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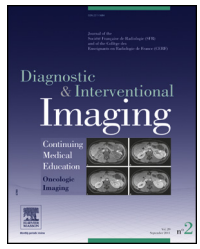

CONTINUING EDUCATION PROGRAM: FOCUS...

Gastrointestinal imaging: Tips and traps in the diagnosis of small HCC

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Abstract Improvement in survival of patients with HCC depends on detecting small lesions. This is possible by screening all patients with cirrhosis for HCC. However, these small lesions are difficult to characterise as only 50 to 80% of lesions less than 3 cm have a typical HCC appearance, depending on the imaging technique used. MRI, with its various possibilities (dynamic sequences, diffusion-weighting, liver-specific contrast agents), is currently the most effective imaging technique for characterising these small HCCs, but at present we do not know the best combination of imaging examinations for diagnosing the condition.

Hepatocellular carcinoma (HCC), the incidence of which continues to increase (11 cases per 100,000 people per year in France), has become the fifth most frequent cancer and the fourth in terms of mortality in the world. In more than 90% of cases it occurs on a background of underlying liver disease — cirrhosis or a chronic liver disease [1—3]. Since there is known to be an environment favouring the occurrence of this cancer, monitoring programmes for cirrhotic patients have been set up in various countries, and it has thus been shown that monitoring improves their survival. The study in a large population (18,816 patients) by Zhang et al. [4] showed an increase in survival in patients whose HCC was discovered while they were in the monitored group of more than 37% compared with patients in the group which was not monitored. This study was confirmed in 2008 by Chan et al. [5] who, in 1136 patients with HCC with cirrhosis, showed overall survival of 61.9 months if the patients had been monitored before the discovery of their HCC and 11.6 months if the patients had not been so monitored.

In France, patients at risk of HCC are monitored by 6-monthly ultrasound examinations [6]. Unfortunately, it is insufficiently prescribed and observed, covering only

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about 20% of the target population [7], but can lead to the detection of small HCC (less than 30 mm or even 20 mm). While curative treatment can be offered for small HCCs, which have a significantly better prognosis than larger ones, diagnosing them with certitude is more difficult. Characterisation of a nodule in cirrhosis discovered by ultrasound depends on contrast-enhanced ultrasound, CT or MRI. Nevertheless, the well-documented characteristics of HCC that permit non-invasive diagnosis [3,8] can be incomplete for small tumours and may thus pose a diagnostic problem that can detract from the benefit of its having been detected early. In addition, the existence of pseudo-lesions and other liver tumours is more often a source of confusion for small HCCs than it is for larger lesions.

The aim of this article is therefore to describe the typical and atypical appearance of small HCCs, to discuss the differential diagnoses, and to provide the technical points and signs that should lead to HCC being suspected.

Typical appearance of hepatocellular carcinoma

During its evolution from the regenerative nodule via the dysplastic nodule to HCC, the vascularisation of the nodule, which, like all the liver parenchyma, is initially mainly portal, gradually becomes arterial by tumour neoangiogenesis, the portal vascularisation at the same time decreasing. This evolution of the tumour vasculature results in the two typical aspects of the image of hepatocellular carcinoma: early enhancement in the arterial phase and washout of the lesion in the portal or late phase (Fig. 1). In a cirrhotic liver, HCC can be diagnosed non-invasively on the basis of observation of these features, and after staging, a therapeutic decision can be taken in a multidisciplinary consultation, without recourse to biopsy [3,8].

While MRI is the most effective technique for showing this typical appearance, it is nevertheless still imperfect, since

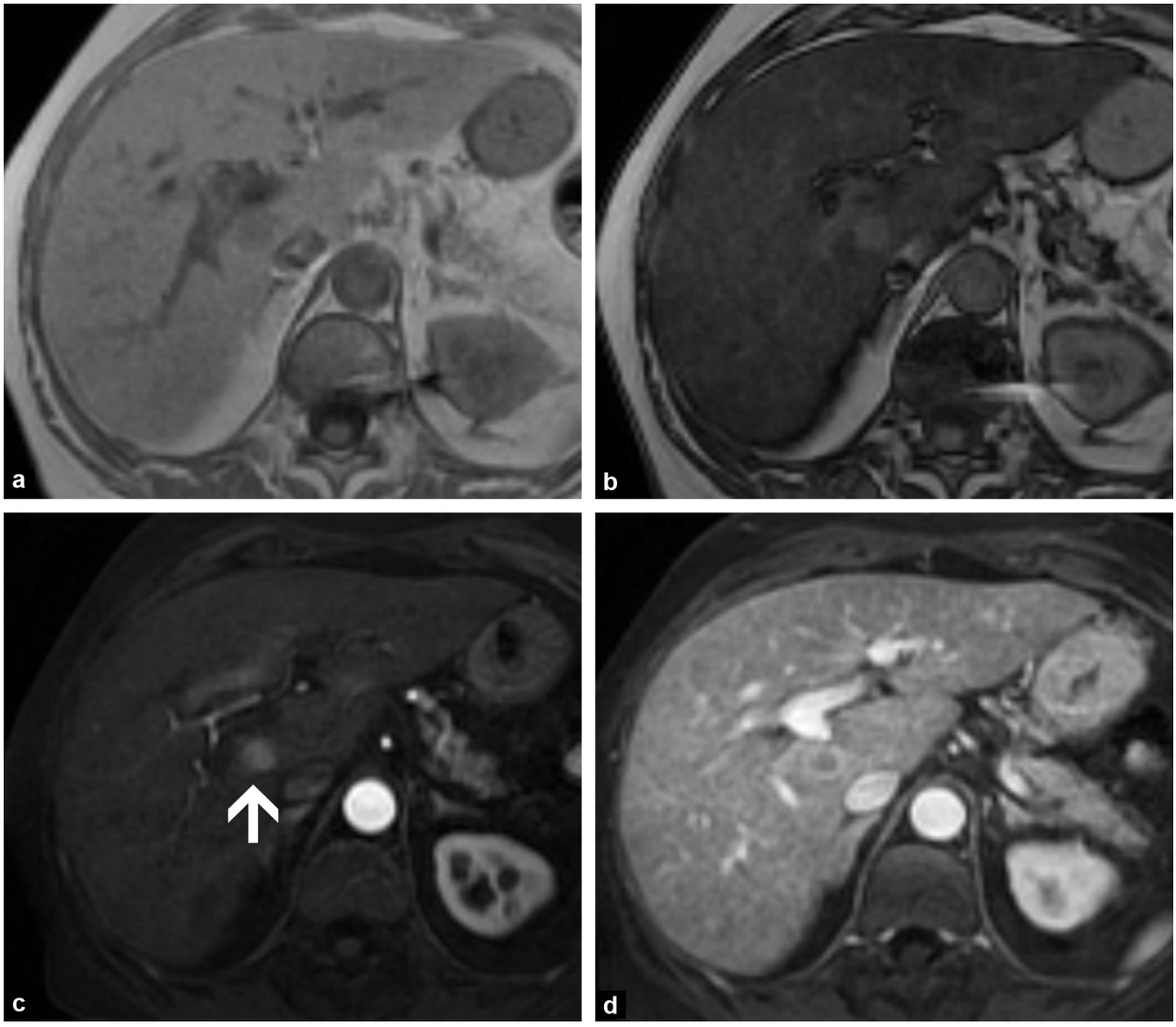

Figure 1. Typical MRI appearance of hepatocellular carcinoma. Monitoring examination for cirrhosis of exogenous origin. T1-weighted MRI in phase (a) and out of phase (b): hepatic steatosis [out-of-phase fall in signal (b)]. T1-weighting with fat saturation after gadolinium injection in the arterial (c) and portal (d) phases: 16 mm lesion (arrow) enhanced in the arterial phase and washed out in the portal phase.

these aspects are observed in less than 60% of nodules of less than 3 cm [9—12]. The sensitivity of the different techniques for diagnosing small HCC is shown in Table 1. At the same time, the specificity of the imaging techniques, particularly of MRI, is high, at between 95 and 96% in the literature, and false positives are frequently high-grade dysplastic nodules [10], treatment of which is probably appropriate because of the high risk of their progressing to HCC [13]. To summarise, when a small nodule is found in liver cirrhosis, the presence of the typical appearance provides virtual certainty of HCC, but its absence does not mean that this diagnosis can be eliminated.

