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Guidelines for the use of contrast-enhanced ultrasound in hepatocellular carcinoma

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ABSTRACT

Surveillance of patients at risk of developing hepatocellular carcinoma (HCC) relies on ultrasound (US) examinations performed at 6-month intervals. Early detection of HCC on a cirrhotic background is a challenging issue, since the US features of the different entities in the multi-step process of hepatocarcinogenesis – such as low-grade and high-grade dysplastic nodule – do overlap. Contrast-enhanced US allows reliable detection of arterial neoangiogenesis associated with the malignant change. Several reports have shown that the ability of contrast-enhanced US to diagnose HCC currently approaches that of optimised multidetector computed tomography (CT) or dynamic magnetic resonance (MR) imaging protocols. The use of contrast-enhanced US to characterise nodular lesions in cirrhosis has recently been recommended by the clinical practice guidelines issued by the European Federation of Societies for Ultrasound in Medicine and Biology and the American Association for the Study of Liver Diseases. Contrast-enhanced US has also been successfully used to assess response of HCC to image-guided percutaneous ablation procedures. In this article, we discuss the advantages and limitations of contrast-enhanced US with respect to the other imaging modalities in the setting of HCC.

1. Introduction

Despite advances in computed tomography (CT) and magnetic resonance (MR) imaging, ultrasound (US) continues to play a key role in the diagnostic management of hepatocellular carcinoma (HCC). According to the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD), US is the recommended tool for surveillance of patients at risk of developing HCC.[1,2] The introduction of US contrast agents and the development of contrast-specific scanning techniques have substantially increased the ability of US to detect and characterise focal liver lesions as well as to assess tumour response to image-guided percutaneous ablation procedures.[3–5] Recently, the European Federation of Societies for Ultrasound in Medicine and Biology has issued recommendations for the use of contrast agents in liver US, and the clinical practice guideline of the AASLD has included contrast-enhanced US – along with contrast-enhanced CT and contrast-enhanced MR imaging – amongst the techniques that can be used for non-invasive diagnosis of HCC in cirrhosis.[2,6]

2. Detection

Surveillance programmes aimed at early detection of HCC in patients at risk are based on US examinations performed at 6–12 months intervals.[1,2,7–11] Early detection of HCC, especially on a cirrhotic background, is a challenging issue. Liver

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cirrhosis is characterised by fibrous septa and regenerative nodules. These features produce a coarse pattern on US, that may impair identification of small tumours. Moreover, a comprehensive assessment of the liver parenchyma may sometimes be impossible because of the patient's body habitus, colonic interposition or morphologic changes induced by cirrhosis – such as retraction of the right liver lobe – that reduce the ability to explore the liver via intercostal scans. The ability to detect the emergence of a small HCC is highly dependent on the expertise of the operator performing the examination and the availability of state-of-the-art equipment. When these requirements are met, surveillance has proved effective in detecting HCC at an early stage.[12,13,14,15] The value of US surveillance performed in a primary care setting by operators who do not have specific skills is questionable. If the expertise is not available, the efficacy of surveillance will be lost. Upon detection of a suspicious nodule, the recommended policy is to evaluate the patient in referral centres with optimal human and technical resources.[1]

Unfortunately, the use of contrast-enhanced US did not prove beneficial in increasing the ability to detect small HCC tumours. As a general rule, contrast-enhanced US techniques are subject to the same limitations as any other US mode: if the baseline scan is disappointing, the contrast-enhanced US study will be disappointing as well.[6] In addition, as described later, the highest contrast between tumour and liver parenchyma is seen during the short time of the arterial phase. Whilst multidetector CT and dynamic MR sequences can automatically image the entire liver parenchyma in a few seconds, a comprehensive manual scanning of the whole liver with US during the arterial phase is hardly possible, even when performing repeated contrast injections. Thus, there is currently no indication to use microbubble contrast agents to increase the detection rate of HCC in patients undergoing US surveillance.[6]

3. Characterisation

Carcinogenesis is often a multi-step process in liver cirrhosis. This process includes progression from cirrhotic nodule, to macroregenerative nodule, to low-grade dysplastic nodule (DN), to high-grade DN, to frank HCC.[16] Progression along the multi-step pathway is characterised by cytological and architectural changes.[17] Unfortunately, these entities show variable and overlapping features at baseline US, making reliable differential diagnosis impossible. Small HCC may appear hyperechoic, hypoechoic or isoechoic with respect to liver parenchyma, and is usually indistinguishable from a macroregenerative nodule or DN. In addition, small hyperechoic HCC may be indistinguishable from a hemangioma.[18]

