The value of contrast enhanced ultrasound (CEUS) in characterizing liver lesions

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Ultrasound contrast agents have been available for a number of years. First generation agents consisted of microbubbles of a perfluorocarbon gas with a lipid shell that can survive multiple passages through the capillary system. These microbubbles oscillate in a non-linear fashion in response to applied ultrasound pulses at their resonant frequency, producing a stream of harmonic echoes. Contrast specific imaging software is required to isolate the echoes from the microbubbles from those of background tissues. The mechanical index (MI) is kept low to avoid bubble disruption and allow real-time imaging of perfusion. The microbubbles act as a blood pool agent and as such are ideal for observing the variable perfusion characteristics of the many different focal liver lesions. The examination is truly dynamic as the enhancement is observed continuously, unlike contrast enhanced CT or MRI examinations where snapshot images are obtained.

**Technique**

The liver lesion requiring characterisation is first identified and ideally should be visible throughout gentle respiration to facilitate observation of the enhancement pattern. Peripheral venous access is obtained using no smaller than a 20G cannula. The contrast bolus is then injected directly through a two-way tap followed by a saline flush through the side arm. This is to minimise bubble disruption within the cannula. The injection is preferably performed by a second person to allow the first person to maintain visualisation of the lesion. A timer is initiated at the moment of injection and the lesion observed throughout usually to a maximum of three minutes. Arterial, portal venous and late phases are observed in contrast enhanced CT or MRI (table 1). Many software packages permit continuous visualisation of the lesion by providing a split screen with a conventional ultrasound and CEUS images side by side.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Time</th>
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<tbody>
<tr>
<td></td>
<td>Start (seconds)</td>
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<tr>
<td>Arterial</td>
<td>10-20</td>
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<tr>
<td>Portal venous</td>
<td>30-40</td>
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<tr>
<td>Late</td>
<td>&gt; 120</td>
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**Benign versus malignant liver lesions**

In many cases, differentiating benign from malignant lesions is often the key requirement in characterisation of an indeterminate liver lesion with further characterisation being of secondary importance, e.g., a patient with an otherwise operable primary cancer and an indeterminate liver lesion detected on a staging CT. Sustained enhancement in the portal and late phases characterises most benign solid lesions while washout in the late phase is typical of a malignant lesion. 

**Further characterisation**

**Haemangioma:** These are considered the most common benign liver tumours and are more common in women. The majority exhibit a characteristic appearance on conventional ultrasound, being small, sharply defined, uniformly hyperechoic focal lesions situated close to blood vessels. A proportion of haemangioma however do not have all these features and hence require further imaging for characterisation. During CEUS, haemangioma show a characteristic enhancement pattern in approximately 75% of cases with early peripheral nodular enhancement, centripetal filling and no washout (figure 1). Larger haemangioma may have a central thrombosed zone that fails to enhance.

**Focal fatty change/sparing:** Fat deposition within the liver can be diffuse, leading to generally increased echogenicity on conventional ultrasound or focal, producing ill-defined, hyperechoic areas with a geographical outline. Likewise, focal areas of sparing within an otherwise fatty liver will result in similarly shaped hypoechoic areas. If more rounded, however, these can raise the suspicion of a metastatic deposit. Following contrast administration, areas of focal fatty deposition and sparing enhance in exactly the same manner as the background liver parenchyma due to the identical vascularity.

**Focal nodular hyperplasia (FNH):** These are generally isoechogenic lesions with a central scar in 50-80% of cases and often an incidental finding in a young female. On CEUS, there is early enhancement via a central feeding vessel with centrifugal filling and no washout. The central scar, when present, does not enhance. This pattern is demonstrated in 50-70% of cases.

**Hepatocellular adenoma (HCA):** These lesions are often isoechogenic to background liver on conventional ultrasound. They usually require differentiation from focal nodular hyperplasia to direct further management as the latter may be managed conservatively whereas hepatic adenomas require resection due to the risk of haemorrhage and malignant transformation. On CEUS, there is homogeneous enhancement in the arterial phase but not during the portal venous phase. This is accounted for by the lack of portal veins within HCA.