Diagnostic difficulties and features providing answers

Atypical appearance of small hepatocellular carcinomas

Absence of typical vascular kinetics

Although less frequently hypervascular in the arterial phase than large HCCs, small HCCs retain this feature in the vast majority of cases (75—85%). On the other hand, the absence of lesion washout in the portal or late phase is common (40—60% of cases depending on the technique used) [10—12]. Lesion washout is most frequently absent in contrast-enhanced ultrasound, and most often present in MRI. The degree of differentiation of the HCC also plays a role, the classic features being most frequently absent in well-differentiated HCCs [9,14].

These enhancement characteristics can however be present in one type of imaging examination and not in another, without there being any clear explanation for this. The first solution to overcome the lack of characteristic appearance of a nodule discovered during an imaging examination is therefore to widen the range of exploration techniques. While contrast-enhanced ultrasound is rarely positive (about 40% according to our own as yet unpublished data), the use of CT or MRI in turn, when one or other of the two techniques is negative, markedly increases imaging sensitivity for the diagnosis of small HCC. The study by Sersté et al. [10] thus reported sensitivity of 74% for CT for showing the typical vascular kinetics and 81% for MRI, and when one or the other technique is used in turn, sensitivity reaches 98% (Fig. 2). Using CT and MRI in turn is the approach recommended in the guidelines of the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD). It should be noted that in these recommendations, even though contrast-enhanced ultrasound may still provide a diagnostic pointer, its use can no longer confirm the diagnosis and defer a biopsy. Only CT and MRI are authorised for providing a non-invasive diagnosis with certainty [3,8].

Hyperintensity with T2-weighting is another feature in the diagnosis of small HCCs (Fig. 3). In making a diagnosis of HCC for lesions measuring less than 20 mm, if the presence of typical vascular kinetics and/or T2 hyperintensity is considered, the sensitivity of MRI is 79.4% and its specificity 76.9%, whereas if typical vascular kinetics are considered alone, the sensitivity of MRI is only 67.6%, with identical specificity [15].

The use of diffusion imaging is also an important element for positive diagnosis of HCC, since more than 75% of small HCCs are hyperintense in diffusion-weighted imaging [9,10]. However, there does not seem to be any correlation between diffusion hyperintensity and tumour differentiation.

The performance of diffusion hyperintensity alone (without the typical enhancement kinetics) is still being discussed in the literature. One team [16] has shown that diffusion-weighted imaging performs better for diagnosis of small HCC than typical appearance (arterial enhancement and portal and/or late washout) recognised by the guidelines; another team could not confirm these results [17].

Even if they are still controversial, it is important to report the results of Piana et al. [16]: for the diagnosis of HCC of less than 2 cm, the use of the combination comprised of arterial hypervascularisation + diffusion-weighted hyperintensity instead of arterial hypervascularisation + lesion washout increases the sensitivity of MRI for diagnosing small HCCs from 60% to 77%, while with joint use of the two combinations (arterial hypervascularisation + lesion washout and + diffusion-weighted hyperintensity) sensitivity is 85% (Fig. 4).

It should be made clear that in diffusion-weighted imaging, there is no place for measurement of apparent diffusion coefficient (ADC) values in the diagnosis of small HCC.

Liver-specific contrast agents, fixed by the hepatocytes and responsible for enhancement of the parenchyma in the late phase (known as the hepatocytic phase) — after 20 min for the most recent product (gadoxetate disodium) — appear to increase detection of small hepatocellular carcinomas [18,19], and the ability, in particular, to differentiate early HCC from dysplastic nodules: in 97% of cases early HCC is not

Table 1 Sensitivity (%) of imaging examinations for the diagnosis of small hepatocellular carcinoma according to the AASLD criteria (arterial hypervascularisation and portal and/or late phase washout).

	Maximum size (cm)	Contrast-enhanced ultrasound	CT	MRI
Forner et al. [12]	2	52		62
Leoni et al. [11]	3	67	64	75
Sestré et al. [10]	2		71	84
Rimola et al. [27]	2			58
Aubé (unpublished data)	3	43	75	80

AASLD: American Association for the Study of Liver Diseases.

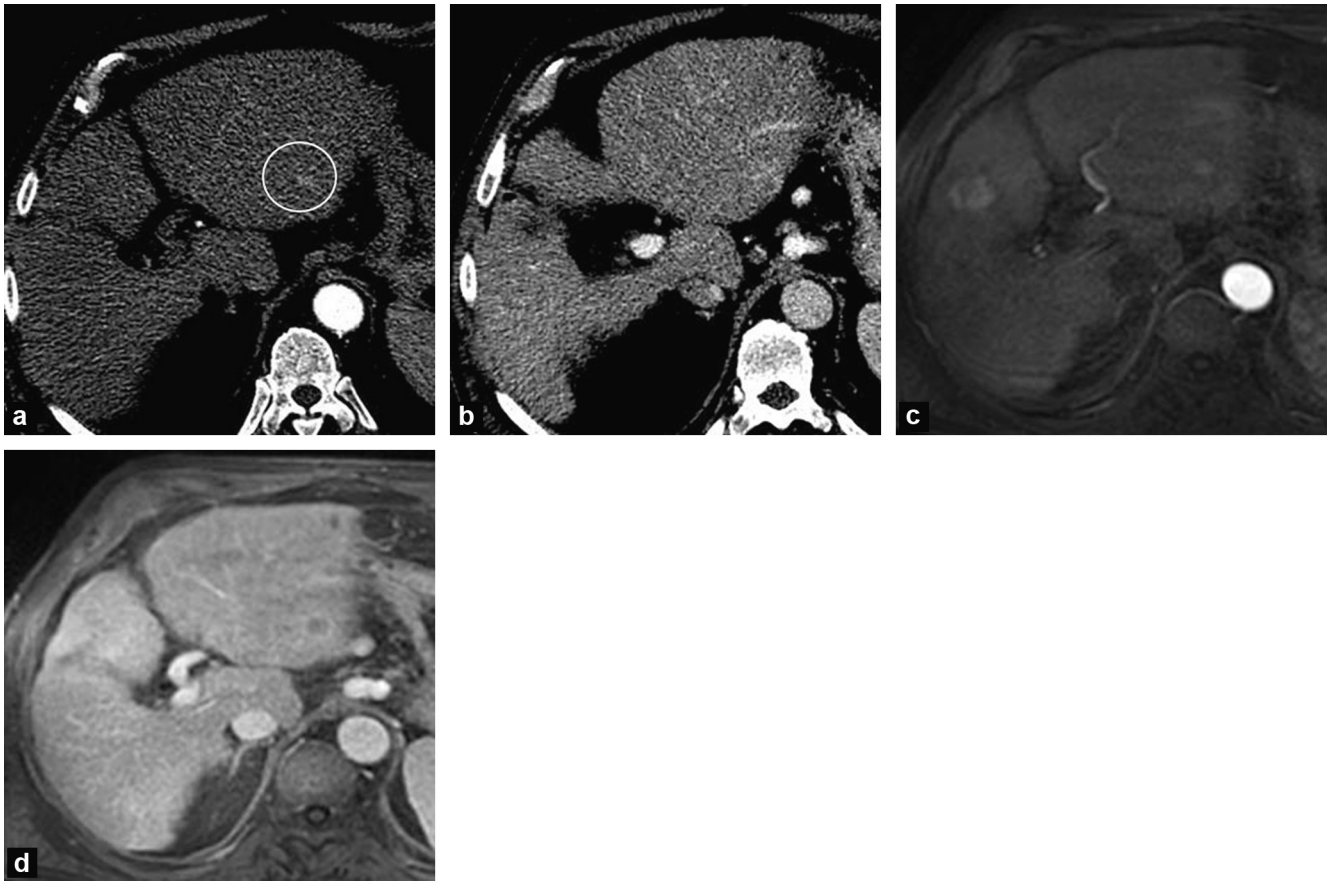

Figure 2. The usefulness of alternative imaging if the lesion is atypical. Monitoring examination for cirrhosis of exogenous and metabolic origin. CT scan in the arterial (a) and portal (b) phases: the lesion is hardly visible in the arterial phase and does not wash out in the portal phase (circle). T1-weighted MRI with fat saturation in the arterial (c) and portal (d) phases: the nodule has a typical appearance, hypervascular in the arterial phase with washout of the lesion.

enhanced in the hepatocytic phase, whereas 100% of dysplastic nodules are iso- or hyperintense in the hepatocytic phase [20] (Fig. 5).

Hypovascular small hepatocellular carcinoma

Small HCCs and well-differentiated HCCs are less often hypervascular than larger HCCs [9,21,22]. 17% of HCC lesions measuring less than 2 cm are reported to be hypovascular [23]. It is difficult to imagine a tumour, which is not enhanced in the arterial phase being a hepatocellular carcinoma, irrespective of the signs associated with it (Fig. 6). In these circumstances, a biopsy must be performed.

