Tips and pitfalls of liver imaging with gadoxetic acid: a pictorial review

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Authors: Y. X. Kitzing, S. McCormack, B. Ng
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Learning Objectives

1. To understand the mechanism of action of Gadoxetic acid (Gd-EOB-DTPA - gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid) and the role of hepatobiliary phase imaging.
2. To be familiar with the classical hepatobiliary phase findings relating to common lesions
3. To be familiar and understand the potential pitfalls due to atypical lesions, background liver disease and early uptake of hepatocyte contrast uptake.
Background

Gadoxetic acid (gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid - Gd-EOB-DTPA) is a hepatocyte specific MRI contrast agent which is designed to optimize lesion detection and characterisation.

Dynamic contrast enhancement

Gadoxetic acid acts as an extra-cellular contrast agent immediately following injection prior to the uptake into the hepatocytes. The recommended dosage of gadoxetic acid is one quarter of conventional extra-cellular contrast (gadopentetate dimeglumine). This theoretically can be associated with weaker extra-cellular enhancement during the dynamic contrast series although this has not been shown in animal models [1]. Recent study has however shown off-label doubling of the dosage of Gadoxetic acid improves the arterial phase lesion-liver conspicuity. [2]

Hepatobiliary phase enhancement

Gadoxetic acid is excreted 50% by the liver and 50% by the kidneys. Functioning hepatocytes take up the gadoxetic acid from the extra-cellular compartment using organic anion transporting polypeptide (OATP8) and excreted into bile by canallicular multi-organic anion transporter (cMOAT) [3].

Gadoxetic acid is accumulated in functioning hepatocytes that express the receptors. This provides the contrast between the lesion and the liver to aid detection. In addition, the lack of uptake by hepatic lesions provides the potential to aid characterisation. The optimal time for maximal signal intensity of normal background liver has been shown to be 10- 20 minutes following the intravenous injection.

The hepatobiliary phase imaging should be used to supplement the T2 and contrast enhanced series. Neglect of the clinical history and the other imaging findings may lead to diagnostic errors.
Imaging Findings OR Procedure Details

Background liver

Imaging findings on hepatobiliary phase varies between cirrhotic and non-cirrhotic patients. In non-cirrhotic livers, the hepatobiliary phase uptake is homogeneous with biliary excretion seen as contrast in the bile ducts. In cirrhotic livers, the hepatobiliary phase uptake is heterogeneous with reticular areas of low signal due to the fibrotic bands. (Fig. 1 on page 9)

Potential pitfall: In patients with severe liver function or biliary obstruction, the excretion of Gadoxetic acid may be predominantly via the kidneys, with poor uptake in the liver on the hepatobiliary phases. (Fig. 2 on page 9). Hepatobiliary phase liver signal intensity is related to the cirrhosis severity [4]. Severely cirrhotic liver provides a poor background for lesion detection. Large infiltrative HCC with subsequent geographic areas of hepatobiliary phase defects may also mimic areas of reduced liver function. (Fig. 3 on page 10)

Hepatocellular Carcinoma (HCC)

The hepatocarcinogenesis pathway includes low grade dysplastic nodules, high grade dysplastic nodules, early HCCs and poorly differentiated HCCs. Hepatocarcinogenesis is associated with reducing expression of the OATP receptors [5].

Majority of the HCCs do not express the receptors for the uptake of Gadoxetic acid and are defects on the hepatobiliary phase (Fig. 4 on page 11). The AASLD recommendation for the diagnosis of HCC is based on the finding of arterial enhancement and portal/delayed phase washout for lesions above 10mm [6].

The hepatobiliary phase finding does not replace the conventional dynamic contrast enhancement in the diagnosis. For lesions below 10mm where diagnosis is less reliable on dynamic contrast enhancement, hepatobiliary phase can provide supportive information.

Potential pitfall: 2.5-8.5% of HCCs take up Gadoxetic acid and may even be hyperintense relative to the background liver (Fig. 5 on page 12). This is thought to be due to the early or well-differentiated HCCs which express the receptors for uptake but reduced excretory capacity [7].
**Potential pitfall:** Due to the early uptake of Gadoxetic acid as early as 90 seconds following injection, there is the potential issue with HCCs which take up Gadoxetic acid to not demonstrate an equilibrium phase (3 min) defect. This issue can potentially be exacerbated if the lesion is T1 hyperintense on the initial pre-contrast study (Fig. 5 on page 12).

