# Contrast-enhanced ultrasound using SonoVue® (sulphur hexafluoride microbubbles) compared with contrast-enhanced computed tomography and contrast-enhanced magnetic resonance imaging for the characterisation of focal liver lesions and detection of liver metastases: a systematic review and cost-effectiveness analysis

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## Executive summary

CEUS vs CECT/CEMRI for focal liver lesions and liver metastases

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# Executive summary

## Background

Ultrasound (US) scanning and other imaging technologies [e.g. computed tomography (CT) and magnetic resonance imaging (MRI)] are important in the management of many patients with liver disease. Imaging sometimes identifies focal abnormalities in the liver that cannot be characterised initially and may need further investigation, the main aim of which is to distinguish between liver cancers and benign abnormalities not likely to require further treatment. One important factor in selecting an imaging test is the ability to provide a rapid diagnosis, both to facilitate prompt treatment in patients who do have cancer and to minimise anxiety in the majority who do not. Most liver lesions are found at an initial unenhanced US scan. If the liver abnormality is not characterised by this test, the patient is usually referred for additional imaging (MRI and/or CT) and may require biopsy when additional imaging remains uncertain. CT and MRI can require additional waiting time, CT uses ionising radiation and the intravenous contrast agent can, on rare occasions, cause kidney damage, and some patients cannot undergo MRI (e.g. because of pacemakers or claustrophobia). The use of contrast agents may improve the ability of US to distinguish between liver cancer and benign abnormalities and, because it can be performed at the same appointment as unenhanced US, more rapid diagnoses may be possible and some CT and MRI examinations may be avoided.

## Objectives

To compare the clinical effectiveness and cost-effectiveness of contrast-enhanced ultrasound (CEUS) using SonoVue® (Bracco UK Ltd, High Wycombe, UK) with that of contrast-enhanced CT (CECT) and contrast-enhanced MRI (CEMRI) for the assessment of adults with focal liver lesions (FLLs) in whom previous liver imaging is inconclusive.

## Methods

A systematic review was conducted to summarise the evidence on the clinical effectiveness of CEUS using the contrast agent SonoVue compared with the clinical effectiveness of CECT and CEMRI for the assessment of adults with FLLs in whom previous liver imaging has been inconclusive. Search strategies were based on the target condition (primary or secondary liver cancer) and intervention (SonoVue CEUS), as recommended in current methodological guidance (www.york.ac.uk/inst/crd/SysRev/!SSL!/WebHelp/SysRev3.htm). Eight bibliographic databases including MEDLINE, EMBASE, Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects were searched from 2000 to September/October 2011. Research registers and conference proceedings were also searched. Systematic review methods followed published guidance (www.york.ac.uk/inst/crd/SysRev/!SSL!/WebHelp/SysRev3.htm). The risk of bias in diagnostic test accuracy (DTA) studies was assessed using a modified version of the QUADAS-2 tool, and in the single controlled clinical trial was assessed using an adaptation of The Cochrane Collaboration's risk of bias tool. Accuracy results were summarised in tables and the text, stratified by clinical indication for imaging [characterisation of FLLs detected on US surveillance of cirrhosis patients, detection of liver metastases, characterisation of incidentally (US) detected FLLs, assessment of response to treatment of liver malignancy] and further stratified by target condition [primary hepatocellular carcinoma (HCC), liver metastases or 'any liver malignancy'] and/or comparator test(s) (CECT, CEMRI, both), as appropriate. The review included only one group of four similar studies (comparable clinical indication, index test and comparator, target condition and diagnostic criteria). Pooled estimates of sensitivity and specificity, with 95% confidence intervals (CIs), were calculated using a random-effects model and a

sensitivity analysis was undertaken to assess the effect of excluding one large study that used a suboptimal reference standard. Between-study clinical heterogeneity was assessed qualitatively.

The health economic analysis focused on populations in whom clinical opinion indicated that there was most likely to be a benefit from the use of CEUS. These were also the populations with most data on test performance. Specifically, most data on the detection of metastases were available from patients with colorectal cancer (CRC). In addition, clinical opinion confirmed that liver metastases from CRC were the main focus of testing. Therefore, the health economic analysis used three models to assess the value of CEUS in the following three populations:

- characterisation of FLLs detected on routine surveillance of patients with cirrhosis
- detection of liver metastases in patients with CRC
- characterisation of incidentally detected FFLs.

