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REVIEW

# Focal liver lesions detection and characterization: The advantages of gadoxetic acid-enhanced liver MRI

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## Abstract

Since its clinical introduction, several studies in literature have investigated gadolinium ethoxybenzhyl diethylenetriaminepentaacetic acid or gadoxetic acid (Gd-EOB-DTPA) properties. Following contrast injection, it provides dynamic vascular phases (arterial, portal and equilibrium phases) and hepatobiliary phase, the latter due to its uptake by functional hepatocytes. The main advantages of Gd-EOB-DTPA of focal liver lesion detection and characterization are discussed in this paper. Namely, we focus on the possibility of distinguishing focal nodular hyperplasia (FNH) from hepatic adenoma (HA), the identification of early hepatocellular carcinoma (HCC) and the pre-operative assessment of metastasis in liver parenchyma. Regarding the differentiation between FNH and HA, adenoma typically appears hypointense in hepatobiliary phase, whereas FNH is isointense or hyperintense to the surrounding hepatic parenchyma. As for the identification of early HCCs, many papers recently published in literature have emphasized the contribution of hepatobiliary phase in the characterization of nodules without a typical hallmark of HCC. Atypical nodules (no hypervascularizaton observed on arterial phase and/or no hypovascular appearance on portal phase) with low signal intensity in the hepatobiliary phase, have a high probability of malignancy. Finally, regarding the evaluation of focal hepatic metastases, magnetic resonance pre-operative assessment using gadoxetic acid allows for more accurate diagnosis.



**Key words:** Magnetic resonance imaging; Liver; Image enhancement; Gadolinium diethylenetriaminepentaacetic acid; Carcinoma; Hepatocellular

**Core tip:** This study highlights the added value of gadoxetic acid-enhanced liver magnetic resonance imaging (MRI) in the detection and characterization of focal liver lesions. Three main topics are summarized: the role of gadoxetic acid in the evaluation of solid benign hepatic lesions, represented by hepatocellular adenoma and focal nodular hyperplasia; the diagnostic capability of hepatobiliary phase of gadoxetic acid-enhanced liver magnetic resonance imaging in the early identification of small hepatocellular carcinoma; the high diagnostic accuracy powered by gadoxetic enhanced-liver MRI in the detection of hepatic metastasis.

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## INTRODUCTION

Since the first studies were reported in literature in 1991-1992, several authors have investigated the potentialities of gadolinium ethoxybenzhyl diethylenetriaminepentaacetic acid or gadoxetic acid (Gd-EOB-DTPA) enhanced magnetic resonance imaging (MRI) liver[1-5]. In a previous article published by Mühler *et al*[5], spin-echo

**Table 1 Imaging features of focal liver lesions in the dynamic vascular phases (after contrast administration) and in the hepatobiliary phase**

| | Phases | | | |
|---|---|---|---|---|
| | Arterial | Portal | Delayed | Hepato-biliary |
| FNH | Hyperintense | Isointense | Isointense | Hyperintense/isointense (hypointense[1]) |
| Adenoma | Hyperintense | Isotense/slightly hypointense | Isotense/slightly hypointense | Hypointense (hyperintense or mixed hypo/hyperintense[1]) |
| Typical HCC | Hyperintense | Hypointense | Hypointense | Hypointense |
| Pre/early HCC (decreased portal supply) | Isointense | Hypointense | Hypointense | Hypointense |
| Pre/early HCC (increased arterial supply) | Hyperintense | Isointense | Isointense | Hypointense |
| Metastasis (hypovascular) | Irregularly hypointense | Irregularly hypointense | Irregularly hypointense | Hypointense |
| Metastasis (hypervascular) | Irregularly hyperintense | Isointense or hypointense | Inhomogeneously hypointense | Hypointense |

[1]Atypical behaviours of focal liver lesions. FNH: Focal nodular hyperplasia; HCC: Hepatocellular carcinoma.

