Characterizing benign liver lesions and trauma 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 benign liver lesions, focal fatty sparing and focal fatty change, and blunt liver trauma.

Microbubbles have been available for over 20 years as a contrast agent in ultrasound. 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; Piscaglia et al, 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, compared to 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 comprises 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.

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

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.

This article discusses the enhancement characteristics of benign liver lesions and trauma 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 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. The enhancement characteristics of malignant liver lesions are discussed separately in the second article of this series.

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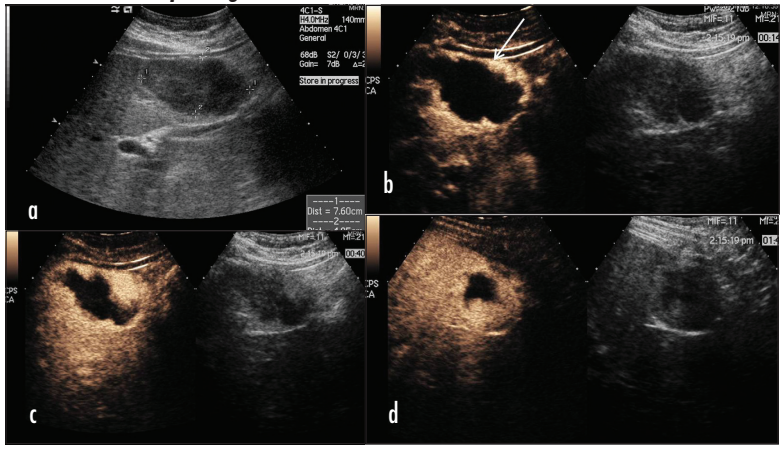
Haemangioma

Haemangiomas are commonly seen on B-mode ultrasound as well-defined echogenic lesions within the liver, and are usually asymptomatic. On contrast-enhanced ultrasound, haemangiomas typically demonstrate gradual peripheral nodular enhancement in the arterial and portal venous phases, with progressive centripetal filling, and become isoenhancing or hyperenhancing to liver parenchyma in the late phase (*Figure 1*). Larger haemangiomas may not fully fill in during the delayed phase as a result of central necrosis or thrombosis (which leaves a central area of non-enhancement). However, these lesions can be confidently diagnosed as haemangiomas by their characteristic centripetal nodular enhancement, and by the fact that the lesions appear smaller on the late phase contrast-enhanced ultrasound images than the B-mode images.

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

	Arterial phase	Venous phase	Late phase
Haemangioma	Peripheral 'nodular' enhancement	Partial or complete centripetal fill in	Complete enhancement or central non-enhancing areas
Focal nodular hyperplasia	Early centrifugal enhancement	Hyper- or isoenhancing 25% central scar	Hyper- or isoenhancing 25% central scar
Hepatic adenoma	Hyperenhancing (heterogeneous)	Isoenhancing	Isoenhancing
Focal fatty sparing or change	Isoenhancing	Isoenhancing	Isoenhancing
Regenerating and dysplastic nodule	Isoenhancing	Isoenhancing	Isoenhancing
Hepatic cyst	Non-enhancing	Non-enhancing	Non-enhancing
Hepatic abscess	Enhancing periphery and/or septa	Hyper- or iso-enhancing rim, enhancing septa, no central enhancement	Hypoenhancing rim, no central enhancement

Figure 1. Haemangioma. a. Baseline B-mode (brightness mode) ultrasound shows an echopoor solid lesion (calipers). b–d. Following intravenous Sonovue the lesion exhibits classic peripheral globular enhancement (arrow in b) with progressive centripetal fill in over time. Imaging performed using a dual display simultaneous real-time coregistered altered B-mode (right screen) and microbubble-specific imaging mode (left screen) (Contrast Pulse Sequencing CPS; Siemens, USA).