In each model, CEUS was compared with CECT, CEMRI using gadolinium contrast agent (Gd-CEMRI) and/or CEMRI using superparamagnetic iron oxide contrast agent (SPIO-CEMRI). The average costs, expected life-years and expected quality-adjusted life-years (QALYs) per patient were calculated for each comparator, if accuracy data were available.

The cirrhosis surveillance model was a modified version of a model produced by the Health Economics Group, Peninsula Technology Assessment Group (PenTAG), Institute of Health Service Research, Peninsula Medical School (the PenTAG cirrhosis surveillance model) [Thompson Coon J, Rogers G, Hewson P, Wright D, Anderson R, Cramp M, *et al*. Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis. *Health Technol Assess* 2007;**11**(34)]. The population of interest was those with a diagnosis of compensated cirrhosis deemed eligible to enter a surveillance programme. It was a probabilistic state transition (Markov) cohort model constructed using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA). The model used a lifetime time horizon and the cycle duration was 1 month. Patients in the model can develop HCC. In the base-case analysis surveillance is every 6 months and stops at age 70 years. During this surveillance (US, combined with CEUS, CECT or CEMRI when inconclusive), the probability of identifying a small (< 2 cm) or medium (2–5 cm) HCC depends on test accuracy. In the base case, accuracy was taken from Leoni *et al.* (Leoni S, Piscaglia F, Golfieri R, Camaggi V, Vidili G, Pini P, *et al*. The impact of vascular and nonvascular findings on the noninvasive diagnosis of small hepatocellular carcinoma based on the EASL and AASLD criteria. *Am J Gastroenterol* 2010;**105**:599–609). Large (> 5 cm) tumours are always identified at surveillance. If the tumour is not identified (false-negatives), it grows and may be identified at the next surveillance or when symptomatic. Patients without HCC who are incorrectly diagnosed (false-positives) were assumed to be rapidly discovered before treatment.

The liver metastases from CRC model is a modified version of the metastatic model developed by Brush *et al.*, adapted to assess the cost-effectiveness of CEUS compared with CECT and CEMRI in detecting metastases from CRC after inconclusive US [Brush J, Boyd K, Chappell F, Crawford F, Dozier M, Fenwick E, *et al*. The value of FDG positron emission tomography/computed tomography (PET/CT) in pre-operative staging of colorectal cancer: a systematic review and economic evaluation. *Health Technol Assess* 2011;**15**(35)]. The population of interest was patients who had previously had surgical treatment for primary CRC and who, during routine follow-up, were identified as potentially having a metastatic recurrence. A decision tree combined with a probabilistic state transition (Markov) cohort model, constructed using Microsoft Excel, was used. The model used a lifetime time horizon and the cycle duration was 1 year. The probability of correctly detecting metastases depends on test accuracy. In the base case, accuracy was taken from Mainenti *et al*. (Mainenti PP, Mancini M, Mainolfi C, Camera L, Maurea S, Manchia A, *et al*. Detection of colorectal liver metastases: prospective comparison of contrast enhanced US, multidetector CT, PET/CT, and 1.5 Tesla MR with extracellular and reticulo-endothelial cell specific contrast agents. *Abdom Imaging* 2010;**35**:511–21). It was assumed that patients with undetected metastases (false-negatives) would be identified within a year if they were still alive. These patients are expected to have a lower quality of life and prognosis, but only in the first year. In the base-case analysis,

patients who are inaccurately diagnosed as having metastases (false-positives) are identified, because it is considered likely that clinicians will require confirmatory biopsy before initiating treatment. They are therefore not unnecessarily treated.

