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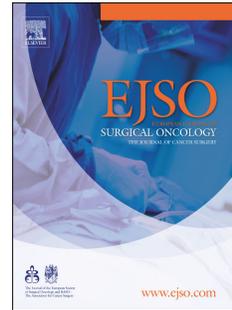
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**CONTRAST ENHANCED ULTRASOUND SHOULD BE THE INITIAL RADIOLOGICAL INVESTIGATION TO CHARACTERISE FOCAL LIVER LESIONS.**

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**ABSTRACT**

**INTRODUCTION** Contrast enhanced ultrasound (CEUS) involves the administration of a microbubble contrast agent followed by an US scan to evaluate the liver lesion through all phases of enhancement. Although technical difficulty and operator dependence can be encountered, CEUS is thought to be superior to conventional US and CT. This study aims to determine how effective CEUS is at characterising focal liver lesions and to establish its role in the diagnostic algorithm.

**METHODS** All patients who underwent a liver CEUS performed by a single consultant radiologist were identified over a 5 year period. The CEUS report, CT, MRI and/or PET report, histopathology report and case notes were reviewed.

**RESULTS** 127 patients were included. CEUS correctly identified 71 of 77 malignant lesions and all of the benign liver lesions. The sensitivity of CEUS for detecting and correctly characterising a malignant FLL is therefore 92% with a specificity of 100%.

**CONCLUSION** Our study shows that CEUS has a high sensitivity and specificity for characterising focal liver lesions. CEUS has advantages over CT and MRI of a high degree of safety, good patient tolerance and often availability at the time of initial detection. We therefore suggest that CEUS should be used as the initial study in the characterisation of FLLs. The study should be followed, as appropriate, by CT and MRI or PET studies. Biopsy, with its risks of tumour seeding and false negative results should only be considered after review of the imaging studies and full MDT discussion.

## INTRODUCTION

The detection and characterisation of a focal liver lesion (FLL) is crucial for effective and appropriate management planning. Initial liver imaging has traditionally been performed by ultrasound (US), but due to its low sensitivity and specificity in assessing FLLs, Computerised Tomography (CT) or Magnetic Resonance Imaging (MRI) are frequently required for further characterisation [1].

The development of microbubble contrast agents and contrast specific USS techniques enables imaging of a FLL through all phases of enhancement: arterial, portal and late parenchymal. Different liver lesions vary in their blood supply, and therefore characterisation of FLLs by contrast enhanced ultrasound (CEUS) has been found to be superior to US [2]. CEUS has also been shown to be superior to US and CT in detecting hepatic metastasis [3]. The European federation of societies for ultrasound in medicine and biology (EFSUMB) recommend the use of CEUS for: incidental findings on routine US, lesion or suspected lesion in chronic hepatitis or cirrhosis, lesion or suspected lesion in patients with known history of malignancy, patients with an inconclusive CT/MRI or cytology/histology result [4].

The aim of this study was to determine how effective CEUS is at characterising focal liver lesions and to establish its role in the diagnostic algorithm.

## METHODS

All patients who underwent a liver CEUS performed by a single consultant radiologist were identified over a 5 year period at the University Hospital Wales, Cardiff. The CEUS report, CT, MRI and/or PET report, histopathology report and case notes were reviewed for each patient. Patients without a confirmed histopathological diagnosis were followed up for at least six months.

CEUS was performed by injecting 2.5ml of SonoVue (Bracco, UK) and using a low mechanical index technique with a Toshiba Aplio XG or Aplio XU US machine and a 3.5 M Hz curved linear transducer. SonoVue is a second generation contrast agent that consists of a stabilised aqueous suspension of sulphur hexafluoride micro bubbles with a phospholipid shell. The mean diameter of the micro bubbles is 2.5 $\mu$ m, which are purported to accumulate in liver sinusoids and have a strong, wideband harmonic response at low mechanical index that is ideal for vascular phase imaging [5]. The liver was evaluated during the three contrast phases: arterial (10-20s after injection), portal venous phase (30-120s post injection) and late (5mins post injection) [6].