(SE) sequences and short tau inversion recovery (STIR) sequences were compared in the detection of experimental liver metastases[5]. Relative enhancement and lesion-to-liver contrast were also analysed in the mentioned study. After contrast administration, the authors reported lesion-to-liver contrast increased by approximately 500% with both SE and STIR sequences. Therefore, we can see that the role of Gd-EOB-DTPA in focal liver lesion (FLLs) detection has been studied from the beginning.

Subsequently, the usefulness of hepatospecific contrast in liver MRI has been confirmed by other studies. In fact, detection and characterization of focal liver tumours have been compared in the same patient using Gd-EOB-DTPA and Gd-DTPA enhanced MRI[6]. In the assessment of FLLs, Gd-EOB-DTPA has also been compared with intra-operative findings in a multicenter analysis[7].

Although research on focal lesions is the most common, some authors have observed that, because of its properties, Gd-EOB-DTPA could be potentially used as a tracer of liver functionality[8-10].

The mechanisms of contrast uptake and excretion have been documented[11-14]. The uptake of Gd-Eob-DTPA is achieved by functional hepatocytes, which have the cloned organic anion transporting polypeptides (OATPs). In humans the contrast is introduced through OATP1 and OATP3 transporters, located at the apical membrane of hepatocytes[15]. Then, the contrast has urinary and biliary excretion rates (the latter up to 50%, much higher than other hepatospecific contrasts). Regarding biliary excretion, the contrast is excreted through Multidrug Resistance-associated Proteins (MRPs) to bile canaliculi (MRP2 = apical transporter) or sinusoidal spaces (MRP3, MRP4 = basolateral transporters)[11-15].

Thus, in normal liver parenchyma starting during dynamic vascular phases, hepatocytes increase the uptake of gadoxetic acid. The uptake process is gradually followed by contrast discharging through the bile canaliculi. Generally, the hepatobiliary phase, where hepatocytes reach maximum signal intensity, is obtained 20 min after contrast administration. The variable contrast uptake by FLLs represents an additional diagnostic tool in liver imaging.

The aim of this topic highlight is to discuss the advantages of gadoxetic acid-enhanced liver MRI in the study of FLLs, focusing on: (1) Evaluation of hepatic adenoma and focal nodular hyperplasia; (2) Identification of early hepatocellular carcinoma (HCC); and (3) Detection of hepatic metastases detection in oncology patients. Typical and atypical behaviours of FLLs using gadoxetic acid-enhanced MRI are summarized in Table 1, which shows imaging features observed also in the hepatobiliary phase.

## EVALUATION OF HEPATIC ADENOMA AND FOCAL NODULAR HYPERPLASIA

The use of Gd-Eob-DTPA allows for characterization of hepatic adenoma (HA) and focal nodular hyperplasia (FNH). In some cases, diagnosis between these solid lesions cannot be reliably achieved using only dynamic vascular phases, and hepatobiliary contrast agents are very useful in their differentiation. In fact, in a previous study, although using gadobenate dimeglumine-a different liver specific contrast from gadoxetic acid-Grazioli *et al*[16] reported an overall accuracy of 98.3% in the differentiation of FNH from HA and liver adenomatosis, with positive predictive value of 100% and negative predictive value of 96.4%.

FNH was described for the first time by Edmondson in 1956[17]. The lesion is considered a non-neoplastic and hyperplastic response of the liver parenchyma to "a pre-existing local arterial spiderlike malformation"[18]. It occurs in asymptomatic women. The relationship between FNH and contraceptives is still unclear as several authors have demonstrated that contraceptives may favour FNH progression[19]. The lesion is generally represented by a solid circumscribed mass, sometimes with lobulated contour (Figure 1), with a central scar surrounded by nodules of hyperplastic hepatocytes and small bile ductuli[20]. FNHs may show a certain degree of histological heterogeneity, due to the variable degree of intra-lesional inflammation, fibrosis or fat content (the latter has been described as steatotic FNH).