Patients with incidentally detected FLLs can have a variety of underlying diseases, for example HCC, metastases and various benign lesions. The prognosis and costs for patients with HCC were modelled using the cirrhosis model, and the prognosis and costs for patients with liver metastases were modelled using the liver metastases model. The FLL model used was a decision-analytic model with a lifetime time horizon. Test accuracy data were taken from the findings of the systematic review. The sensitivity and specificity of CEUS and CECT in identifying any malignancy were based on the results of a meta-analysis of four studies. CEUS and CEMRI could be compared using only one study. For different reasons it was assumed that patients with an incorrect test result (i.e. false-positive and false-negative results) would be correctly identified within 1 year. This was a conservative assumption biased against CEUS.

The impact of uncertainty about the various input parameters on the outcomes was explored through sensitivity analyses.

## Results

Of the 854 references identified, 19 (describing 18 studies) were included in the review. Hand searching of conference proceedings identified a further three studies. Twenty of the 21 studies included in the systematic review were DTA studies. The majority of these were judged to be at low or unclear risk of bias with respect to the 'index test', 'comparator test' and 'reference standard' domains. Reporting quality was poor and a number of studies were reported only as conference abstracts. High risk of bias ratings for the 'patient selection' domain arose from retrospective study design or inappropriate exclusions (e.g. patients with a low probability of malignancy). High risk of bias ratings for the 'flow and timing' domain most frequently arose from exclusion of >10% of patients from analyses. Test accuracy studies varied in terms of target condition, definitions of a positive imaging test and lesion size assessed. Overall, there was no clear indication that any of the imaging modalities considered (CEUS, CECT or CEMRI) offered superior performance for any of the populations or clinical applications considered.

Studies conducted in cirrhosis patients undergoing routine surveillance all concerned the differentiation of HCC from other lesion types. The definition of a positive test varied across studies and estimates of sensitivity and specificity were inconsistent, even when studies used similar definitions. There was no consistent evidence for any significant difference in performance between the three imaging modalities and three MRI contrast media assessed. It is unclear whether or not CEUS alone is adequate to rule out HCC for FLLs of <30 mm in this population; one study indicated that CEUS may be better at ruling out HCC for FLLs of 11–30 mm, with very small FLLs (<10 mm) not considered.

Studies of the diagnosis of liver metastases using contrast-enhanced imaging with vascular contrast media (CEUS, CECT and Gd-CEMRI) gave similar definitions of a positive test when reported. Two studies reported data for SPIO-CEMRI. There was no consistent evidence for any difference in test performance between the three imaging modalities and different contrast media assessed. The limited data available indicate that CEUS alone may be adequate to rule out liver metastases in patients with CRC.

Studies of patients with incidentally detected FLLs mainly reported data on diagnosis of 'any malignancy'. Studies were consistent in their definitions of the criteria for HCC, which were similar to those reported in published guidelines. Studies reported per-patient or equivalent data. All studies reported no significant difference in the accuracy of CEUS and CECT or CEMRI for the characterisation of focal FLLs. The pooled estimates of sensitivity for the identification of 'any liver malignancy' using CEUS and CECT were 95.1% (95% CI 93.3% to 96.6%) and 94.6% (95% CI 92.7% to 96.1%), respectively, and the corresponding specificity estimates were 93.8% (95% CI 90.4% to 96.3%) and 93.1% (95% CI 89.6% to 95.8%), based

on data from four studies. The single study comparing CEUS with CEMRI reported similar sensitivity and lower specificity for both modalities. High estimates of sensitivity indicate that CEUS alone may be adequate to rule out liver malignancy in this population.

In the surveillance of cirrhosis, CEUS was found to be as effective as but £379 (95% CI £324 to £1060) less costly than CECT. This indicates that CEUS dominates CECT. Gd-CEMRI was found to be £1063 (95% CI £449 to £1492) more costly than CEUS and gained 0.022 (95% CI –0.002 to 0.050) more QALYs. This resulted in an incremental cost-effectiveness ratio (ICER) of £48,545 per QALY gained. This ICER would be deemed unacceptable given a willingness-to-pay threshold of £20,000 per additional QALY. CEUS can therefore be considered the most cost-effective option when used after inconclusive US. Changing the source of accuracy data corroborated the dominance of CEUS over CECT. CEUS was cost-effective compared with Gd-CEMRI in most sensitivity analyses.