The problem of hypovascular HCCs can be associated with fat-containing HCCs. Fat content is highly suggestive of HCC in the context of cirrhosis, but other tumours with a fat content (adenoma, angiomyolipoma, etc.) cannot be formally ruled out [24]. Apart from the fact that fat is present, arterial hypervascularisation remains moderate or non-existent and lesion washout cannot be detected. Non-invasive diagnosis following the international recommendations cannot therefore be made in these cases (Fig. 7). The frequency of these fatty HCCs among small (less than 2 cm) HCCs has been reported as 12% [9].

Pseudotumours

In chronic liver disease, the two pseudotumours that will pose problems for differential diagnosis with small HCC are vascular disorders, particularly arterioportal fistulas and confluent fibrosis. These abnormalities have quite characteristic radiological signs, which usually allow them to be recognised.

In liver cirrhosis, micro-emboli of the portal vasculature are frequently associated with arterioportal fistulas, in the absence of any tumour.

They are typically well defined, sub-capsular, enhanced in the arterial phase, then becoming homogeneous with the adjacent parenchyma in the portal phase.

However, in some cases they can acquire a nodular appearance, while usually remaining peripheral. In addition, they can maintain a positive contrast gradient in the portal phase [25]. They are only visible on injected sequences and are not seen without contrast injection, whatever MRI sequence is used (Fig. 8).

Confluent fibrosis is often larger. It frequently has a peripheral starting point, accompanied by retraction of the capsule. It appears hyperintense with T2-weighting, enhances gradually and is mainly visible in the late phases (after 3 min) (Fig. 9).

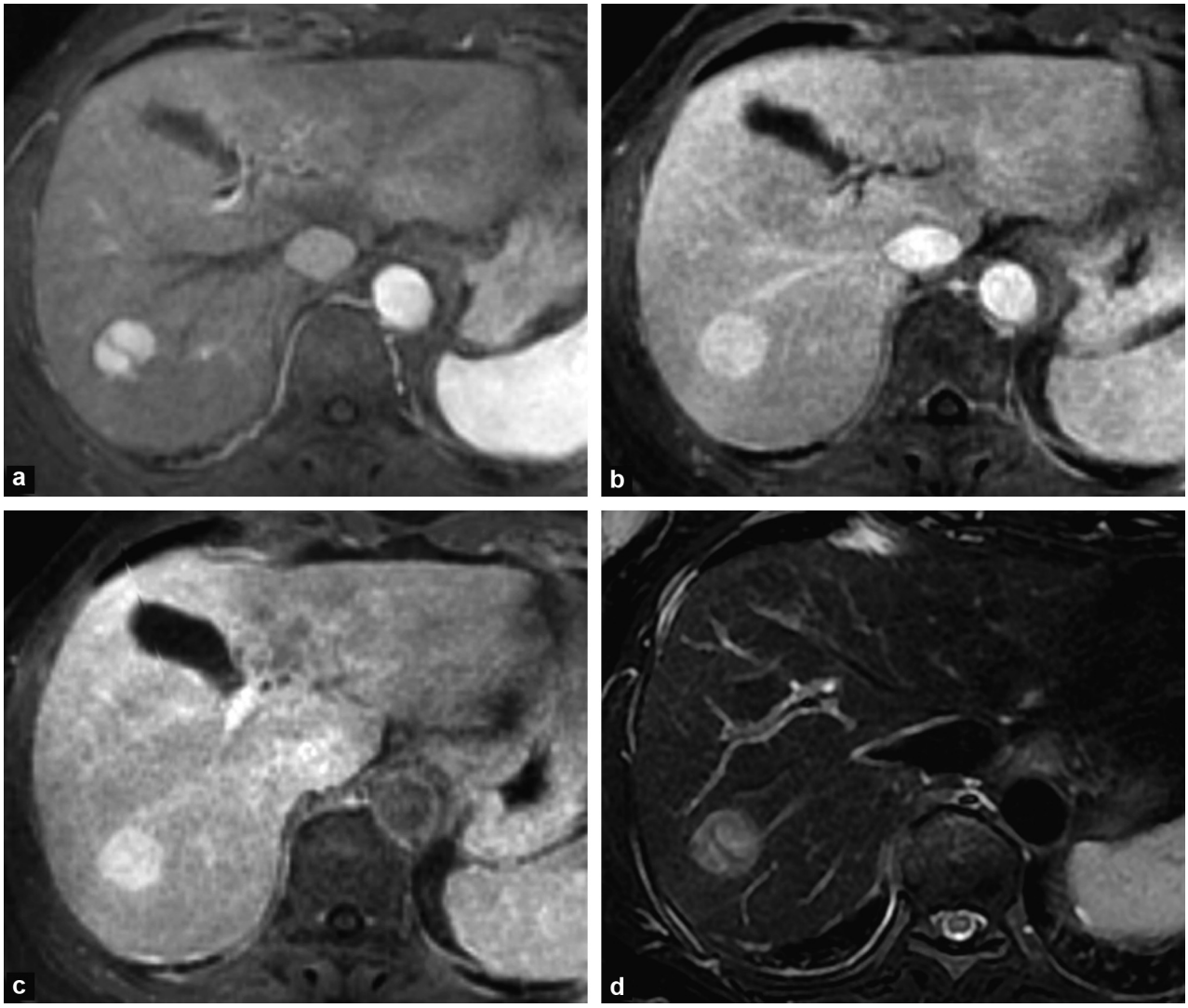

Figure 3. The usefulness of T2-weighting. Monitoring examination for cirrhosis of exogenous origin. T1-weighted MRI with fat saturation after gadolinium injection in the arterial (a), portal (b) and late (c) phases, and with T2-weighting (d): hepatocellular carcinoma enhanced in the arterial phase after injection, without washout of the lesion in the portal and late phases, but with hyperintensity with T2-weighting.

Other tumours

While the appearance of a nodule in liver cirrhosis should in the first instance suggest HCC, other tumours can be encountered in a cirrhotic liver.

Some are hypovascular (peripheral cholangiocarcinoma, metastasis), and will not therefore immediately suggest a hepatocellular carcinoma; others, hypervascular in the arterial phase (hypervascular haemangioma, adenoma, focal nodular hyperplasia), will be the differential diagnoses for an atypical small HCC. Dysplastic nodules may appear to be very similar to small HCC.

Peripheral cholangiocarcinoma is a tumour promoted by cirrhosis. Hypervascularisation in the arterial phase is rare, but possible. It has been reported recently that intrahepatic cholangiocarcinomas in liver cirrhosis were more hypervascularised than those occurring in non-cirrhotic livers [26]. In this case washout may be present.

However, the appearance of a peripheral cholangiocarcinoma is usually of a tumour with slow, often incomplete, peripheral enhancement (Fig. 10) [27,28].

Hypervascular haemangiomas are common. In the arterial phase, their appearance can be perfectly attributed to a small HCC (Fig. 11), but there is no lesion washout. On the contrary, the lesion tends to retain the contrast agent in the interstitial phase, the enhancement kinetics being the same as that of large arteries such as the aorta. Another pointer is the evident arterial hypervascularisation of the parenchyma around the nodule. In the end, the convincing argument is provided by definite hyperintensity in a T2-weighted MR image [29].

There can also be focal nodular hyperplasia in a cirrhotic liver. With the exception of lesion washout, its appearance perfectly mimics the appearance of an HCC (Fig. 12). Hyperintensity with T2 and diffusion-weighting is possible. The use of a liver-specific contrast agent showing FNH fixation and the absence of fixation by HCC could be a means of non-invasive diagnosis [30,31].