**Potential pitfall:** Clustered satellite HCC nodules which are small individually may not have perceptible hepatobiliary defects matching the overall arterial enhancing area (Fig. 6 on page 13). This can be exacerbated by the background liver cirrhosis and heterogeneity.

**Hepatocellular carcinoma versus Dysplastic nodules**

Distinction between early HCC and high grade dysplastic nodules on dynamic contrast enhancement can occasionally be difficult due to hypovascular HCCs and arterially enhancing dysplastic nodules. Similarly, there is variable uptake of Gadoxetic acid by nodules bordering between early HCC and high grade dysplastic nodules. The information from the dynamic contrast enhancement and the hepatobiliary phase can supplement each other.

Dysplastic nodules comprises of atypical hepatocytes but without overt malignancy. Majority of dysplastic nodules take up Gadoxetic acids with few losing the ability to express the receptors for uptake [8] (Fig. 7 on page 14). The hepatobiliary phase has been useful in our clinical practice in characterising large hypovascular nodules and distinguishing hypovascular HCCs from hypovascular dysplastic nodules. (Fig. 8 on page 14)

Isolated hepatobiliary phase defects are presumed to represent dysplastic nodules or early HCCs. Some reports have shown that these over time develop conventional arterial enhancement features of HCC and follow-up is required. Lesion size and intra-lesion fat are associated with higher risk of subsequent arterialisation [9].

**Regenerative nodules**

Regenerative nodules are focal hepatocellular proliferations without atypia. They are mostly isointense to the background liver parenchyma.

**Potential pitfall:** In our experience, regenerative nodules can occasionally be mildly hypointense relative to the background liver, presumably secondary to disturbed
hepatocyte function. Their hypointensity is however less marked compared to HCCs (Fig. 4 on page 11).

**Arterially Enhancing Pseudolesions**

Pseudolesions can develop from arteriportal shunts or vascular disturbances leading to transient hepatic attenuation differences. They are often but not necessarily subcapsular in location. They do not have portal venous/equilibrium phase defects. Hepatobiliary phase can help to distinguish between true lesions and arterially enhancing pseudolesions [10] (Fig. 9 on page 15).

**Potential pitfall:** Chronic vascular disturbances due to portal vein thrombosis or arteriportal shunts can lead to hepatocyte dysfunction in the supplied segment, reduced Gadoxetic acid uptake and relative hypointensity on the hepatobiliary phase. (Fig. 10 on page 16)

**Metastases**

Metastases show up as hepatobiliary phase defects due to the lack of hepatocytes. The hepatobiliary phase improves visibility of metastases compared to conventional dynamic enhanced series. (Fig. 11 on page 17)

**Potential pitfalls:** Some metastases have been reported to show central hyperintensity on the hepatobiliary phase presumably due to extra-cellular leakage into central areas of necrosis or ischaemia [11, 12].

**Haemangioma**

Haemangiomata are recognised by their conventional imaging features of marked T2 hyperintensity and peripheral nodular arterial enhancement with progressive washout. Hemangiomata are defects on the hepatobiliary phase. Interpretation of the hepatobiliary phase defect should be made in conjunction with the T2 findings.

**Potential pitfalls:** Pseudowashout (Fig. 12 on page 17) due to the early uptake of the Gadoxetic acid by the background liver in as early as 90 seconds following injection, a small rapidly filling haemangioma may have a relative defect on the equilibrium phase (3minutes) and mimic a hypervascular tumour [13]. Correlation with T2 or imaging with extracellular MRI contrast would be helpful.
Focal nodular hyperplasia and hepatic adenoma

Focal nodular hyperplasia and hepatic adenoma are arterially enhancing lesions which are both more commonly seen in the female population. The management is however different with large hepatic adenoma subject to surgical resection due to risk of haemorrhage and malignant transformation.

Focal nodular hyperplasia express OATP and may be isointense or hyperintense to the background liver on the hepatobiliary phase. The pattern may be homogeneous or heterogeneous. If there is a central scar, there will be a hepatobiliary phase defect centrally. Occasionally, there may be a thin rim of hypointensity peripherally due to adjacent compressed hepatocytes. Fig. 13 on page 18

**Potential pitfall:** There is a reported rate of 2% of focal nodular hyperplasia that do not take up the Gadoxetic acid [14]. Close follow-up or biopsy for tissue confirmation is suggested where suspected FNH do not take up the contrast agent.

