Characterizing malignant liver lesions with contrast-enhanced ultrasound

Microbubbles as an ultrasound contrast agent allow characterization of focal liver lesions. This article summarizes the ultrasound appearances and enhancement characteristics of malignant liver lesions, and also discusses its potential use for ultrasound-guided intervention and ablation of liver lesions.

Contrast-enhanced ultrasound allows focal liver lesions to be detected and characterized by their enhancement patterns. Contrast-enhanced ultrasound can be used to diagnose hepatocellular carcinoma in a cirrhotic liver, or to detect liver metastases in a patient with a known primary malignancy. This article discusses how the radiologist can establish the malignant nature of focal liver lesions. The enhancement characteristics of benign liver lesions and trauma were discussed separately in the previous article of this series (Wills et al, 2014).

Microbubbles as a contrast agent in ultrasound have been available for over 20 years. They are licensed for clinical use in most parts of the world. Characterization of focal liver lesions is the most important application of contrast-enhanced ultrasound, with an accuracy rivalling that of contrast-enhanced computed tomography and magnetic resonance imaging (Quaia et al, 2004; Cosgrove, 2010; Wilson and Burns, 2010; National Institute for Health and Care Excellence, 2012; Claudon et al, 2013).

Microbubbles consist of a low solubility complex gas such as a perfluoro gas surrounded by a shell, typically composed of phospholipids. They are similar in size to red blood cells, in comparison with the molecular sizes of computed tomography and magnetic resonance contrast agents. Following an intravenous injection they last for about 5 minutes in the circulation. By serendipity, microbubbles of this size resonate in an ultrasound field at the frequencies used in everyday diagnostic sonography. During resonance they emit 'fingerprint like' harmonic signals (overtones) which can be selectively detected by the microbubble-specific software available on commercial ultrasound systems. Microbubbles are usually imaged using low acoustic power modes to reduce their destruction and thus allow real-time imaging. They are better tolerated than magnetic resonance and computed tomography agents with fewer and less severe adverse effects and are not nephrotoxic. The most widely used agent in Europe is Sonovue (Bracco, Italy) which is composed of sulphur hexafluoride gas surrounded by a phospholipid monolayer. It is used in doses of 1–2 ml.

The liver (and incidentally the spleen) demonstrates three phases of enhancement after an intravenous bolus injection: the arterial, portal-venous and late phases (*Table 1*). The late phase occurs as the vascular phases subside, when the microbubbles are sequestered in the sinusoids of the liver and spleen.

Enhancement is visualized in real time either alongside or superimposed upon B-mode (brightness mode) fundamental greyscale images. The enhancement characteristics of liver lesions at contrast-enhanced ultrasound are similar to those seen on contrast-enhanced computed tomography and contrast-enhanced magnetic resonance imaging, but microbubbles are confined to the vascular space whereas computed tomography and magnetic resonance contrast media diffuse into the extracellular compartment. Thus the elimination of contrast from a liver lesion may differ slightly between contrast-enhanced ultrasound and computed tomography or magnetic resonance. In addition, as contrast-enhanced ultrasound operates in real time, fast changes during the arterial phase are better captured than on contrast-enhanced computed tomography or contrast-enhanced magnetic resonance imaging.

This article discusses the enhancement characteristics of malignant liver lesions that are commonly encountered in clinical practice (their typical features are summarized in *Table 2*). Enhancement should be assessed in all phases in order to fully characterize a lesion. As a general rule, however, lesions which do not washout in the late phase (i.e. remain hyperenhancing or isoenhancing to liver

Table 1. Time windows for the three phases of enhancement at contrast-enhanced ultrasound

Phase	Time window
Arterial	10–30 seconds
Portal venous	>30–120 seconds
Late	>120 seconds–5+ minutes

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Table 2. Typical enhancement characteristics of malignant liver lesions at contrast-enhanced ultrasound