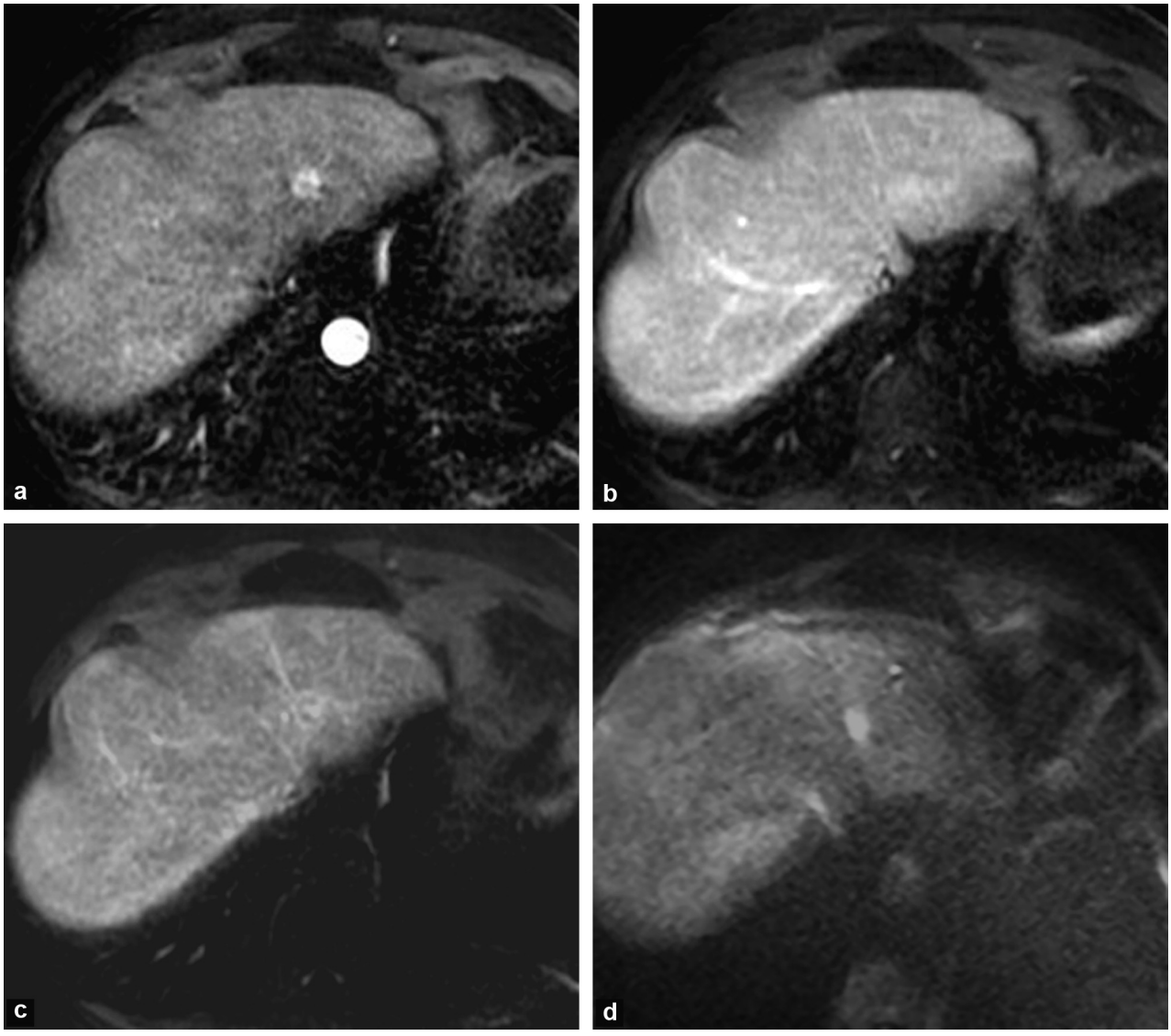

Figure 4. The usefulness of diffusion-weighted sequences. Monitoring examination for HBV cirrhosis. T1-weighted MRI with fat saturation after gadolinium injection in the arterial (a), portal (b) and late (c) phases and with diffusion-weighting (d): hepatocellular carcinoma enhanced in the arterial phase after injection, without washout of the lesion in the portal and late phases, but with hyperintensity with diffusion-weighting.

Dysplastic nodules are often hypervascular in the arterial phase: a recent study [15] showed this to be the case in 63% of them. In the same study, lesion washout was present in 16% of cases. However, dysplastic nodules are not generally hyperintense with T2 or diffusion-weighting. Fixation of the liver-specific contrast agent in the hepatocytic phase has been reported as constant [20]. The evolution of dysplastic nodules has been little studied in the literature, and their current management is often little different from management of HCC, but they do not seem to develop systematically into HCC [13]. In this context, the use of gadoxetic acid currently appears to be the most efficient technique for differentiating between these lesions [20].

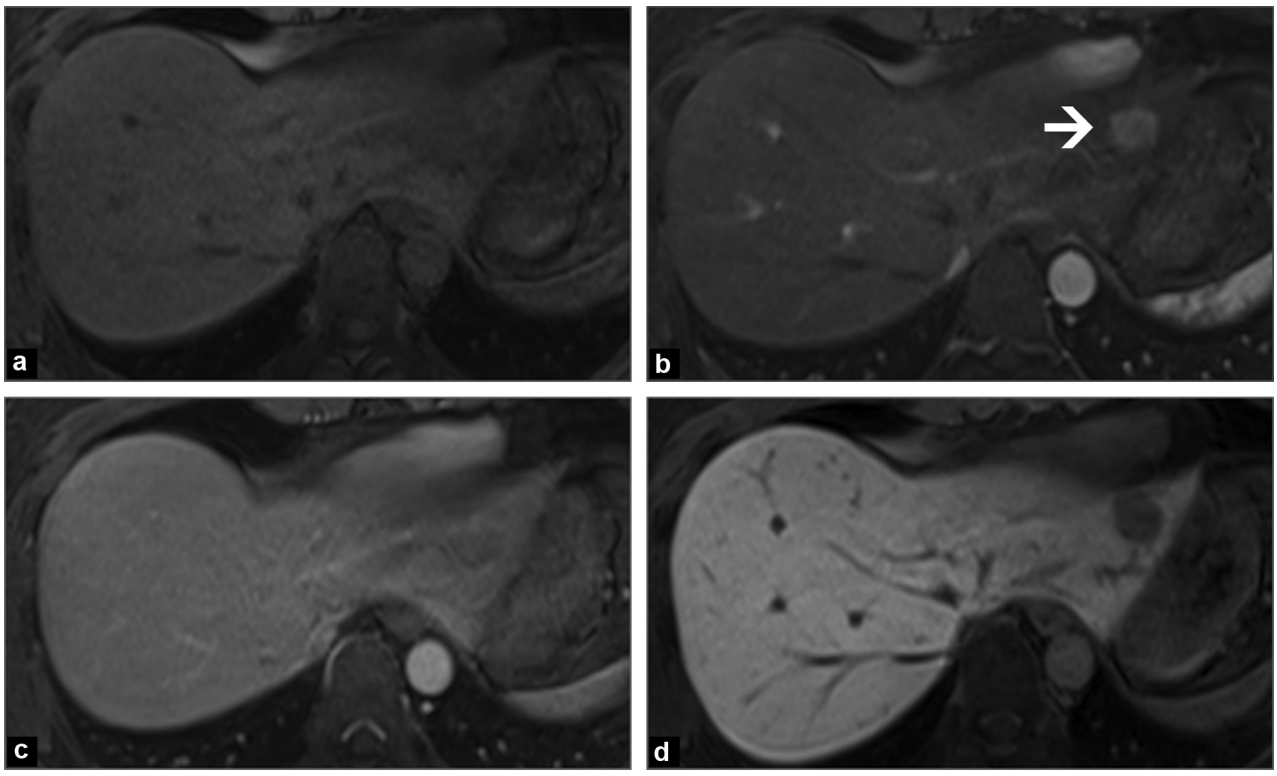

Figure 5. The usefulness of liver-specific contrast agents. T1-weighted MRI without (a) then after injection of gadoxetic acid in the arterial (b), portal (c) and hepatobiliary (d) phases. Hepatocellular carcinoma of the left lobe of the liver (arrow), enhanced in the arterial phase, without lesion washout and no fixation of the contrast agent in the hepatobiliary phase.
Images from Myeon-Jin Kim (MD), Seoul, Republic of Korea.

