RADIOLOGÍA

www.elsevier.es/rx

RADIOLOGÍA

UPDATE AND GOOD PRACTICE IN THE CONTRAST MEDIA USES

Hepatobiliary contrast agents for Liver Magnetic Resonance Imaging

A. Perez-Girbes [a],[*], J.M. Lee [b], L. Martí-Bonmatí [a]

[a] Área Clínica de Imagen Médica, Hospital Universitario y Politécnico La Fe, Valencia, Spain
[b] Department of Radiology, Seoul National University Hospital, Seoul, South Korea

Abstract The use of hepatobiliary-specific contrast agents in liver MRI is a crucial diagnostic tool for evaluating liver disease, enabling the detection and characterisation of focal lesions and vascular alterations, as well as the assessment and grading of chronic hepatopathy. Paramagnetic hepatobiliary-specific contrast agents are gadolinium-based, partially taken up by hepatocytes, and excreted via both renal and biliary pathways. There are two linear ionic molecules that are currently commercially available: gadobenic acid (Gd-BOPTA) and gadoxetic acid (Gd-EOB-DTPA). Their main clinical indications include distinguishing and characterising focal liver lesions on healthy liver tissue, diagnosing and staging hepatocellular carcinoma in patients with chronic hepatopathy, and increasing reliability in the detection of hepatic metastases in oncology patients, especially prior to surgery. They are also useful in the evaluation of the biliary tract and in assessing complications of hepatic surgery such as bile leaks.

Medios de contraste específicos para el estudio del hígado en resonancia magnética

Resumen La resonancia magnética hepática con medios de contraste hepatoespecíficos es una herramienta diagnóstica crucial para evaluar las enfermedades hepáticas. Permite la detección y la caracterización de lesiones focales y alteraciones vasculares hepáticas, así como laevaluación y gradación de la hepatopatía crónica. Los contrastes hepatoespecíficos paramagnéticos están basados en el gadolinio, se incorporan parcialmente a los hepatocitos, y se excretan tanto por la vía renal como por la biliar. Actualmente se dispone comercialmente de dos moléculas lineales iónicas: el ácido gadobénico (Gd-BOPTA) y el ácido gadoxético (Gd-EOB-DTPA). Sus principales indicaciones clínicas incluyen diferenciar y caracterizar lesiones focales

* Corresponding author.
  E-mail address: perez_alegir@gva.es (A. Perez-Girbes).

hepáticas sobre hígado sano, diagnosticar y estadificar el carcinoma hepatocelular en pacientes con hepatopatía crónica, e incrementar la fiabilidad en la detección de metástasis hepáticas en pacientes oncológicos, especialmente antes de la cirugía. También son útiles en la evaluación anatómica de la vía biliar y las complicaciones de la cirugía hepática como la fuga biliar.

Introduction

Liver Magnetic Resonance Imaging (MRI) with intravenous contrast is an indispensable diagnostic tool for the evaluation of liver diseases, and allows for improved detection and characterisation of focal lesions and hepatic vascular abnormalities in patients with incidental lesions, chronic hepatopathy, vascular disorders or cancer.

Contrast media are administered intravenously and can generally be classified by their mechanism of action (paramagnetic or superparamagnetic) or by their distribution in the body after administration. The contrast media currently used are paramagnetic and gadolinium based. In the study of the liver, both extracellular and hepatobiliary contrasts can be used.[1]

Extracellular contrast media are the most commonly used in MRI studies. After intravenous administration, they are initially distributed in the vascular compartment and progressively diffuse into the extravascular and extracellular interstitial space, without being incorporated into the interior of the cells. From this space they return to the vessels for renal excretion. In the liver, these contrasts may have a prolonged distribution phase in areas with increased vascular space, such as in haemangiomas, or with increased extracellular space with affinity for the contrast, such as in fibrosis. There are several extracellular contrast media on the market, with differences based on their molecular structure, their physical/chemical characteristics and their pharmacokinetic properties.[2] The contrast agents in use have a macrocyclic structure and are extremely safe, even in patients with impaired renal function.[3] They are typically administered as a rapid intravenous bolus, at a dose of 0.1 mmol/kg (equivalent to 0.2 ml/kg at the usual concentration of 0.5 mmol/ml), followed by a push bolus of normal saline solution at the same rate.[2,4]

Hepatobiliary contrast agents were historically developed as gadolinium- and manganese-based paramagnetic contrast agents or as iron-based superparamagnetic contrast agents. Nowadays, only gadolinium-based paramagnetic contrast agents are used.[1] Hepatobiliary paramagnetic contrast agents using gadolinium partially incorporate in the hepatocyte. It is excreted both through the kidneys and the bile ducts. The partial incorporation of contrast into the hepatocyte and its excretion through the bile canaliculus is what enables a highly reliable evaluation of the hepatic parenchyma and characterisation of its anatomy, focal lesions and alterations in the vascular and biliary tree.[5] This review will discuss the properties and characteristics of hepatobiliary gadolinium contrast agents in MRI, their clinical indications, and the criteria for radiological interpretation of the main findings.

Types of hepatobiliary contrast agents used in liver studies with magnetic resonance imaging

Hepatobiliary contrast media are incorporated into hepatocytes through an active transport mechanism by membrane proteins. Once inside the hepatocyte, they can return to the sinusoidal vascular space or be excreted into the bile canaliculus. This movement marks the different visualisation phases in the vessels, the liver parenchyma and the biliary tree. The uptake by hepatocytes occurs through the organic anion transporting polypeptide (OATP1) group of transporters, particularly the OATP1B1/B3 (also called OATP8) located in the sinusoidal membrane of the hepatocyte. From inside the hepatocyte (Fig. 1), part of this intracellular contrast is excreted into the bile through the multidrug resistance-associated protein 2 (MRP2) transporter located in the canalicular membrane.[6,7] Another part of the contrast returns to the vascular space through the sinusoidal multidrug resistance-associated protein transporter 3/4 (MRP3/MRP4). Clearance towards the sinusoid depends on the portal flow.[8] Liver lesions whose cellularity has lost the expression of these transporters and lesions whose origin is not hepatocellular will not incorporate this contrast into their cells.

There are currently two hepatobiliary contrast agents available for clinical use in Europe. Both contrasts are administered intravenously, are gadolinium-based, and undergo partial hepatic uptake and excretion, which allows images to be obtained in the phase in which the contrast is predominantly inside the hepatocyte, called the hepatobiliary phase (HBP). These contrasts are gadobenic acid (Multihance®, Braco, Italy) and gadoxetic acid (Primovist/Eovist®, Bayer-Schering Pharma, Germany). In this paper, the names Gd-BOPTA and Gd-EOB-DTPA are used for these contrasts, given their greater familiarity in radiological language.

Structurally, both Gd-BOPTA and Gd-EOB-DTPA are ionic linear molecules with the ability to bind to plasma proteins. In the case of Gd-BOPTA, the formulation has a concentration of 0.5 mmol/ml, with a usual dose of 0.1 ml/kg body weight. The approved dose of Gd-EOB-DTPA is 0.1 ml/kg body weight, although its concentration is lower, at 0.25 mmol/ml.
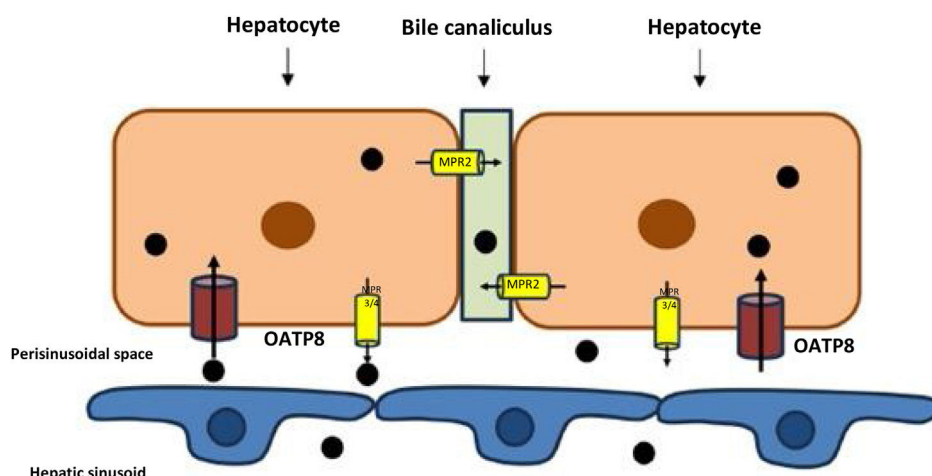
Figure 1   Diagram of the transport and accumulation of hepatobiliary contrast inside the hepatocyte. There is active uptake from the sinusoidal membrane through the OATP8 transporter (=OATP1 B1/B3) and excretion into the bile canaliculus through the MPR2 channel. Part of the intracellular contrast may return to the vascular space via the sinusoidal transporter MRP3/MRP4.