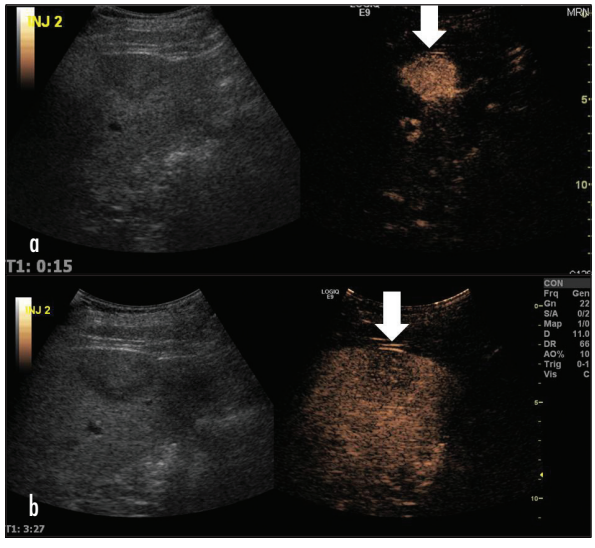
	Arterial phase	Venous phase	Late phase
Hypovascular metastases (e.g. colon, pancreas cancer)	Peripheral rim enhancement	Hypo or non-enhancement	Hypo or non-enhancement
Hypervascular metastases (e.g. neuroendocrine)	Hyperenhancement	Hypo or non-enhancement	Hypo or non-enhancement
Hepatocellular carcinoma	Hyperenhancement	Hypo or non-enhancement	Hypo or non-enhancement
Cholangiocarcinoma	Variable hyperenhancement	Hypo or non-enhancement	Hypo or non-enhancement
Lymphoma	Variable hyperenhancement	Hypo or non-enhancement	Hypo or non-enhancement

parenchyma) tend to be benign (with the exception of simple cysts, haematomas, ablation cavities and abscesses, which do not enhance in any phase), whereas lesions which do not retain contrast in the late phase (i.e. demonstrate washout) are usually malignant.

Metastases

Hepatic metastases have a varied appearance on B-mode ultrasound, ranging from hypoechoic (most common) to hyperechoic. On contrast-enhanced ultrasound, hypervascular metastases (e.g. from neuroendocrine, melanoma, renal and thyroid cancers) typically show avid enhancement throughout the lesion in the arterial phase, with washout in the portal and late phases so that they become hypoenhancing or non-enhancing (*Figure 1*). A typical enhancement pattern of hypovascular metastases (e.g. from colon, pancreas, lung cancers) is rim enhancement in the arterial phase (*Figure 2*), followed by hypo- or non-enhancement in the portal venous and late phases. Metastases that contain cystic or necrotic components show no enhancement at all in these regions, while the solid component will follow the enhancement pattern described above. Contrast-enhanced ultrasound significantly increases the conspicuity of metastases compared to B-mode ultrasound, allowing detection of isoechoic and subcentimetre lesions down to 3 mm. Conventional ultrasound has a false negative rate of up to 30% in the detection of liver metastases. Contrast-enhanced ultrasound increases the sensitivity and specificity of ultrasound in the detection of liver metastases to rival those of contrast-enhanced computed tomography and contrast-enhanced magnetic resonance (*Figure 3*).

Figure 1. Hypervascular metastasis from a phaeochromocytoma. a. Following intravenous Sonovue arterial phase imaging (15 seconds post injection) shows avid enhancement of the metastasis (arrow). b. The metastasis (arrow) appears as a defect in the late phase (3 minutes 27 seconds). Imaging performed using a dual display simultaneous real-time coregistered B-mode (left screen) and microbubble-specific imaging mode (right screen)(GE Healthcare, UK).



Hepatocellular carcinoma

Hepatocellular carcinoma occurs most commonly in cirrhotic livers. Cirrhosis is a major risk factor, and such

Figure 2. Dual display contrast-enhanced ultrasound showing rim enhancement (arrow on contrast enhanced image) around a colorectal metastasis (27 seconds post contrast injection). (Contrast Pulse Sequencing CPS mode (left screen); Siemens, USA.)

