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Small liver lesions in oncologic patients: characterization with CT, MRI and contrast-enhanced US

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Abstract

Focal liver lesions (FLLs) are frequently discovered during ultrasound examinations either in healthy subjects without a clinical history of cancer or during staging or follow-up procedures in oncologic patients or in routine surveillance of hepatopathic patients. In oncologic patients, the liver is the most common target of metastatic disease and accurate detection and characterisation of FLLs is prognostically fundamental during the initial staging as well as before and after pre-operative chemotherapy, as it can help to identify patients who are most likely to benefit from liver surgery. Moreover, early detection of primary or secondary liver malignancies increases the possibility of curative surgical resection or successful percutaneous ablation. As many FLLs in these patients are benign, a precise and preferably non-invasive method of differentiation from malignant metastatic nodules is needed. Moreover, the continuous follow-up of cancer patients requires an easily available, reliable and cost-effective diagnostic tool for the detection and characterization of FLLs.

Keywords: *Focal liver lesion; cancer; detection; characterisation.*

Focal liver lesions (FLLs) are frequently discovered during ultrasound examinations either in healthy subjects without a clinical history of cancer or during staging or follow-up procedures in oncologic patients or in routine surveillance of hepatopathic patients. In oncologic patients, the liver is the most common target of metastatic disease and accurate detection and characterisation of FLLs is prognostically fundamental during the initial staging as well as before and after pre-operative chemotherapy, as it can help to identify patients who are most likely to benefit from liver surgery. Moreover, early detection of primary or secondary liver malignancies increases the possibility of curative surgical resection or successful percutaneous ablation[1,2]. As many FLLs in these patients are benign, a precise and preferably non-invasive method of differentiation from malignant metastatic nodules is needed. Moreover, the continuous follow-up of cancer patients requires an easily available, reliable and cost-effective diagnostic tool for the detection and characterisation of FLLs.

Ultrasound is a widely used method for the detection of FLLs; however there are limitations to conventional grey scale B mode ultrasound, especially when the lesions are small (<2 cm), when cirrhosis is present or in patients undergoing chemotherapy. Colour and power Doppler have increased sensitivity for detection of FLLs compared to conventional B mode, but sensitivity is still inferior to contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI)[1,3–5]. To improve the detection of FLLs, sonography must also provide information on vascularity, exploiting differences in blood supply between normal and pathologic tissue.

The introduction of microbubble contrast agents and the development of contrast-specific techniques have opened new perspectives in liver ultrasound (US). Contrast-enhanced ultrasound (CEUS) represents a significant breakthrough in sonography. Its unique feature of non-invasive assessment in real-time of liver perfusion throughout the different vascular phases has led to a dramatic improvement in diagnostic accuracy of US in the detection and characterisation of FLLs, as well as in the guidance and evaluation of response to therapeutic procedures. The technique is based on a new class of intravascular microbubble agent, consisting

1470-7330/08/000132 + 04

of perfluoro-gases combined with multipulse scanning modes sensitive to non-linear (harmonic) responses of the microbubbles and enabling tissue signal suppression[6,7].

With harmonic ultrasound imaging, thanks to blood-pool contrast agents, it is possible to have real-time observation of the contrast-enhancement in the different phases with high spatial and contrast resolution, thus allowing precise evaluation of tumoral vascularisation, outlining both macro- and micro-circulation.

Unlike contrast agents used for CT and MR, second generation contrast media may truly distribute intravascularly without any interstitial phase. In the delayed phase of CEUS, microbubbles are entrapped in the sinusoids, giving the so called 'sinusoidal phase', which is the ideal phase for hepatic staging by CEUS, as it allows the evaluation of the entire liver parenchyma.

