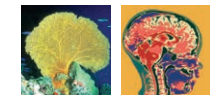
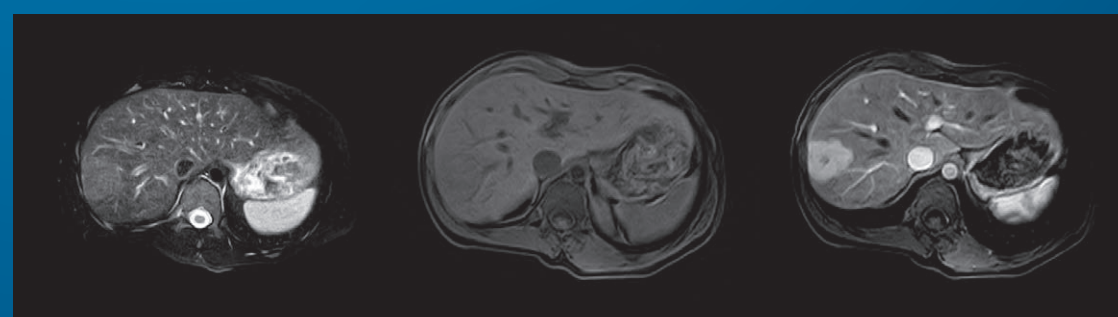


DOTAREM®

Gadoteric acid

Liver imaging



- Dr. Onorina Bruno,
- Pr. Bernard Van Beers,
- Pr. Valérie Vilgrain,
Hôpital Beaujon, Clichy, France

Guerbet

Contrast for Life

References

- Keogan MT, Edelman RR. Technologic advances in abdominal MR imaging. Radiology 2001;220:310-320.
- Semelka RC, Martin DR, Balci NC. Magnetic resonance imaging of the liver: how I do it. J Gastroenterol Hepatol 2006;21:632-637.
- Ito K, Mitchell DG, Matsunaga N. MR imaging of the liver: techniques and clinical applications. Eur J Radiol 1999;32:2-14.
- Scheffler K, Lehnhardt S. Principles and applications of balanced SSFP techniques. Eur Radiol 2003;13:2409-2418.
- Yu JS, Park JG, Jeong EK, Park MS, Kim KW. Hepatic MRI using the double-echo chemical shift phase-selective gradient-echo technique. AJR Am J Roentgenol 2007;188:W49-56.
- Merkle EM, Nelson RC. Dual gradient-echo in-phase and opposed-phase hepatic MR imaging: a useful tool for evaluating more than fatty infiltration or fatty sparing. Radiographics 2006;26:1409-1418.
- Koh DM, Collins DJ. Diffusion-weighted MRI in the body: applications and challenges in oncology. AJR Am J Roentgenol 2007;188:1622–1635.
- Banner R. Basic principles of diffusion-weighted imaging. Eur J Radiol 2003;45:169-184.
- Taouli B, Koh DM. Diffusion-weighted MR imaging of the liver. Radiology 2010;254:47-66.
- Parikh T, Drew SJ, Lee VS, et al. Focal liver lesion detection and characterization with diffusion-weighted MR imaging: comparison with standard breath-hold T2-weighted imaging. Radiology 2008;246:812-822.
- Gandhi SN, Brown MA, Wong JG, Aguirre DA, Sirlin CB. MR contrast agents for liver imaging: what, when, how. Radiographics 2006;26:1621-1636.
- Bellin MF, Van Der Molen AJ. Extracellular gadolinium-based contrast media: an overview. Eur J Radiol 2008;66:160-167.
- Silva AC, Evans JM, McCullough AE, et al. MR imaging of hypervascular liver masses: a review of current techniques. Radiographics 2009;29:385-402.
- Hussain SM, Zondervan PE, Jzermans JN, Schalm SW, de Man RA, Krestin GP. Benign versus malignant hepatic nodules: MR imaging findings with pathologic correlation. Radiographics 2002;22:1023-1036.
- Mortele KJ, Ros PR. Benign liver neoplasms.Clin Liver Dis 2002;6:119-145.
- Hussain SM, Terkivatan T, Zondervan PE, Lanjouw E, de Rave S, Ijzermans JN, de Man RA. Radiographics 2004;24:3-17.
- Dokmak S, Paradis V, Vilgrain V et al. A single-center surgical experience of 122 patients with single and multiple hepatocellular adenomas. Gastroenterology 2009;137:1698-1705.
- Paradis V, Champault A, Ronot M, et al. Telangiectatic adenoma: an entity associated with increased body mass index and inflammation. Hepatology. 2007;46:140-146.
- Grazioli L, Federle MP, Brancatelli G, Ichikawa T, Olivetti L, Blachar A. Hepatic adenomas: imaging and pathologic findings. RadioGraphics 2001; 21:877-892.
- Taouli B, Losada M, Holland A, Krinsky G. Magnetic resonance imaging of hepatocellular carcinoma. Gastroenterology 2004;127:S144-152.
- Sainani NI, Catalano OA, Holalkere NS, Zhu AX, Hahn PF, Sahani DV. Cholangiocarcinoma: current and novel imaging techniques. Radiographics 2008;28:1263-1287
- Danet IM, Semelka RC, Leonardou P, et al. Spectrum of MRI appearances of untreated metastases of the liver. AJR Am J Roentgenol 2003;181:809-817.
- Kanematsu M, Kondo H, Goshima S, et al. Imaging liver metastases: review and update. Eur J Radiol. 2006;58:217-228.

Contents

Introduction

Recent technical advances in imaging hardware and pulse sequence design increase the role of magnetic resonance (MR) imaging in evaluation of the liver, allowing the acquisition of MR images with an excellent anatomic detail largely free of artifacts in a reduced image acquisition time.

Clinical MR imaging sequences for hepatic imaging continue to evolve at a fast rate. Still, the basic demands for MR imaging of the liver are the following: to improve parenchymal contrast, to suppress respiratory motion artifact, and to ensure complete anatomic coverage.

Lesion enhancement after intravenous administration of chelates of gadolinium is essential for characterization of focal liver lesions, improving the sensitivity, specificity, and accuracy of MR imaging of the liver.

MR imaging also permits exquisite hepatic tumor detection, especially for the detection of metastases with diffusion-weighted imaging (DWI).

Therefore MR imaging has emerged as the method of choice in the diagnostic workup of focal liver lesions, in particular at the pretherapeutic stage.

Scanning technique

HARDWARE and SOFTWARE High field strength (3 Tesla) significantly improves signal-to-noise ratio in fast sequences. Scanner hardware developments such as high performance gradient coils, multi transmit radiofrequency, and phased-array coils as well as evolution of softwares have increased the performance of diagnostic techniques for liver disease. Images of the liver are obtained using dedicated phased-array coils that significantly improve the signal-to-noise ratio, allowing faster and higher resolution sequences. High performance gradient coils enable to use sequences as fast gradient echo (GRE), fast spin-echo (FSE), single shot FSE (SSFSE) and echo-planar imaging (EPI).

All T1-weighted sequences are breath-hold sequences allowing reduction of most image artifacts including respiratory motion.

T2-weighted sequences are performed either breath-hold or with respiratory gating and with 2D or 3D acquisition depending of vendors.

Parallel imaging comprises a set of techniques (ex. sensitivity encoding SENSE) in which half or fewer of the usual number of lines of k-space are sampled while simultaneously preserving spatial resolution and have the ability to reduce acquisition times by half or more.

A great variety of pulse sequences for MR imaging are now available to study the liver. Our routine MR imaging protocol commonly includes respiratory-triggered turbo-spin-echo T2-weighted, breath-hold single-shot T2-weighted, in- and opposed-phase T1-weighted gradient-echo, diffusion-weighted single shot spin-echo echo-planar and breath-hold fat-suppressed 3D T1-weighted sequences before and after intravenous administration of chelates of gadolinium. The entire study can be completed within 30 minutes.

Unenhanced MRI

Non-contrast enhanced T1-weighted imaging provide information on the presence of subacute blood, concentrated protein, and/or fat in tissues.

The underlying principle of T1-weighted imaging is to use the shortest possible TE in order to maximize hepatic contrast as well as the number of sections attainable during a breath-hold examination.

Non-contrast enhanced T1-weighted MR imaging study is commonly obtained by two or three-dimensional spoiled gradient-echo sequence with frequency- selective fat-saturation. Images are acquired in a single breath-hold in cooperative patients, removing artifacts secondary to bowel peristalsis or respiratory motion. Gradient-echo sequences are also used to obtain in- and opposed-phase images (chemical shift imaging).

In- and opposed-phase imaging

T1-weighted gradient-echo in-phase and opposed-phase sequences are useful for demonstrating tissue in which mixtures of fat and water protons are present within the same voxel.