Table 1   Main physical/chemical characteristics of the two hepatobiliary contrast agents marketed in Europe: Gd-BOPTA and Gd-EOB-DTPA.

	Gd-BOPTA	Gd-EOB-DTPA
Trade name	Multihance®	Primovist/Eovist®
Excess ligand[a]	0%	0.5%
Osmolality (mOsm/kg H_2O, 37 °C)	1970	688
Viscosity (mPa s, 37 °C)	5.3	1.2
Thermodynamic stability constant (Log K_{therm})	22.6	23.5
Conditional stability constant (Log K_{cond})	18.4	18.7
$T_{1/2}$	<5 s	<5 s
Relaxation (r1/r2, 1.5 T)[b]	6.0−6.6/7.8−9.6	6.5−7.3/7.8−9.6
Relaxation (r1/r2, 3.0 T)[b]	5.2−5.8/10.0−12.0	5.9−6.5/10.0−12.0
Elimination	96% kidney	50% kidney
	4% liver	50% liver

Source: Adapted from Hao et al.[9]

   [a] Excess ligand as a percentage of the molar concentration of contrast agent (at pH 7.4).
   [b] Values in $l \times mmol^{-1}s^{-1}$.

The hepatic excretion of Gd-BOPTA is approximately 4% of the administered dose. For HBP imaging, images should be acquired at 90−120 min. to maximise uptake by the liver parenchyma. This contrast enables a dynamic study with the early and late arterial, portal and equilibrium phases between the vascular and interstitial compartments, all of which are separated from the HBP, which comes much later. The biliary excretion of Gd-EOB-DTPA is approximately 50%, which makes it possible to obtain images in the HBP starting 20 min. after intravenous administration. Gd-EOB-DTPA also enables a complete dynamic study with the early arterial phase, late arterial phase and portal phase. The transition phase represents a mixture of contrast in the interstitium and in the hepatocyte, so it differs from the traditional equilibrium phase presented by the other contrasts. A summary of the main physical/chemical characteristics of both compounds, Gd-BOPTA and Gd-EOB-DTPA, is shown in Table 1. In this paper, protocols for the acquisition of dynamic sequences after contrast administration are defined with a contrast injection speed of 2 ml/s and a weight-adjusted volume (0.1 ml/kg), as instructed in the package leaflet.

Protocols and phases in dynamic liver studies

Following administration of the contrast medium, MRI images are acquired at a time interval determined by the main compartment, where there is a higher concentration of the injected compound. Given the differences in the dynamic behaviour of hepatobiliary contrasts, the naming of some of the phases after administration depends on the contrast used.

Most of the parameters used in the acquisition protocols for liver MRI with hepatobiliary contrast agents are similar to those used for extracellular contrast agents, except for the images obtained in HBP, the delay of which will, as mentioned, depend on the specific type of contrast agent used. Sometimes it may only be necessary to acquire HBP in what we know as abbreviated protocols for the presurgi-
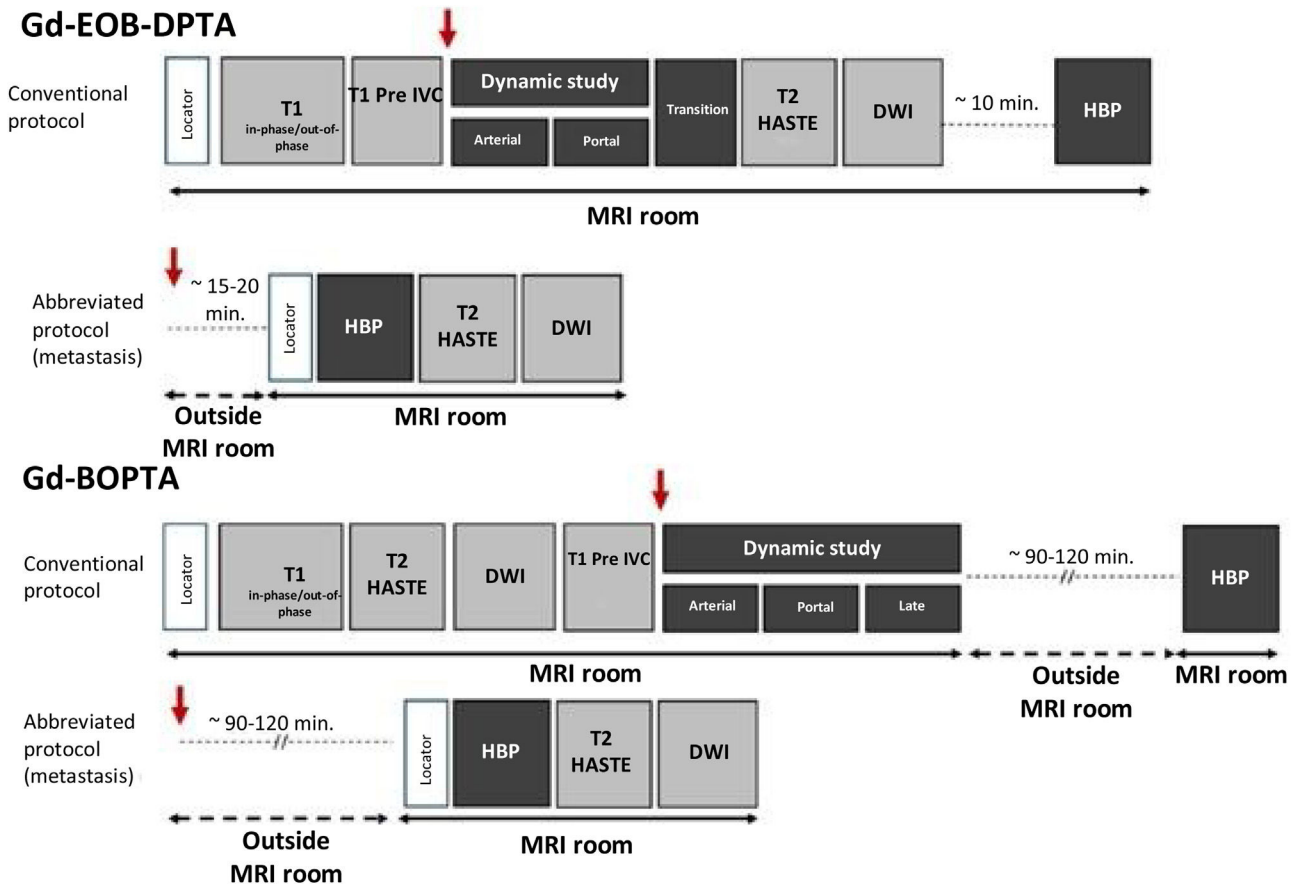
Figure 2 Standard liver MRI protocols for hepatobiliary contrasts. A conventional protocol and an abbreviated protocol that can be used in the detection of liver metastases are shown, in both cases injecting the contrast outside the MRI equipment and waiting 15–20 min. with Gd-EOB-DPTA and 90–120 min. with Gd-BOPTA. In all cases, the red arrow indicates intravenous injection of contrast. DWI: diffusion-weighted image; HBP: hepatobiliary phase.

cal detection of liver metastases, especially in patients with colorectal cancer.[10] A summary of the usual protocols used with hepatobiliary contrasts is shown in Fig. 2. The main sequence for the pre-contrast, dynamic and HBP study is based on a 3D gradient echo with very short TR/TE times, a flip angle between 13 and 30°, and usually with fat suppression to maximise the intensity of the contrast signal.

Hepatic arterial phase

At this stage, the hepatic artery and its branches show complete enhancement while the contrast has not yet reached the suprahepatic veins. ACR-LI-RADS[11] definition distinguishes two arterial phases: 1) the early arterial phase, in which the portal vein is not opacified; and 2) the late arterial phase, in which opacification is already present in the portal vein, but not in the suprahepatic veins.

The time we must wait between the start of the injection of contrast into an upper limb peripheral vein and the acquisition of the images is a very important parameter. In general, it is preferred to acquire the early arterial phase once the contrast is detected in the abdominal aorta in studies with bolus tracking. The region of interest (ROI) to identify the arrival of the contrast bolus should be located at the centre of the vessel, usually in the abdominal aorta near

the start of the coeliac trunk. For the highest quality arterial study in dynamic acquisition, a 25-ml saline push bolus is used immediately after completing the contrast injection and at the same speed.

Usually two arterial phases are acquired, one early and one late. The early arterial phase is acquired approximately 5 s. after detecting the arrival of contrast to the aorta (this is the time required to cancel the bolus tracing sequence and start the acquisition). If this sequence is not available, the early arterial phase could be obtained about 15 s. after injection, although the quality of the arterial phase will not be guaranteed. In the case of the late arterial phase, this is acquired at approximately 20 s. in studies with bolus detection, or approximately 30−35 s. after peripheral venous administration.