Hepatic adenomas are defects on hepatobiliary phase imaging. Gadoxetic acid is well established in distinguishing between hepatic adenoma and focal nodular hyperplasia. There are reported cases of hepatic adenoma showing uptake and may relate to the subtype of adenoma but the aetiology is not yet elucidated [11].

**MRI sequences**

Hepatobiliary phase imaging is obtained using a T1 weighted sequences with associated issues of fat and iron altering the liver signal.

**Potential Pitfalls:**

**Iron:** Severe iron overloading of the liver leads to marked hypointensity of the liver on both dynamic contrast enhanced series and hepatobiliary phase. HCCs do not contain iron and are therefore hyperintense relative to the liver on all sequences including the hepatobiliary phase. (Fig. 14 on page 19) Assessment for the enhancement of HCC in patients with hemochromatosis and severe iron load would be more appropriate with dynamic contrast enhanced CT.

**Siderotic** nodules within cirrhotic liver are hypointense on both T1 and T2 and may also be visible as multiple defects on hepatobiliary phase imaging. (Fig. 15 on page 20)
**Fat:** Focal steatosis may show as hepatobiliary phase hypointensity if the MRI sequence is with fat saturation and out-phase imaging (Fig. 16 on page 21). It is important to distinguish this from fat containing early HCCs (Fig. 17 on page 22). Morphology, usual site of involvement, risk factors and correlation to the dynamic contrast enhanced series and T2 imaging are important.

[14]
Images for this section:

**Fig. 1:** A. 20 min hepatobiliary phase T1 imaging in a non-cirrhotic patient shows homogeneous uptake with biliary contrast excretion. B. Hepatobiliary phase 20 minute T1 imaging in a patient with cirrhosis. There is heterogeneous uptake of the contrast with reticular coarsening.

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**Fig. 2:** Patient with biliary obstruction. 20 minute hepatobiliary phase shows central hypointensity of the liver parenchyma. There is no contrast in the bile duct.

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Fig. 3: Patient with cirrhosis secondary to hepatitis C. A. Arterial phase shows a vague area of arterial enhancement in segment 2 in addition to a typical hepatocellular carcinoms in the right lobe of the liver (not shown). B. Hepatobiliary phase 20 minute T1. There is mild hypoattenuation of the region which did not stand out from background cirrhotic signal variation. Subsequent disease progression showed this area to be infiltrative HCC.

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Fig. 4: Patient with a 12 mm HCC and regenerative nodules (pathology proven). A. T2 FSEFS sequence shows hyperintensity of lesion. B & C. Dynamic contrast enhanced series showed arterial enhancement and portal venous washout D. DWI B800 images shows diffusion restriction of the HCC. E. Hepatobiliary phase 20 minute T1 sequence shows marked hypointensity of the HCC against the background liver. F. Near the HCC, in a subcapsular location of segment 8, there is a further small nodule of relative hypointensity on the hepatobiliary phase imaging. This was proven to be multiacinar regenerative nodule. On the other sequences, there was no evidence of arterial enhancement, T2 hyperintensity or diffusion restriction. Note the background mild hypointense nodules elsewhere.

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Fig. 5: Hepatocellular carcinoma with uptake of Gadoxetic acid. A. Hepatobiliary phase 20 minutes T1 sequence shows avid homogeneous uptake in a nodule. There was arterial enhancement within the nodule (not shown). B. 5 minute equilibrium phase with Gadoxetic acid shows that the lesion is isointense relative to the background liver without washout. C. 5 minute equilibrium phase imaging on CT shows washout of the lesion which is now classified as a hepatocellular carcinoma. The lack of washout on the MRI sequences was presumed to be a combination of early uptake of Gd-EOB-DTPA and baseline T1 hyperintensity of the lesion. The time interval between the CT and the MRI was 2 months.

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Fig. 6: Infiltrative HCC in segment 5 without matching hepatobiliary phase defect (biopsy proven). A. Arterial phase T1 shows a poorly defined area of arterial enhancement in segment 5 of the liver. No definite portal venous defect (not shown). B. Hepatobiliary phase 20 minutes T1 sequence shows no corresponding defect. C. DYNA CT angiogram from hepatic arterial injection and hepatic angiogram (not shown) show that the region of arterial enhancement is due to constellation of subcentimeter arterial enhancing foci.
Fig. 7: Patient with dysplastic nodule. A. Hepatobiliary phase T1 shows uptake of Gadoxetic acid by the nodule. The nodule did not show arterial enhancement and was hypovascular. B. Arterial phase CT. The dysplastic nodule remained stable until the development of an HCC foci with nodule in nodule appearance.
Fig. 8: Hypovascular HCC recurrence. Dynamic contrast enhanced imaging shows no arterialisation of this newly developed hypovascular mass near the resection margin. T1 hepatobiliary phase 20 minute shows that the lesion does not take up Gadoxetic acid. Subsequent explant analysis confirmed a HCC.