One of the key pathologic factors for differential diagnosis between HCC and non-malignant hepatocellular lesions that is reflected in imaging appearances is the vascular supply to the nodule. Through the progression from macroregenerative nodule to low-grade DN, to high-grade DN, to frank HCC, one sees loss of visualisation of portal tracts and development of new arterial vessels, termed non-triadal arteries, which become the dominant blood supply in overt HCC lesions.[19,20,21] This arterial neoangiogenesis is the landmark of HCC and is the key for imaging diagnosis.[22,23]

Doppler US techniques have long been used in attempts to evaluate tumour vascularity in HCC.[24,25,26,27] At colour or power Doppler US, a large HCC is usually displayed as a vascular-rich lesion containing intratumoural flow signals with an arterial Doppler spectrum. A basket pattern, which is a fine blood-flow network surrounding the nodule, and tumour vessels flowing into the lesion and branching within it, are typically observed. Doppler interrogation shows a pulsatile Doppler waveform with high frequency shifts (>1 kHz) and abnormally elevated resistive index (>0.71).[25,27] In contrast, macroregenerative nodule and DN either do not have any detectable intratumoural vascularity or show arterial vessels with low frequency shifts and a normal resistive index.[28] However, in small HCC tumours, the sensitivity of Doppler US in showing arterial neovascularity is low, and abnormal flow can be demonstrated in less than 50% of the lesions.[24,28] In addition, the technique is quite cumbersome and the positive predictive value is not high.[29]

Several reports have shown that contrast-enhanced US is a tool to show arterial neoangiogenesis in HCC.[30,31,32,33] HCC typically shows strong intratumoural enhancement in the arterial phase, whilst macroregenerative nodule and DN usually do not show any early contrast uptake, and resemble the enhancement pattern of liver parenchyma. The ability of contrast-enhanced US to show arterial hypervascularisation appears to approach that of optimised multidetector CT or dynamic MR imaging protocols, provided that the nodule can be clearly identified on baseline scans (Table 1). In one study, in which only HCC tumours showing arterial hypervascularity at CT were included, the sensitivity of contrast-enhanced US in the detection of arterial hyperenhancement was 91%.[34] In two comparative analyses including consecutive patients with small nodules in cirrhosis detected during surveillance, contrast-enhanced US was superior to multidetector CT and slightly inferior to dynamic MR imaging in showing the presence of arterial hypervascularity (Table 1).[35,36]

Unfortunately, the sole detection of arterial hypervascularity in a small nodular lesion emerged in a cirrhotic liver – although suspicious for HCC – may not be considered as a conclusive finding. It is well established that non-malignant hepatocellular lesions – especially high-grade DN – may show arterial hypervascularisation on imaging.[37,38] Small, high-flow hemangiomas may also appear as hyperenhancing nodule.[39] A recent investigation has shown that in the setting of cirrhotic patients undergoing surveillance, the sole imaging finding of arterial hypervascularisation in small solitary nodules of 2 cm or less has a specificity of 86% and a positive predictive value of 92% for the diagnosis of HCC.[36] To increase the specificity of imaging diagnosis, it is mandatory to evaluate contrast wash-out during the portal venous and the late phase, as recently recommended by the 2005 EASL conference on HCC and the AASLD practice guideline.[2] Contrary to non-malignant entities, HCC is characterised by rapid wash-out of the contrast agent, and usually appears hypoenhanced in the portal venous or the late phase[36,37,38] (Fig. 1).

Table 1 – Studies comparing contrast-enhanced US with multidetector CT or dynamic MR imaging in the ability to detect arterial hypervascularisation in nodular lesions in cirrhosis

Author	No. of lesions	Lesion size	Detection rate	
			Contrast US	CT/MRI
Gaiani et al. [34]	103	2.8 ± 1.3 cm	91%	CT, 100%[a]
Bolondi et al. [35]	41	1–2 cm	61%	CT, 49%
	31	2–3 cm	97%	CT, 87%
Forner et al. [36]	60	0.5–2 cm	78%	MRI, 85%

a This series included only tumours showing arterial hypervascularity at multidetector at CT.