Fat and water protons have different resonance frequencies. Depending on echo time used, images may be acquired when fat and water protons are resonating either in-phase or 180 degrees opposed-phase with respect to each other. In voxels containing a mixture of fat and water, the signal generated from fat and water protons is additive when the tissue is imaged in phase, and mutually destructive when the tissue is imaged on opposed- phase. Areas of focal or diffuse fat loose signal on opposed- phase images compared to in-phase images.The boundaries between tissues with different water or fat content appear black on opposed-phase images, an artifact known as India ink or chemical shift artifact of the second kind.

Opposed-phase imaging is therefore extremely useful for detecting focal or diffuse fatty infiltration and identifying lesions containing fat. In-phase and opposed-phase images are obtained in a single breath-hold as a double-echo acquisition, reducing or eliminating misregistration artifacts. This sequence is also helpful in detecting liver iron owing to the double-echo approach, such as hemochromatosis or hemosiderosis.

T2-weighted imaging

T2-weighted sequences provide information about the presence of increased fluid, fibrosis, and/or iron deposition in tissues. Therefore, T2-weighted images are useful for detection of focal hepatic lesions that are mostly hyperintense relative to the surrounding liver parenchyma. Excellent contrast between tissues and fluids is observed on fast spin-echo images, but the contrast between solid tumors and liver is low because of magnetisation transfer effects related to the multiple 180° pulses. On single-shot fast spin-echo images obtained with a long TE, only the signal of fluids is retained, a property that is used for performing MR cholangiography. Rapid T2-weighted single-shot echo-planar acquisition enables T2-weighted imaging with better tumor-to-liver contrast than fast spin-echo imaging.

Balanced steady-state free-precession sequences

Balanced steady-state free-precession sequences (FIESTA, true FISP or balanced FFE) are based on a gradient-echo sequence with a steady state developing for transverse and longitudinal magnetization, as well as a chosen TR that is shorter than hepatic T1 and T2 relaxivity parameters. Images show mixed image weightings, usually with T2* over T1 MR image characteristics. A major advantage of this sequence type is its insensitivity to motion artifacts. This sequence is mainly used as a bright blood technique.

Scanning technique

Fat suppression techniques

Most MRI sequences benefit from fat saturation, which improves conspicuity of solid liver lesions and reduces ghosting artifact from abdominal fat, particularly in respiratory-triggered and echo-planar sequences. Different techniques are available to achieve fat signal saturation. The most common is spectral fat saturation, in which a frequency fat-selective excitation pulse is applied to the whole volume before the imaging sequence to saturate the signal from fat. Therefore only water spins contribute to the signal in the imaging sequence. This sequence is commonly used in clinical practice. The second method is an inversion recovery technique, which employs an inversion pulse and an optimal inversion time delay to null the signal of fat. This technique is not lipid-specific because it can also suppress signal of non fatty tissue with similar T1 behaviour. Inversion recovery sequences offer improved fat saturation in the setting of poor magnetic field homogeneity or magnetic susceptibility artifact. The third method is known as water-excitation, which uses selective spectral and spatial saturation composite pulses to obtain a selective excitation of water protons at any location, while lipid spins do not generate any signal. This sequence is commonly used in clinical practice. Fat suppression can also be obtained by adding an in-phase and an opposed-phase image. For example, this method is used in a sequence known as iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL).

Diffusion-weighted imaging

Diffusion is a physical process that results from the thermally driven, random motion of water molecules. Diffusion-weighted MR imaging is a MR imaging technique that derives its image contrast on the basis of differences in the mobility of water molecules between tissues. It enables differentiation between tissues that are highly cellular such as tumors where the water diffusion is restricted, and cystic or necrotic tissues where the water diffusion is less restricted. Single shot spin-echo echo-planar imaging is the most frequently used sequence for DWI. Diffusion sensitizing gradients are symmetricaly applied on either side of the 180° refocusing pulse. The b value depends on the gradient amplitude, the gradient diffusion length, and the time between the two pulses. Small b values (< 100 sec/mm^2) are helpful for lesion detection whereas long b values (up to 1000 sec/mm^2) are interesting for tissue characterization. To eliminate the impact of T1, T2, TR, and TE, apparent diffusion coefficient (ADC) maps can be calculated to obtain pure diffusion information. ADC maps are calculated for each pixel with at least two diffusion-weighted imaging data sets with different b values (ideally two b values ≥ 150 sec/mm^2 to avoid the perfusion effects). DWI should be part of routine MR examination for focal liver lesions. This sequence is very useful in the detection of both benign and malignant hepatic lesions, and might be superior to T2-weighted imaging.

Contrast enhanced dynamic MRI

Contrast enhanced T1-weighted imaging

Contrast enhanced imaging significantly increases the diagnostic confidence of MR imaging for the detection and characterization of focal liver lesions and the assessment of the liver vasculature .

Breath-hold 2D or 3D T1-weighted spoiled gradient-echo sequences are used for multiphase image acquisition after gadolinium administration.

Compared with a two-dimensional GRE imaging approach, the 3D method provides several advantages. 3D T1-weighted spoiled gradient-echo sequence with an intravenously administered contrast agent permits the acquisition of a volumetric data set of thinner sections (1–3-mm) with contiguous slices and near-isotropic pixel size (≤2.3 mm), enabling images post-processing into different imaging planes, allowing greater accuracy in diagnosis of small hepatic tumors. The combination of high-resolution isotropic pixels and accurate timing also permits angiographic reconstructions of the 3D images, producing MR angiography and venography that can be useful in therapeutic planning.

DotaremⓇ (gadoterate meglumine, Gd-DOTA) is a highly paramagnetic ionic MRI contrast agent with extracellular distribution which shortens T1, T2 and T2* relaxation time. This effect produces signal enhancement on T1-weighted MR images. Extracellular contrast agents such as **DotaremⓇ** can be bolus injected because of their low rate of side effects and excellent safety profile in patients with normal and degraded renal function.

The recommended dose of gadolinium chelate for liver imaging is 0.1 mmol/kg of body weight, or 0.2 mL/kg. A dose of 15-20 mL is effective in nearly all adults for liver imaging. Due to its rapid redistribution from the intravascular compartment to the extracellular space, the contrast agent must be administered as a rapid bolus typically at 2mL/sec. At least three sets of dynamic images of the liver are obtained during the arterial, portal venous, and equilibrium phases of contrast enhancement. The sequences should be bolus-triggered, especially for the assessment of hypervascular liver lesions such as hepatocellular carcinomas.

Timing of the arterial phase images is critical for lesion characterization. Specifically, the acquisition should be done in the hepatic arterial phase of extracellular contrast enhancement, when the portal vein is only slightly enhanced. Demonstration of contrast medium in hepatic arteries and in the portal vein and absence of contrast medium in the hepatic veins are reliable landmarks of an optimal arterial phase.

Typically, maximal enhancement of the hepatic parenchyma is seen in the portal-venous phase. In this phase, the hepatic parenchyma is maximally enhanced so that hypovascular lesions, such as cysts, hypovascular metastases and scar tissue, are most clearly shown as hypointense lesions. Patency or thrombosis of portal vessels is also best shown during this phase. The delayed phase is acquired 3 to 5 min after the initiation of contrast injection. In this phase, focal liver lesions display several features that contribute to lesion characterization, including persistent absence of enhancement of cysts, centripetal progression of enhancement in hemangiomas, homogeneous fading of enhancement of adenomas and focal nodular hyperplasia to near isointensity with surrounding liver parenchyma, late enhancement of central scars in focal nodular hyperplasia, heterogeneous wash-out of contrast in liver metastases, complete wash-out in small liver metastases and hepatocellular carcinoma, and delayed capsule enhancement in hepatocellular carcinoma.

Focal liver lesions

MR imaging provides information concerning the soft tissue characteristics as well as the vascularisation of the lesions using a variety of different MR sequences coupled with dynamic contrast enhancement.