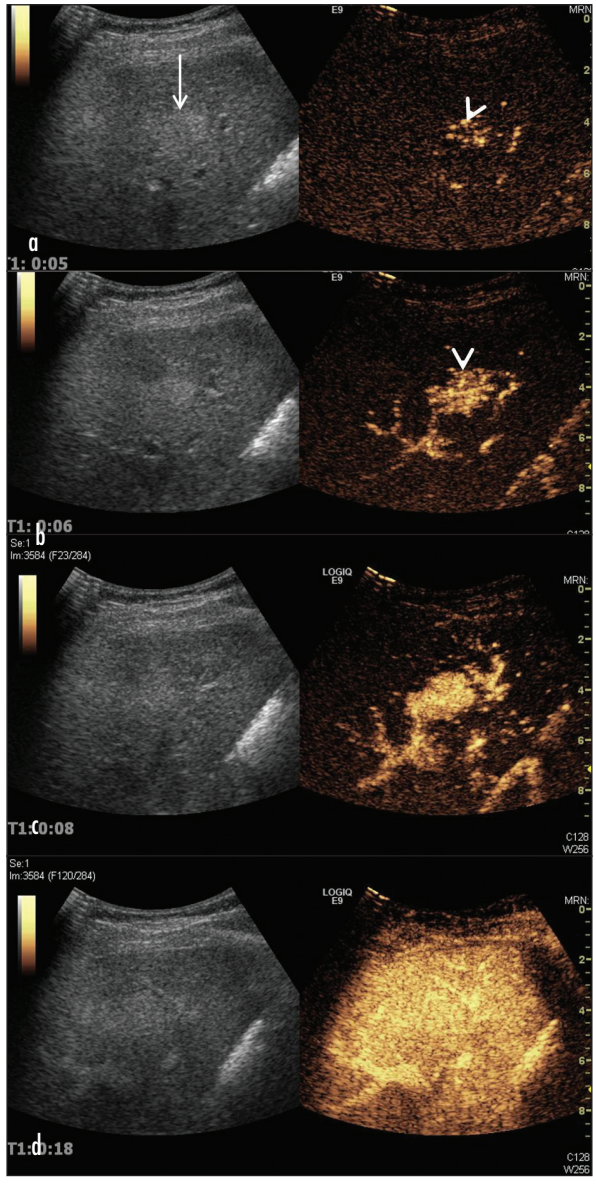


Small 'high flow' haemangiomas may show brief avid enhancement and then become isoechoic with adjacent liver.

Focal nodular hyperplasia

Focal nodular hyperplasia is slightly less common than haemangiomas, and occurs more commonly in women than men. Usually these lesions are isoechoic to liver parenchyma on B-mode ultrasound, but may be visible as faintly echogenic liver lesions. Focal nodular hyperplasia typically demonstrates centrifugal enhancement in a 'spoke wheel' pattern (*Figure 2*), arising from a central

Figure 2. Focal nodular hyperplasia. a–d. Dual display contrast-enhanced ultrasound showing rapid avid arterial phase centrifugal enhancement of a subtle focal liver lesion (arrow on B-mode (left screen) in a) from a central feeding vessel in a spoke wheel pattern (arrowhead in a, b). The lesion becomes isoechoic with the rest of the liver by 18 seconds (d) and does not wash out in the late phase. (Contrast Pulse Sequencing CPS mode (right screen); Siemens, USA).



feeding vessel. These lesions usually appear hyperenhancing to liver parenchyma very rapidly (usually this occurs in the arterial phase, and 25% may have a central non-enhancing 'scar' which does not appear until the late phase). Focal nodular hyperplasia then becomes isoenhancing to liver by the portal venous or late phase. The key to diagnosing focal nodular hyperplasia is their early arterial enhancement, as they usually become invisible in the portal venous and late phases and this often requires review of the stored cine loop. Similarly, focal nodular hyperplasia is often not perceptible on a portal venous phase computed tomography of the liver.

Hepatic adenoma

Hepatic adenomas are more common in females than males, particularly in young women who take the oral contraceptive pill. While benign, these lesions often present with pain as a result of haemorrhage (the risk of which increases with the size of the adenoma) and a small proportion undergo malignant change, hence the recommendation for close surveillance or surgical excision. On B-mode ultrasound, adenomas present as heterogeneous lesions within homogeneous liver parenchyma, containing anechoic components as a result of foci of haemorrhage, although they are sometimes difficult to discern and may only be evident by the mass effects they produce (capsular and vascular distortion).