Distribution and retention of the contrast microbubbles in the sinusoidal network without passage into the interstitial space make the CEUS sinusoidal phase fundamental in distinguishing between benign and malignant lesions. During this phase, lesions with liver-like (focal nodular hyperplasia (FNH), adenoma) or angiomatous (cavernous and capillary hemangiomas) vascular structures appear isoechoic or hyperechoic due to the retention of microbubbles similar or superior to that in the adjacent liver parenchyma. Conversely, in lesions with neoangiogenic vascular structures (hepatocellular carcinoma (HCC), cholangiocarcinoma, metastases), a similar degree of retention of the microbubbles compared to the liver parenchyma cannot be present. In particular, metastases are easily differentiated from benign lesions by their hypoechoic appearance in the late sinusoidal phase compared to the liver parenchyma, which is homogenously enhanced during the sinusoidal CEUS phase, even though metastatic lesions may show various contrast enhancement patterns in the arterial phase (absent, rim-like, dotter or diffuse), similar to that of the benign lesions[8–10]. The identification of a hypoechoic defect during the sinusoidal CEUS phase allows the correct characterisation of the majority of malignant focal liver lesions[9,11]. However, a clear hypoechoic defect in the sinusoidal CEUS phase is expected to be imaged even within fibrotic or necrotic areas of liver lesions, due to the absence of delayed fibro-interstitial enhancement, based on the absence of the pooling of microbubble contrast agent. For this reason a sclerosed hemangioma and a necrotic intrahepatic area, appearing as a clear hypoechoic defect in the sinusoidal CEUS phase, can be wrongly diagnosed as malignant lesions.

Several studies have shown an improved diagnostic performance and confidence of CEUS in diagnosing liver metastases when compared with baseline US. With up-to-date technologies CEUS sensitivity, specificity and accuracy in the detection of liver metastases is comparable or superior to that obtained with contrast-enhanced CT, with similar results to state of the art liver MRI. CEUS has been shown to be particularly useful to improve the conspicuity and detection rate of metastases smaller than 1 cm or those lesions which are isoechoic to the adjacent liver parenchyma and thus barely visible at B mode ultrasound[7,12–14]. Real-time observation gives to the CEUS technique high sensitivity in discovering hypervascular lesions (such as small metastasis due to hyper-vascularised tumours or small HCC). Other techniques such as CT and MRI can often fail in this purpose due to wrong arterial contrast timing[9]. Moreover, microbubble-based contrast agents allow diagnostic problems to be solved directly in the US unit, without employing other imaging techniques, with a consequent reduction in the waiting and hospital time for the patient.

However, there are some intrinsic limitations in CEUS, similar to those of B mode sonography: e.g. obese patients with abundant meteorism, or deep lesions. Furthermore, it is an operator dependent procedure and a less reproducible and a less panoramic tool than CT or MRI, especially when routine follow-up examination is needed. For these reasons CEUS is less widely used than should be for detection and is often confined to its better encoded role in characterising an equivocal lesion discovered during the B mode exam or as a 'second-look' tool for atypical lesions studied with CT and/or MRI, due to the intravascular and non-interstitial distribution of the microbubbles[3,10,15,16].

CT is an easy access technique, due to wide availability and patient-friendly protocols allowing even a chest–abdomen–pelvis examination in less than 20 s breath hold using multidetector CT technology. It has high sensitivity and specificity for detecting hepatic metastases and it is able to characterise the vast majority of focal liver lesions, such as haemangiomas. However, it often happens that a lesion is indeterminate on contrast-enhanced CT. In this case, the principal technique for additional liver evaluation after CEUS and contrast-enhanced CT is MRI and it is rapidly emerging as the imaging modality of choice for detection and characterisation of focal liver lesions due to high sensitivity and specificity, resulting from the optimal lesion-to-liver contrast and no exposure to radiation. Improvement in breath-hold T1 weighted fast spoiled gradient echo, respiratory trigger applied to T2-weighted FSE sequences and parallel imaging are crucial to obtain high quality MRI liver images, reducing the most important artefacts that derive from respiratory motion.

MRI gadolinium-chelate contrast agents provide critical tumour characterisation, with high contrast and spatial resolution information, and can be safely used in patients allergic to iodine contrast agents. The advent of liver-specific contrast agents, which are targeted to enhance hepatocytes (hepato-specific contrast-agent such as Gd-BOPTA, Gd-EOB-DTPA, Mn-DPDP) or Kupffer cells (superparamagnetic iron oxide (SPIO) and ultrasmall superparamagnetic iron oxide (USPIO),

e.g. ferumoxide and ferucarbotran) has facilitated an increase in accuracy of MRI in detection and characterisation of FLLs[17–23].