Hemangioma

On unenhanced T1-W MR images, hemangiomas are most commonly visualized as well-defined homogeneous slightly hypointense masses, with lobulated borders. On T2-weighted images, they characteristically show marked homogeneous hyperintensity with occasional areas of low intensity corresponding to areas of fibrosis (Figure 1 a, c).
Because hemangiomas are fluid-filled lesions, the water diffusion is less restricted than that of surrounding liver. Consequently, the ADC value is high and exceeds 2.1–3 mm^2/sec. They typically show hyperintensity on small b value images (due to the T2 effect) and decrease in signal intensity on long b values (Figure 1 d, e). Occasionally, they are still hyperintense on long b values due to the persistent T2 effect (shine-through effect).
After administration of a contrast agent, enhancement of hemangiomas generally follows the enhancement pattern of the aorta. More specifically, three types of enhancement patterns may be identified, depending on the size of the lesion.
The majority of lesions less than 1.5 cm in diameter show homogeneous enhancement during the arterial phase. The key findings for hemangioma are the strong hyperintensity on T2-weighted imaging and the persistent enhancement on delayed-phase imaging. Medium-sized lesions (between 1.5 and 5 cm in diameter) show either uniform early enhancement or peripheral nodular enhancement progressing centripetally to uniform enhancement in the delayed phase (Figure 1 f, g). Large hemangiomas (i.e., lesions larger than 5 cm) demonstrate peripheral nodular enhancement with persistent central hypointensity that correlates with regions of fibrosis and/or cystic areas. Peripheral nodular enhancement, detected during the arterial phase, is very useful to distinguish hemangiomas from metastases.

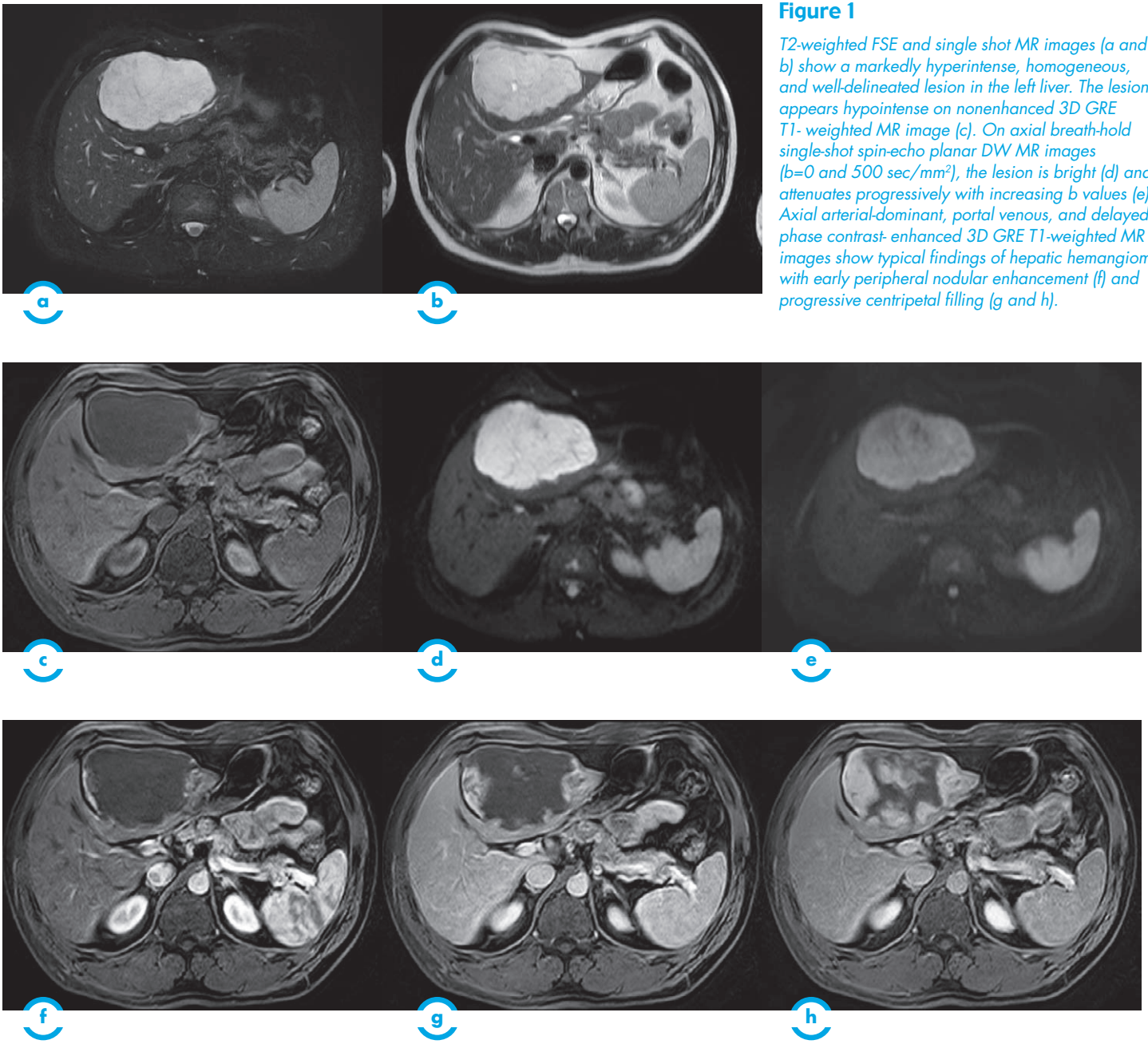


Figure 1

T2-weighted FSE and single shot MR images (a and b) show a markedly hyperintense, homogeneous, and well-delineated lesion in the left liver. The lesion appears hypointense on nonenhanced 3D GRE T1- weighted MR image (c). On axial breath-hold single-shot spin-echo planar DW MR images (b=0 and 500 sec/mm^2), the lesion is bright (d) and attenuates progressively with increasing b values (e) Axial arterial-dominant, portal venous, and delayed phase contrast- enhanced 3D GRE T1-weighted MR images show typical findings of hepatic hemangioma with early peripheral nodular enhancement (f) and progressive centripetal filling (g and h).

Focal liver lesions

Focal Nodular Hyperplasia (FNH)

Typical FNH is iso- or hypointense on T1-weighted images and slightly hyper- or isointense on T2-weighted images (Figure 2 a, b). In most cases, FNH has a central scar that is hyperintense on T2-weighted images and hypo-intense on precontrast T1-weighted images. The FNH composition is similar to normal liver tissue. This explains why the mean ADC value of FNH is similar to that of the liver. Yet, FNH may appear slightly hyperintense on DWI, because of a T2 effect (Figure 2 c).

After administration of gadolinium chelates, FNH shows intense and homogeneous enhancement during the arterial phase (with the exception of the scar) and has a signal

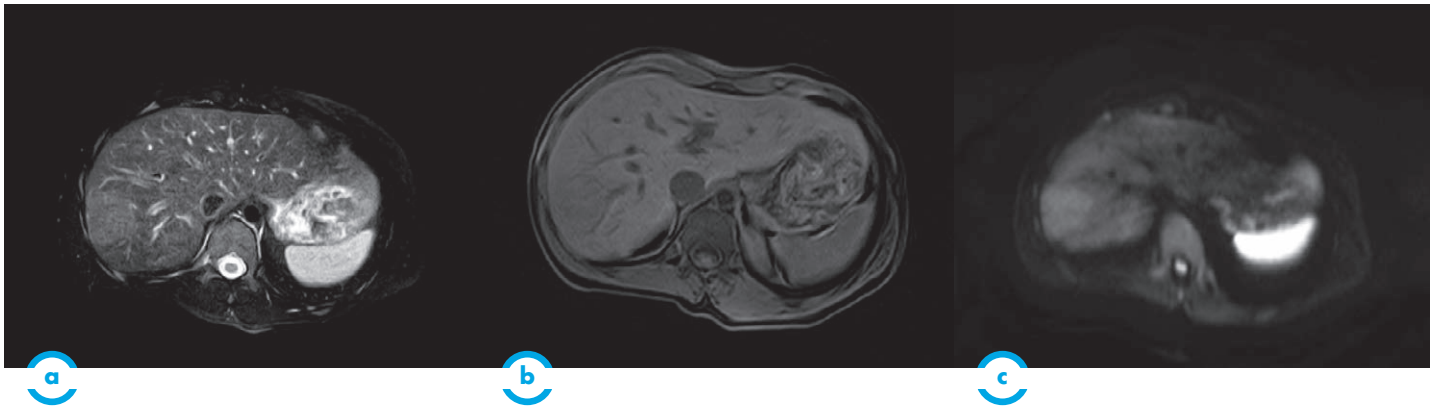


Figure 2

Axial fat-suppressed T2-weighted fast SE and T1-weighted GRE images (a and b) show a large FNH lesion in the right liver that is slightly hyperintense and hypointense relative to the surrounding liver parenchyma. The central scar has slightly higher signal intensity than the lesion in T2-weighted image (a). Axial breath-hold single-shot spin-echo planar diffusion weighted image (c) shows slight hyperintensity of the lesion at high b value (b=600 sec/mm²).

intensity approaching that of the surrounding liver parenchyma during portal and delayed phase imaging (Figure 2 d-f). The central scar demonstrates progressive enhancement in the later phases of gadolinium-enhanced imaging (Figure 2 f). None of the imaging findings is specific for the diagnosis of FNH, therefore the diagnosis is based on the combination of imaging findings (absence of capsule, signal intensity, lesion homogeneity, strong arterial enhancement, and central scar). The challenge is to diagnose FNH that does not exhibit all typical findings, especially small FNH with no central scar.