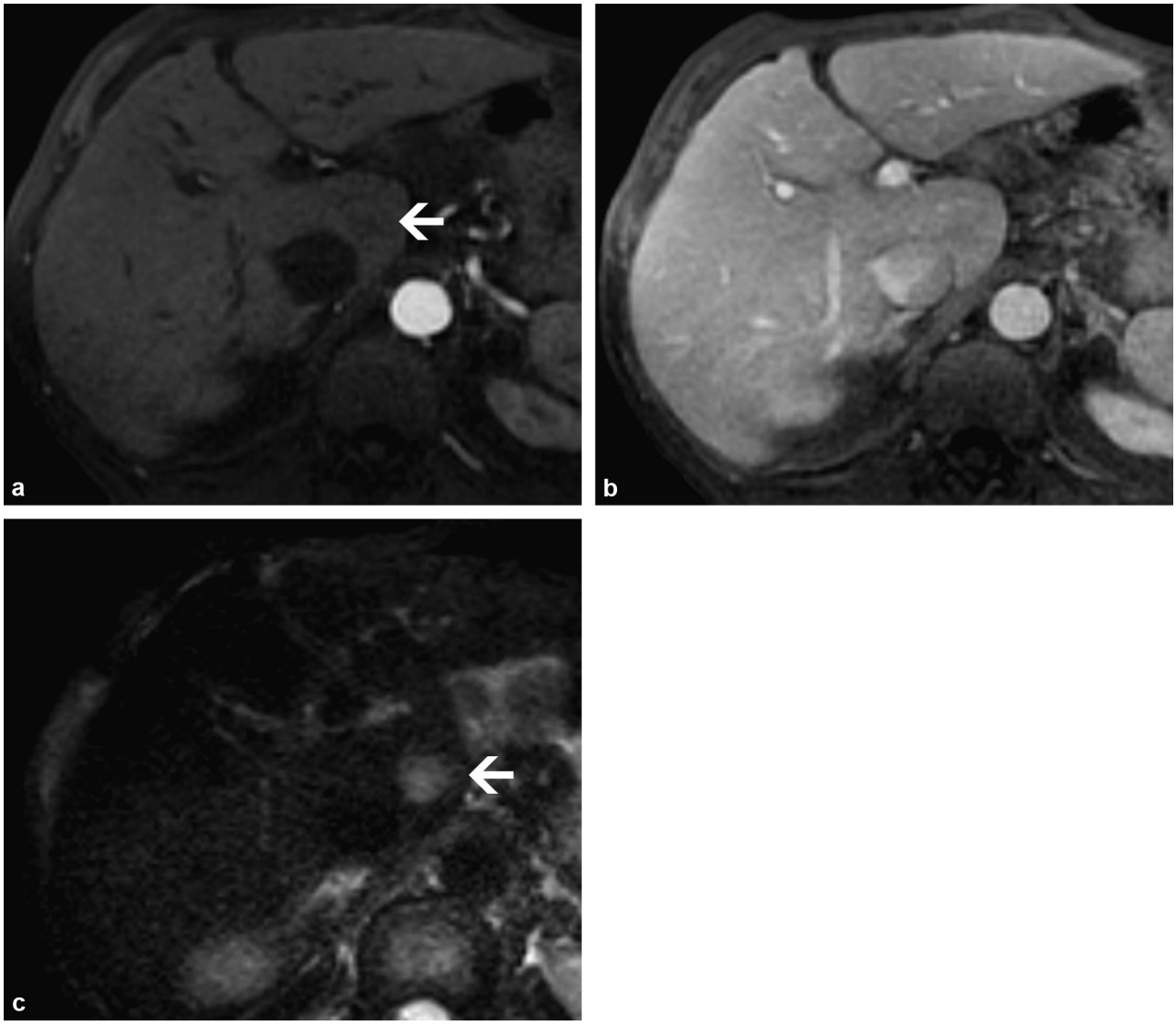

Figure 6. Hypovascular hepatocellular carcinoma (HCC). Monitoring examination for cirrhosis of exogenous origin. T1-weighted MRI with fat saturation in the arterial (a) portal (b) phases and diffusion-weighted sequence (c). The HCC is hypovascular but hyperintense in the diffusion-weighted sequence (arrow).

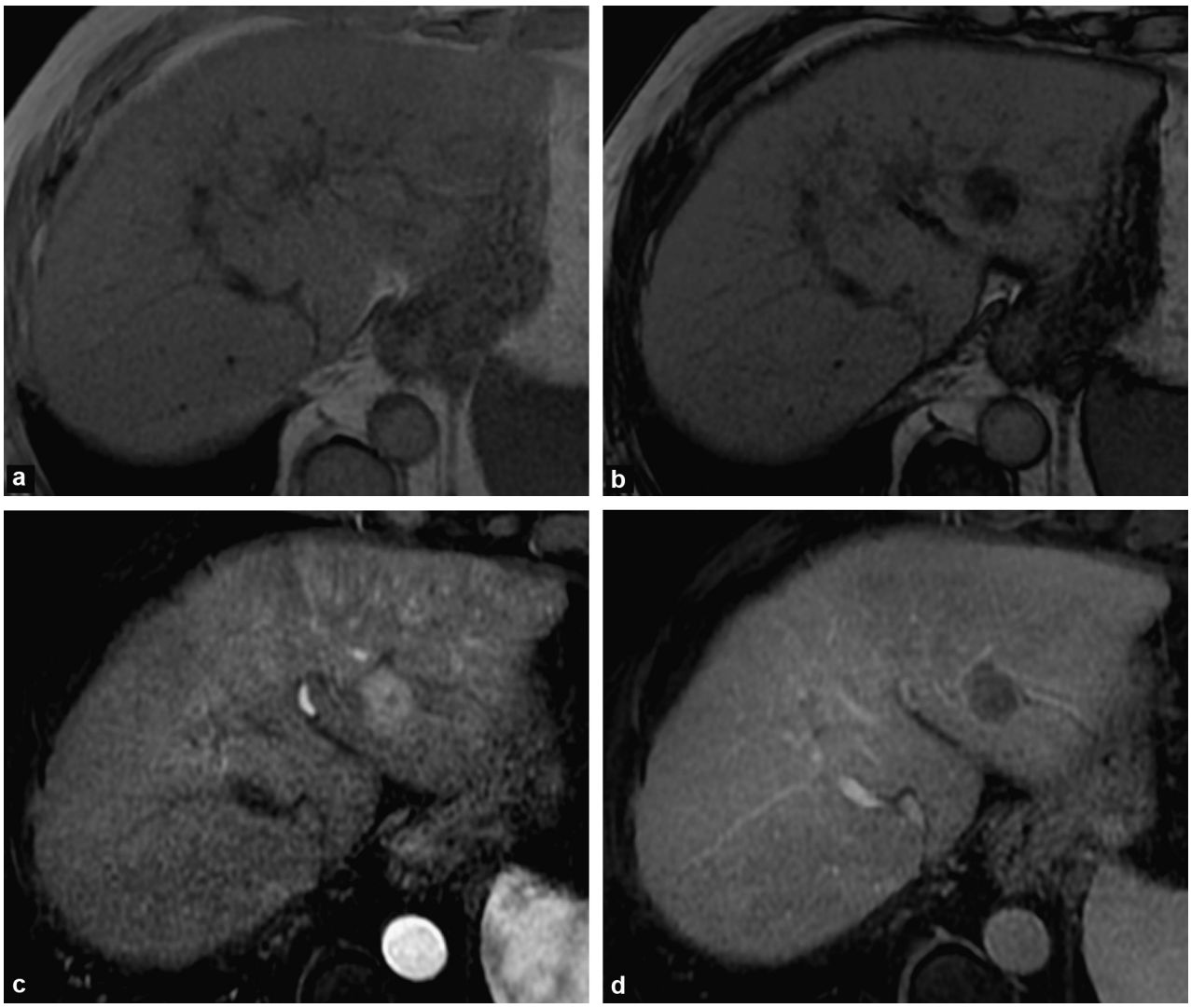

Figure 7. Hepatocellular carcinoma with a fatty component. Monitoring examination for cirrhosis of metabolic origin. T1-weighted MRI in phase (a) and out of phase (b): out-of-phase fall in signal indicating its fat content. T1-weighted image with fat saturation after gadolinium injection in the arterial (c) and portal (d) phases: enhanced in the arterial phase with lesion washout accentuated by the fat content.

