weighted fat suppressed axial image a small nodule barely hyperintense is shown. ***B,*** At dynamic imaging, in the arterial phase, the nodule is hypervascular. ***C,*** The nodule is slightly hypointense in the venous phase. ***D,*** In delayed phase imaging the nodule is definitely hypointense relative to surrounding liver parenchyma

biliary contrast agents, improve the characterization of small nodules in liver cirrhosis. However, despite the progress in MRI with liver-specific contrast agents, at present, the radiologic diagnosis of HCC relies exclusively on contrast enhancement features with either multidetector CT or MRI, regardless of the imaging modalities and is based on the assessment of arterial enhancement, due to the presence of non-triadal neoangiogenetic arteries and portal/venous wash-out, due to the loss of sinusoidal vascularization. Occasionally, small HCC can be isointense or hypointense in the arterial phase as cellular changes can precede the development of neovascularity. This probably reflects the stage of carcinogenesis with the partial or complete loss of the normal portal tract but no associated increased non-triadal arterializations. These neoplastic nodules, known as hypovascular HCCs, because of the lack of arterial enhancement, are often misdiagnosed at dynamic imaging with either CT or MRI but can be properly recognized because of hypointensity in DPI (Figure 8). Conversely, some DN, particularly HGDNs receiving increasing supply from the hepatic artery, can enhance in the arterial phase and can be misdiagnosed as HCC.

We think that, in relation to many scientific evidences, a new imaging diagnostic algorithm for HCC diagnosis would be required. Nevertheless, the guidelines of the main hepatological societies, such as the American Association for the Study of Liver Diseases[22,23], and the European Association for the Study of the Liver[24] do not recognize the diagnostic superiority of MRI over CT in the diagnosis of HCC and do not emphasize the usefulness of MRI hepatospecific contrast media. In contrast, the Japan Society of Hepatology (JSH) guidelines have recognized the superiority of Gd-EO-DTPA MRI over dynamic CT in the diagnosis of HCC in patients with chronic liver disease[25].

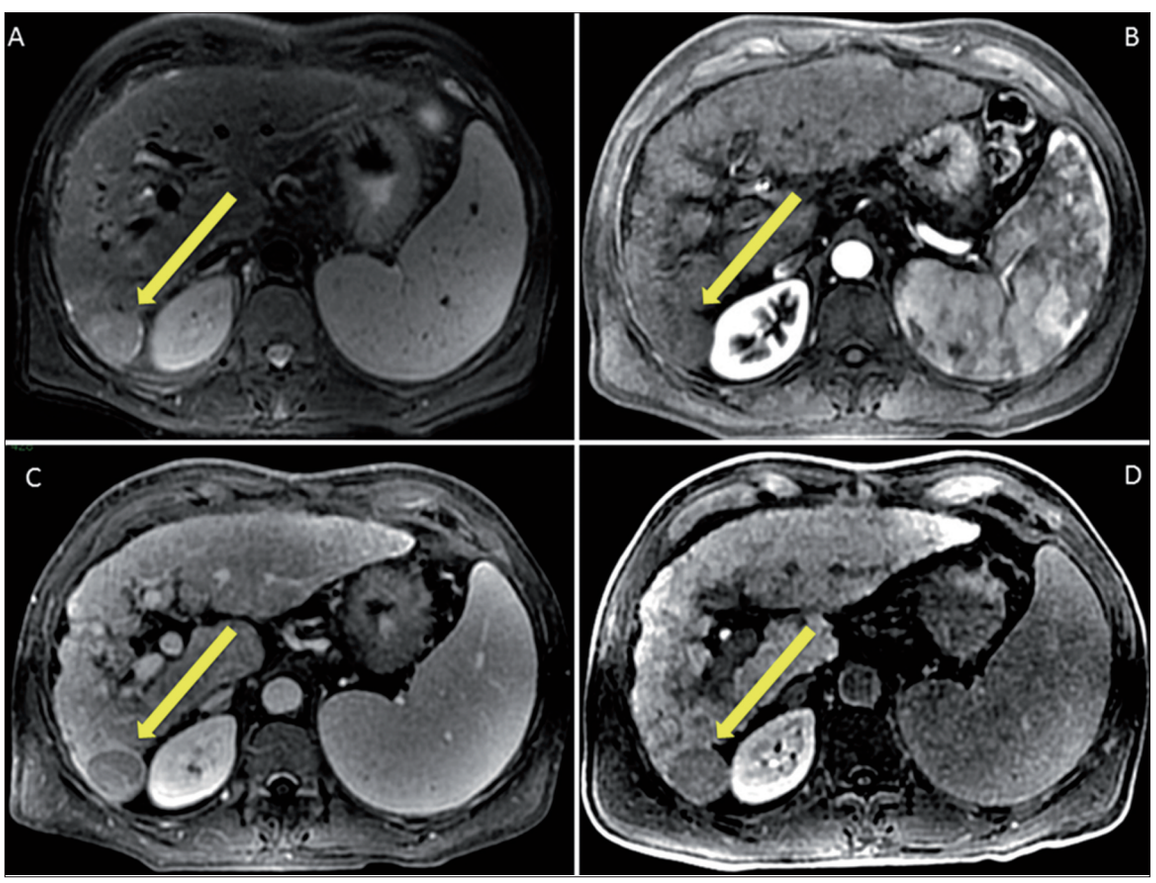

Figure 8. Hypovascular HCC. ***A,*** On T2-weighted fat suppressed axial image an hyperintense lesion is shown in the VI segment. ***B,*** At dynamic imaging, in the arterial phase, the lesion is hypovascular. ***C,*** The nodule appears hypointense in the venous phase. ***D,*** In delayed phase imaging the nodule is definitely hypointense relative to surrounding liver parenchyma.