The solid components of an adenoma demonstrate enhancement (from the periphery) in the arterial phase, and usually become isoenhancing to liver parenchyma by the portal venous and late phases (although this is variable) (*Figure 3*). The haemorrhagic components of an adenoma are avascular, and therefore do not enhance in any phase.

Focal fatty sparing and focal fatty change

Areas of focal fatty sparing and focal fatty change within the liver appear on B-mode ultrasound as echopoor and echogenic areas respectively, in comparison to background liver parenchyma. Thus these can be mistaken for focal liver masses, and are particularly worrying in the context of a patient with a known malignancy where the presence of liver metastases may preclude potentially life-saving surgery. Focal fatty sparing and focal fatty change are areas of essentially normal hepatic parenchyma, and thus on contrast-enhanced ultrasound demonstrate identical enhancement to the surrounding liver parenchyma (*Figures 4* and *5*) and disappear on the contrast-enhanced ultrasound images.

Regenerating and dysplastic nodules

A regenerating nodule is an area of regenerating liver parenchyma within a cirrhotic liver. These are of variable echogenicity on B-mode imaging, and may appear isoechoic to liver parenchyma (only being apparent because of the 'mass-like' appearance of the nodule). Like focal fatty sparing and focal fatty change, regenerating nodules demonstrate identical enhancement characteristics to adjacent liver parenchyma on all phases of contrast-enhanced ultrasound (*Figure 6*). Dysplastic nodules are similar to regenerating nodules, but contain dysplastic cells (which may be low or high grade, when examined histologically). Again, these demonstrate similar enhancement characteristics to the adjacent liver parenchyma on contrast-enhanced ultrasound. Unfortunately some well-differentiated hepatocellular carcinomas have identical enhancement characteristics to regenerating or dysplastic nodules but may exhibit delayed washout after 5 minutes. For suspicious lesions additional factors (such as serological tumour markers or lesion growth over serial ultra-

Figure 3. Adenoma. a. Dual display contrast-enhanced ultrasound showing enhancement of a focal liver lesion (arrow in B-mode (right screen)). b. There is little wash out in the late phase indicating benignity. Biopsy revealed an adenoma. (Toshiba Ultrasound Contrast Imaging, Japan.)

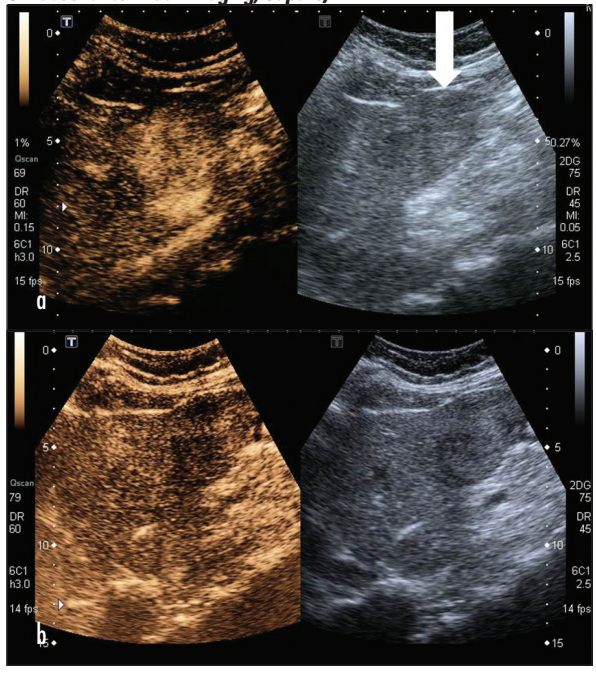
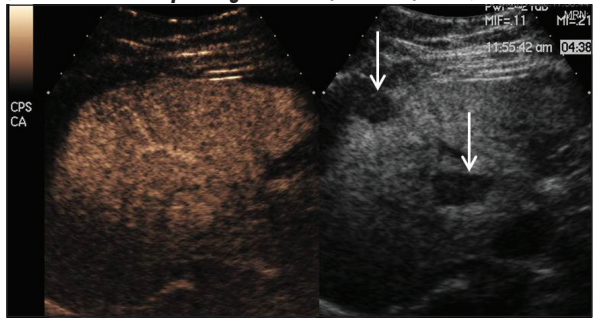