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## RESULTS

One hundred and forty one patients were identified of whom 14 were excluded due to insufficient information or follow-up. Of the 127 patients studied 68 were male. Seventy seven patients had a malignant diagnosis and 50 patients a benign diagnosis. The distributions of diagnoses for the malignant and benign lesions are detailed in tables 1 and 2 respectively.

CEUS correctly identified 71 of 77 malignant lesions. Of these malignant lesions, the diagnosis was confirmed by histopathology in 54 cases and by imaging (CT, MRI and/or PET) in 15 cases. The diagnosis was confirmed by follow-up alone in 2 cases.

Of the 6 incorrectly characterised malignant lesions 5 CEUS scans did not identify a lesion and one CEUS diagnosed a cholangiocarcinoma as focal nodular hyperplasia. Four of the 6 lesions were identified as malignant by another imaging modality.

All of the benign FLLs were correctly identified as being benign. The diagnosis was confirmed by histopathology in 17 cases and by imaging in 23 cases. The diagnosis was confirmed by follow-up alone in 10 cases. One FLL was identified as an adenoma on CEUS and MRI but subsequently found to be an angiomyolipoma on histology.

The sensitivity of CEUS for detecting and correctly characterising a malignant FLL is therefore 92% with a specificity of 100%. The positive predictive value was 92% and the negative predictive value was 100%.

## DISCUSSION

Ultrasound contrast agents were initially introduced when imaging vessels in poor conditions or when low velocity flow resulted in difficulties obtaining a Doppler signal. It then became evident that the liver parenchyma enhanced with contrast and that FLLs had individual enhancement patterns through the various contrast phases enabling their characterisation [6] (see table 3 and figure 1).

The use of conventional US to characterise liver lesion has limitations, including: identifying small lesions (<2cm), in cirrhotic livers, and in patients undergoing chemotherapy [9]. CEUS has increased diagnostic performance when compared with conventional US and the advantage of dynamic vascular assessment [2]. When compared with CT and MRI, CEUS utilises a contrast agent that is safer, non-nephrotoxic, and has a lower incidence of hypersensitivity or allergy and is without the radiation exposure of CT. It is often possible to perform CEUS at the time of initial detection of the lesion and CEUS also provides information which may be similar to that obtained by CT and MRI, but in other cases gives additional, complementary information.

In this series of CEUS there were no reported side effects from the contrast. SonoVue is, however, contraindicated in patients with recent myocardial infarction, angina, cardiac insufficiency, severe pulmonary hypertension and acute respiratory distress syndrome [6]. Technical difficulties in CEUS arise in obese patients, as for conventional USS, and when imaging segment 8 of the liver. CEUS is strongly operator dependent and the results can be reliant upon the radiologist's skill and experience as well as the quality of the equipment.

In this series of CEUS performed by an individual radiologist, the specificity for identifying a malignant liver lesion was 100%. This compares favourably with previous studies by Leen (2006), von Herbay (2004) and Soye (2007) who demonstrated specificities of 81%, 92% and 98% respectively [10,11,12]. The lesions that were misdiagnosed characteristically have similar enhancement patterns on CEUS: cholangiocarcinoma and FNH.

## CONCLUSION

Our study shows that CEUS has a high sensitivity and specificity for characterising focal liver lesions. CEUS has advantages over CT and MRI of a high degree of safety, good patient tolerance and often availability at the time of initial detection. We therefore suggest that CEUS should be used as the initial study in the characterisation of FLLs. The study should be followed, as appropriate, by CT and MRI or PET studies (see fig 2). Biopsy, with its risks of tumour seeding and false negative results should only be considered after review of the imaging studies and full MDT discussion [13].