Recently, Renzulli et al[26] have proposed a new diagnostic algorithm based on JSH guidelines for HCC diagnosis in patients under surveillance for chronic liver disease. Their policy includes the use of MRI hepatospecific contrast media, providing different diagnostic strategies for all possible types of nodules identified by these contrast agents. Accordingly, the European Society of Gastrointestinal and Abdominal Radiology (ESGAR)[2] panel of experts has recently stated that the combined interpretation of dynamic and DPI improves the diagnostic accuracy of MRI for the detection of HCC.

Assessment of the Biliary Tract

Hepatobiliary contrast agents are excreted into the biliary tree, shorten the T1 relaxation time of the bile and allow for the performance of a high-resolution T1-weighted contrast-enhanced cholangiography[3,10] (Figure 9). In combination with conventional T2-weighted MR cholangiopancreatography (MRCP), valuable informations can be obtained about biliary anatomy and anatomic variants and may affect the preoperative planning in patients candidates to surgery[3,6,10,18]. Moreover, this technique allows accurate detection of postoperative complications such as biliary fistulas and bilomas which present progressive fill-in during the DPI[10,18] (Figure 10). In the postoperative follow-up, accidental ductal ligation can also be easily recognized in the DPI as an abrupt interruption of the biliary tract[3,18].

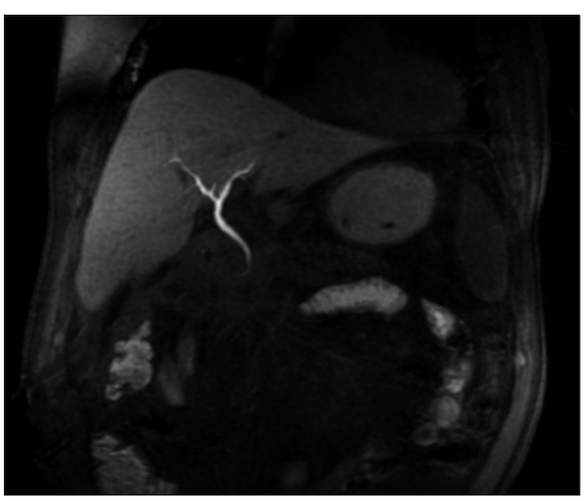

Figure 9. T1-weighted contrast-enhanced cholangiography. Maximum Intensity Projection (MIP) reconstructed T1-weighted image, in the hepatobiliary phase shows the biliary tree, hyperintense because of the excretion of the contrast agent.

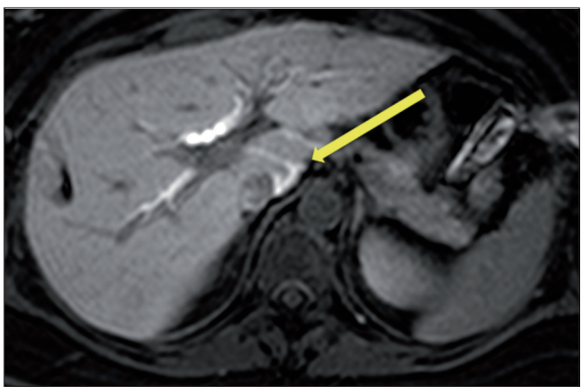

Figure 10. Biliary fistula and biloma. Axial T1-weighted fat suppressed image shows a biliary fistula and bile extravasation around the caudate lobe.

Other applications of hepatobiliary contrast agents include the study of biliary duct obstructions and the evaluation of the biliary flow dynamics[3,10,27]. The diagnosis of sphincter of Oddi dysfunction can be based on the finding of the absent or delayed passage of the hepatobiliary contrast through the ampulla of Vater. Furthermore, hepatobiliary contrast allows the differentiation between biliary and extrabiliary cistic lesions through the depiction of the communication of biliary cystic lesions with the bile ducts[10].

Assessment of Liver Function

Recently there has been increased interest in the use of hepatobiliary-specific agents for quantitative evaluation of liver function. Normal hepatocytes are progressively replaced by fibrotic tissue in the cirrhotic liver and, for this reason, the hepatic parenchymal enhancement in DPI is decreased. A good correlation between signal intensity, liver function and stage of fibrosis has been recently demonstrated[3,10]. In particular, Haimerl et al[28] found that the relative enhancement during DPI in Gd-EOB-DTPA MRI correlates with the model for an end stage liver disease (MELD) score which is currently used to assess the functional reserve in liver cirrhosis and to manage the waiting list for liver transplantation.

Further potential hepatobiliary contrast applications include the evaluation of the functional hepatic reserve before partial hepatectomy[3].

Conclusions

Hepatobiliary contrast agents combining interpretation of dynamic and DPI increase the MRI

accuracy in the differential diagnosis of focal lesions in both normal and cirrhotic liver and in the evaluation of the biliary tract. The major drawbacks are represented by the inadequate depiction of liver parenchyma and biliary system in patients with severe liver dysfunction.

The use of hepatobiliary contrast agents may reduce the necessity of invasive diagnostic procedures as well as of further investigation with other imaging methods, so decreasing the overall diagnostic costs and the anxiety of both patients and medical team[10].

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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