Figure 4. Focal fatty sparing. A 65-year-old woman with colon cancer who was referred for a contrast-enhanced ultrasound following the finding of echopoor liver lesions in an echogenic fatty liver. Contrast-enhanced ultrasound at 4 minutes 38 seconds (late phase) shows two focal lesions (arrows) on B-mode (right screen) which do not wash out, consistent with focal fatty sparing. (Contrast Pulse Sequencing CPS mode; Siemens, USA.)



sound studies) must be taken into account or the lesion followed up at 3-monthly intervals.

Figure 5. Focal fatty change. a. Echogenic focal liver lesion on baseline B-mode (calipers). b. Dual display contrast-enhanced ultrasound showed homogeneous iso-enhancement with the adjacent liver in all phases, consistent with focal fatty change (arrow). (GE Healthcare, UK.)

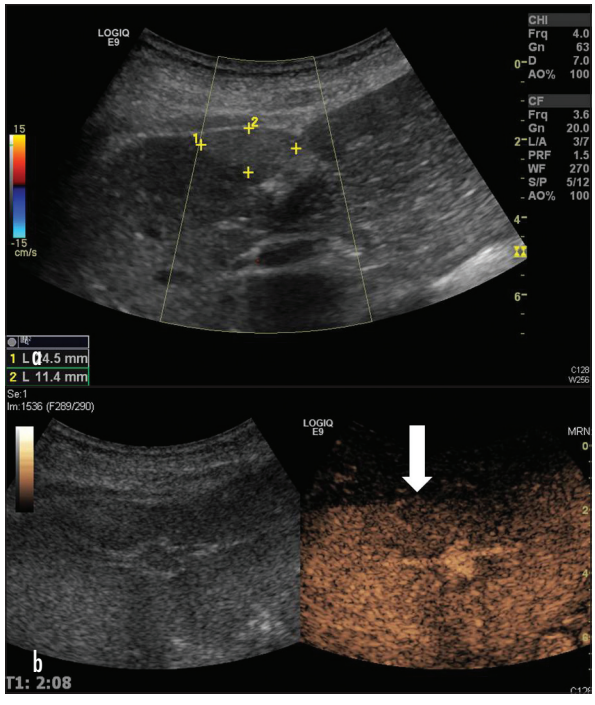
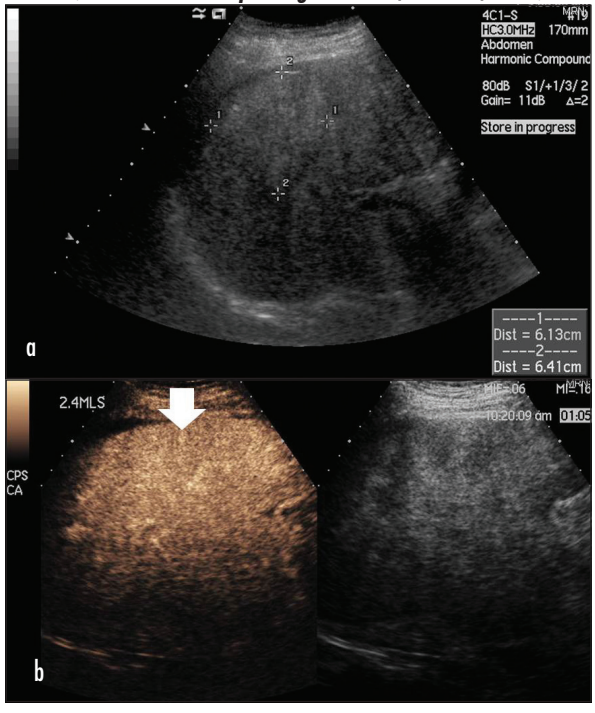


Figure 6. Regenerating nodule. a. Focal lesion in a cirrhotic liver on baseline B-mode (calipers). b. Dual display contrast-enhanced ultrasound showed homogeneous iso-enhancement (arrow) with the adjacent liver in all phases consistent with a regenerating nodule. (Contrast Pulse Sequencing CPS mode; Siemens, USA.)