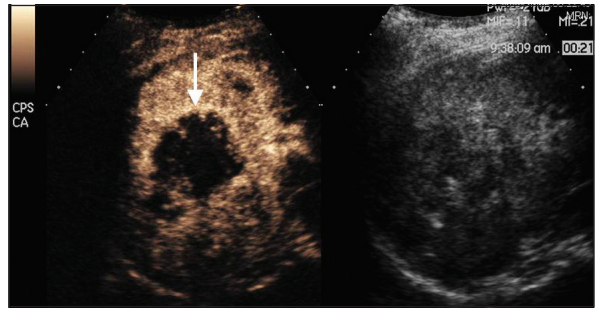
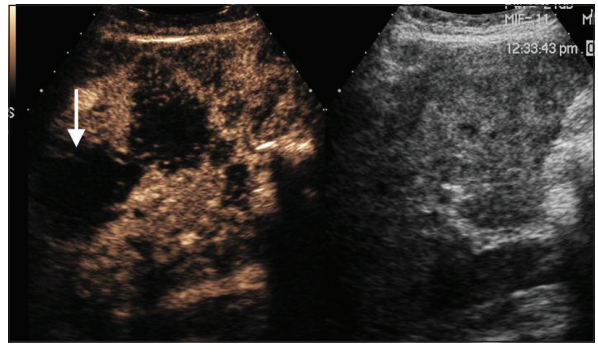


Figure 3. Dual display contrast-enhanced ultrasound demonstrating increased conspicuity of colorectal metastases (arrow) in the late phase (2 minutes 26 seconds post contrast injection) compared to conventional B-mode (right screen). (Contrast Pulse Sequencing CPS mode (left screen); Siemens, USA.)



patients undergo regular 'screening' ultrasound for hepatocellular carcinoma. Hepatocellular carcinoma typically appears as a hypoechoic lesion on B-mode ultrasound, although may be heterogeneous in echotexture as a result of necrosis. On contrast-enhanced ultrasound, hepatocellular carcinoma typically demonstrates hyperenhancement in the arterial phase, in a chaotic 'basket weave' pattern, followed by hypoenhancement or non-enhancement (i.e. washout) in the portal venous and late phases (*Figures 4* and *5*).

Unfortunately some well-differentiated hepatocellular carcinomas have identical enhancement characteristics to those of regenerating or dysplastic nodules (showing isoenhancement with the adjacent liver in all phases). Some hepatocellular carcinomas may only exhibit delayed washout after 5 minutes (especially with newer longer-lasting contrast agents).

Figure 4. Dual display contrast-enhanced ultrasound enhancement of a hepatocellular carcinoma demonstrating chaotic 'basket weave' pattern in the arterial phase. (GE Healthcare, UK.)

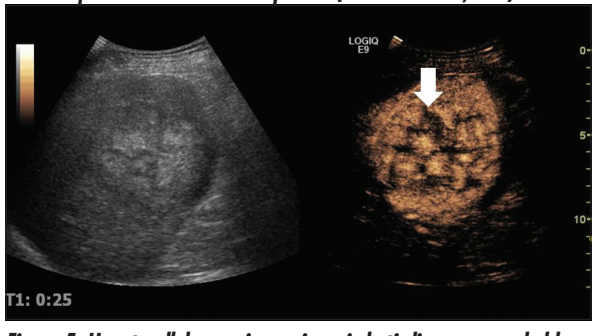
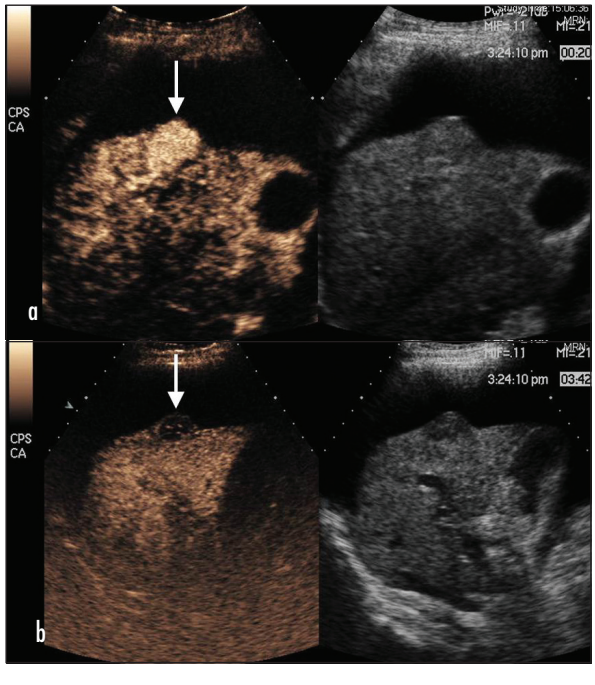