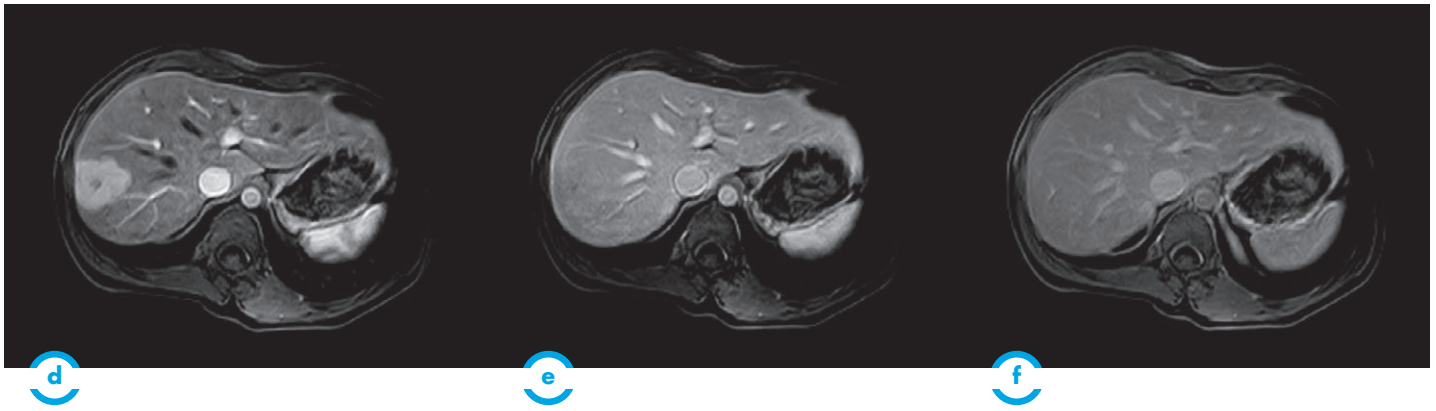


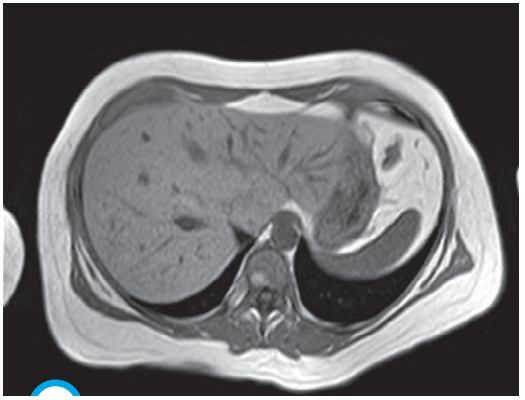
Figure 2

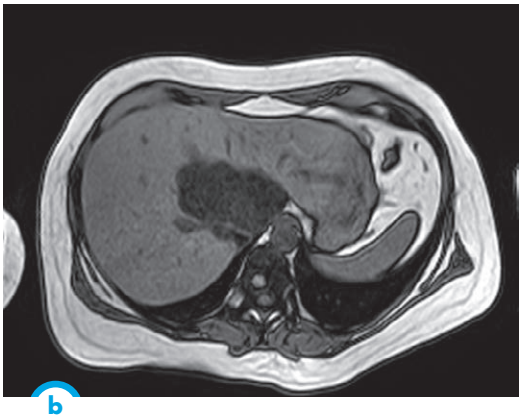
Axial arterial-dominant, portal venous, and delayed phase contrast-enhanced 3D GRE T1-weighted MR images show an intense homogeneous enhancement of the entire lesion during the arterial phase (d); the lesion becomes isointense relative to the surrounding liver parenchyma during the portal phase (e). The central scar enhances during delayed phase (f).

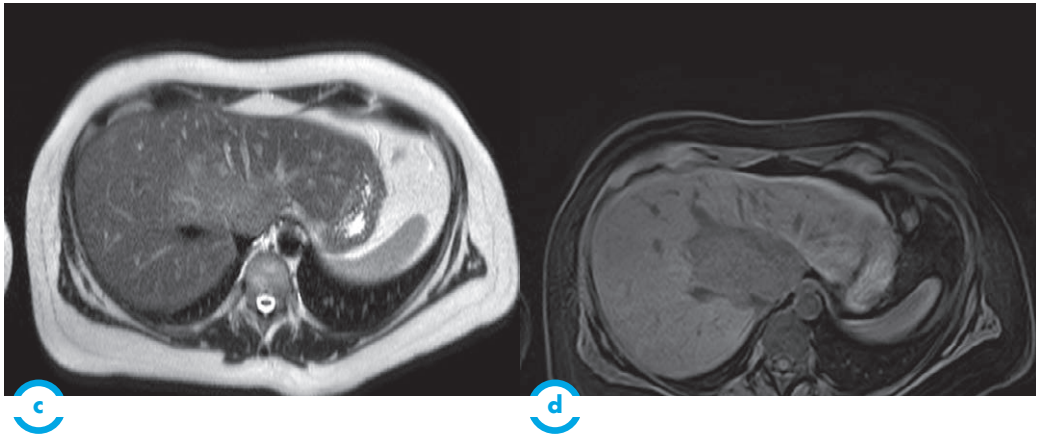
Hepatocellular adenoma

Hepatocellular adenomas are benign liver tumors that have been recently divided in three groups according to their different molecular pattern: (1) hepatocyte nuclear factor-1alpha (HNF-1alpha)-inactivated, (2) beta-catenin-activated, and (3) inflammatory or telangiectatic.

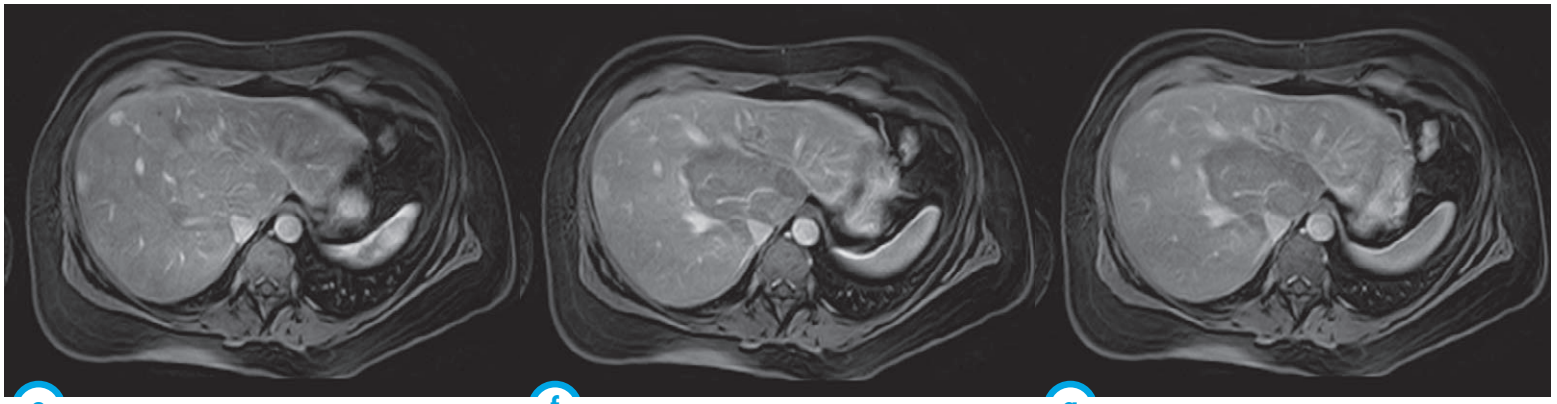
- The HNF-1alpha-inactivated group so called "steatotic group"corresponds to lesions with: (i) diffuse signal dropout on T1-weighted chemical shift images because of steatosis (Figure 3 a, b), (ii) iso-intensity or slight hyperintensity on T2-weighted images and hypo-intensity on fat suppressed T1-weighted images (Figure 3 c, d), and (iii) moderate enhancement in the arterial phase, with no persistent enhancement in the portal venous and delayed phases (Figure 3 e-g).







c d



e f g

Figure 3

On axial in-phase T1-weighted GRE MR image the lesion is isointense relative to liver parenchyma (a) ; on corresponding axial opposed-phase T1-weighted GRE MR image the lesion shows a significant and homogeneous drop in signal intensity (b) which indicates lipid intracellular content.
On axial T2-weighted MR image without fat suppression (c), the lesion is slightly hyperintense relative to liver parenchyma. On axial T1-weighted fat suppressed GRE MR image (d), the lesion is hypointense relative to liver parenchyma.
Axial arterial-dominant, portal venous, and delayed phase contrast-enhanced 3D GRE T1-weighted MR images show a slight enhancement on arterial phase (e). On portal venous and delayed phases (f and g) the lesion shows a wash-out and appears hypointense relative to liver surrounding parenchyma.