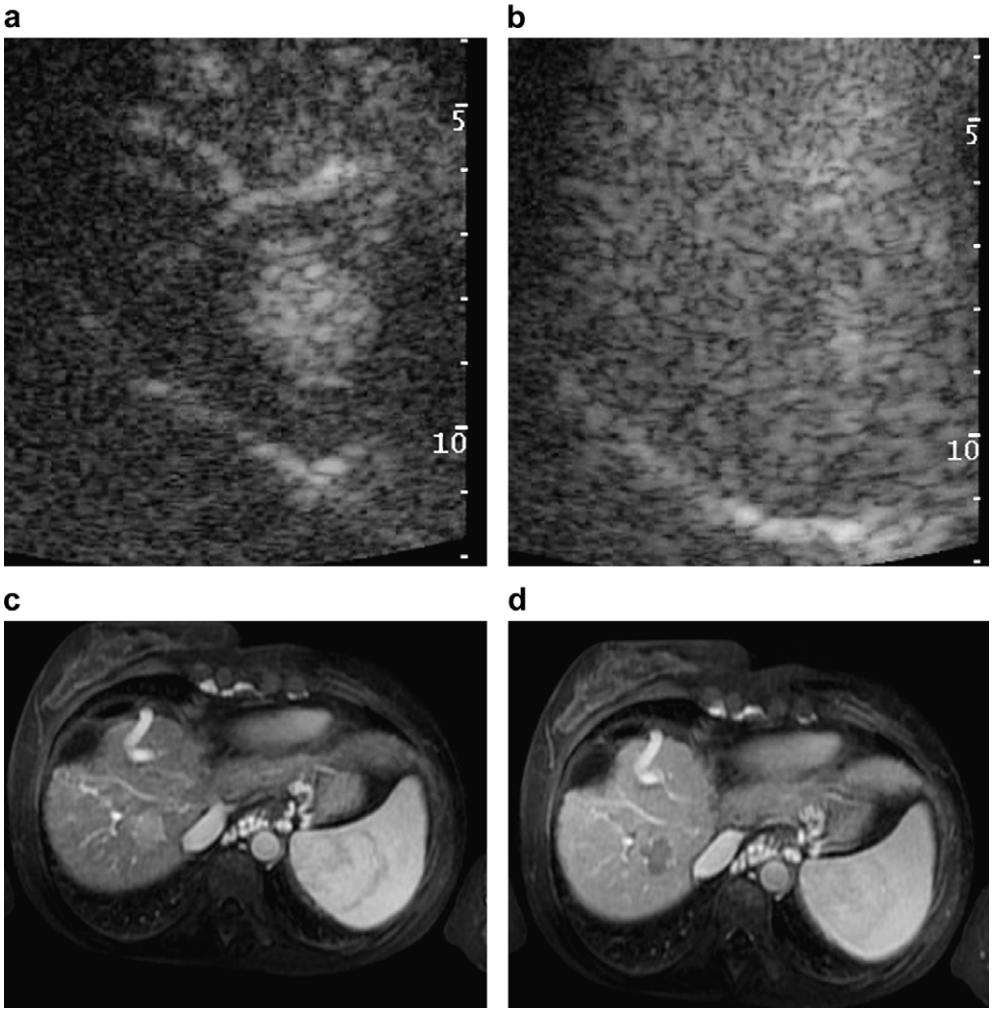

Fig. 1 – Non-invasive diagnosis of very-early HCC in cirrhosis. Contrast-enhanced US shows clear-cut enhancement in the arterial phase (a) with rapid wash-out in the portal venous phase (b) in a 2-cm nodule in cirrhosis. The same findings are observed on dynamic contrast-enhanced MR images obtained in the arterial phase (c) and the portal venous phase (d).

If strict criteria – including hypervascularisation in the arterial phase with wash-out in the portal venous or the late phase – are used to diagnose HCC, the very high specificity that can be obtained has the downside of a reduced sensitivity in the diagnosis of malignancy. In fact, the timing of contrast wash-out in HCC appears to be correlated with the degree of tumour differentiation. Whilst moderately or poorly differentiated tumours have fast contrast wash-out and appear as defects in the portal venous or the late phase, well-differentiated tumours may wash out slowly and be iso-enhanced with respect to the liver parenchyma in the portal venous or the late phase.[41,42,43] Thus, diagnosis of small, well-differentiated tumours remains a challenge. Nevertheless, this is the case for any dynamic imaging technique, and the diagnostic accuracy of contrast-enhanced US for the diagnosis of HCC appears to be similar to that of multidetector CT or dynamic MR imaging (Table 2)[36,40].