Table 1: Malignant liver lesions

<b>Diagnosis</b>	<b>No. of patients</b>
Metastasis	60
Hepatocellular carcinoma	13
Cholangiocarcinoma	3
Lymphoma	1

Table 2: Benign liver lesions

<b>Diagnosis</b>	<b>No. of patients</b>
Haemangioma	18
Focal nodular hyperplasia	11
Abscess	6
Focal fatty change	4
Simple cyst	2
Regenerating nodule	1
Hydatid	1
Angiomyolipoma	1
Other	6

Table 3. Contrast Ultrasound characterisation of focal liver lesions

<b>Focal Liver Lesion</b>	<b>Arterial Phase</b>	<b>Portal Phase</b>	<b>Late Phase</b>
<b>Metastasis</b>	Enhancement usually centripetal	No portal flow. Appear as holes	Appear as sharply delineated areas
<b>Hepatocellular carcinoma</b>	Hypervascular with septae, basket-like or irregular pattern	Washout, but isoechoic in well differentiated HCC	Echo poor
<b>Cholangio-carcinoma</b>	Hyper-perfused	Punched out defects	
<b>Lymphoma</b>	Variable arterial perfusion	Hypo-enhancement	
<b>Haemangioma</b>	Peripheral nodular enhancement	Centripetal filling with iso or hyperenhanced area	Isoenhanced
<b>Focal nodular hyperplasia</b>	Hyperenhanced with spoke wheel filling from artery	Iso or hyperenhanced central scar	Iso or hyperenhanced central scar
<b>Abscess</b>	Cyst-like. May have echogenic debris and hypervascularity in thickened wall		
<b>Focal fatty change</b>	Isoenhancement	Isoenhancement	Isoenhancement
<b>Cyst</b>	Absence of contrast with posterior enhancement	Absence of contrast with posterior enhancement	Absence of contrast with posterior enhancement

[7&amp;8]