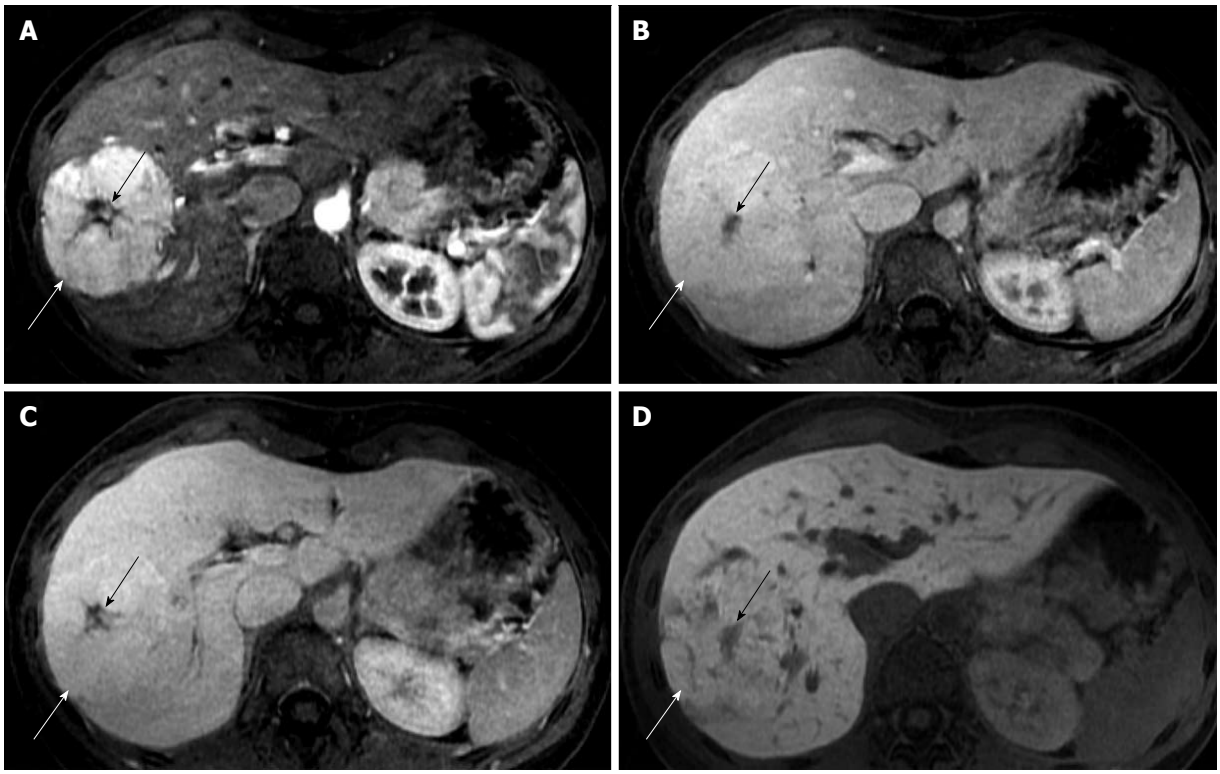


**Figure 1 Typical imaging features of focal nodular hyperplasia in a 29-year-old woman.** Gadoxetic acid-enhanced magnetic resonance imaging; axial images (A-D) were obtained in dynamic phases and hepatobiliary phase. A shows a solid circumscribed mass (white arrow), lobulated in contour, with a central scar (black arrow); the lesion is hyperintense on the arterial phase (A) and persists slightly hyperintense in the portal and venous phases (B and C respectively). In hepatobiliary phase (D) the mass is slightly hyperintense or isointense to the surrounding liver. The presence of biliary canaliculi, even if not functioning, leads to retention of gadoxetic acid in comparison to the surrounding parenchyma.