Table 2 – Studies comparing contrast-enhanced US with multidetector CT or dynamic MR imaging in the diagnosis of HCC in nodules 2 cm or smaller detected during US surveillance

Author	No. of patients	No. of lesions	Lesion size	Sensitivity	Specificity
Forner et al. [36]	60	60[a]	0.5–2 cm		
Contrast US				52%	93%
Dynamic MRI				62%	97%
Dai et al. [40]	72	103	1–2 cm		
Contrast US				91%	87%
Multidetector CT				80%	98%

Note. Figures refer to detection of typical enhancement pattern of HCC, i.e., arterial hypervascularizarion with venous wash-out.
a This series included only patients with solitary small tumours.

4. Staging

Accurate intrahepatic staging is essential for the proper clinical management of patients with HCC, particularly given the propensity of HCC, even at early stages, to produce satellite lesions via invasion of peripheral portal vein branches.

It is well established that US has limited sensitivity in the detection of tiny satellite lesions. When careful imaging with pathologic correlation on explanted livers was performed, the sensitivity of US was as low as 14% in the detection of lesions smaller than 2 cm, and as low as 0% for cancerous foci smaller than 1 cm.[44,45] Although these data have been collected mainly in patients with advanced cirrhosis who underwent liver transplantation (and therefore may not be applicable to the general population of cirrhotic patients with HCC) the rate of underestimation of the extent of the disease with US is clearly unacceptable. Unfortunately, as discussed earlier, the use of contrast agents did not result in any significant improvement in the ability of US to detect small tumours.[6] The duration of the arterial phase – during which HCC tumours stand out against the faintly enhanced liver parenchyma – is far too short to allow a comprehensive manual scanning of the entire organ. In the portal venous and the late phase, contrary to hepatic metastases, the contrast between tumour and liver is usually low, preventing identification of small tumours not detected on baseline scans. Thus, even in the era of contrast-enhanced US, the use of either multidetector CT or dynamic MR imaging for intrahepatic staging of HCC is a mandatory step before therapeutic planning.[23,46]

In large HCC tumours, thrombosis of portal vein branches due to tumour invasion is commonly observed on imaging. However, in the setting of liver cirrhosis, portal vein thrombosis has a prevalence of about 5%, even in the absence of HCC.[47] In patients with HCC, distinction between malignant and non-malignant portal vein thrombosis is of paramount importance, as vascular invasion determines the shift from intermediate-stage to advanced-stage according to the Barcelona Clinic Liver Cancer (BCLC) staging system.[48] Recent observations have shown that contrast-enhanced US may be a tool for this purpose.[49,50] Unlike bland thrombosis, malignant thrombi show the typical features of HCC, and demonstrate rapid enhancement in the arterial phase due to the presence of hypervascularized tumour tissue. In one study including 54 consecutive patients who had cirrhosis, biopsy-proven HCC, and thrombosis of the portal trunk or the main right or left branches, contrast-enhanced US showed absolute specificity and higher sensitivity than fine-needle biopsy in demonstrating the malignant nature of the thrombus.[49] In another series of 34 patients listed for transplantation for HCC on cirrhosis, who also showed thrombosis of the portal trunk or intrahepatic branches, contrast-enhanced US was able to accurately exclude the malignant nature of the thrombus, as confirmed by pathologic analysis of the explanted organs.[50]

5. Diagnostic work-up

The detection of a nodular lesion during US surveillance should always raise the suspicion of HCC.[1,2] However, pathologic studies have shown that a significant proportion of small nodules detected by US in cirrhotic livers do not correspond to HCC, but rather to non-malignant hepatocellular nodules. Percutaneous US-guided biopsy might be considered as the most straightforward approach to differentiate HCC from non-malignant hepatocellular lesions. Unfortunately, biopsy of small nodular lesions in cirrhosis is not entirely reliable. In fact, needle placement may be difficult and a sampling error may occur. Moreover, it is very difficult to distinguish well-differentiated HCC from DN on small biopsy specimens, as there is no clear-cut dividing line between dysplasia and a well-differentiated tumour.[51] Therefore, a positive biopsy, as assessed by an expert pathologist, is helpful, but a negative biopsy can never rule out malignancy.[1,2] In addition, biopsy is associated with a low but not negligible rate of complications, including tumour seeding along the needle track.