- The beta-catenin-activated group is less characteristic at MR imaging. The most common appearance is enhancement during the arterial phase and wash-out during the portal venous and delayed phases.

- The inflammatory or telangiectatic group corresponds to lesions with: (i) absence or only focal signal dropout on chemical shift images (Figure 4 a, b); (ii) marked hyperintensity on T2-weighted images, with a stronger signal in the outer part of the lesions, correlating with areas of sinusoidal dilatation (Figure 4 c); and (iii) strong arterial enhancement, with persistent enhancement in the portal venous and delayed phases (Figure 4 e-g).

The two latter (inflammatory or telangiectatic and beta-catenin-activated groups) may undergo malignant transformation which is mostly observed in large lesions (> 5 cm) and in male patients. Diagnosis of malignant transformation is difficult at imaging.
As FNH, hepatocellular adenoma is a benign hepatocellular lesion. Its mean ADC is similar to that of the liver.

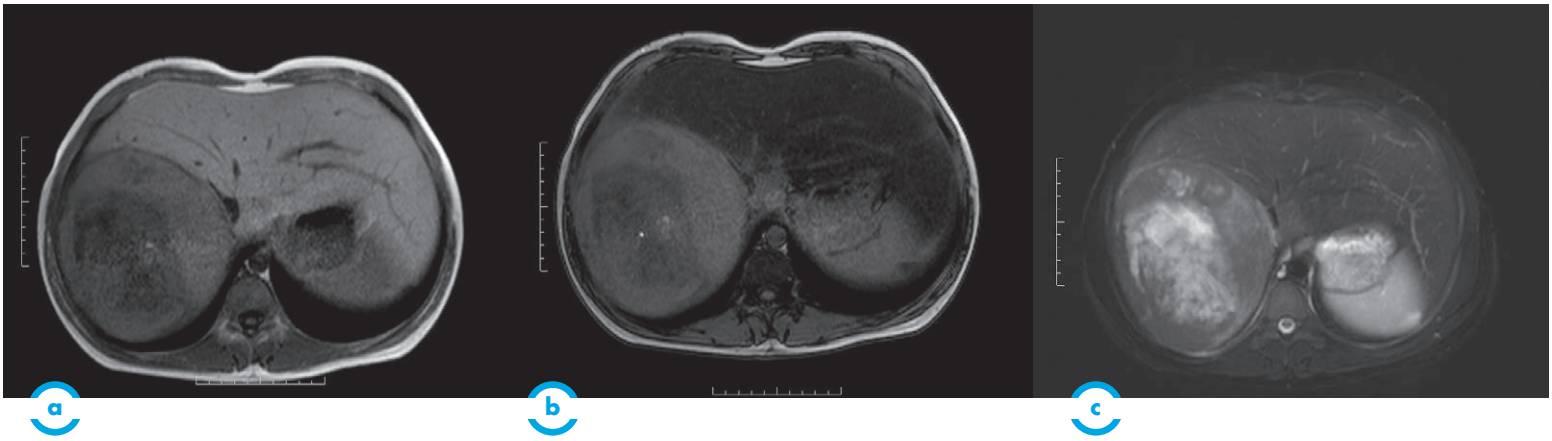


Figure 4

Axial in-phase and opposed-phase T1-weighted GRE MR images (a and b). On opposed-phase image, there is no signal dropout within the lesion. Conversely, the surrounding liver parenchyma shows a loss of signal characteristic of steatosis. On axial T2-weighted MR image (c) the lesion is markedly hyperintense relative to liver parenchyma.

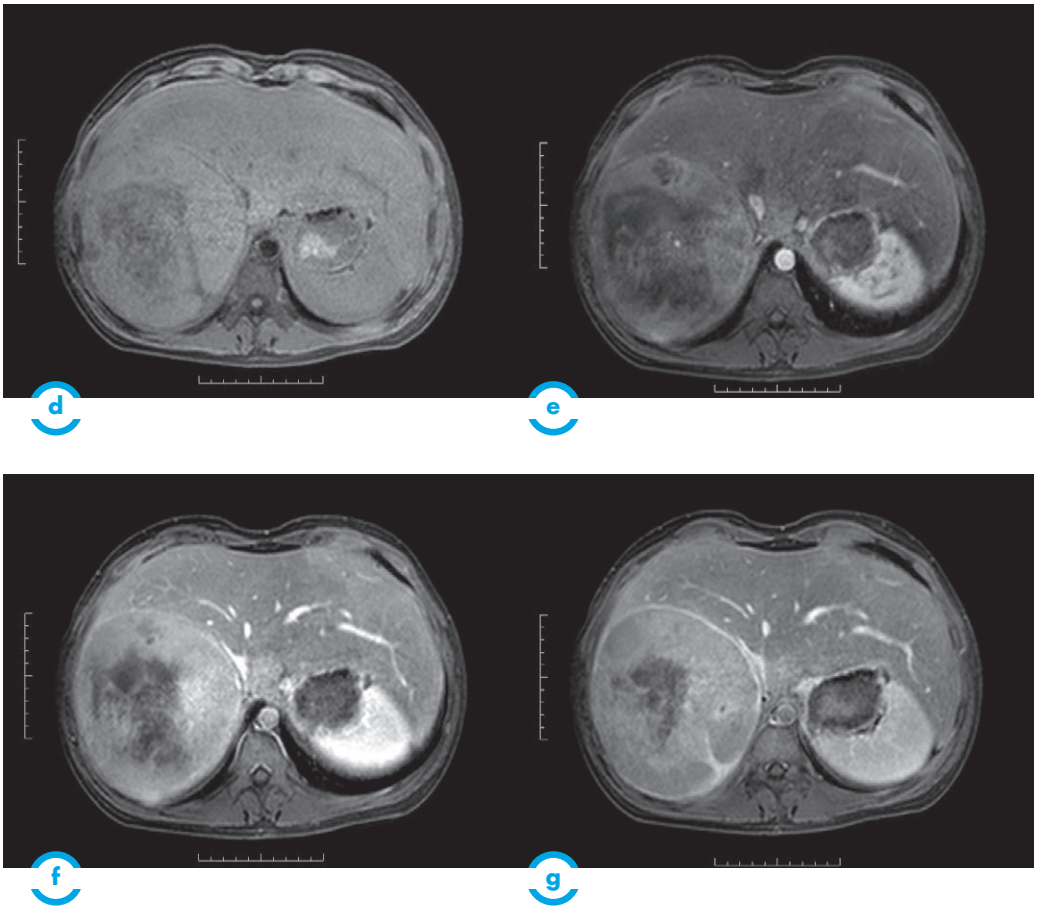


Figure 4

Axial non enhanced and arterial-dominant, portal venous, and delayed phase contrast-enhanced 3D GRE T1-weighted MR images (d, e, f, g) show strong arterial enhancement, with persistent enhancement in the portal venous and delayed phases.

Hepatocellular carcinoma (HCC)

Hepatocellular carcinoma has a variable appearance at MR imaging, the most common features being hyperintensity on T2-weighted images, and hypointensity on T1-weighted images (Figure 5 a, b, c). Lesions less than 1.5 cm are often isointense on T1-weighted MR images, whereas larger lesions may be hyperintense. Hyperintensity on T1-weighted images is mostly caused by intralesional fat or hemorrhage and less commonly by copper, proteins, glycogen, and clear cell formation. Signal intensity on T2-weighted images is related to tumor differentiation and hypointense HCCs are predominantly seen in well-differentiated tumors. Most HCCs, including HCCs ≤ 2 cm, are seen on DWI and are hyperintense relative to the surrounding hepatic parenchyma (Figure 5 d). On contrast-enhanced T1-weighted MR images, most small (< 2 cm) HCCs demonstrate homogeneous and intense enhancement during the arterial phase, whereas larger lesions often show heterogeneous enhancement and a mosaic pattern. Typically, HCCs show contrast agent wash-out during the portal venous and/or delayed phases, becoming hypointense relative to the surrounding liver (Figure 5 e, f). A peripheral capsule, which appears hypointense on T2- and precontrast T1-weighted images and hyperintense on delayed phase images, is highly suggestive of HCC (Figure 5 g, h) and is mostly observed in medium size tumors (3-5 cm). Non-invasive diagnosis of HCC is possible in patients with cirrhosis. The major criteria are tumor enhancement during arterial phase and wash-out on portal venous or delayed phases. Such association is highly specific for the diagnosis. Combination of imaging such as MR, CT and contrast-enhanced ultrasound is required in lesions smaller than 2 cm in diameter.