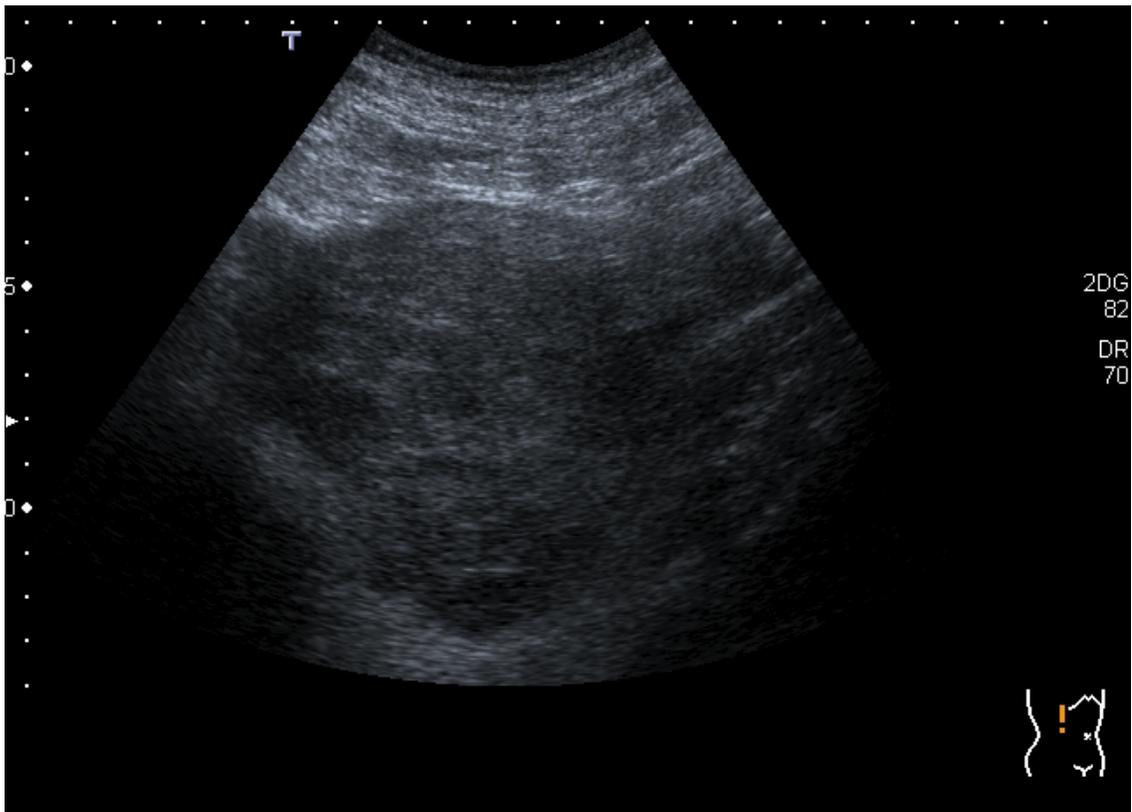
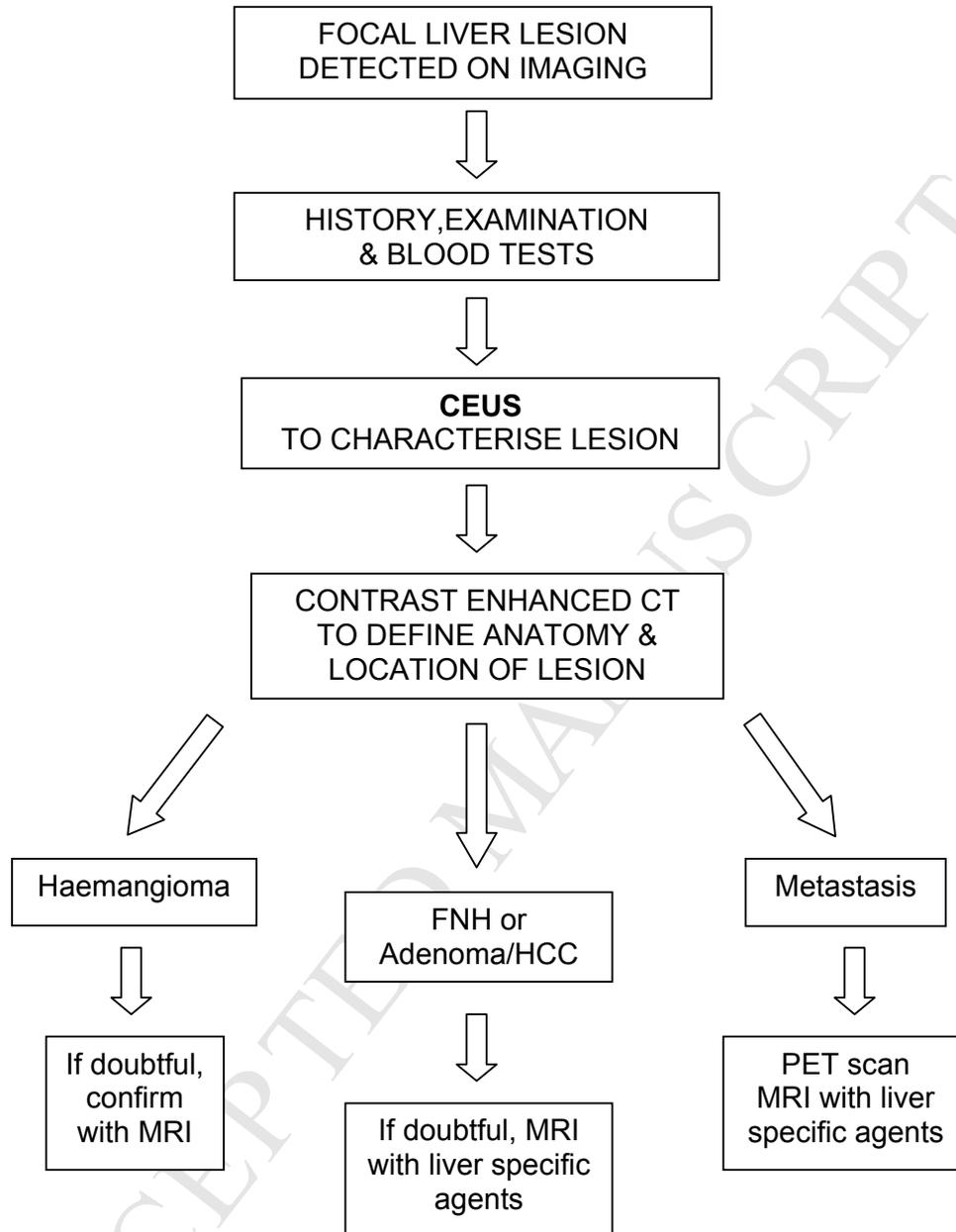


Figure 1. Hepatocellular Carcinoma

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Figure 2



**Conflict of interest**

The authors state that they have no conflict of interest.

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