The late arterial phase is critical to having the best detection and characterisation of hepatocellular carcinoma (HCC),[12] so obtaining diagnostic-quality images during this phase is critical. For this reason, liver imaging protocols are currently performed with multiple acquisitions during the arterial phase, which minimises study variability. These multiple arterial acquisitions minimise the problems associated with self-limiting transient dyspnoea that can occur during arterial phase acquisition after Gd-EOB-DTPA administration, which causes motion artifacts, limiting the

quality of the acquisition. A recent meta-analysis[13] found a 13% incidence of severe transient artifacts in single arterial acquisition, compared to 3% in multiphase acquisitions, with a statistically significant difference. A significant difference was also found in the incidence of these transient artifacts between studies performed with Western populations (Europe and the USA, 16%) and Eastern populations (Asia-Pacific, 9%).[13] Age over 65 years, a body mass index $\geq 25\,kg/m^2$, having chronic obstructive pulmonary disease and the existence of moderate or severe pleural effusion are independent risk factors for the appearance of these artifacts in arterial acquisition after the administration of Gd-EOB-DPTA.[14]

Portal phase or portal venous phase

The image series acquired in the portal phase is obtained approximately 60 s. after the administration of intravenous contrast in the upper limb or approximately 50 s. after the trigger threshold in studies with bolus tracking. During this phase, there is maximum enhancement of the liver parenchyma, and both the portal vein and the suprahepatic veins are completely opacified. These images allow assessment of the presence of tumour washout in patients with HCC, regardless of the contrast medium. It is also the phase of the dynamic study with the highest diagnostic yield in the detection of liver metastases.

Late or equilibrium phase

This series is obtained approximately 3 min. after administration of extracellular contrast and Gd-BOPTA. In this phase the portal vein and suprahepatic veins are opacified, but less so than in the portal venous phase. Enhancement of the liver parenchyma is also observed, but in a lower intensity than during the portal phase. In studies performed with extracellular media or with Gd-BOPTA, the presence of washout can be determined during this phase according to LI-RADS criteria in patients with chronic liver disease.

This phase does not exist if Gd-EOB-DPTA is used as a contrast.

Transition phase

This phase is obtained in studies with Gd-EOB-DPTA, as this contrast is incorporated early into the hepatocytes and there is no pure extracellular phase beyond the portal phase. This phase is not considered in studies performed with Gd-BOPTA. In general, it is obtained between 2 and 5 min. after administration of the contrast, where there is a transition with contrast extending to both extracellular and intracellular compartments. In this phase, the vessels and liver parenchyma have similar signal intensity. For the characterisation of focal lesions in patients with chronic liver disease, the presence of hypointensity during this transition phase is not considered washout in most international guidelines, with the exception of the KLCA-NCC guideline from South Korea.[15,16]

Hepatobiliary phase

The delay in obtaining HBP depends on the contrast medium used. With Gd-EOB-DPTA, a quality HBP can be obtained as early as 15−20 min. after intravenous administration. In some centres, DWI and T2-WI sequences are performed after the dynamic study to optimise the protocol and reduce the study acquisition time.[17]

Studies using Gd-BOPTA require a longer waiting time to obtain the HBP, between 90−120 min. In these cases, the patient usually waits outside the MRI room for its acquisition. This adds time to the study, although the acquisition of the second part is rapid and hardly upsets the timing of appointments when controlled.

The HBP is considered to be of adequate quality when the liver parenchyma clearly shows hyperintensity compared to the blood vessels. The presence of contrast excreted into the biliary tract does not equate to maximum enhancement of the liver parenchyma, and by itself does not imply a quality HBP.[11,12,18]

In patients with liver disease, due to the loss of functionality of hepatocyte membrane transporters, it is common to observe decreased parenchymal enhancement in this HBP, as well as a slower realisation of maximum liver enhancement. Furthermore, a heterogeneous enhancement pattern may be observed in this situation if there is significant liver fibrosis or sinusoidal perfusion disturbance. A pattern of reduced uptake with periportal distribution has also been described in other chronic liver diseases, especially in primary biliary cirrhosis and idiopathic portal hypertension.[18]

Some studies have used this enhancement of the liver parenchyma to make a qualitative and quantitative determination of liver function, which may be useful in long-term follow-up and monitoring after treatment.[19] For example, relative liver enhancement is directly related to the likelihood of one-year survival in liver transplant patients.[20]

Clinical indications

Most focal liver lesions do not have normal and functioning hepatocytes and will not show uptake of hepatobiliary contrast media, so most lesions appear hypointense in HBP.

Some lesions show contrast media uptake through OATP8 transporters, which is a valuable feature for the characterisation of focal lesions. Table 2 shows a summary of the behaviour of the main lesions usually evaluated using hepatobiliary contrast media in different clinical contexts.

Differentiation of focal hepatic lesions in non-cirrhotic liver

The main indications in this section are related to the characterisation of hepatocellular tumours.

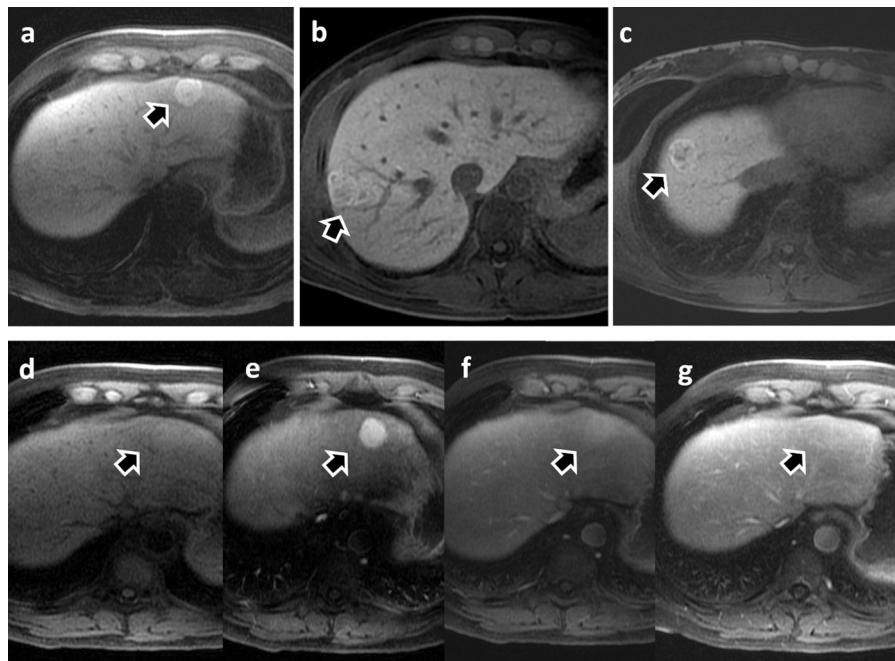### Focal nodular hyperplasia and hepatocellular adenoma

Differentiation between focal nodular hyperplasia (FNH) and hepatocellular adenoma (HCA) is one of the main indications in routine clinical practice for performing MRI studies and obtaining images in HBP. Both entities present similar characteristics in conventional imaging studies and it can be difficult to differentiate between them (Figs. 3 and 4).

Table 2 Classification of the main types of focal liver lesions based on the clinical context and their usual behaviour in the hepatobiliary phase.

Clinical context	Type of lesion	Typical behaviour during HBP	Additional comments
Non-cirrhotic patients	Focal nodular hyperplasia (FNH)	Iso/hyperintense in 97% Some lesions may display a hyperintense peripheral ring	Benign lesion that rarely requires surgical treatment.
	Hepatocellular adenoma (HCA)	*Hypointensity:* 100% of HNF-1α-inactivated HCA *Iso/hyperintensity:* 59% of β-catenin-mutated; 14% of inflammatory HCA; 11% of unclassified HCA	Benign hepatocellular neoplasia with different molecular subtypes. Different risk of bleeding and malignant transformation depending on the subtype.
Patients with cirrhosis	Hepatocellular carcinoma (HCC)	*Hypointensity:* usual behaviour, majority of HCC *Iso/hyperintensity:* 8.8−14.4% of HCC	Normal enhancement behaviour in the arterial phase and washout during the portal or equilibrium phase (Gd-BOPTA). Transition phase (2−5 min) obtained with GD-EOB-DPTA not valid for washout detection, except in South Korean guidelines.
	Intrahepatic cholangiocarcinoma	Typically hypointense, although the centre may show hyperintensity due to contrast accumulation.	EOB-cloud phenomenon less common than on healthy liver.
	Regeneration nodules	Typically isointense to the rest of the parenchyma	
	Dysplastic nodules	Up to 30% hypointense; the rest iso/hyperintense	
	Cirrhotic doughnut nodules	Doughnut-shaped with peripheral hyperintense ring enhancement	They do not show enhancement in the arterial phase.
Cancer patients	Liver metastases	*Hypointensity:* Common behaviour in most liver metastases *Iso/hyperintensity:* Retention of contrast material in the central area	HBP also useful for detection of metastasis of neuroendocrine tumours.
	FNH-type lesion	Typically hyperintense or isointense. Occasionally hypointense with a hyperintense ring	Patients treated with oxaliplatin-containing chemotherapy regimens.
	Intrahepatic cholangiocarcinoma	Hyperintense central zone with hypointense peripheral ring (EOB-cloud phenomenon)	
Vascular abnormalities	FNH-type lesion (Budd-Chiari)	Typically hyperintense or isointense.	Usually hyperintense in T1 and hypointense in T2 compared to the rest of the parenchyma.
	FNH-type lesion (Fontan)	Typically hyperintense or isointense.	Occasionally they may show washout during the portal phase.