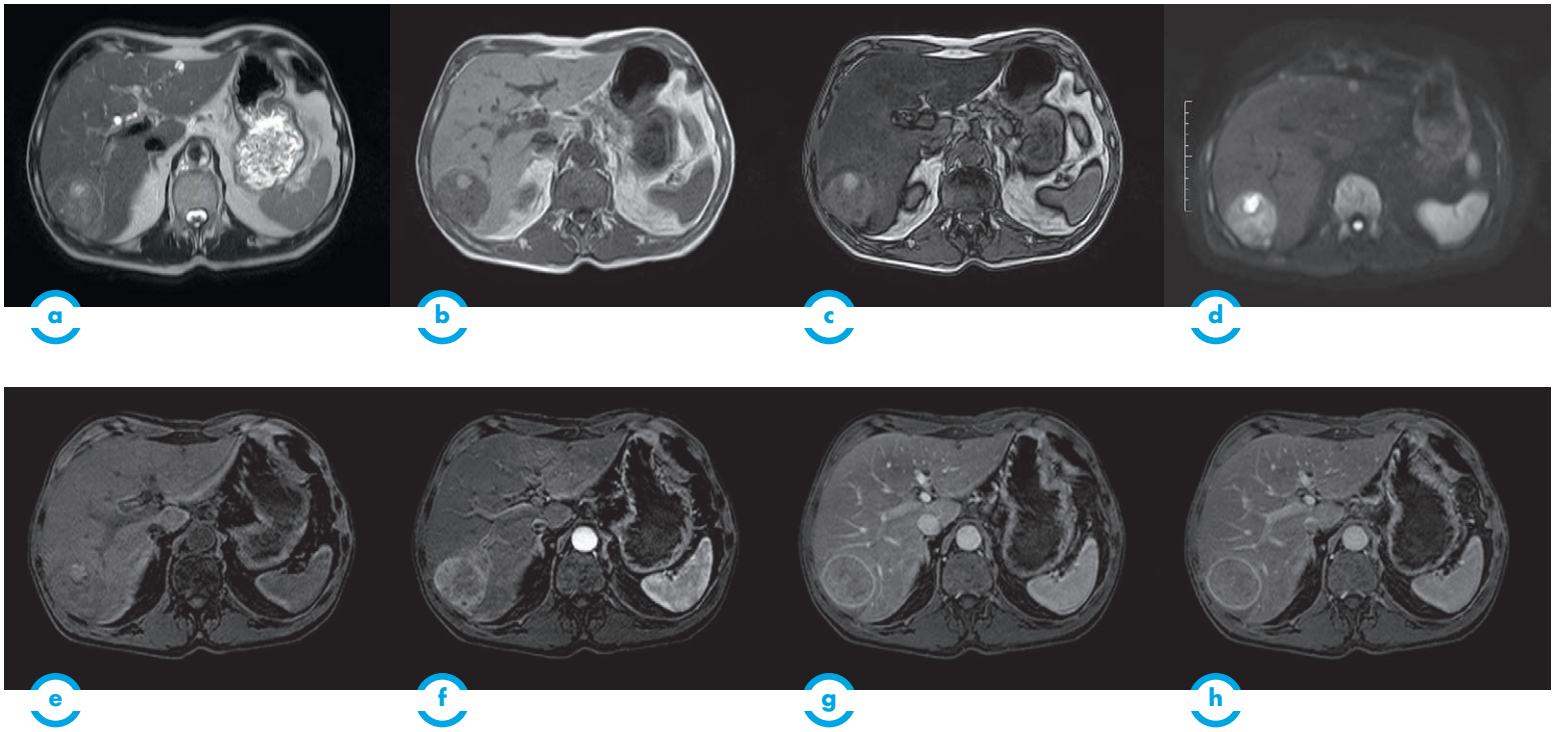


Figure 5

T2-weighted single-shot image (a) shows a slightly hyperintense lesion in the right liver. In- and opposed-phase T1-weighted GRE (b, c). The intralesional hyperintense portion does not drop on opposed-phase indicating focal hemorrhage. Note the decreased signal intensity of the liver steatosis. On axial fat-suppressed breath-hold single-shot spin-echo planar diffusion image (d) (b=600 sec/mm²), the lesion shows restricted diffusion.
Axial unenhanced, arterial-dominant, portal venous, and delayed phase contrast-enhanced 3D GRE T1-weighted MR images (e, f, g, h). There is a heterogeneous and marked enhancement of the lesion at the arterial phase (f); the lesion exhibits wash out of contrast material on portal and delayed phase images (g, h). The fibrous capsule surrounding the lesion is very suggestive of HCC.

Cholangiocarcinoma

Most intrahepatic or peripheral cholangiocarcinomas are mass-forming, whereas hilar or extrahepatic cholangiocarcinomas are predominantly periductal or polypoid. Peripheral cholangiocarcinoma is either isointense or hypointense relative to the normal liver on T1-weighted MR images, but may range from markedly to mildly hyperintense on T2-weighted MR images depending on the amount of mucinous material, fibrous tissue or necrosis within the tumor (Figure 6 a, b). On DWI, peripheral cholangiocarcinoma often exhibits heterogeneous signal intensity with the most hyperintense component at the periphery representing active growing neoplastic tissue.
On dynamic T1-weighted MR images acquired after intravenous administration of gadolinium, minimal or moderate heterogeneous enhancement is seen at the tumor periphery on early images, whereas progressive central enhancement is observed on later images (although the central area may show incomplete enhancement). Progressive enhancement is related to dense fibrous stroma. Small-sized cholangiocarcinomas may show homogeneous and complete enhancement during the early phase and a prolonged enhancement during the equilibrium phase (Figure 6 c-f).The diagnosis of peripheral cholangiocarcinoma is not only based on the presence of fibrous stroma, but also on ancillary findings such as satellite nodules, capsular retraction, portal or venous encasement, and peripheral bile duct dilatation.