Figure 5. Hepatocellular carcinoma in a cirrhotic liver surrounded by ascites. a. Dual display contrast-enhanced ultrasound showing avidly enhancing capsular hepatocellular carcinoma (arrow) in the arterial phase (20 seconds post contrast injection) with large feeding vessels. b. Late phase image shows washout of the hepatocellular carcinoma (arrow). (Contrast Pulse Sequencing CPS mode; Siemens, USA.)



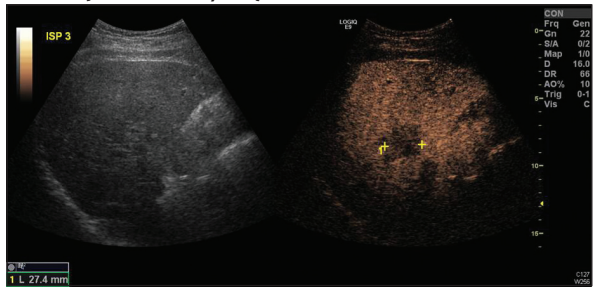
Because of the variable enhancement pattern of hepatocellular carcinoma and the fact that the whole liver cannot be adequately surveyed in the brief arterial phase to look for hepatocellular carcinoma enhancement, contrast-enhanced ultrasound is not currently indicated for screening but is used in the assessment of focal lesions once detected. Contrast-enhanced ultrasound can be used alone to diagnose hepatocellular carcinoma in lesions greater than 2 cm and in conjunction with contrast-enhanced computed tomography or contrast-enhanced magnetic resonance for lesions greater than 1 cm. For suspicious lesions additional factors (such as serological tumour markers or lesion growth over serial ultrasound studies) must be taken into account or the lesion followed up at 3-monthly intervals.

Cholangiocarcinoma and gall bladder cancer

Cholangiocarcinomas are a form of adenocarcinoma arising from the bile ducts, and are categorized as hilar (Klatskin) tumours (*Figure 6*), which tend to infiltrate the central bile ducts, or peripheral tumours arising from smaller intrahepatic bile ducts which tend to have a mass-like appearance within the liver parenchyma. The appearance of cholangiocarcinomas on B-mode ultrasound is highly variable, although the parenchymal mass of peripheral tumours is most commonly hyperechoic. In some cases, hilar cholangiocarcinomas may only be manifest as segmental dilatation of intrahepatic bile ducts without a perceptible mass. The enhancement pattern of cholangiocarcinomas in the arterial phase is also variable, in that some demonstrate avid arterial enhancement whereas others do not. The key characteristic (as with hepatic metastases) is washout of the contrast agent with the lesion becoming hypo- or non-enhancing in the portal venous and late phases. In some cases of cholangiocarcinoma, an enhancing intraductal component of the tumour may be seen at contrast-enhanced ultrasound.

Gall bladder cancer is a rarer form of adenocarcinoma. It may manifest as an intraluminal mass, diffuse mural thickening or a mass replacing the gall bladder. The clinical presentation depends on its direction of growth; spread into the colon or small bowel may cause bowel obstruction and extension into the liver may produce obstructive jaundice. Contrast-enhanced ultrasound may

Figure 6. Klatskin cholangiocarcinoma. Dual display contrast-enhanced ultrasound showing a defect on the contrast mode (calipers on right screen) which is invisible on the coregistered B-mode. (GE Healthcare, UK.)



show variable enhancement in arterial phase with hypoenhancement or non-enhancement in the portal venous phase and late phase (*Figure 7*).