HBP: hepatobiliary phase.

Figure 3 Focal nodular hyperplasia (FNH). Arrows in images a-c show three contrast-enhancing lesions from three different patients characterised as FNH during the hepatobiliary phase with Gd-BOPTA. Images d–g show the dynamic study of the patient in image a. The lesion appears slightly hyperintense on non-contrast T1 (d), marked enhancement during the arterial phase (e) and progressive homogenisation with the liver parenchyma in the portal (f) and late (g) phases.
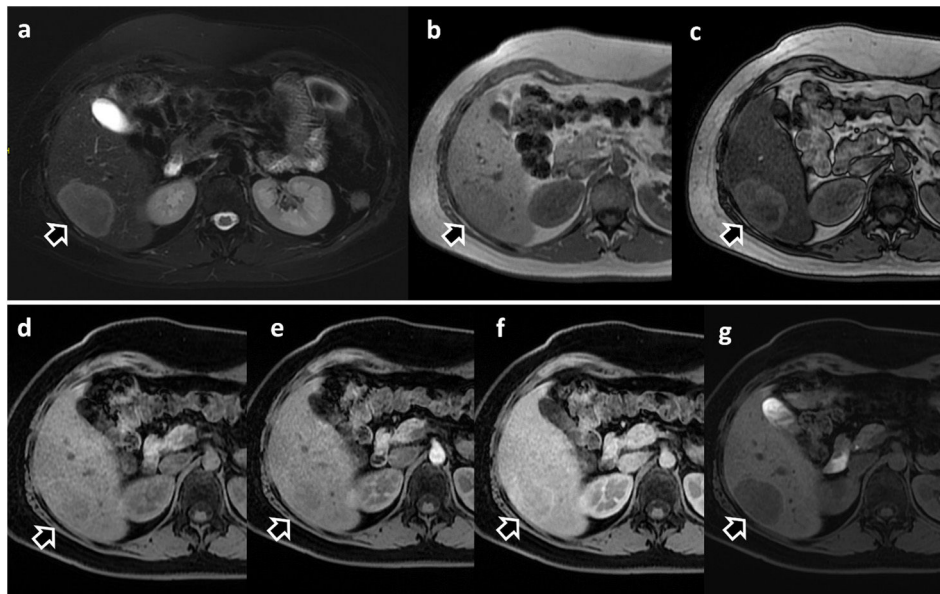
Figure 4 Inflammatory subtype hepatocellular adenoma (biopsy-confirmed) in a 35-year-old patient on oral contraceptives. The lesion appears hyperintense on T2-WI (a) compared to the liver parenchyma, a typical finding with the inflammatory subtype. In the in-phase and out-of-phase sequences (b and c), a drop in signal can be seen in part of the lesion due to the presence of intracellular fat (also see a drop in signal in the liver parenchyma due to c). In the dynamic study (d, T1-WI without IVC; e, arterial phase; f, portal phase; and g, hepatobiliary phase) note the marked hypointensity during the hepatobiliary phase (g).

Establishing the distinction is important, as FNH is a benign disorder that rarely requires treatment, while HCA is a benign tumour which carries a risk of bleeding and malignant transformation, which may require surgical treatment. Furthermore, HCA are not homogeneous and there are different pathological subtypes with different behaviour and prognosis. The most recent version of the molecular and gene expression classification of HCA, published in 2017, classifies them into eight subtypes.[21] However, most groups and publications consider four main subtypes:

HFN1α-inactivated adenoma (*HFN1α; hepatocyte nuclear factor 1α*); inflammatory adenoma; β-catenin mutated adenoma; and unclassified adenoma.

HFN1α-inactivated adenoma has a low risk of complications when less than 5 cm in size. Its association with the use of oral contraceptives and obesity is lower than in the case of inflammatory adenoma, which is strongly associated. Both subtypes have a higher incidence in females and are the most common subtypes.

Beta-catenin-mutated adenomas are a group of adenomas with mutations in the CTNNB1 (catenin β-1) gene in exon 3 or in exon 7/8. The mutation in exon 3 leads to a high risk of malignancy (up to 40%) and mutation in exon 7/8 means a high risk of bleeding with a lower risk of malignancy. The exon 3 mutation is associated with the use of anabolic steroids and males.[21,22]

A classic systematic review concluded that the signal intensity of the tumour in the HBP had a high diagnostic performance for differentiating FNH from HCA, with a sensitivity of 91–100% and a specificity of 87–100% for the diagnosis of FNH.[23] FNH is the most common disorder presenting with iso- or hyperintensity uptake by the lesion during HBP. However, this feature is not exclusive to FNH and can also be observed in certain HCA subtypes and even in some well-differentiated HCC. For example, up to 83% of mutated β-catenin adenomas show iso- or hyperintensity during HBP.[24]

A more recent systematic review[25] included 410 cases of HCA and found that 14% exhibited iso- or hyperintensity during HBP. When this behaviour was analysed based on pathological subtypes, the percentage varied from 0% of HNF1α-inactivated adenomas to 59% of mutated β-catenin. In inflammatory and unclassified adenomas, the proportion was 14% and 11% respectively. In this same review, the specificity of iso- or hyperintensity of the lesion in the HBP to differentiate FNH from HCA was 89% if all HCA subtypes were included. However, this specificity dropped to 65% if only mutated β-catenin and unclassified subtypes were included. The authors concluded that the high diagnostic yield of iso- or hyperintensity in HBP was due to the low prevalence of these subtypes, especially of mutated β-catenin. This may be a significant problem in clinical practice since, as previously mentioned, the β-catenin subtype mutated in exon 3 is the subtype with the highest risk of malignancy among adenomas.

Therefore, although signal intensity in HBP has traditionally been used as a simple way of differentiating HCA from FNH, most of these studies did not consider adenoma subtypes and these two disorders cannot be differentiated solely by signal intensity in HBP. For precise characterisation, this must be combined with other characteristics, such as the presence of intracellular lipids in the HNF1α-inactivated adenoma, or the marked hyperintensity in T2-weighted images and the atoll sign in the inflammatory adenoma.[22]

Focal nodular hyperplasia-like lesions

Chemotherapy treatments, especially those based on oxaliplatin used in patients with pancreatic or colorectal cancer, can induce the formation of regenerative lesions similar to focal nodular hyperplasia (FNH-like) in the liver. The development of FNH-like lesions and their detection in follow-up studies of patients with gastrointestinal cancer can lead to errors, as they can be confused with metastasis, with the risk of inappropriate treatment changes and even unnecessary invasive procedures. FNH-like lesions have a typical behaviour on MRI, with the presence of enhancement during the arterial phase and hyper- or iso-intensity during the HBP.[26] The presence of a hyperintense ring at the periphery of the regenerative lesion in HBP is also characteristic of up to 50% of oxaliplatin-induced lesions.[27]

In patients with liver disease after Fontan surgery, a flow diversion technique between the inferior vena cava and the pulmonary artery for patients with congenital heart defects, it is common for benign hypervascular regenerative lesions to develop with an appearance similar to FNH. In this context, in addition to the appearance described above, some of these FNH-like lesions may show features typical of HCC, such as washout during the portal phase, which sometimes makes diagnosis difficult.[28,29]

Over 30% of patients with Budd-Chiari syndrome develop FNH-like lesions.[30] Unlike FNH, these lesions may appear hyperintense on T1-weighted images and hypointense on T2-weighted images, when compared with the rest of the liver parenchyma. It is typically common to find arterial enhancement and contrast retention in the lesion during HBP (Fig. 5).[26,30]