Hepatic adenoma is a rare monoclonal benign liver tumour, predominantly found in young females and associated with the use of contraceptives[21]. It generally appears as an uncapsulated mass, formed by large plats or cord cells very similar to hepatocytes. In a work by Grazioli *et al*[22], they are defined as "these plats are separated by sinusoids, which consist of small capillaries perfused through the arterial pressure". This histological architecture explains the morphological behaviour of adenomas during the dynamic phases after contrast administration. In fact, lesions often appear hypervascular in the arterial phase, and are generally isointense or hypointense to the surrounding liver in the portal phase. The vascular supply in the portal phase is not observed because of the adenomas lack of a portal vascularization[22]. Adenomas have a poor number of Kupfer cells, and this histological feature could explain the absence of technetium (Tc)-99m sulfur colloid uptake. In addition, HAs do not have bile canaliculi[23,24].

The significant capability of Gd-Eob-DTPA in distinguishing FNH from adenomas depends on histological features and cellular expression of molecular transporters. Bile ductuli are present in FNHs, whereas they are missing in HAs. The molecular transporter Organic Anion Transporting Polypeptide 8 (OATP 8) is usually absent or minimally expressed in cellular adenomas. This transporter is instead expressed in FNH, explaining the uptake of Gd-Eob-DTPA[25].

Thus, typically HAs appear hypointense, whereas FNHs are isointense or hyperintense to the surrounding hepatic parenchyma (Figures 1 and 2, Table 1). Several studies have described the mentioned imaging features.

In a work published in 2001, all three adenomas studied in the hepatobiliary phase by Grazioli *et al*[22] showed hypointense appearance following liver contrast agent administration. Zech *et al*[25] reported enhancement in the hepatobiliary phase in the 90% of FNH examined in their series where only a minority of lesions showed no enhancement or peripheral enhancement. The presence of biliary canaliculi, even if not functioning, leads to a "slower excretion in comparison to the surrounding parenchyma", and this gadoxetic acid retention explains the hyperintense appearance of FNH[26] (Figures 1 and 2).

Nevertheless, atypical lesions are very difficult to diagnose, even using Gd-EOB-DTPA. In fact, the heterogeneity of FNH could also explain the atypical imaging presentation that has recently been well described in many articles[27,28]. In another case series published in literature, Grazioli *et al*[29] found that 62 out of 68 FNHs (91.2%) were hyperintense or isointense to the surrounding liver, with only 6 lesions showing an atypical pattern[29]. One atypical enhancement pattern explanation was the presence of a large central scar. These lesions appeared hypointense in hepatobiliary phase, showing only a little marginal enhancement. Two atypical lesions, in the series reported by Grazioli *et al*[29], were hypointense for

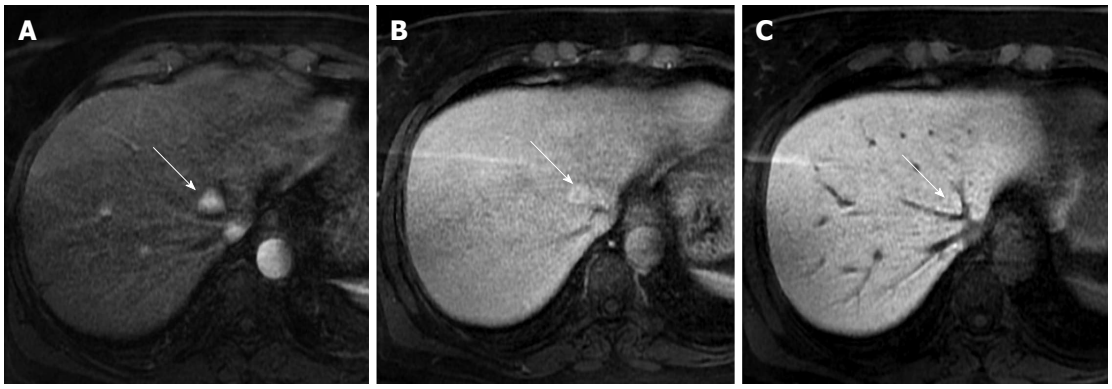


**Figure 2 Magnetic resonance imaging of a small focal nodular hyperplasia.** Arterial, venous and hepatobiliary phases (A, B and C), acquired in a 44-year-old woman shows the typical enhancement of a small focal nodular hyperplasia (white arrows). The lesion is located in the fourth liver segment, between medium and left sovrahepatic vein. In hepatobiliary phase (C) the lesion is slightly hyperintense to the surrounding liver parenchyma, due to uptake of hepatospecific contrast.

the presence of large fibrous components and abundant fat contents (steatotic FNH).