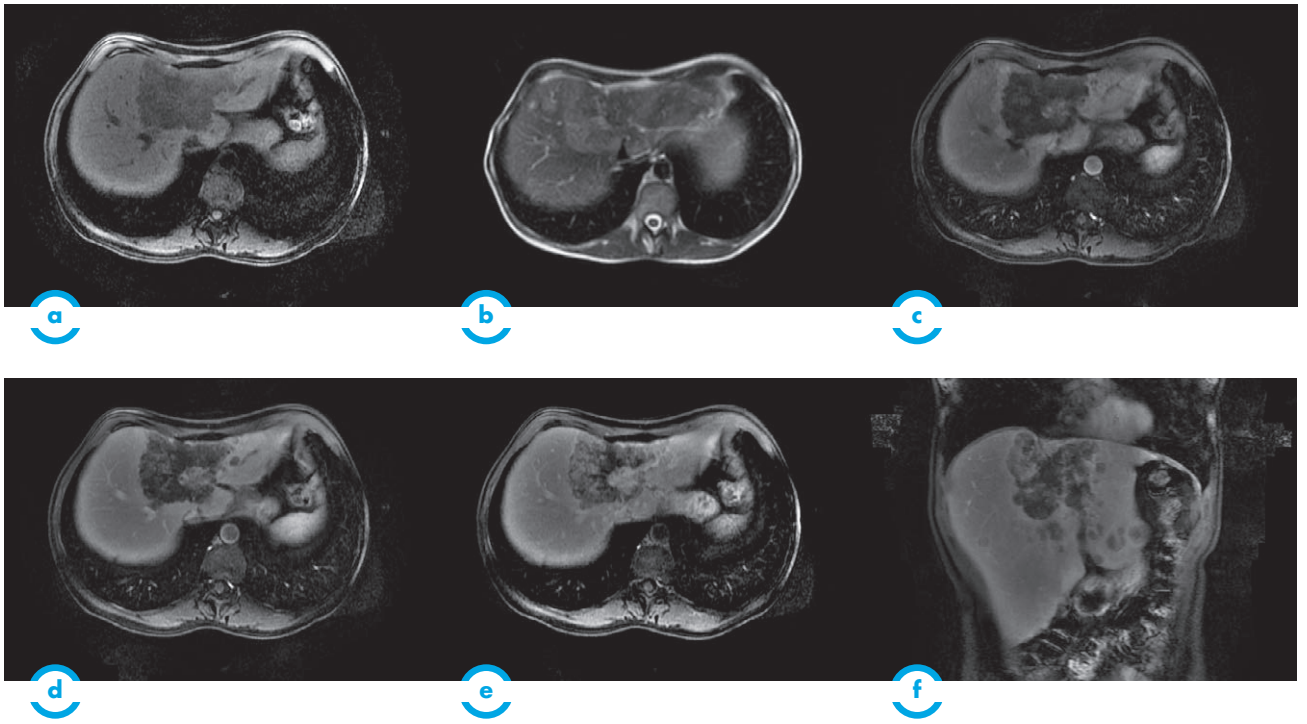


Figure 6

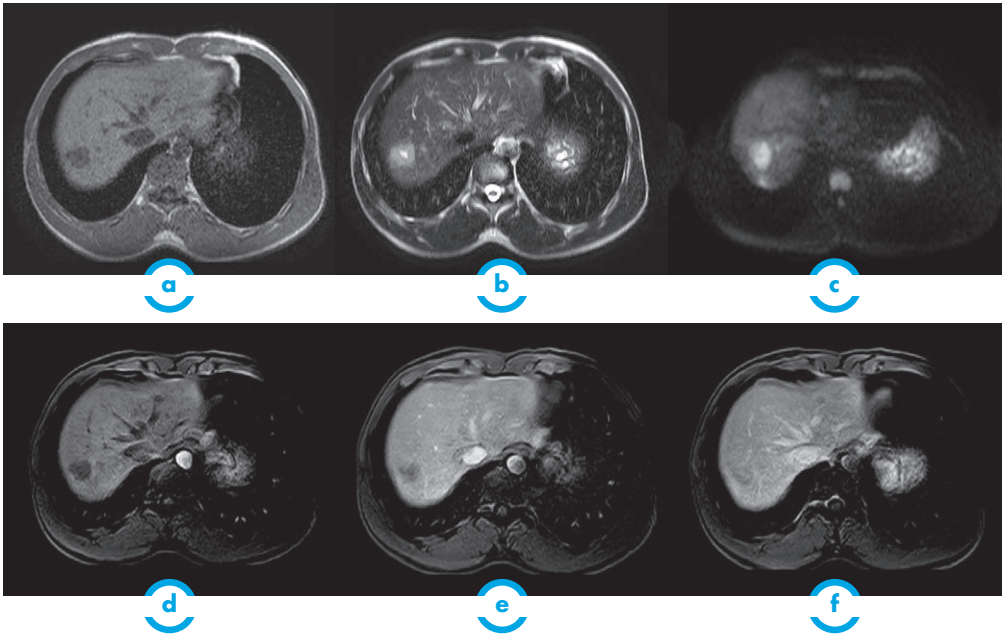
Non-enhanced fat suppressed GRE T1-weighted image (a) shows a hypointense mass with irregular margins in the left liver; T2-weighted FSE image (b) shows a slightly hyperintense lesion.
Axial arterial-dominant, portal venous, and delayed phase contrast-enhanced 3D GRE T1-weighted MR images (c, d, e). There is an irregular peripheral enhancement of the lesion during arterial phase imaging (c) followed by progressive and heterogeneous enhancement of the fibrous content of the lesion on portal and delayed phase images (d and e). Note the multiple intrahepatic satellite nodules that are characteristic of peripheral cholangiocarcinoma on coronal delayed phase (f).

Metastases

The signal intensity of metastases on MR images varies considerably, depending on the degree of vascularity, hemorrhage, and necrosis. Liver metastases generally have a low signal intensity on T1-weighted images and a high signal intensity on T2-weighted images relative to the surrounding parenchyma (Figure 7 a, b). Lesion hyperintensity on T1-weighted images may be seen when tumors contain areas of hemorrhage. Less commonly, such changes are explained by the presence of melanin, mucin and even more rarely by fat. On T2-weighted MR images, liver metastases usually show high signal intensity relative to the surrounding liver parenchyma, although the signal is lower than that observed in hemangiomas or cysts. Metastases with liquefactive necrosis may have a cystic appearance. In contrast, low signal intensity on T2-weighted MR images may be seen in hemorrhagic tumors, melanin-containing lesions, or in metastases with a large amount of fibrous matrix, calcifications or dessicated mucinous secretions. Metastases may often demonstrate a characteristic "doughnut" or "target" sign on T2-weighted images, in which the central area is surrounded by a peripheral rim, corresponding to the growth margin of the tumor.

Figure 7

T1-weighted GRE image (a) shows a hypointense metastatic lesion from colorectal cancer with irregular margins in the right hepatic lobe. On axial fat-suppressed T2-weighted FSE image (b), the lesion is heterogeneous and contains a hyperintense necrotic central area. Axial fat-suppressed breath-hold single-shot spin-echo planar diffusion image (c) (b=600 sec/mm^2) shows restricted diffusion in the metastatic lesion. Axial arterial-dominant, portal venous, and delayed phase contrast-enhanced 3D GRE T1-weighted MR images (d, e, f). Dynamic studies show irregular peripheral enhancement of the mass on arterial phase (d), and progressive and heterogeneous enhancement of the lesion on portal and delayed phase images (e and f).



The vast majority of liver metastases is strongly hyperintense on DWI (Figure 7 c). Several studies have shown that DWI is more sensitive for tumor detection than conventional imaging.

Most liver metastases are described as hypovascular. There is usually a weak and peripheral enhancement during the arterial phase after administration of the contrast agent, followed by delayed enhancement of fibrous components. This halo sign is highly characteristic of liver metastases secondary to colorectal cancer (Figure 7 d, f).

Hypervascular metastases often show high signal intensity on T2-weighted images and low signal intensity on T1-weighted images (Figure 8 a, b). Due to the restricted water diffusion, they are mostly hyperintense on DWI with high b values (Figure 8 c). Intense enhancement in the arterial-dominant phase followed by wash-out in the portal-venous and delayed phases is commonly observed (Figure 8 d, e, f). This pattern is mainly seen in endocrine liver metastases. Some of them may mimic the appearance of FNH with a central scar. However, they are much more intense than FNH on T2-weighted images.

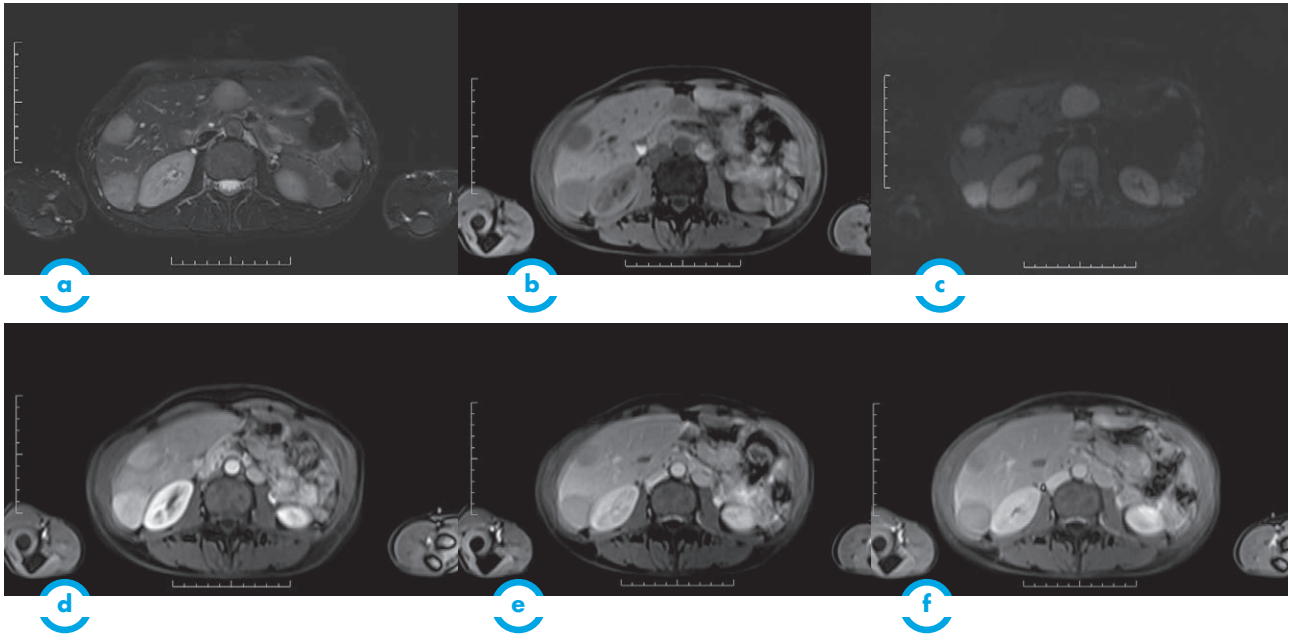


Figure 8

Fat-suppressed T2-weighted FSE image (a) show multiple hyperintense lesions in right hepatic lobe, which are hypointense on axial fat suppressed T1-weighted GRE image (b). Axial fat-suppressed breath-hold single-shot spin echo-planar diffusion image (c) (b=600 sec/mm²) shows multiple lesions with restricted diffusion in the right hepatic lobe. Axial arterial-dominant, portal venous, and delayed phase contrast-enhanced 3D GRE T1-weighted MR images show multiple hypervascular metastases with marked enhancement at early phase (d) and washout on portal and delayed phases (e and f).