Characterisation of focal liver lesions in liver cirrhosis
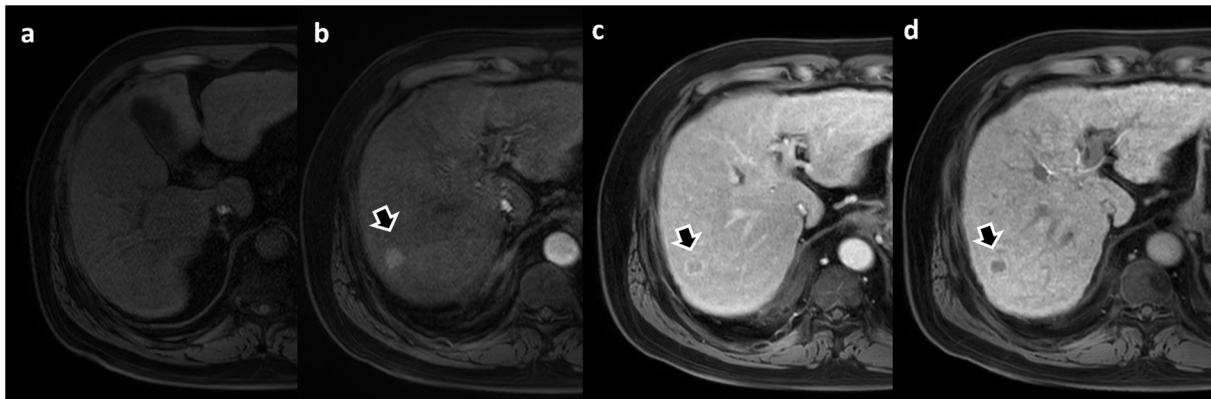
Hepatocellular carcinoma

The vast majority of hepatocellular carcinomas (HCC) develop in patients with liver cirrhosis. The non-invasive diagnosis of this primary liver cancer is accepted in patients with chronic liver disease when specific characteristics are demonstrated in the dynamic behaviour of the lesion after the administration of the contrast medium. According to the European EASL guidelines,[31] a non-invasive diagnosis of HCC can be established when all these criteria are met: nodules larger than 1 cm that show hyperenhancement in the arterial phase; and washout during the portal or equilibrium phase. The LI-RADS v2018[11] criteria allow for the definitive diagnosis of HCC and also include other imaging features such as the presence of pseudocapsules during the portal phase and nodule growth in serial studies (Fig. 6).

Unlike the previous EASL and LI-RADS criteria, in which the presence of hypointensity in the HBP is not considered a major criterion and it differs in the tumour washout, some of the main Asian diagnostic guidelines, such as the KLCA-NCC from South Korea[16] or the JSH-HCC from Japan,[32] consider hypointensity in the HBP as washout, provided it can be ruled out that the session is behaving like a haemangioma, due to its high signal intensity on T2-weighted images, or an intrahepatic cholangiocarcinoma, due to its target appearance on the diffusion-weighted image. This discrepancy between the European/US and Asian guidelines is based on the fact that the diagnostic criteria seek high specificity ör high sensitivity respectively, depending on the incidence of the disease in each region[33] and on the therapeutic approach, liver transplantation or local treatments.[15,34]
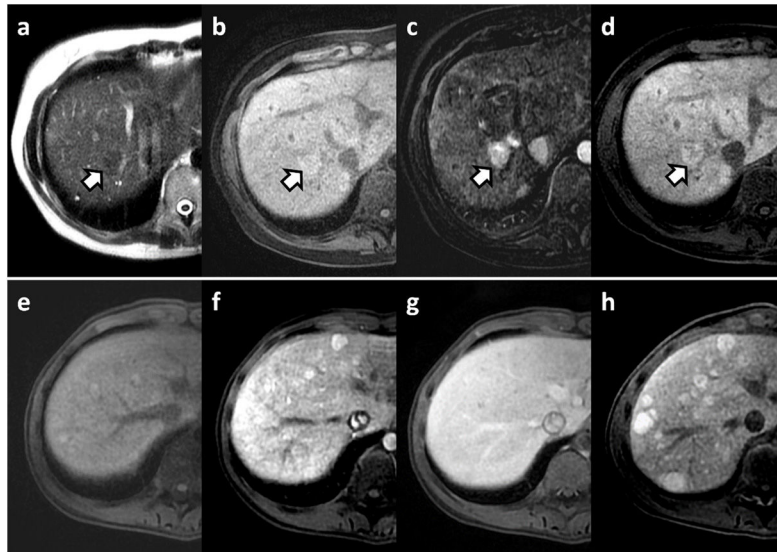
Figure 5 Focal nodular hyperplasia-like (FNH-like) lesions in two different patients. (a) 45-year-old woman with Budd-Chiari syndrome and multiple FNH-like lesions, with Gd-BOPTA. Note the presence of the lesion marked with an arrow, hypointense compared to the rest of the parenchyma in T2-WI sequence (a) and hyperintense in T1 (b). The lesion shows arterial enhancement (c); arterial phase with subtraction) and hyperintensity during HBP (d). (e–g) 23-year-old man with Fontan procedure and liver MRI with Gd-EOB-DPTA. Multiple focal hepatic lesions with FNH-like features may be seen. They show hyperintensity in T1 without IV contrast (e) with enhancement during the arterial phase (f), isointensity during the portal phase (g) and marked hyperintensity during the hepatobiliary phase (h).


Figure 6 Patient with HBV cirrhosis. Dynamic liver MRI with Gd-EOB-DPTA. Focal liver lesion with definitive criteria for hepatocellular carcinoma: presence of enhancement in the arterial phase (b), with washout and pseudocapsule formation during the portal phase (c) and hypointensity during the hepatobiliary phase (d).

The hypointensity of HCC lesions is due to the loss of membrane transporters with cell dedifferentiation. Decreased expression of OATP1B3 is one of the alterations that occur in hepatocarcinogenesis, which is why most HCC appear hypointense in HBP.[35] The LI-RADS criteria consider hypointensity during this phase as an auxiliary criterion suggestive of malignancy, and isointensity or hyperintensity of the lesion during this phase as a criterion that suggests it may be benign. However, we must remember that 9%–14% of HCC can show hyperintensity in the HBP due to over-expression of the OATP8 transporter, with these being well-differentiated HCC with a better prognosis.[36,37]

In recent years, the widespread use of hepatobiliary contrast media has generated a growing interest in hypointense nodules in HBP which do not show enhancement in the arterial phase.[38] It is generally recognised that these lesions may represent early stages of HCC, as during the process of hepatocarcinogenesis, the decreased expression of the OATP8 transporter[37] occurs before the development of the characteristic changes in tumour vascularisation. Adequately identifying and characterising these nodules and their progression to hypervascularised nodules through closer follow-up enables early treatment of HCC.

In a retrospective multicentre study with patients at high risk of developing HCC, nodules ≤ 30 mm which were hypointense on HBP and without enhancement in the arterial phase corresponded in 44% of cases to advanced HCC, in 20% to early HCC, in 28% to high-grade dysplastic nodules, and
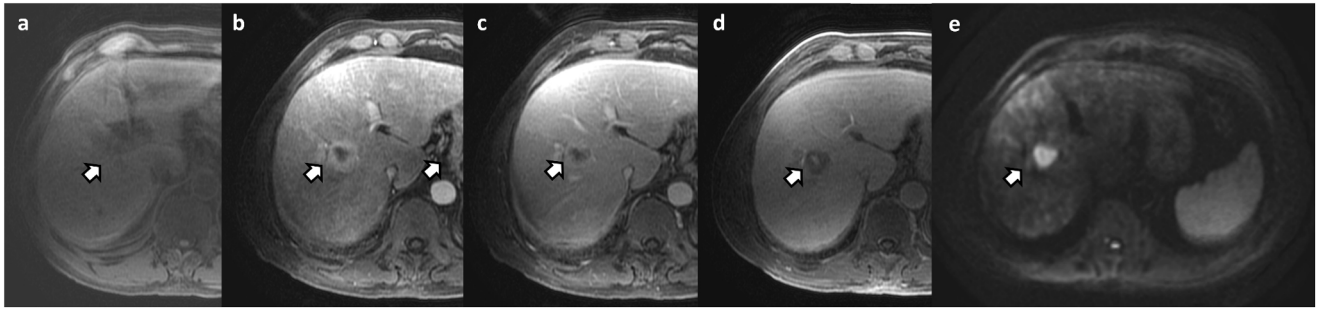
Figure 7 Intrahepatic cholangiocarcinoma in a patient with liver cirrhosis. Liver MRI with Gd-BOPTA (a), without contrast; (b) arterial phase; (c) portal phase; (d) hepatobiliary phase; (e) diffusion with b = 800) showed a lesion with arterial ring enhancement (b) that persisted during the portal phase (c). In the hepatobiliary phase (d), note the hypointensity of most of the lesion with a hyperintense central zone, probably due to contrast retention in the extracellular matrix. Restricted diffusion can also be seen (e). The lesion was biopsied and the diagnosis of intrahepatic cholangiocarcinoma was confirmed.
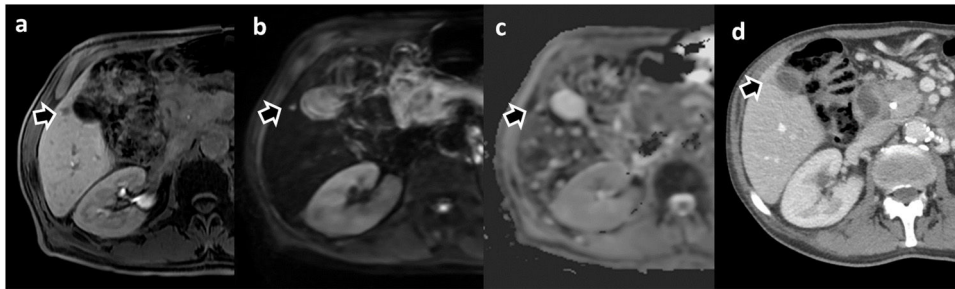
Figure 8 Small liver metastasis in a patient with pancreatic adenocarcinoma detected on liver MRI with Gd-BOPTA. (a) Hepatobiliary phase, (b) Diffusion-weighted sequence (b = 800) and (c) Apparent diffusion coefficient (ADC) map. In a prior CT study performed for local staging (d), the lesion was not detected and is difficult to identify. The metastatic lesion was confirmed by biopsy.