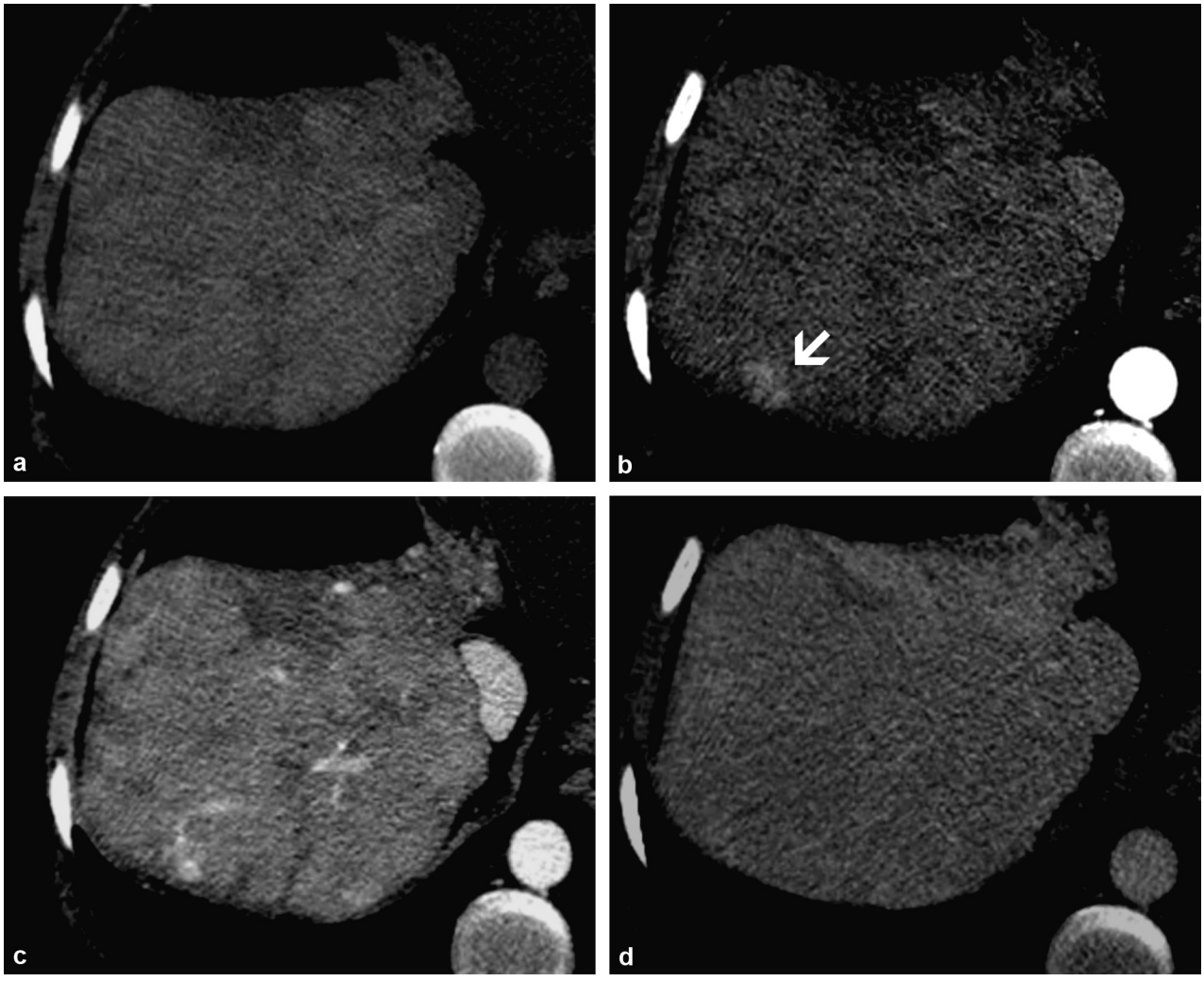

Figure 8. Arterioportal fistula. Monitoring examination for cirrhosis of exogenous origin. CT scan without (a) and after injection of an iodinated contrast agent in the arterial (b), portal (c) and late (d) phases: small peripheral arterioportal fistula (arrow) spontaneously isodense (a), responsible for parenchymal enhancement from the arterial phase, and which became homogeneous in the portal and late phases.

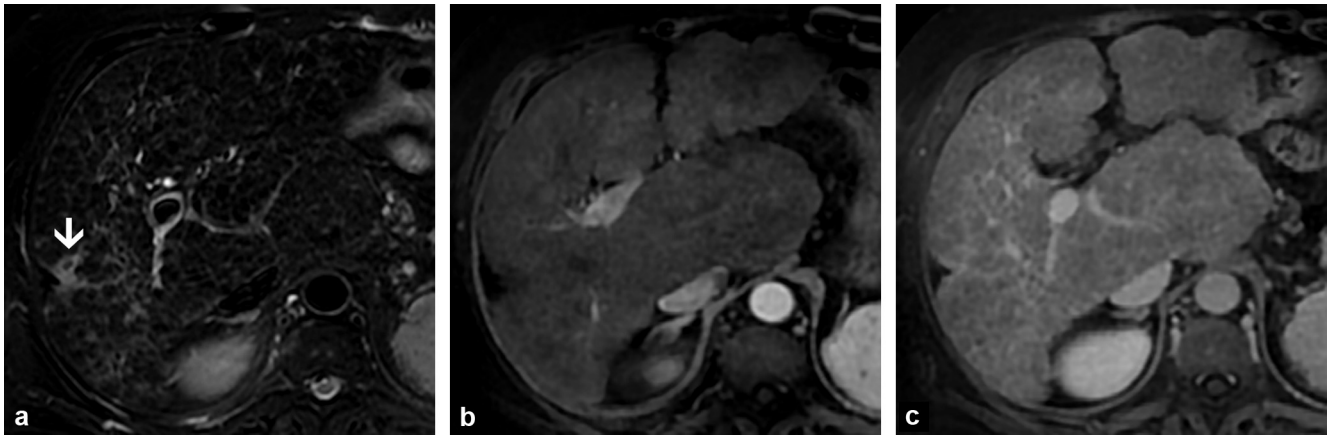

Figure 9. Peripheral confluent fibrosis. Monitoring examination for cirrhosis of exogenous and metabolic origin. T2-weighted (a) and T1-weighted MRI with fat saturation in the arterial (b) and late (c) phases: peripheral confluent fibrosis with capsule retraction (arrow) with T2-weighted hyperintensity, with no enhancement in the arterial phase but gradually enhancing in the late phase (after 3 min).

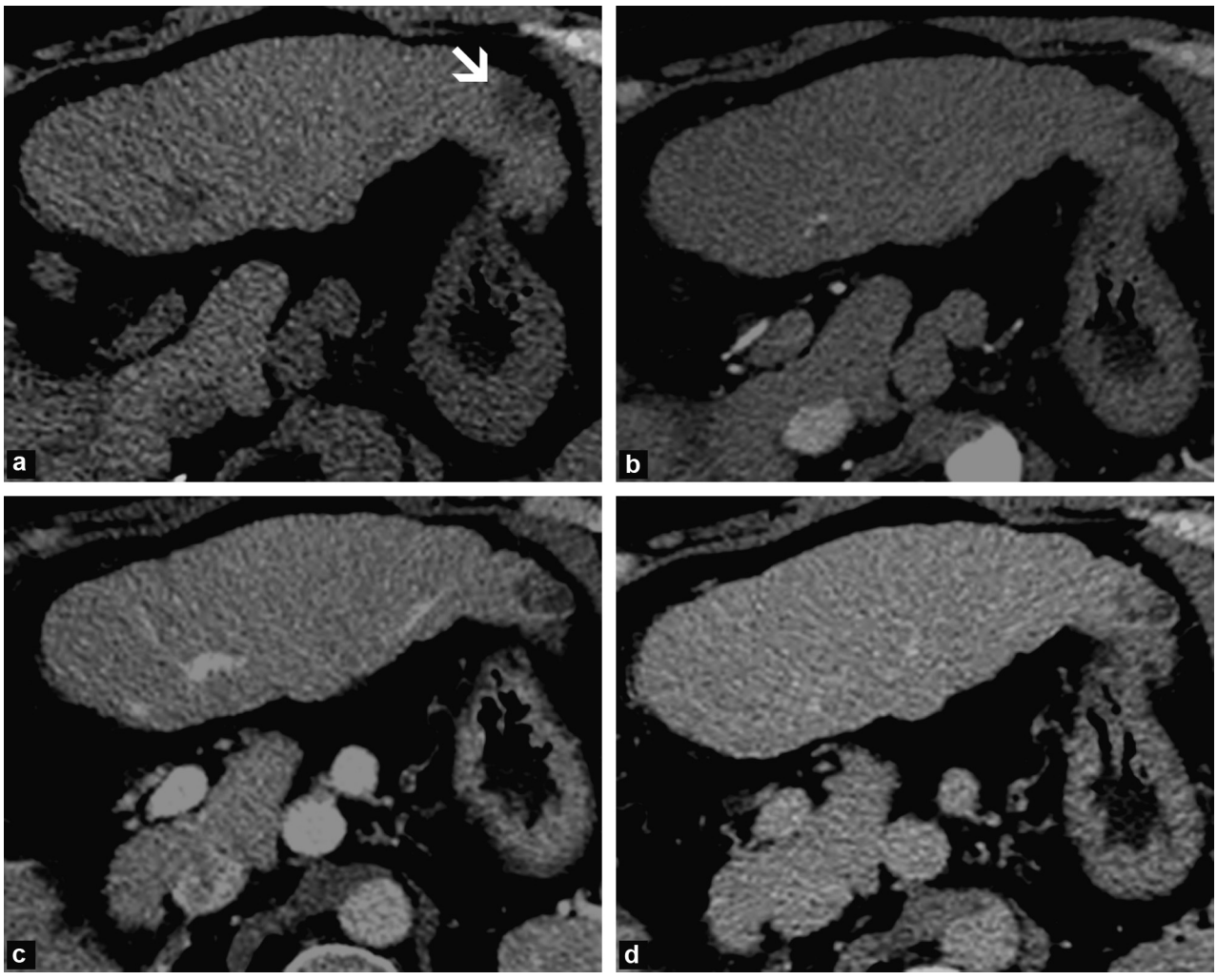

Figure 10. Cholangiocarcinoma. Monitoring examination for cirrhosis of exogenous origin. CT scan without (a) and after injection of an iodinated contrast agent in the arterial (b), portal (c) and late (d) phases: peripheral cholangiocarcinoma of the tip of the left lobe of the liver (arrow), spontaneously hypodense, without arterial hypervascularisation, with incomplete peripheral enhancement in the late phase (d).