On the other hand, atypical HAs may not appear hypointense in the hepatospecific phase. Atypical behaviours, appearing as hyperintense lesions, have been reported in literature[15]. In fact, inflammatory adenomas could enhance in the hepatospecific phase. Hyperintense HAs in the hepatobiliary phase have been observed in the series by Denecke *et al*[15]. They reported one hepatic adenoma homogeneously hyperintense and two HAs with a mixed pattern (hypo-/hyperintense). In the subgroup of fatty hepatic adenomas, 14 adenomas were hypointense and 1 was mixed hyper-/hypointense. Also, Huppertz *et al*[30] describe in their FLLs series two out of three adenomas with hyperintense appearance in comparison to the surrounding liver. However, based on a quantitative analysis, all HAs, with hypointense signal to the surrounding liver on hepatobiliary phase, showed a certain degree of increase in signal intensity[15]. This could probably be explained by contrast retention in the interstitium or fibrotic tissue.

In addition, in the series reported by Denecke *et al*[15], the proportion between hyperintense and hypointense adenomas in hepatobiliary phase was approximately equal both in the non-steatotic group and in the steatotic of fatty adenomas[29]. The mechanism of Gd-EOB-DTPA uptake in these minority HAs is still unclear and further studies with histological correlation are needed.

## IDENTIFICATION OF EARLY HCC

The progressive differentiation of a regenerative nodule to a dysplastic nodule, and then to an early-HCC has been well investigated[31-34]. In this differentiation, the nodule increases its arteriolar supply progressively and reduces the portal vascularization[32,33]. This vascular change is a crucial step in the carcinogenesis. In view of this consideration, HCC diagnosis with imaging techniques is based on a "vascular analysis" of enhancing pattern, with an increased signal intensity or "wash-in" during the arterial phase and a "wash-out" pattern in the portal or equilibrium phase[35] (Table 1).

In 2012 the European Association for the Study of the Liver (EASL) and European Organization for Research and Treatment of Cancer (EORTC) provided common guidelines for the management of the liver[36]. The joint committee established that non-invasive assessment for HCC could be made only by applying a 4-phase multidetector computed tomography (CT) scan or dynamic contrast-enhanced MRI. In addition, the guidelines postulated that diagnosis is based on a typical morphological hallmark of HCC (Figure 3), with hypervascular pattern in the arterial phase and wash-out in the portal venous or delayed phases[36]. It has to be remarked that while only one technique is required for nodules greater than 1 cm in diameter (evidence 2D, recommendation 2B), a more conservative approach using 2 techniques is recommended in suboptimal settings[36].

Similarly, in 2010 an update of The American Association for the Study of Liver Disease (AASLD) recommended that nodules greater than 1 cm should be investigated with either 4-phase multidetector CT scan or dynamic contrast enhanced MRI[37]. In case of atypical nodules, a second contrast methodical is required (level Ⅱ), or alternatively a biopsy.

Nevertheless, the characterization of a nodule, based on these approaches, is not possible if both mentioned imaging features, "wash-in" and "wash-out", are not observed. Nodules may have hypervascular appearance in arterial phase, without evident wash-out in the portal or equilibrium phase (Figure 4). They could also have the same attenuation or signal intensity to the surrounding liver parenchyma during the dynamic arterial phase on CT and MRI images respectively, and may manifest a wash-out only in the portal phase. In this case the diagnosis is difficult and so, a further analysis is usually required in order to evaluate other important features such as a change in size or a tumour marker. A more invasive approach could be also adopted by choosing a biopsy.