only in 8% to low-grade dysplastic nodules or regenerative nodules.[39] In an attempt to more accurately determine the likelihood of malignancy, predictive factors for hypervascular transformation of these nodules have been described: size > 10 mm; the presence of hyperintensity on T2-weighted images; restriction on diffusion-weighted images; and the existence of a previous HCC.[13]

Intrahepatic cholangiocarcinoma

In patients with cirrhosis, image screening for HCC also enables the detection of intrahepatic cholangiocarcinoma lesions in early stages. Intrahepatic cholangiocarcinoma usually presents as a lesion with peripheral or ring enhancement in images obtained in the arterial phase and with centripetal enhancement in the portal or late phases, although sometimes it is difficult to differentiate between the two conditions in patients with cirrhosis (Fig. 7). In HBP, intrahepatic cholangiocarcinoma has been described to behave as a tumour with a poorly defined central area of greater signal intensity at its edges, called an ËOB-cloud¡, and surrounded by a hypointense margin.[40] However, this behaviour is not common in cholangiocarcinomas on cirrhotic liver.

Other lesions in liver cirrhosis

The International Working Party Classification of Hepatocellular Lesions divides lesions in this context into regenerative and dysplastic/neoplastic.[41] Regenerative lesions include monoacinar regenerative nodules, 1—3 mm in size and consisting of a single portal space, and multiacinar or large regenerative nodules, consisting of more than one portal space. When these lesions are found in liver cirrhosis, they are called monoacinar or multiacinar cirrhotic nodules, respectively.[42] Regenerative nodules associated with liver cirrhosis usually show a signal intensity similar to that of the liver parenchyma in the images obtained in HBP, although occasionally they may appear hyperintense. Within the regenerative lesions, in up to 6% of patients with cirrhosis, so-called HBP-doughnut nodules can be observed. These nodules do not enhance during the arterial phase and correspond to the multiacinar cirrhotic nodules described in histology.[42] Dysplastic nodules are often iso- or hyperintense in HBP due to preserved expression of OATP1B3 transporters. However, up to a third of these high-grade dysplastic nodules may be hypointense in HBP.[35] We see that hypointensity of a nodule in the HBP in the presence of chronic liver disease is a warning sign and criterion for early follow-up.

Detection of liver metastases

Metastases are the most common type of malignant liver tumour.[43] The use of MRI with hepatobiliary contrast media and the acquisition of images in HBP has improved the diagnostic performance in metastasis detection, with a
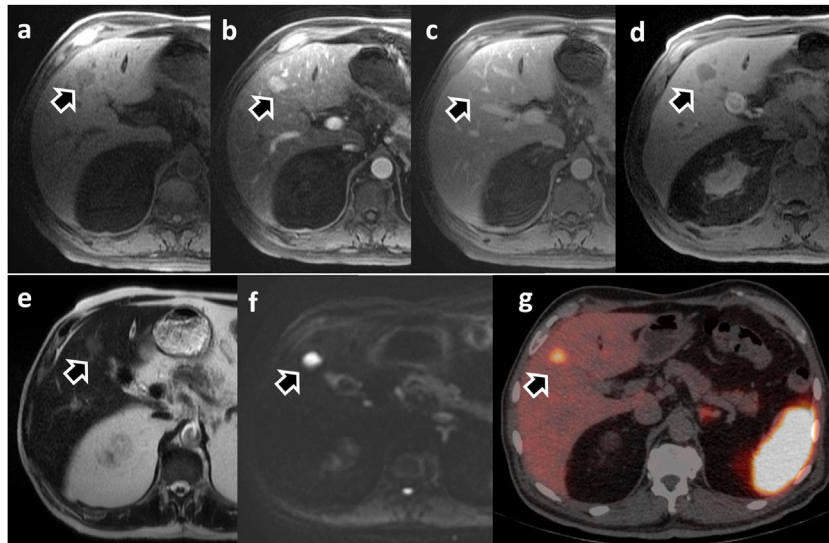
Figure 9 Patient with liver metastasis from ileal neuroendocrine tumour. Dynamic liver MRI with Gd-BOPTA (a–f): a) non-contrast phase; (b) arterial phase; (c) portal phase; (d) hepatobiliary phase; (e) T2-WI; (f) diffusion with b = 800); and PET/CT with Ga-68-DOTATATE (g). The lesion is hypervascular during the arterial phase (b), barely visualised during the portal phase (c), and is markedly hypointense in HBP (d), as well as hyperintense in the diffusion sequence (f). The PET/CT confirmed the presence of somatostatin receptors in the lesion (g).

diagnostic yield superior to CT and MRI with extracellular contrast media (Fig. 8).

The combination of diffusion-weighted and HBP imaging is the best strategy for maximising the detection of metastases. In a meta-analysis that included 39 studies, the combination of diffusion sequencing and HBP obtained the highest sensitivity, with 96% for metastasis detection. The combination improved sensitivity compared to the isolated use of either (87% and 91% respectively).[44] This study showed similar results even for metastases smaller than 1 cm in size. Other studies have compared the use of conventional MRI protocols with full dynamic study versus abbreviated protocols (including T2-weighted, diffusion-weighted and HBP images) for the detection of metastases in colorectal cancer, and obtained similar metastasis detection rates with both protocols.[45]

In the investigation of liver metastases from neuroendocrine tumours, the combination of HBP and the diffusion sequence also had the highest detection rate compared to the rest of the sequence combinations and showed sensitivity and specificity of 86% and 94% respectively.[46] In the same study, this combination was statistically significant in showing the highest interobserver agreement. Another study showed that the HBP sequence had the highest contrast/noise ratio for the detection of liver metastases from neuroendocrine tumours.[47] These studies suggest using hepatobiliary contrasts in the assessment of patients with suspected metastasis from neuroendocrine tumours (Fig. 9).

Most liver metastases are hypointense in HBP due to the absence of hepatocytes and membrane transporters. However, some lesions, mainly adenocarcinoma metastases, show a relatively hyperintense central zone during HBP, which has the same cloud enhancement behaviour as that observed in cholangiocarcinoma. This uptake is probably due to the accumulation of contrast in the extracellular matrix with fibrosis or its diffusion in the area of central necrosis.[36]

Assessment of the biliary tract and liver function

Obtaining images during biliary excretion of hepatobiliary contrast enables a detailed study of the biliary tree, both for preoperative assessment in procedures considered complex and to demonstrate the presence of bile leaks, even from small branches.

In the assessment of living liver donors for liver transplantation, the addition of 3D T1-weighted cholangiogram sequences after hepatobiliary contrast administration improved visualisation of second-order bile ducts and increased diagnostic confidence in the assessment of biliary anatomy compared with T2-weighted MR-cholangiogram sequences.[48]

Bile leak is one of the main complications of liver surgery, and occurs with an incidence of 4–10%. It causes an increase in morbidity with prolonged hospital stay and an increased mortality rate.[49] In a study evaluating hepatobiliary contrast-enhanced MR cholangiography in patients with bile leaks lasting more than one week, 100% accuracy was achieved in detection and localisation.[49] This avoided the need for invasive direct cholangiography and identified peripheral leaks amenable to conservative treatment.

In our experience, in patients strongly suspected of having bile leak who also have perihepatic collections, it is advisable to perform an MR cholangiogram, acquiring the images later than the usual HBP, as sometimes the excretion is slowed and the leaks may go undetected in the early stages of biliary excretion (Fig. 10).