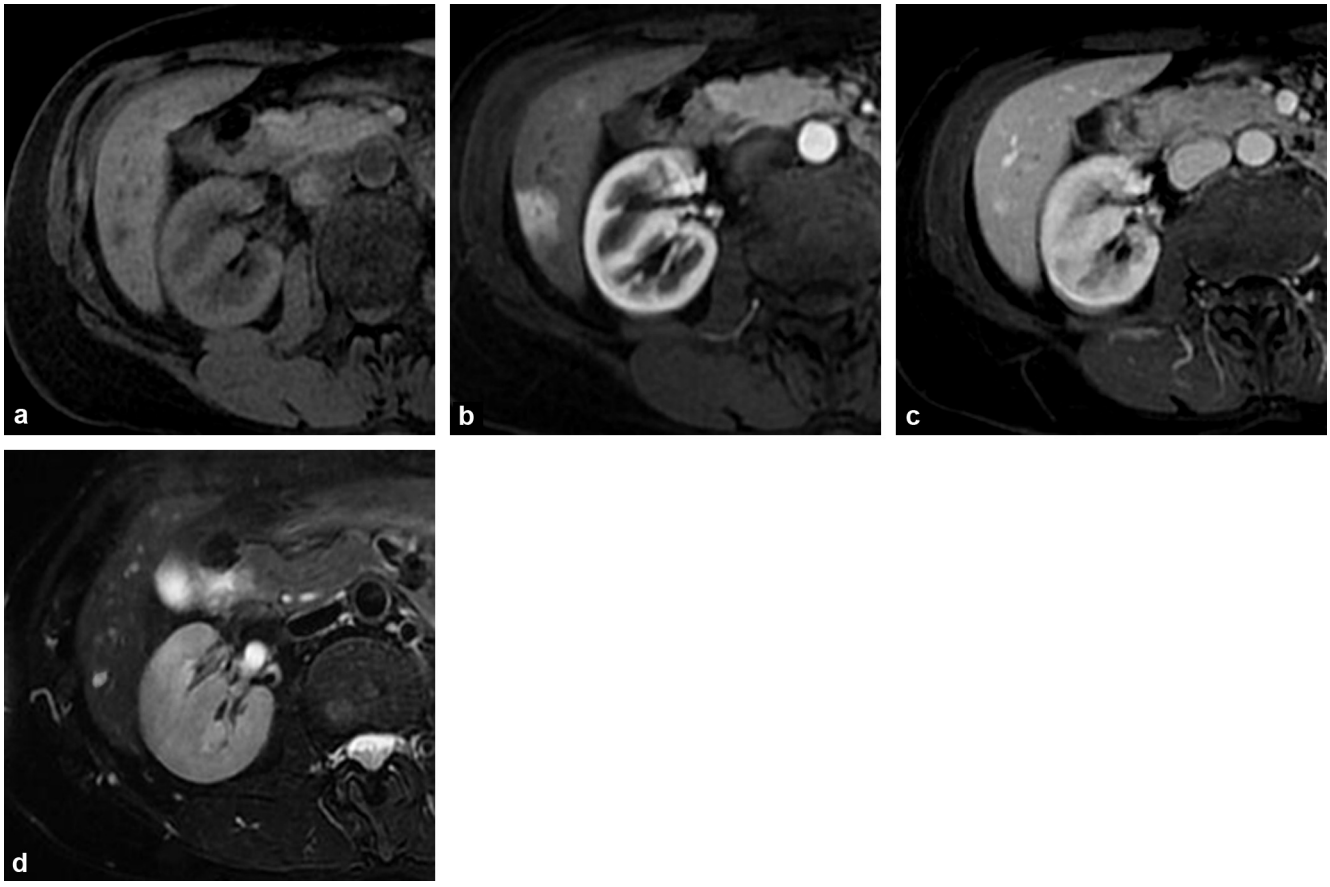

Figure 11. Haemangioma. Monitoring examination for cirrhosis of viral origin. T1-weighted MRI with fat saturation without (a), then after gadolinium injection in the arterial (b) and portal (c) phases and with T2-weighting (d). Hypervascular lesion in the arterial phase, with persistent enhancement in the portal phase. Note the parenchymal enhancement around the lesion in the arterial phase due to high arterial flow. The clear hyperintensity with T2-weighting confirms the diagnosis of haemangioma.

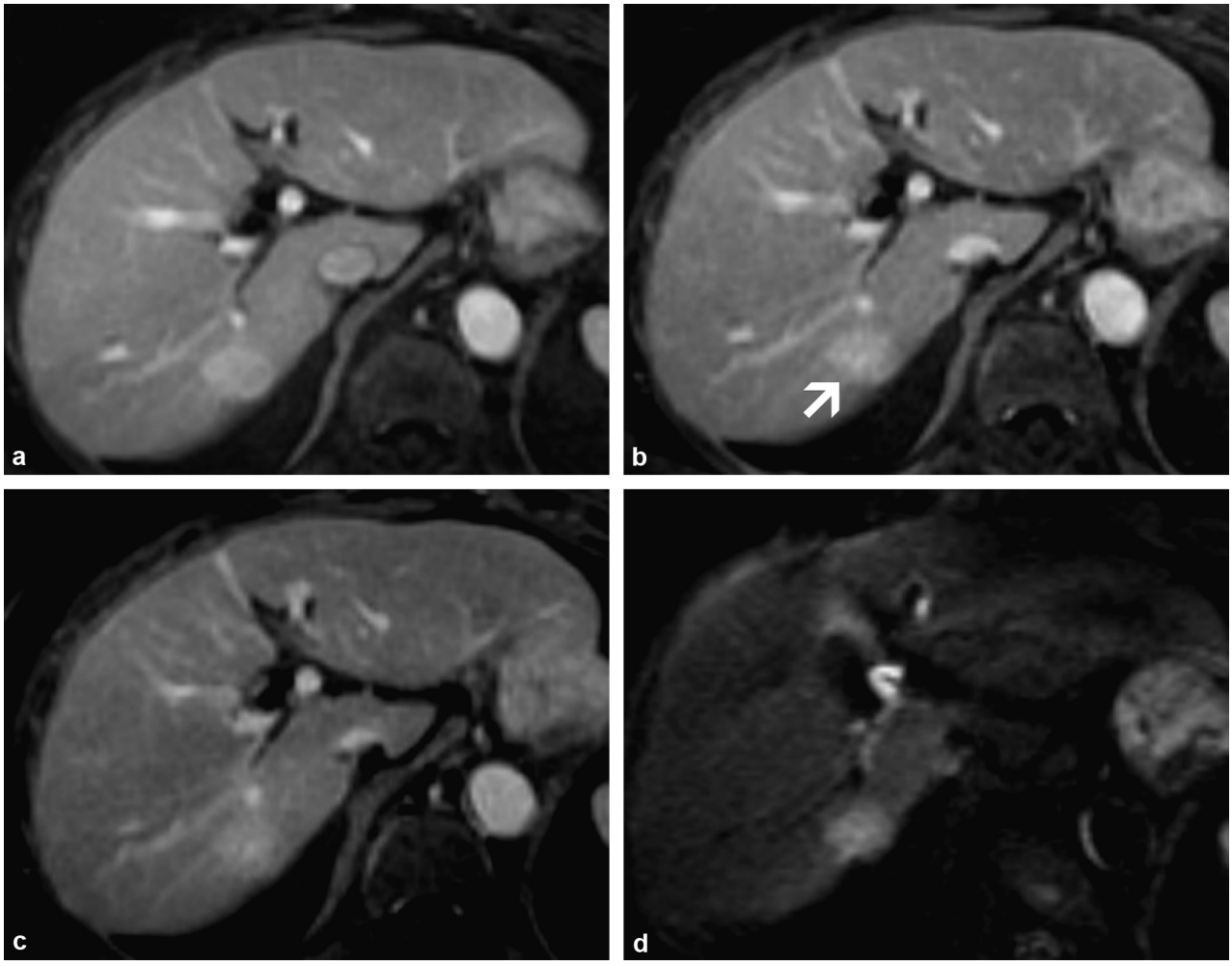

Figure 12. Focal nodular hyperplasia (FNH). Monitoring examination for cirrhosis of viral origin. T1-weighted MRI with fat saturation after gadolinium injection in the arterial (a), portal (b), late (c) phases and with diffusion-weighting (d): focal nodular hyperplasia (arrow), enhanced in the arterial phase with persistence of the enhancement in the portal and late phases. A small central area enhanced in the late phase is visible helping to suggest a diagnosis of FNH. Note the misleading hyperintensity of the lesion with diffusion-weighting.