**Metastases:** The liver is frequently the site of metastatic disease and accurate detection of disease is critical in providing optimal treatment and prognosis for an individual patient. The accuracy of CEUS is comparable with contrast enhanced CT. An individual metastatic deposit demonstrates variable enhancement during the arterial phase but is typically hypoechoic on the portal venous and delayed phases. In addition, it is common for additional metastases not visualised on conventional ultrasound to be identified during a ‘sweep through’ of the entire liver following characterisation of the initial lesion.

**Hepatocellular carcinoma (HCC):** Cirrhosis is the main risk factor for HCC, therefore identification of focal liver lesions within this group of patients requires differentiation from regenerative nodules and other benign lesions. Earlier detection leads to less invasive treatments and better outcomes. On CEUS, HCCs demonstrate strong, homogeneous enhancement during the arterial phase followed by a slow washout best visualised approximately two minutes after contrast administration (figure 2). Hypovascular HCCs remain a diagnostic challenge as they fail to demonstrate a characteristic enhancement pattern.

**Cholangiocarcinoma:** These tumours are relatively rare and often advanced at the time of diagnosis. They demonstrate varying degrees of enhancement in the arterial phase but are hypoechoic relative to the background liver in the portal venous and delayed phases.

**Conclusion**

CEUS is a complementary imaging modality to CT and MRI in the characterisation of focal liver lesions. Advantages
include being potentially available in every ultrasound department, relatively low cost, extremely safe including in patients with renal impairment, quick examination times, minimal additional training required for existing ultrasound personnel and a high accuracy (two recent large multicentre trials demonstrated accuracy of 86-90%).

There are several situations where CEUS could be considered as the first line characterisation investigation. First is the incidental liver lesion. With ever-improving ultrasound equipment technology and skilled operators as well as increasing referrals, the detection of incidental liver lesions has increased steadily. Many of these will have a characteristic appearance on conventional ultrasound allowing dismissal, eg haemangiomata, however, many will have non-specific features and require further characterisation. This can involve an interval ultrasound examination, CT, MRI, biopsy or often a combination of these. Even then, a significant number of lesions remain indeterminate and follow-up is required. These further investigations are time consuming, invasive, expensive and potentially hazardous.

A major, and perhaps less appreciated consequence, is the degree of anxiety and overall adverse effect on quality of life that this experience has for the individual patient. A common scenario is of detection of a single hypoechoic focal liver lesion in a young female having an ultrasound for non-specific symptoms. CEUS is the ideal modality for characterisation as it can be performed at the time of the examination and the patient leaves the department generally with a reassuring diagnosis of a benign lesion and no further investigation required.

Second is the detection of an indeterminate focal liver lesion on a background of cirrhosis. The recognition of high risk groups for hepatocellular carcinoma and improved outcomes associated with early detection has led to widespread conventional ultrasound screening of patients with cirrhosis. Characterisation of an indeterminate focal lesion in this group of patients is therefore vital to differentiate early HCCs requiring intervention from regenerative nodules and other benign lesions.

Third is the characterisation of an identified indeterminate liver lesion in a patient with a known malignancy. The nature of such a lesion has a major influence on further treatment and prognosis. Accurate characterisation of such a lesion at the time of detection allows efficient and appropriate cancer management.

Finally, although not first line, CEUS has a role to play in the characterisation of lesions that have remained indeterminate on previous imaging such as CT or MR and even following biopsy. It is still quite possible for a lesion that has shown no characteristic pattern on other imaging modalities to demonstrate pathognomonic features on CEUS.

CEUS, despite its availability and many advantages, remains underutilised in many centres and characterisation of focal liver lesions is just one of the most successful of its many potential applications.

References