The degree of liver enhancement is directly related to the mass of functioning hepatocytes and their efficiency in incorporating the contrast medium. Areas of the liver with reduced function or damaged hepatocytes will show less enhancement. This differential behaviour makes it possible to assess liver function. HBP MRI has become integrated

Figure 10 62-year-old patient with collection detected on ultrasound after cholecystectomy. Dynamic liver study with Gd-EOB-DPTA. Top row: (a) without contrast; (b) arterial phase; (c) portal phase; (d) late phase; (e) transition phase. Bottom row: sequential uptakes during the hepatobiliary phase and additional uptakes that allow the identification of extravasation of the contrast material (arrows) towards the collection in the images at minutes 26, 30 and 40.

into clinical practice and offers an excellent non-invasive method for assessing liver function. Several studies have shown that the combination of radiomics and clinical variables with deep learning models can effectively stratify hepatic functional reserve in patients with liver disease.[50,51]

Conclusions

Hepatobiliary contrast media enable better detection and characterisation of focal liver lesions in most clinical situations, both in cancer patients, patients with chronic liver disease and patients with lesions likely to be of hepatocellular origin. In addition, they facilitate the assessment of bile duct lesions and of the functional capacity of the liver parenchyma, which significantly increases confidence and safety in the diagnosis.

Authorship

1. Responsible for the integrity of the study: APG, JML and LMB.
2. Study conception: not applicable.
3. Study design: not applicable.
4. Data collection: not applicable.
5. Data analysis and interpretation: not applicable
6. Statistical processing: not applicable
7. Literature search: APG, JML and LMB.
8. Drafting of the article: APG, JML and LMB.
9. Critical review of the manuscript with intellectually relevant contributions: APG, JML and LMB.
10. Approval of the final version: APG, JML and LMB.

Conflicts of interest

The authors declare that they have no conflicts of interest.

References

1. Koh D-M. Liver-specific contrast agents. Cancer Imaging. 2012;12:363–4, http://dx.doi.org/10.1102/1470-7330.2012.9022.
2. Bellin MF, Vasile M, Morel-Precetti S. Currently used non-specific extracellular MR contrast media. Eur Radiol. 2003;13:2688–98, http://dx.doi.org/10.1007/s00330-003-1912-x.
3. Weinreb JC, Rodby RA, Yee J, Wang CL, Fine D, McDonald RJ, et al. Use of intravenous gadolinium-based contrast media in patients with kidney disease: Consensus Statements from the American College of Radiology and the National Kidney Foundation. Radiology. 2021;298:28–35, http://dx.doi.org/10.1148/radiol.2020202903.
4. Kambadakone AR, Fung A, Gupta RT, Hope TA, Fowler KJ, Lyshchik A, et al. LI-RADS technical requirements for CT, MRI, and contrast-enhanced ultrasound. Abdom Radiol. 2018;43:56–74, http://dx.doi.org/10.1007/s00261-017-1325-y.
5. Cannella R, Zins M, Brancatelli G. ESR Essentials: diagnosis of hepatocellular carcinoma-practice recommendations by ESGAR. Eur Radiol. 2024;34:2127–39, http://dx.doi.org/10.1007/s00330-024-10606-w.
6. Van Beers BE, Pastor CM, Hussain HK. Primovist, Eovist: what to expect? J Hepatol. 2012;57:421–9, http://dx.doi.org/10.1016/j.jhep.2012.01.031.
7. van Montfoort JE, Stieger B, Meijer DK, Weinmann HJ, Meier PJ, Fattinger KE. Hepatic uptake of the magnetic resonance imaging contrast agent gadoxetate by the organic anion transporting polypeptide Oatp1. J Pharmacol Exp Ther. 1999;290:153–7.
8. Daire J-L, Leporq B, Vilgrain V, Van Beers BE, Schmidt S, Pastor CM. Liver perfusion modifies Gd-DTPA and Gd-BOPTA hepatocyte concentrations through transfer clearances across sinusoidal membranes. Eur J Drug Metab Pharmacokinet. 2017;42:657–67, http://dx.doi.org/10.1007/s13318-016-0382-x.
9. Hao D, Ai T, Goerner F, Hu X, Runge VM, Tweedle M. MRI contrast agents: basic chemistry and safety. J Magn Reson Imaging. 2012;36:1060–71, http://dx.doi.org/10.1002/jmri.23725.

10. Canellas R, Patel MJ, Agarwal S, Sahani DV. Lesion detection performance of an abbreviated gadoxetic acid-enhanced MRI protocol for colorectal liver metastasis surveillance. Eur Radiol. 2019;29:5852–60, http://dx.doi.org/10.1007/s00330-019-06113-y.

11. Chernyak V, Santillan CS, Papadatos D, Sirlin CB. LI-RADS® algorithm: CT and MRI. Abdom Radiol (NY). 2018;43:111–26, http://dx.doi.org/10.1007/s00261-017-1228-y.

12. Neri E, Bali MA, Ba-Ssalamah A, Boraschi P, Brancatelli G, Alves FC, et al. ESGAR consensus statement on liver MR imaging and clinical use of liver-specific contrast agents. Eur Radiol. 2016;26:921–31, http://dx.doi.org/10.1007/s00330-015-3900-3.

13. Kim DW, Choi SH, Park T, Kim SY, Lee SS, Byun JH. Transient severe motion artifact on arterial phase in gadoxetic acid-enhanced liver magnetic resonance imaging: a systematic review and meta-analysis. Invest Radiol. 2022;57:62–70, http://dx.doi.org/10.1097/RLI.0000000000000806.

14. Jang EB, Kim DW, Choi SH, Hong SB, Park T, Ko Y, et al. Transient severe motion artifacts on gadoxetic acid-enhanced MRI: risk factor analysis in 2230 patients. Eur Radiol. 2022;32:8629–38, http://dx.doi.org/10.1007/s00330-022-08885-2.

15. Koh D-M, Ba-Ssalamah A, Brancatelli G, Fananapazir G, Fiel MI, Goshima S, et al. Consensus report from the 9th International Forum for Liver Magnetic Resonance Imaging: applications of gadoxetic acid-enhanced imaging. Eur Radiol. 2021;31:5615–28, http://dx.doi.org/10.1007/s00330-020-07637-4.

16. 2022 KLCA-NCC Korea practice guidelines for the management of hepatocellular carcinoma. Clin Mol Hepatol. 2022;28:583–705, http://dx.doi.org/10.3350/cmh.2022.0294.

17. Kalor A, Girometti R, Maheshwari E, Kierans AS, Pugliesi RA, Buros C, et al. Update on MR contrast agents for liver imaging: what to use and when. Radiol Clin North Am. 2022;60:679–94, http://dx.doi.org/10.1016/j.rcl.2022.04.005.

18. Hui CL, Mautone M. Patterns of enhancement in the hepatobiliary phase of gadoxetic acid-enhanced MRI. Br J Radiol. 2020;93:20190989, http://dx.doi.org/10.1259/bjr.20190989.

19. Poetter-Lang S, Bastati N, Messner A, Kristic A, Herold A, Hodge JC, et al. Quantification of liver function using gadoxetic acid-enhanced MRI. Abdom Radiol (NY). 2020;45:3532–44, http://dx.doi.org/10.1007/s00261-020-02779-x.

20. Bastati N, Wibmer A, Tamandl D, Einspieler H, Hodge JC, Poetter-Lang S, et al. Assessment of orthotopic liver transplant graft survival on gadoxetic acid-enhanced magnetic resonance imaging using qualitative and quantitative parameters. Invest Radiol. 2016;51:728–34, http://dx.doi.org/10.1097/RLI.0000000000000286.

21. Nault J-C, Couchy G, Balabaud C, Morcrette G, Caruso S, Blanc J-F, et al. Molecular classification of hepatocellular adenoma associates with risk factors, bleeding, and malignant transformation. Gastroenterology. 2017;152:880–94.e6, http://dx.doi.org/10.1053/j.gastro.2016.11.042.

22. Tse JR, Felker ER, Naini BV, Shen L, Shen J, Lu DSK, et al. Hepatocellular adenomas: molecular basis and multimodality imaging update. Radiographics. 2023;43:e220134, http://dx.doi.org/10.1148/rg.220134.

23. McInnes MDF, Hibbert RM, Inácio JR, Schieda N. Focal nodular hyperplasia and hepatocellular adenoma: accuracy of gadoxetic acid-enhanced MR imaging—a systematic review. Radiology. 2015;277:413–23, http://dx.doi.org/10.1148/radiol.2015142986.

24. Ba-Ssalamah A, Antunes C, Feier D, Bastati N, Hodge JC, Stift J, et al. Morphologic and molecular features of hepatocellular adenoma with gadoxetic acid-enhanced MR imaging. Radiology. 2015;277:104–13, http://dx.doi.org/10.1148/radiol.2015142366.