Lymphoma

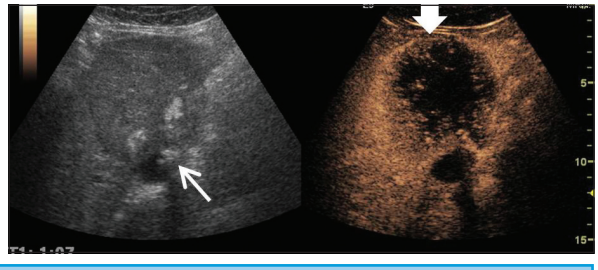
On B-mode ultrasound, lymphomatous deposits within the liver typically appear as hypoechoic masses, similar to the appearance of hepatic metastases. On contrast-enhanced ultrasound, these lesions show variable enhancement in the arterial phase, but show the typical 'malignant' appearance of 'washout' in the portal venous and late phases.

Contrast-enhanced ultrasound and intervention

In some instances, a focal liver lesion (e.g. that may have been diagnosed on contrast-enhanced computed tomography or contrast-enhanced magnetic resonance) will not be clearly visible on B-mode ultrasound. In such cases, the use of contrast-enhanced ultrasound may allow better visualization of the lesion on ultrasound, and thus allow the radiologist to perform a targeted ultrasound-guided biopsy (*Figure 8*). Even if such a procedure requires more than one bolus of contrast agent, microbubbles have no nephrotoxicity and patients can safely receive multiple doses.

Contrast-enhanced ultrasound may also be used before and after interstitial ablation of a focal malignant liver lesion. The operator is able to perform repeated injections of microbubbles in order to establish whether viable (enhancing) tumour remains (*Figure 9*), and whether further on-table ablative therapy is required. However, ablation therapy usually results in the formation of gas bubbles within the target tissue (which may block the ultrasound beam) although these usually resolve in minutes. BJHM

Figure 7. Gall bladder carcinoma. Dual display contrast-enhanced ultrasound showing rim enhancement around a large tumour (thick arrow) with a non-enhancing necrotic centre arising from the gall bladder which contains echogenic stones (thin arrow). (GE Healthcare, UK.)



KEY POINTS

- Contrast-enhanced ultrasound allows characterization of focal, indeterminate liver lesions.
- Malignant liver lesions almost always appear as defects (hypoenhancing to the adjacent liver parenchyma) on contrast-enhanced ultrasound in the late phase (>2 minutes).
- Hypervascular metastases (e.g. from neuroendocrine, renal, melanoma and thyroid cancers) are hyperenhancing in the arterial phase, whereas most other metastases are hypoenhancing in the arterial phase.
- Hepatocellular carcinomas are usually hyperenhancing in the arterial phase, and washout in the portal venous and late phases. Unfortunately, some well-differentiated hepatocellular carcinomas do not washout in the late phase.
- Cholangiocarcinomas, gallbladder cancers and lymphoma have a variable appearance in the arterial phase, but washout in the portal venous and late phases.
- Contrast-enhanced ultrasound may be used to guide the operator when performing biopsies of a focal liver lesion.
- Contrast-enhanced ultrasound may be used to establish almost immediately whether ablation of a liver lesion has been extensive enough, or whether further ablative treatment is required.

Conflict of interest: none.

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Figure 8. Dual display contrast-enhanced ultrasound showing a targeted biopsy (needle labelled with arrowheads) of a cholangiocarcinoma metastasis (arrow) which cannot be visualized on B-mode (left screen). (GE Healthcare, UK.)

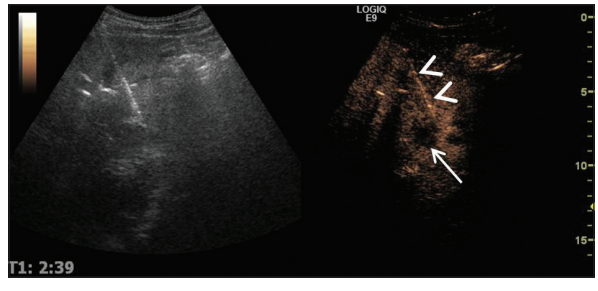

Figure 9. Dual display contrast-enhanced ultrasound showing a crescent of viable tumour (arrows on contrast enhanced image-right screen) following radiofrequency ablation of a colorectal metastasis. The rest of the tumour is necrotic (seen as a defect). (GE Healthcare, UK.)