Frequently the first step in MRI imaging is performing a basal pre-contrast liver evaluation, followed by the contrast dynamic imaging with an injection bolus of liver-specific gadolinium-chelates like Gd-BOPTA or Gd-EOB-DTPA, that have high T1 relaxivity properties, allowing enhancement pattern analysis. Moreover, these contrast agents are taken up by functioning hepatocytes; thus after a variable amount of time after the injection (20–120 min, depending on the contrast agent), the normal liver shows increased signal intensity on T1 images, while a liver lesion becomes hyper-, iso- or ipo-intense due to the presence or absence of normal hepatocytes, often allowing the correct differentiation between benign hepatocellular lesions and malignant non-hepatocellular lesions.

Recently the rising importance of diffusion-weighted imaging (DWI) in abdominal pathology has been reported. Diffusion is a natural physical phenomenon, due to brownian motion that is arbitrary and irregular, caused by thermal movement. Despite the effect of molecular diffusion, movement is weak, and it can result in the MR signal missing convergence with the degree of attenuation in the MR gradient intensity and the amplitude of molecular movements. The diffusion coefficient of the living body is affected by many factors of macrocirculation such as cellular osmosis and temperature, diffusion of capillaries, glutinous degree and proportion of intra- and extracellular water and direction of cellular transitions. It is also affected simultaneously by macro factors and circadian rhythms, such as breath, pulsation and peristalsis. The apparent diffusion coefficient (ADC) has been used to replace diffusion[24].

Recently DWI has been applied to regions of the body to detect malignant lesions, due to high sensitivities of this technique in the visualisation of lesions with higher cellular density[25]. For DWI breath-hold single-shot (SS) spin-echo (SE) or echo-planar imaging (EPI) with fat saturation is widely employed because of its speed and relatively high signal-to-noise ratio. Parallel imaging is crucial to reduce the acquisition time or increase the matrix, improving spatial resolution, without altering the acquisition time and without significant loss of image quality[26].

In the post-processing phase, the DW images are used to calculate the ADC maps on which the signal analysis is performed by positioning a region of interest (ROI) on the lesion being studied.

The choice of the degree of diffusion weighting (b-value) is still an unresolved problem. In the literature different b-values are used with different results[27]. Recently, different authors suggest acquiring three sets of DW images with three different b-values[28–30]. To improve sensitivity in detection of small solid lesions (<1 cm) respiratory triggered SS-EPI-DWI is particularly useful[30].

In liver imaging DWI is useful in the detection and characterisation of focal lesions. It has recently been shown that DWI is a very sensitive tool with higher values compared to that of T2-weighted turbo spin echo (TSE) or short tau inversion recovery (STIR) or half-Fourier single-shot turbo spin echo (HASTE) images, in the detection of solid focal liver lesions[30]. In characterisation, the ADC values have a good accuracy (83–88%) in discriminating between malignant and benign lesions, due to the fact that ADCs of metastases are significantly lower in most cases than those of benign lesions like hemangiomas, FNHs and cysts, even if some difficulties in differentiation are due to some overlap of ADC values (i.e. high ADC values in metastatic lesions with a high necrotic component or intermediate ADC values in hepatic abscesses with dense viscous content)[28,31,32].

Measurement of the ADCs of focal liver lesions may constitute a useful supplementary method for lesion characterisation both in healthy and oncologic patients, improving the information from basal pre-contrast MR sequences, contrast-dynamic imaging and delayed imaging with hepato-specific contrast agents.

In conclusion, the first step in the follow-up of oncologic patients is still B mode ultrasound, followed by CEUS when an incidental focal liver lesion is discovered.

Even if contrast-enhanced CT, due to its wide diffusion and good sensitivity and specificity, is still the method of choice for the evaluation of oncologic patients, MRI should be considered the imaging modality of choice when characterisation of a focal liver lesion is crucial for therapeutic decisions, especially when a benign liver lesion in suspected in a patient with cancer, due to its high specificity derived from multimodality MR imaging (dynamic contrast imaging, hepato-specific contrast agents delayed imaging and diffusion-weighted imaging).

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