25. Kim T-H, Woo S, Ebrahimzadeh S, McInnes MDF, Gerst SR, Do RK. Hepatic adenoma subtypes on hepatobiliary phase of gadoxetic acid-enhanced MRI: systematic review and meta-analysis. AJR Am J Roentgenol. 2023;220:28–38, http://dx.doi.org/10.2214/AJR.22.27989.

26. LeGout JD, Bolan CW, Bowman AW, Caserta MP, Chen FK, Cox KL, et al. Focal nodular hyperplasia and focal nodular hyperplasia-like lesions. Radiographics. 2022;42:1043–61, http://dx.doi.org/10.1148/rg.210156.

27. Furlan A, Brancatelli G, Dioguardi Burgio M, Grazioli L, Lee JM, Murmura E, et al. Focal nodular hyperplasia after treatment with oxaliplatin: a multiinstitutional series of cases diagnosed at MRI. AJR Am J Roentgenol. 2018;210:775–9, http://dx.doi.org/10.2214/AJR.17.18867.

28. Wells ML, Hough DM, Fidler JL, Kamath PS, Poterucha JT, Venkatesh SK. Benign nodules in post-Fontan livers can show imaging features considered diagnostic for hepatocellular carcinoma. Abdom Radiol (NY). 2017;42:2623–31, http://dx.doi.org/10.1007/s00261-017-1181-9.

29. Yang HK, Jang H-J, Khalili K, Wald RM, Yoo S-J, Kim TK. CT and MR imaging findings of the livers in adults with Fontan palliation: an observational study. Abdom Radiol. 2020;45:188–202, http://dx.doi.org/10.1007/s00261-019-02119-8.

30. Vilgrain V, Lewin M, Vons C, Denys A, Valla D, Flejou JF, et al. Hepatic nodules in Budd-Chiari syndrome: imaging features. Radiology. 1999;210:443–50, http://dx.doi.org/10.1148/radiology.210.2.r99fe13443.

31. Galle PR, Forner A, Llovet JM, Mazzaferro V, Piscaglia F, Raoul J-L, et al. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. J Hepatol. 2018;69:182–236, http://dx.doi.org/10.1016/j.jhep.2018.03.019.

32. Hasegawa K, Takemura N, Yamashita T, Watadani T, Kaibori M, Kubo S, et al. Clinical Practice Guidelines for Hepatocellular Carcinoma: The Japan Society of Hepatology 2021 version (5th JSH-HCC Guidelines). Hepatol Res. 2023;53:383–90, http://dx.doi.org/10.1111/hepr.13892.

33. Choo SP, Tan WL, Goh BKP, Tai WM, Zhu AX. Comparison of hepatocellular carcinoma in Eastern versus Western populations. Cancer. 2016;122:3430–46, http://dx.doi.org/10.1002/cncr.30237.

34. Kim T-H, Kim SY, Tang A, Lee JM. Comparison of international guidelines for noninvasive diagnosis of hepatocellular carcinoma: 2018 update. Clin Mol Hepatol. 2019;25:245–63, http://dx.doi.org/10.3350/cmh.2018.0090.

35. Kitao A, Matsui O, Yoneda N, Kozaka K, Shinmura R, Koda W, et al. The uptake transporter OATP8 expression decreases during multistep hepatocarcinogenesis: correlation with gadoxetic acid enhanced MR imaging. Eur Radiol. 2011;21:2056–66, http://dx.doi.org/10.1007/s00330-011-2165-8.

36. Vernuccio F, Gagliano DS, Cannella R, Ba-Ssalamah A, Tang A, Brancatelli G. Spectrum of liver lesions hyperintense on hepatobiliary phase: an approach by clinical setting. Insights Imaging. 2021;12:8, http://dx.doi.org/10.1186/s13244-020-00928-w.

37. Kim JY, Kim M-J, Kim KA, Jeong HT, Park YN. Hyperintense HCC on hepatobiliary phase images of gadoxetic acid-enhanced MRI: correlation with clinical and pathological features. Eur J Radiol. 2012;81:3877–82, http://dx.doi.org/10.1016/j.ejrad.2012.07.021.

38. Brandi N, Renzulli M. Liver lesions at risk of transformation into hepatocellular carcinoma in cirrhotic patients: hepatobiliary phase hypointense nodules without arterial phase hyperenhancement. J Clin Transl Hepatol. 2024;12:100–12, http://dx.doi.org/10.14218/JCTH.2023.00130.

39. Joo I, Kim SY, Kang TW, Kim YK, Park BJ, Lee YJ, et al. Radiologic-pathologic correlation of hepatobiliary phase hypointense nodules without arterial phase hyperenhancement at gadoxetic acid-enhanced mri: a multicen-

ter study. Radiology. 2020;296:335–45, http://dx.doi.org/10.1148/radiol.2020192275.

40. Kim SH, Lee CH, Kim BH, Kim WB, Yeom SK, Kim KA, et al. Typical and atypical imaging findings of intrahepatic cholangiocarcinoma using gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid–enhanced magnetic resonance imaging. J Comput Assist Tomogr. 2012;36:704, http://dx.doi.org/10.1097/RCT.0b013e3182706562.

41. International Working Party. Terminology of nodular hepatocellular lesions. Hepatology. 1995;22:983–93, http://dx.doi.org/10.1016/0270-9139(95)90324-0.

42. Kozaka K, Kobayashi S, Yoneda N, Kitao A, Yoshida K, Inoue D, et al. Doughnut-like hyperintense nodules on hepatobiliary phase without arterial-phase hyperenhancement in cirrhotic liver: imaging and clinicopathological features. Eur Radiol. 2019;29:6489–98, http://dx.doi.org/10.1007/s00330-019-06329-y.

43. Kaur H, Hindman NM, Al-Refaie WB, Arif-Tiwari H, Cash BD, Chernyak V, et al. ACR Appropriateness Criteria® Suspected Liver Metastases. J Am Coll Radiol. 2017;14:S314–25, http://dx.doi.org/10.1016/j.jacr.2017.01.037.

44. Vilgrain V, Esvan M, Ronot M, Caumont-Prim A, Aubé C, Chatellier G. A meta-analysis of diffusion-weighted and gadoxetic acid-enhanced MR imaging for the detection of liver metastases. Eur Radiol. 2016;26:4595–615, http://dx.doi.org/10.1007/s00330-016-4250-5.

45. Ghorra C, Pommier R, Piveteau A, Rubbia-Brandt L, Vilgrain V, Terraz S, et al. The diagnostic performance of a simulated ''short'' gadoxetic acid-enhanced MRI protocol is similar to that of a conventional protocol for the detection of colorectal liver metastases. Eur Radiol. 2021;31:2451–60, http://dx.doi.org/10.1007/s00330-020-07344-0.

46. Hayoz R, Vietti-Violi N, Duran R, Knebel J-F, Ledoux J-B, Dromain C. The combination of hepatobiliary phase with Gd-EOB-DTPA and DWI is highly accurate for the detection and characterization of liver metastases from neuroendocrine tumor. Eur Radiol. 2020;30:6593–602, http://dx.doi.org/10.1007/s00330-020-06930-6.

47. Morse B, Jeong D, Thomas K, Diallo D, Strosberg JR. Magnetic resonance imaging of neuroendocrine tumor hepatic metastases: does hepatobiliary phase imaging improve lesion conspicuity and interobserver agreement of lesion measurements? Pancreas. 2017;46:1219–24, http://dx.doi.org/10.1097/MPA.0000000000000920.

48. Cai L, Yeh BM, Westphalen AC, Roberts J, Wang ZJ. 3D T2-weighted and Gd-EOB-DTPA-enhanced 3D T1-weighted MR cholangiography for evaluation of biliary anatomy in living liver donors. Abdom Radiol (NY). 2017;42:842–50, http://dx.doi.org/10.1007/s00261-016-0936-z.

49. Citterio D, Vaiani M, Sposito C, Rossi RE, Flores M, Battiston C, et al. Improved management of grade B biliary leaks after complex liver resections using gadoxetic acid disodium-enhanced magnetic resonance cholangiography. Surgery. 2021;170:499–506, http://dx.doi.org/10.1016/j.surg.2021.02.018.

50. Hu J, Wang X, Prince M, Wang F, Sun J, Yang X, et al. Gd-EOB-DTPA enhanced MRI based radiomics combined with clinical variables in stratifying hepatic functional reserve in HBV infected patients. Abdom Radiol (NY). 2024;49:1051–62, http://dx.doi.org/10.1007/s00261-023-04176-6.

51. Park HJ, Yoon JS, Lee SS, Suk H-I, Park B, Sung YS, et al. Deep learning-based assessment of functional liver capacity using gadoxetic acid-enhanced hepatobiliary phase MRI. Korean J Radiol. 2022;23:720–31, http://dx.doi.org/10.3348/kjr.2021.0892.