In addition, small nodules (< 2 cm) very often lack the typical behaviour of HCC. Arterial neovascularization or reduced portal supply cannot be identified on imaging techniques, probably because these vascular changes are not significant. Adopting only hypervascularity criteria in

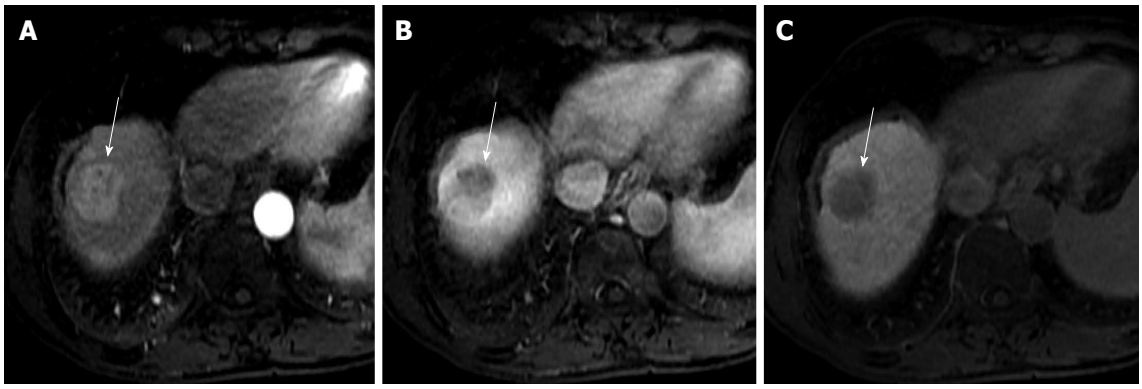


**Figure 3 Imaging features of a typical hepatocellular carcinoma.** Axial magnetic resonance images show a hypervascular lesion in the arterial phase (A, white arrow), located in the top of the liver, with wash-out clearly in the portal venous phase (B, white arrow). This enhancement pattern represents the typical morphological hallmark of hepatocellular carcinoma. The nodule has an increased arteriolar supply and reduced portal vascularization. In hepatobiliary phase, the lesion appears hypointense to the surrounding liver parenchyma.

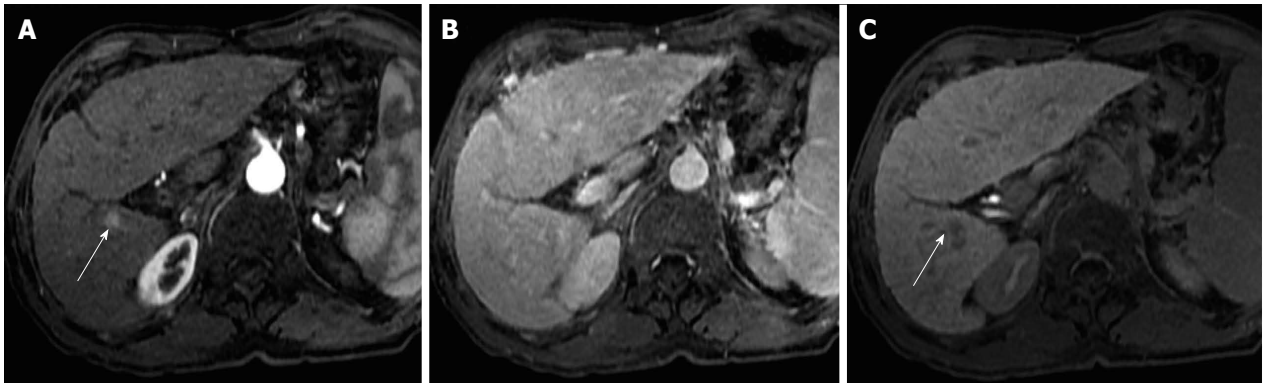


**Figure 4 Imaging features of a small hepatocellular carcinoma.** The lesion (white arrow), located in the fifth segment of right hepatic lobe, is detectable in the arterial and hepatobiliary phase. It has hypervascular appearance in arterial phase (A), without evident wash-out in the portal phase (B). The lesion is hypointense in the hepatobiliary phase (C). As reported in literature, the low or absence of gadolinium ethoxybenzhyl diethylenetriaminepentaacetic acid or gadoxetic acid uptake could precede the decrease of portal vascularization in malignant differentiation.