Hepatic cysts

Simple hepatic cysts are extremely common, benign lesions. These can usually be fully characterized on B-mode ultrasound where they appear as well-defined, smooth walled, anechoic lesions with through-transmission of sound without Doppler-detected vascularity. Contrast-enhanced ultrasound is rarely required to characterize a simple hepatic cyst, but cysts may be present in patients undergoing contrast-enhanced ultrasound for an additional, indeterminate liver lesion or may be complex, with internal echoes, requiring further assessment with contrast-enhanced ultrasound (*Figure 7*). Simple cysts demonstrate no enhancement on any phase of contrast-enhanced ultrasound.

Hepatic abscess

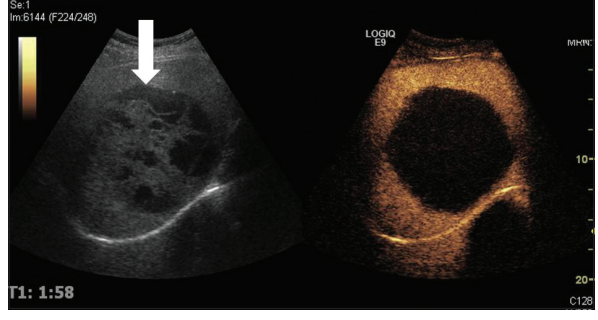
A hepatic abscess is a focal area of infection within the liver, and the patient will usually display clinical signs and symptoms of sepsis and often have a clinical history of exposure, for example to amoeba. On B-mode ultrasound, as a liver abscess matures, it progresses from an isoechoic (and thus invisible) area to a necrotic, hypoechoic (almost 'cystic') lesion. At contrast-enhanced ultrasound, a hepatic abscess may demonstrate avid enhancement in the periphery and in its septa (*Figure 8*). The necrotic region does not enhance. Usually abscesses are suspected clinically before imaging, and rarely present as incidental findings in asymptomatic patients.

Hepatic trauma

Traditionally computed tomography is the modality of choice for imaging abdominal trauma. However, it has drawbacks in terms of ionizing radiation, nephrotoxic contrast media and accessibility. Contrast-enhanced ultrasound is more sensitive than B-mode and almost as sensitive as computed tomography in the detection of solid organ injury in blunt abdominal trauma.

Lacerations (*Figure 9*), haematomas, contusions and infarcts are seen as non-enhancing areas surrounded by normal enhancing parenchyma. Pseudoaneuryms and active bleeding can also be diagnosed. Scanning contrast-enhanced ultrasound protocols allow assessment of

Figure 7. Complex cyst. Dual display contrast-enhanced ultrasound showed no rim or internal enhancing septi of a complex cyst (arrow on B-mode image). Aspiration revealed old blood but no pathogens. (GE Healthcare, UK.)



all the abdominal organs in the arterial phase for active bleeding and in the late phase for lacerations. Contrast-enhanced ultrasound has the advantages of being quick and allowing repeated real-time examination of the solid organs for several minutes without needing ionizing radiation and nephrotoxic contrast. It can also be performed at the bedside in casualty and in the intensive care unit. Current guidelines (Piscaglia et al, 2012) recommend contrast-enhanced ultrasound may be used in isolated moderate energy injuries in haemodynamically stable patients (not high energy injuries), where computed tomography is not available, contraindicated or inconclusive (as a result of artefacts), minor trauma (especially children) and for follow up of injuries and in renal impairment. Contrast-enhanced ultrasound can be added to a FAST (focused assessment and sonography in trauma) scan which is primarily used for the detection of free abdominal fluid. BJHM

Figure 8. Liver abscess. a. Ill-defined focal liver lesion on baseline B-mode (calipers). b. Dual display contrast-enhanced ultrasound showed enhancement of thickened septi in the abscess (not detected on B-mode) as well as increasing the conspicuity of two subcapsular collections (arrows). (Contrast Pulse Sequencing CPS mode; Siemens, USA.)