Both the 2005 EASL conference on HCC and the AASLD practice guideline have recommended that further investigation of nodules detected during US surveillance with dynamic imaging techniques, including contrast-enhanced US, multidetector CT, or dynamic MR imaging, is required to highlight the different vascular supply of HCC as compared to non-malignant entities.[2] However, the diagnostic protocol should be structured according to the actual risk of malignancy and the possibility of achieving a reliable diagnosis. Since the prevalence of HCC amongst US-detected nodules is strongly related to the size of the lesion, the diagnostic work-up depends on the size of the lesion.[2] Lesions smaller than 1 cm in diameter have a low likelihood of being HCC. However, such minute nodules may become malignant with time. Therefore, these lesions need to be followed up in order to detect growth suggestive of malignant transformation. A

reasonable protocol is to repeat US every 3 months, until the lesion grows to more than 1 cm, at which point additional diagnostic techniques are applied.[1,2] It has to be emphasized, however, that the absence of growth during the follow-up period does not rule out the malignant nature of the nodule because an early HCC may occasionally take more than 1 year to increase in size.[1]

When the nodule exceeds 1 cm in size, the lesion is more likely to be HCC and diagnostic confirmation should be pursued. It is accepted that the diagnosis of HCC can be made without biopsy in a lesion larger than 1 cm that shows characteristic vascular features of HCC – i.e. arterial hypervascularisation with wash-out in the portal venous or the late phase –even in patients with normal alpha-fetoprotein value.[2] In lesions above 2 cm a single imaging technique showing the characteristic vascular profile of HCC mentioned above may confidently establish the diagnosis. In lesions ranging between 1 and 2 cm, AASLD guidelines recommend that typical imaging findings confirmed by two coincident dynamic imaging modalities to allow a non-invasive diagnosis are required.[2] Such lesions ranging between 1 and 2 cm are the true target of screening programmes, as they identify the population of patients with very-early HCC tumours, who have the highest likelihood for cure with surgical resection or percutaneous ablation.[52] Specificity of imaging diagnosis is crucial to prevent therapeutic mistakes due to a false positive diagnosis of malignancy.

The combination of contrast-enhanced US and multidetector CT (or contrast-enhanced US and dynamic MR imaging) appears the most reliable for non-invasive diagnosis of small tumours. This is clearly the most cost-effective combination, as the contrast-enhanced US study can be performed immediately upon detection of a focal lesion at baseline US, and only one additional examination (either CT or MR imaging) is needed as a confirmatory test. In addition, given the different pharmacokinetics of US contrast agents (blood-pool compounds) with respect to CT and MR imaging contrast agents (extracellular fluid space compounds), such combination provides complementary information. In a prospective validation of AASLD criteria conducted in a series of consecutive patients with a solitary focal lesion smaller than 2 cm detected during US surveillance, the combined use of contrast-enhanced US and dynamic MR imaging achieved 100% specificity for the diagnosis of HCC.[36]

If the lesion does not show typical features of HCC, or the vascular profile does not coincide with the imaging techniques, biopsy is recommended.[2] It is important to point out that the absence of arterial hypervascularisation on imaging