the diagnosis of HCC, MR sensitivity for nodules < 20 mm is about 63%[38,39].

An important diagnostic tool for the evaluation of lesions in the hepatospecific phase has now been added. In fact, papers have recently emphasized the contribution of hepatobiliary phase in the characterization of nodules without a typical hallmark of HCC. In a recent paper by Iannicelli *et al*[40], a total of 120 nodules were retrospectively evaluated using gadoxetic acid-enhanced liver MRI. In this study, 92 out of 120 nodules (76.6%) reported typical vascular behaviour of HCC, with hypervascularization appearance in the arterial phase. In the hepatobiliary phase, 90/92 nodules showed low signal intensity, whereas two nodules were hyperintense. The other 28 cases, with non-hypervascular behaviour in the arterial phase, were hypointense in hepatobiliary phase. Among these non-hypervascular nodules, only 15 cases had hypointense signal in the equilibrium phase. In the follow-up study, 50% of non-hypervascular nodules with low signal intensity in the hepatobiliary phase acquired the typical vascular behaviour of HCC.

The high accuracy in the identification of early HCCs will probably change the diagnostic algorithm in hepatocellular carcinoma[41]. It facilitates the diagnosis of hypervascular advanced HCC and the differentiation of early HCC and dysplastic nodules from pseudovascular lesions.

The hypointense appearance in hepatobiliary phase will probably be considered a "radiological marker of nodule differentiation". In the study by Golfieri *et al*[42], 62 out of 215 nodules were atypical for radiological behaviour. Their histological analysis showed 20 high-grade dysplastic nodules (HGDN)/early HCC, 21 low-grade nodules dysplasia, 17 regenerative nodules and 4 nodular regenerative hyperplasia. Nineteen out of 20 HGDN/early HCC nodules were hypointense in hepatobiliary phase. In another work, Kogita *et al*[43] found that low or absence of Gd-EOB-DTPA uptake precedes the decrease of portal vascularization in malignant differentiation (Figure 4).

In conclusion, gadoxetic acid-enhanced liver MRI could be very helpful in the early identification of HCC. However, differentiation between HCC and dysplastic nodule remain very difficult. Atypical nodules require better investigation, studying their behaviour in the hepatospecific phase.

## LIVER METASTASES DETECTION IN ONCOLOGY PATIENTS

Detection of liver metastases in oncology patients is essential in order to choose the best possible management and treatment. In this regard, many studies have demonstrated the high diagnostic accuracy of liver MRI[44]. Nevertheless, routine liver MRI is generally not performed for the staging of extra-hepatic oncology diseases. For example, the American College of Radiology Appropriateness Criteria for pre-treatment staging of colorectal cancer recommended CT of the chest, abdomen and pelvis for the initial evaluation of disease[45]. In the majority of the cases, staging liver MRI is required to evaluate doubtful FLLs.

The identification of liver involvement by metastases disease is essential because surgical resection has improved patient survival, especially in cases of colorectal cancer[46,47].