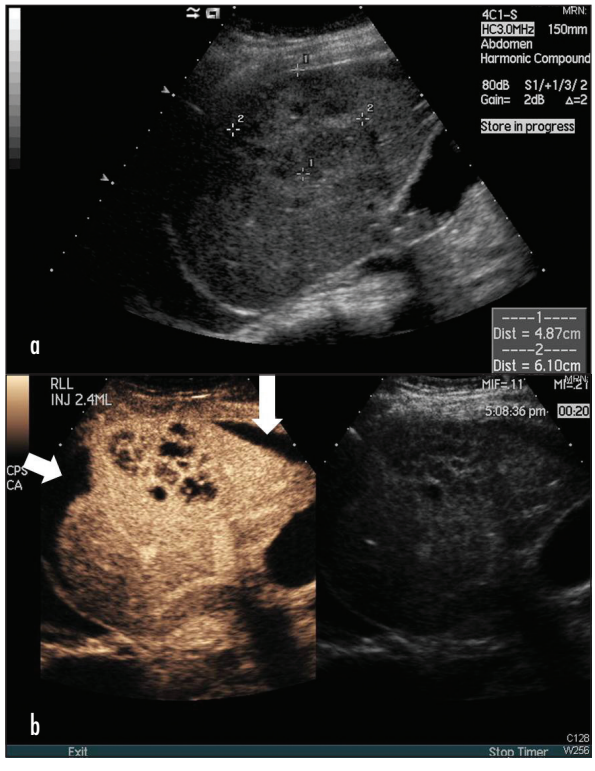
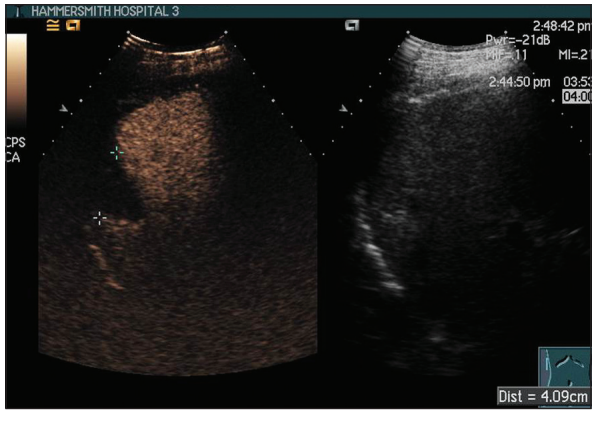


Figure 9. Dual display contrast-enhanced ultrasound showing a liver laceration, following a rugby injury. The laceration is seen as a devitalized area (calipers on left screen) on contrast-enhanced ultrasound which is very subtle on B-mode (right screen). (Contrast Pulse Sequencing CPS mode; Siemens, USA.)



Conflict of interest: none.

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KEY POINTS

- Contrast-enhanced ultrasound allows characterization of focal, indeterminate liver lesions.
- Benign liver lesions usually appear hyperenhancing or isoenhancing to liver parenchyma in the late phase (>2 minutes), with the exception of liver cysts and abscesses.
- Haemangiomas typically demonstrate peripheral 'nodular' centripetal enhancement and this pathognomonic pattern needs no further investigation, although the patient may need to be counselled that she/he has a 'birth mark' of no significance but that it may arouse concern on future investigations.
- Focal nodular hyperplasia demonstrates early centrifugal enhancement from a central feeding vessel, with a 'spoke-wheel' appearance.
- Hepatic adenomas may appear as heterogeneous lesions (from central haemorrhage) with enhancement of the solid components which may persist into the late phase. Their risk of bleeding and malignant potential require follow-up or surgical intervention.
- Focal fatty sparing, focal fatty change, regenerating nodules and dysplastic nodules have an enhancement pattern that is identical to adjacent liver parenchyma.
- Contrast-enhanced ultrasound is more sensitive than B-mode and almost as sensitive as computed tomography in detecting solid organ injury in blunt abdominal trauma. Contrast-enhanced ultrasound can detect laceration, contusions, haematomas, pseudoaneurysms and active bleeding.