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Fig. 9: Patient with Hepatitis B. Arterial phase showed multiple subcentimeter arterial enhancement. There is no defect on the 20minute hepatobiliary phase T1. These are likely areas of pseudolesion from shunting. The imaging findings have been stable for 5 years.

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Fig. 10: Patient with thrombosed right posterior portal vein. A. Portal venous phase T1 shows thrombosis of the right posterior portal vein. B. Hepatobiliary phase shows a wedged shaped hypointensity relative to the adjacent normally perfused liver. Chronic
perfusional disturbance presumably leads to hepatocyte dysfunction and reduced Gadoxetic acid uptake.

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**Fig. 11:** Patient with metastatic adenocarcinoma. A & B. Hepatobiliary phase T1 FSPGR. Multiple hypointense nodules relative to the background liver due to metastases. C. Portal venous phase T1. The slice is comparable to image B. Note the higher lesion-to-liver contrast on the hepatobiliary phase compared to the portal venous phase.

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**Fig. 12:** Patient with two hemangioma. A. T2 sequence shows T2 hyperintensity. B. Arterial T1 sequence shows nodular arterial enhancement for the large haemangioma and early rapid filling of the smaller haemangioma. C. 3 minute equilibrium T1 sequence shows pseudo-washout of the smaller haemangioma due to the bright background liver from Gadoxetic acid uptake. D. 20 minute hepatobilliary phase shows both lesion hypointense relative to the liver.

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Fig. 13: Patient with focal nodular hyperplasia. A: T2. Lesion is isointense to background liver with central hyperintense scar. B: Arterial phase T1 following Gadoxetic acid: Lesion shows arterial enhancement. C: Hepatobiliary phase T1: Note the uptake of Gadoxetic acid in the focal nodular hyperplasia without uptake centrally in the scar. There is a peripheral rim of hypointensity which may be due to adjacent compressed liver tissue.

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Fig. 14: Patient with hemochromatosis. T1 hepatobiliary phase 20 minutes shows no parenchymal hyperintensity due to the liver iron content leading to T1 signal distortion. Due to the loss of iron accumulation, the HCC is the hyperintense nodule relative to the background liver.

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Fig. 15: Patient with hepatitis B and siderotic nodules. A & B. T1 (in and out of phase) imaging shows conspicuity of the siderotic nodules on in-phase imaging due to the associated longer TE and higher susceptibility to the iron content of the nodules. C. Hepatobiliary phase T1 shows multiple corresponding hypointense nodules against the liver parenchyma.

Fig. 16: Patient with breast carcinoma and presumed focal fatty infiltration. CT showed area of hypointensity adjacent to gallbladder fossa. A & B. In and out of phase T1 shows focal signal suppression consistent with intralesional fat. Dynamic contrast series shows no enhancement (not shown). C. Hepatobiliary phase T1 FSPGR Fat suppressed 20 minutes shows hypointensity of the region relative to the background liver. This was treated as focal fatty infiltration with uneventful follow-up.
**Fig. 17:** Patient with hepatocellular carcinoma with intralesional fat. A & B. In and out of phase T1 imaging shows signal suppression in keeping with intralesional fat. Dynamic contrast enhanced series (not shown) demonstrated arterial enhancement and portal venous phase washout. C. Hepatobiliary phase T1 FSPGR shows mild hypointensity of the lesion. On follow-up, the lesion enlarged and was treated as HCC.
Conclusion

Utilisation of Gd-EOB-DTPA in hepatobiliary phase imaging should be as a supplement to the T2 and contrast enhanced series. Understanding of the hepatocyte specific action of the contrast agent, the hepatocarcinogenesis sequence, the patient’s background liver status and the MRI techniques are important in the anticipation of potential pitfalls.


10. Sun HY, Lee JM, Shin CI et al. Gadoxetic acid-enhanced magnetic resonance imaging for differentiating small hepatocellular carcinomas (< or =2 cm in diameter) from arterial enhancing pseudolesions: special emphasis on hepatobiliary phase imaging. Invest Radiol. 2010 Feb;45(2):96-103.