Conclusion

The diagnosis of small HCC poses two major difficulties. Firstly, the typical vascular kinetics of HCC allowing it to be diagnosed non-invasively are often absent. Secondly, lesions that can mimic HCC (an arterioportal fistula, confluent fibrosis, a hypervascular haemangioma, benign hepatocellular tumours, etc.) are often small and they appear similar to an atypical small HCC.

There are two broad solutions to the problem: first of all, widen the range of examinations. This increases the possibility of detecting the characteristic vascular kinetics of HCC. Secondly, signs other than those provided by the vascular kinetics must be used, namely from T2 and diffusion-weighting, and liver-specific contrast agents. In some cases these tools will provide differential diagnoses (confluent fibrosis, hypervascular haemangioma, benign hepatocellular tumour). In other cases they will strengthen the suspicion of HCC.

It is possible (and without doubt desirable) that in the future these solutions will form part of the algorithm for non-invasive diagnosis of HCC in a cirrhotic liver.

It is important to remember that, whatever the diagnostic tools used, whenever a tumour is discovered in a cirrhotic liver, even (and particularly) if it is small, our attitude should not be to monitor its evolution but to make a careful radiological examination of its appearance. If a certain diagnosis of HCC or another lesion cannot be made with imaging, a biopsy must be performed without fail.

TAKE-HOME MESSAGES

- Six-monthly ultrasound monitoring of patients with cirrhosis should lead to the detection of small HCCs.
- Non-invasive diagnosis of HCC in cirrhotic patients is possible using CT and/or MRI.
- The characteristic appearance of HCC is arterial hypervascularisation followed by lesion washout in the portal and/or late phase.
- Small HCCs have an atypical CT or MRI appearance in 20 to 50% of cases.

- In the absence of the characteristic appearance of HCC in one examination (CT or MRI) the other type of examination should be carried out.
- The use of diffusion-weighted and T2-weighted imaging and liver-specific contrast agents can help in the diagnosis of small HCCs, but these methods are not yet recognised by the guidelines as non-invasive diagnostic tools.
- Lesions other than HCC occur in the cirrhotic liver: a hypervascular nodule is not necessarily HCC, and a hypovascular nodule does not eliminate HCC.
- If the characteristic appearance of HCC is not seen in imaging, a biopsy must be performed.

Clinical case

This 58-year-old patient was being monitored for cirrhosis of exogenous origin: he had been weaned from the cause for 5 years. During the six-monthly ultrasound monitoring, a 16 mm nodule was discovered in the left lobe of the liver. T2-weighted (Fig. 13a) and T1-weighted MRI after injection of gadolinium with acquisition in the arterial (Fig. 13b) and portal phases (Fig. 13c) was performed to characterise the nodule.

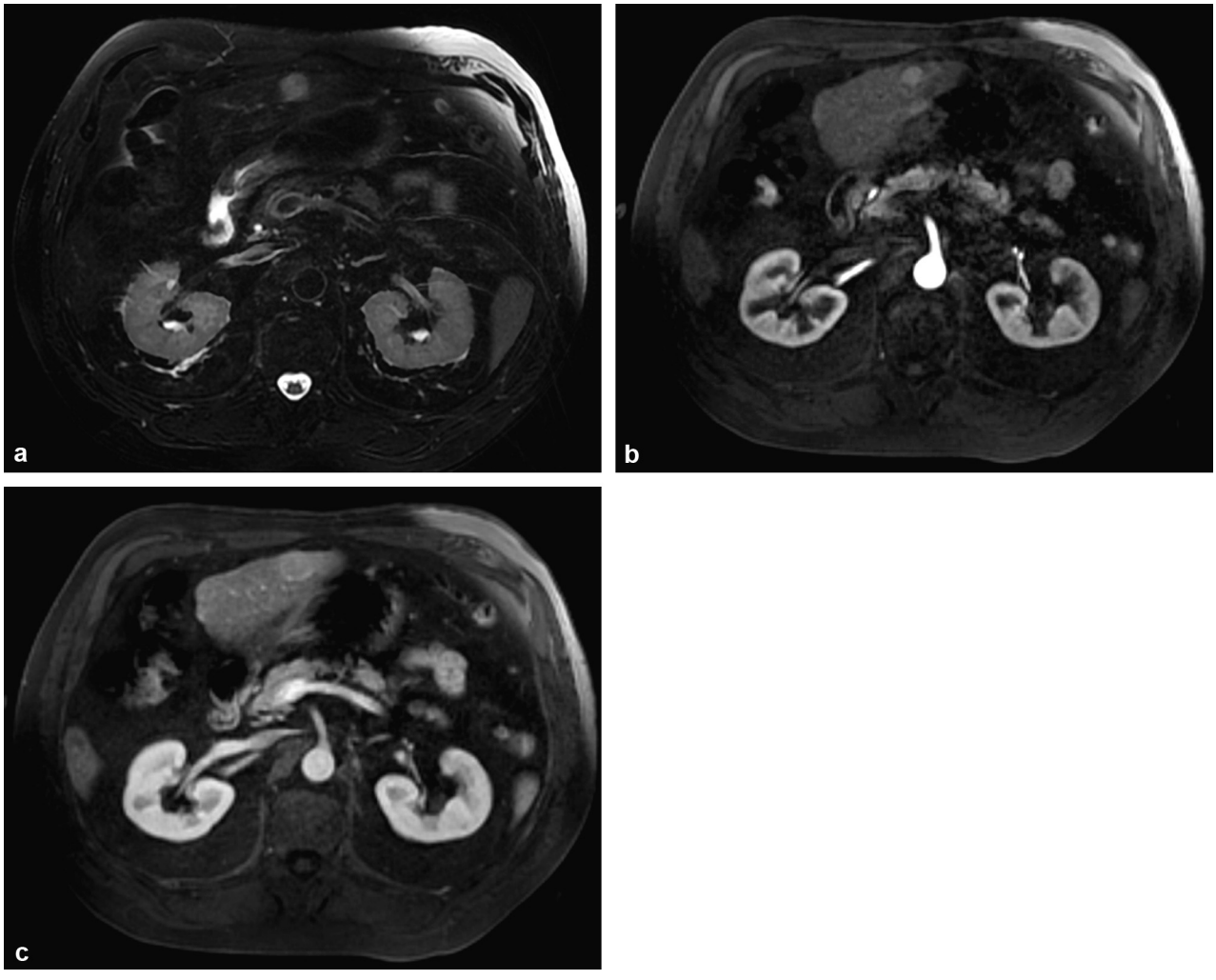

Figure 13. T2-weighted sequence with fat saturation (a), T1-weighted sequence with fat saturation after gadolinium injection and acquisition in the arterial (b) and portal (c) phases.

Questions

1. Why can we not make the diagnosis of HCC?
2. What do you do in practice?
3. Is there a feature on one of these sequences, which could point towards a diagnosis of HCC?
4. If you cannot make a diagnosis with imaging, what would you recommend for this patient?

Answers

1. No diagnosis of HCC can be made because there is no lesion washout.
2. Another type of examination should be performed (CT scan) as recommended by the guidelines for non-invasive diagnosis of HCC.
3. The hyperintensity with T2-weighting suggests HCC, but cannot be considered to positively confirm it according to the current guidelines.
4. A biopsy is essential; simply monitoring the lesion is not acceptable.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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