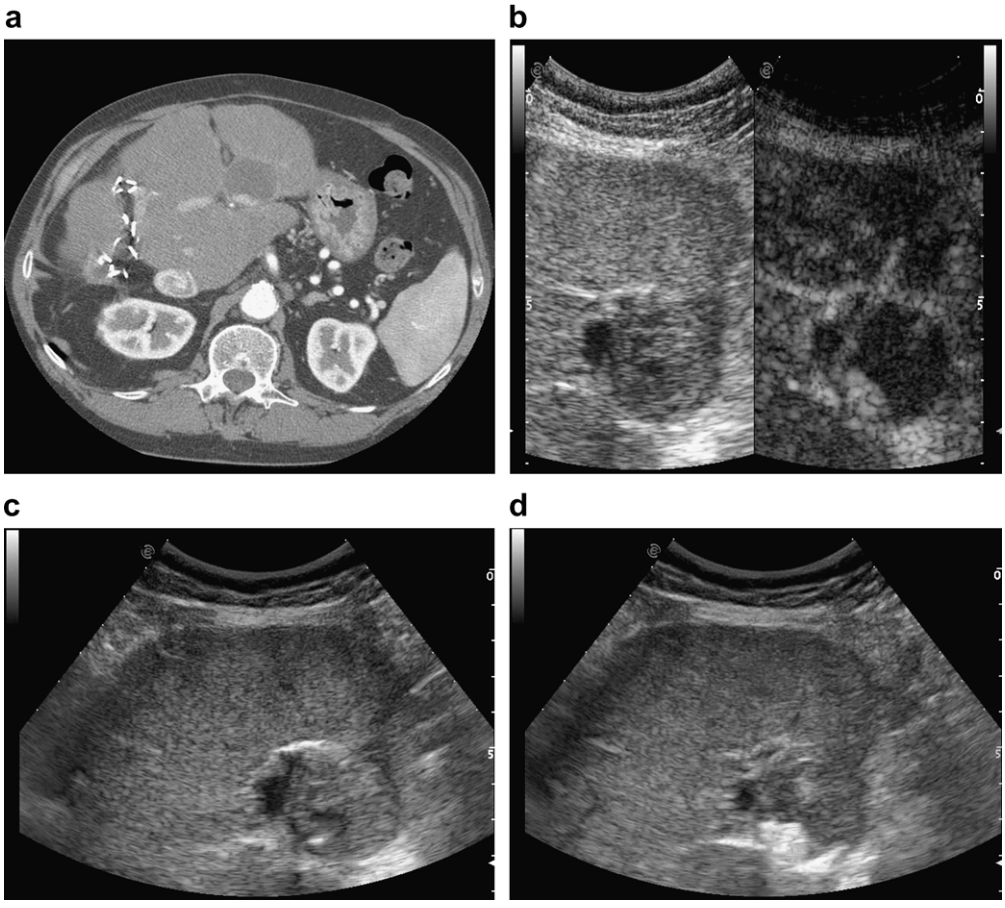

Fig. 2 – Percutaneous ablation of HCC. Multidetector CT image acquired after RF ablation shows small focus of residual, arterially enhancing viable tumour (a). Contrast-enhanced US clearly shows the area of residual disease as clear-cut enhancing nodule within the non-enhancing coagulated tumour (b). Precise real-time needle targeting of the tiny area of residual disease is easily achieved (c) and additional treatment with ethanol injection is administered (d).

does not rule out HCC. It is well established that HCC tumours at a very early stage may not exhibit the characteristic vascular features of overt HCC.[35] Delaying the diagnosis of HCC until imaging detection of arterial hypervascularisation occurs could reduce the chances of radical cure, since the incidence of microscopic vascular invasion and satellite nodules significantly increases when the tumour exceeds 2 cm and develops imaging-detectable neoangiogenesis.[17] In the setting of cirrhotic patients in whom a solitary nodule smaller than 2 cm is detected during US surveillance, biopsy is still needed in about two-thirds of the cases, and, given the well-known limitations of pathology interpretation, repeated biopsies are needed in as many as 30% of the cases.[36] This is the area where advances in imaging techniques based on liver-specific contrast agents (including hepatocyte-targeted agents and reticuloendothelial system-targeted agents) should be further investigated[53] and research on new diagnostic tools – based on immunostaining, gene expression assessment, or protein profiling – should be focussed.[54]

6. Response to image-guided ablation

Image-guided percutaneous ablation is currently accepted as the best therapeutic choice for non-surgical treatment of early-stage HCC.[1,2] Over the past two decades, several methods for chemical ablation or thermal tumour destruction through localised heating or freezing have been developed and clinically tested. Radiofrequency (RF) ablation is currently established as the primary ablative modality at most institutions on the basis of a more consistent local tumour control.[55,56,57,58] US is an ideal tool to guide percutaneous ablation as it allows real-time monitoring of the procedure.

When US is used as the imaging modality for guiding ablations, the addition of contrast agent can provide additional important information. Firstly, it improves delineation and conspicuity of lesions poorly visualised on baseline scans thus facilitating targeting; secondly it allows immediate assessment of the outcome of treatment by showing disappearance of any previously visualised intralesional enhancement; and finally it may be useful in the follow-up protocol for early detection of local tumour recurrence.[6]

Contrast-enhanced images obtained shortly after treatment demonstrate successful ablation as a non-enhancing area with or without a peripheral enhancing rim. The enhancing rim that may be observed along the periphery of the ablation zone appears as a relatively concentric, symmetric and uniform process in an area with smooth inner margins. This is a transient finding that represents reactive hyperemia and needs to be differentiated from irregular peripheral enhancement due to residual tumour that occurs at the treatment margin. In contrast to benign peri-ablational enhancement, residual unablated tumour often grows in scattered, nodular or eccentric patterns (Fig. 2).

Later follow-up imaging studies should be aimed not only at detecting the recurrence of the treated lesion but also the development of new hepatic lesions or the emergence of extrahepatic disease. Contrast-enhanced CT or MR imaging are recognised as the standard modalities in this situation.[6]

Conflict of interest statement

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