Gadoxetic acid-enhanced liver MRI allows for a vascular dynamic study of the hepatic parenchyma and adds hepatospecific phase for characterization of FLLs[46,48-50]. Lee *et al*[46] evaluated Gd-EOB-DTPA liver MRI and triple-phase multidetector computed tomography (MDCT) in the detection of suspected hepatic metastases, reporting that dynamic MR images with or without hepatospecific phase show better diagnostic performance than MDCT images. The sensitivity increased significantly with the addition of hepatobiliary phase in gadoxetic acid-enhanced MRI ($P < 0.0001$). In particular, the diagnostic accuracy was greater for small lesions (< 1 cm)[46]. Gadoxetic acid-enhanced liver MRI showed higher capability than enhanced MDCT in detection liver metastases from pancreatic carcinoma. In fact, in a recent work by Motosugi *et al*[48], higher values of sensitivity for detection of metastases were reported, with values of 85% for MRI and 69% for MDCT.

Acquisition of hepatospecific phase takes some time in a liver MRI protocol because it is generally performed 20 min after contrast administration. Less time would be important, in order to reduce the length of a liver MRI protocol. Diagnostic accuracy for metastases detection and lesion conspicuity was evaluated in hepatospecific images obtained 10 min and 20 min after gadoxetic acid administration[51]. In the study performed by Jeong *et al*[51], the hepatobiliary phase images obtained at 10 and 20 min after Gd-EOB-DTPA administration improve detection of metastases in comparison with pre-contrast images and dynamic acquisitions only. It has been demonstrated that sensitivity in the detection of metastases does not differ significantly using delay images acquired at 10 min and 20 min after contrast injection. However, in our opinion, the interval time between dynamic acquisitions and 10-min hepatobiliary phase, and between the 10-min and 20-min hepatobiliary phases, could be maintained in a standard liver MRI protocol. In fact, these intervals offer the possibility to acquire other sequences, thus acquiring a more complete liver MRI protocol. Diffusion weighted imaging (DWI) using multiple *b* values could require more time for its acquisition. In line with what has previously been reported in literature[52], morphological T2-weighted sequences, including axial breath-hold steady-state free-precession, axial breath-hold single shot spin-echo and axial breath-hold fast spin-echo sequences are acquired after dynamic imaging in our protocol. After these T2-weighted sequences, radiologists may acquire the first hepatospecific phase (10 min after contrast administration). Then, between 10-min and 20-min hepatobiliary phases, DWI could be placed without any considerable influence on imaging quality[52].

Recently in the field of FLL detection and characterization, it has been evaluated whether diagnostic performance of gadoxetic acid-enhanced liver MRI could be enriched by DWI. The contribution of DWI has been widely applied in different radiology fields[53-58]. In detection and characterization of FLLs, diffusion imaging reported higher scores in comparison with conventional T2-weighted sequences. In view of these results, several studies have compared the diagnostic capability of DWI and gadoxetic acid-enhanced liver MRI in detection FLLs. Donati *et al*[59] found that adding DWI to Gd-EOB-DTPA did not significantly increase diagnostic accuracy compared to Gd-EOB-DTPA imaging alone. Considering the detection of small metastases, Shimada *et al*[60] reported higher diagnostic accuracy of Gd-EOB-DTPA in comparison to DWI. Probably, both imaging modalities represent very important diagnostic tools in the evaluation of FLLs, as recently described in a study by Macera *et al*[61]. They found that the combination of DWI with Gd-EOB-DTPA-enhanced MRI imaging significantly increases the diagnostic accuracy sensitivity in patients with colorectal liver metastases treated with pre-operative chemotherapy[61].

## CONCLUSION

The topics discussed clearly demonstrate the importance of gadoxetic acid-enhanced liver MRI in the evaluation of FLLs. In fact, it significantly increases diagnostic accuracy in the detection and characterization of FLLs. Furthermore, it allows for the diagnosis of benign solid hepatic lesions such as FNH and HA, thanks to the different contrast uptake observed in hepatobiliary phase.

Some atypical nodules in vascular behaviours could be diagnosed as HCC if they lack Gd-EOB-DTPA retention in the hepatobiliary phase. The HCC guidelines need to underline the recent use of a liver hepatospecific agent. Finally, MR pre-operative assessment using gadoxetic acid allows for higher diagnostic accuracy in the detection of hepatic metastases.

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