Conclusion

MR imaging of the liver is an excellent tool for the detection and characterization of focal liver lesions. Diagnosis is based on lesion signal intensity on T1- and T2- weighted images, and lesion behaviour on dynamic studies after intravenous administration of gadolinium chelates. DWI has become very helpful, especially for the detection of liver metastases, and contributes to tumor characterization.

Summary of signal intensity obtained for different lesions and according to sequences used

	T1 pre	T2	T1 post	DWI	ADC
Hemangioma	Strongly hypointense	Strongly hyperintense	Hyperintense at arterial and portal phases	Decreased signal on long b values	High
Focal Nodular Hyperplasia (FNH)	Iso- or hypointense (central scar)	Iso- or slightly hyperintense (central scar)	Strongly hyperintense at arterial phase	Slightly hyperintense	Similar to liver
Hepatocellular adenoma	Variable	Variable	Moderately hyperintense at arterial phase, wash-out or persistent enhancement at portal and late phase	Slightly hyperintense	Similar to liver
Hepatocellular carcinoma (HCC)	Hypointense	Hyperintense	Hyperintense on arterialphase; wash-out at portal phase and / or late phase	Hyperintense	Low
Cholangio carcinoma	Hypointense	Hyperintense	Moderate, heterogenous, centripetal and progressive hyperintense	Hyperintense	Low
Metastases	Hypointense	"doughnut" hyperintense	Mostly irregular hyperintense and peripheral enhancement (halo sign), variable at portal phase	Hyperintense	Low

Resume of product characteristics

DOTAREM 0.5 mmol/mL, solution for injection. **Composition:** For 100 mL of solution: active ingredient: Gadoteric Acid 27.932 g corresponding to: DOTA 20.246 g corresponding to gadolinium oxide 9.062 g. **Indications (*):** Medicinal product for diagnostic use only: Magnetic Resonance Imaging for cerebral and spinal disease, diseases of the vertebral column, and other whole-body pathologies (including angiography). **Posology and method of administration:** The recommended dose is 0.1 mmol/kg, i.e. 0.2 mL/kg in adults and children. In angiography, depending on the results of the examination being performed, a second injection may be administered during the same session if necessary. Angiography with Gadoteric acid is not recommended in children (0-18 years). In Encephalic and spinal MRI, in some exceptional cases, as in the confirmation of isolated metastasis or the detection of leptomeningeal tumours, a second injection of 0.2 mmol/kg may improve tumor characterisation and facilitate therapeutic decision making. For patients with impaired renal function and paediatric population (0-18 years) more than one dose should not be used during a scan, injections should not be repeated unless the interval between injections is at least 7 days. The product must be administered by strict intravenous injection. Depending on the amount of gadoteric acid to be given to the child, it is preferable to use gadoteric acid vials with a single use syringe of a volume adapted to this amount in order to have a better precision of the injected volume. In neonates and infants the required dose should be administered by hand. **Contraindications:** Hypersensitivity to gadoteric acid, to meglumine or to any medicinal products containing gadolinium. **Special warnings and precautions for use:** Dotarem must not be administered by subarachnoid (or epidural) injection. The usual precaution measures for MRI examination should be taken such as exclusion of patients with pacemakers, ferromagnetic vascular clips, infusion pumps, nerve stimulators, cochlear implants or suspected intracorporal metallic foreign bodies, particularly in the eye. **General particulars corresponding to all gadolinium contrast agents:** All gadolinium based contrast media can cause minor or major hypersensitivity reactions that can be life-threatening. These can occur immediately (within 60 minutes) or be delayed (within 7 days) and are often unpredictable. Because of the risk of major reactions, emergency resuscitation equipment should be available for immediate use. Hypersensitivity reactions can be aggravated in patients on betablockers and particularly in the presence of bronchial asthma. These patients may be refractory to standard treatment of hypersensitivity reactions with beta agonists. Impaired renal function: Prior to administration of gadoteric acid, it is recommended that all patients are screened for renal dysfunction by obtaining laboratory tests. There have been reports of Nephrogenic Systemic Fibrosis (NSF) associated with use of some gadolinium-containing contrast agents in patients with severe renal impairment (GFR < 30 ml/min/1.73 m^2). As there is a possibility that NSF may occur with Dotarem, it should only be used in these patients after careful consideration. CNS disorders: As with other contrast agents containing gadolinium, special precautions should be taken in patients with a low seizure threshold. Precautionary measures, e.g. close monitoring, should be taken. All equipment and drugs necessary to counter any convulsions which may occur must be made ready for use beforehand. **Interactions with other medicinal products and other forms of interaction:** No interactions with other medicinal products have been observed. Formal drug interaction studies have not been carried out. **Fertility, pregnancy and lactation:** Gadoteric acid should not be used during pregnancy unless the clinical condition of the woman requires use of gadoteric acid. Continuing or discontinuing breast feeding for a period of 24 hours after administration of gadoteric acid, should be at the discretion of the doctor and lactating mother. **Effects on ability to drive and use machines:** No studies on the effects on the ability to drive and use machines have been performed. Ambulant patients while driving vehicles or operating machinery should take into account that nausea may incidentally occur. **Undesirable effects:** Uncommon (≥1/1000 to <1/100): hypersensitivity, headache, dysgeusia, dizziness, somnolence, paraesthesia (including burning sensation), hypotension, hypertension, nausea, abdominal pain, rash, feeling hot, feeling cold, asthenia, injection site reactions (extravasation, pain, discomfort, oedema, inflammation, coldness). Rare (≥1/10 000 to <1/1 000): anxiety, presyncope, eyelid edema, palpitations, sneezing, throat tightness, vomiting, diarrhea, salivary hypersecretion, Urticaria, pruritus, hyperhidrosis, chest pain, chills. Very rare (<1/10 000): anaphylactic reaction, anaphylactoid reaction, agitation, coma, convulsion, syncope, tremor, parosmia, conjunctivitis, ocular hyperaemia, vision blurred, lacrimation increased, tachycardia, cardiac arrest, arrhythmia, bradycardia, flushing, pallor, vasodilatation, hot flush, cough, dyspnoea, nasal congestion, respiratory arrest, bronchospasm, throat irritation, laryngospasm, pharyngeal oedema, dry throat, pulmonary oedema, erythema, angioedema, eczema, muscle cramps, muscular weakness, back pain, arthralgia, malaise, chest discomfort, pyrexia, face oedema, injection site necrosis (in case of extravasation), phlebitis superficial, decreased oxygen saturation, Not known : nephrogenic systemic fibrosis. **Overdose:** Gadoteric acid can be removed by haemodialysis. However there is no evidence that haemodialysis is suitable for prevention of nephrogenic systemic fibrosis. **Please note:** The peel-off tracking label on the vials or syringes should be stuck onto the patient record to enable accurate recording of the gadolinium contrast agent used. The dose used should also be recorded. If electronic patient records are used, the name of the product, the batch number and the dose should be entered into the patient record. **Pharmacological properties:** Pharmacotherapeutic group: paramagnetic contrast media for MRI, ATC code: V08CA02. Presentation (*): 5, 10, 15, 20, 60 & 100 mL in vial (glass) and 10, 15 & 20 mL in a prefilled syringe (glass). **Marketing authorization holder: (*) Information:** Guerbet - BP 57400 - F-95943 Roissy CdG cedex – FRANCE. Tel: 33 (0) 1 45 91 50 00. **Date of revision of this document:** September 2016.

For current and complete prescribing information refer to the package insert and/or contact your local Guerbet organization.

(*) Indications, presentations and marketing authorization holder may differ from country to country.

Reporting of suspected adverse reactions is important as it helps to continuously assess the benefit-risk balance. Therefore, Guerbet encourages you to report any adverse reactions to your health authorities or to our local Guerbet representative.

www.guerbet.com

Guerbet

P17 053 DOT - February 2017 - © escapades - Realisation: communication