In the diagnosis of liver metastases from CRC, CEUS was found to cost £1 (95% CI –£1.26 to £1.28) more than CECT and at a lifetime time horizon they yielded equal QALYs per patient. Both Gd-CEMRI and SPIO-CEMRI were dominated by CECT because they were more costly and equally as effective. When increasing the proportion of patients with metastases or changing the source of accuracy data, CEUS was found to dominate CECT. In these additional analyses, Gd-CEMRI was not cost-effective compared with CEUS, or dominated by CEUS. If it is not assumed that patients incorrectly diagnosed with metastases are identified by biopsy before any unnecessary treatment, the lower specificity of CEUS has greater consequences. CEUS is then the most costly and the least effective option, and Gd-CEMRI dominates. However, it is questionable whether or not this would happen in practice.

In the characterisation of incidentally detected FLLs, CEUS was found to be very slightly more effective (0.0002 QALYs; 95% CI –0.00110 to 0.00140) than CECT and £52 (95% CI –£81 to –£22) less costly. Compared with CEMRI, CEUS was also slightly more effective (0.0026 QALYs; 95% CI –0.0058 to 0.0135 QALYs) and less costly (–£131; 95% CI –£194 to –£69). An increased prior probability of malignant lesions increased the QALYs gained by CEUS compared with both CECT and CEMRI, thereby confirming its dominance. When the consequences of an incorrect diagnosis of HCC and metastases were made more or less severe, CEUS dominated CECT and CEMRI. When the data source for the performance of CEUS and CECT was switched from the meta-analysis to one of the four studies used in the meta-analysis, the cost-effectiveness results changed only slightly, and did not alter the dominance of CEUS over CECT.

## Conclusions

The results of our systematic review suggest that SonoVue CEUS could provide similar diagnostic performance to other imaging modalities (CECT and CEMRI) for the three main clinical applications considered: characterisation of FLLs detected on US surveillance of cirrhosis patients, detection of liver metastases in patients with CRC and characterisation of incidentally detected FLLs. However, some caution is required in the interpretation of these findings as studies were generally small and heterogeneous with respect to the target condition (HCC, liver metastases or 'any malignancy'), definitions of a positive imaging test and lesion size assessed.

The cost-effectiveness analysis indicated that the use of CEUS instead of CEMRI was cost-effective. The use of CEUS instead of CECT was considered cost-effective in the surveillance of cirrhosis and the characterisation of incidentally detected FLLs, with similar costs and effects for the detection of liver metastases from CRC. Although conclusions can be very dependent on the management of incorrectly diagnosed lesions, it is expected that CEUS can reduce costs without reducing quality of life and survival. It should be noted that, although no data were available on this issue, experience with CEUS could have an important impact on diagnostic accuracy; availability of experienced operators and training requirements are likely to be important considerations for the implementation of this technology.

If the main use of liver imaging is considered to be the rapid rule-out of malignancy, equivalent diagnostic performance may be sufficient for SonoVue CEUS to be preferred over other imaging modalities. A potential advantage of using SonoVue CEUS would be the option of completing the assessment at the same time as the initial unenhanced US. Although this would be unlikely to reduce waiting times (compared with other imaging modalities) sufficiently to change clinical outcome, the potential to provide more rapid diagnosis without repeat hospital visits is likely to be preferred by patients and may also reduce costs.

## Suggested research priorities

The ideal study to address questions of clinical effectiveness would be a large multicentre RCT in which patients are randomised to receive further testing/monitoring, therapeutic planning and/or treatment based on different imaging strategies (SonoVue CEUS, CECT, CEMRI). Long-term observational studies assessing the clinical consequences of incorrect initial diagnoses may also be informative for future cost-effectiveness analyses. Standardisation of the definition of a positive imaging test for each target condition (HCC, liver metastases) followed by further, high-quality DTA studies is needed to confirm our findings on test accuracy. Future DTA studies should ideally compare the performance of all three imaging modalities (SonoVue CEUS, CECT and CEMRI) in the same patient group and report numbers of non-diagnostic images and imaging-related adverse events. Studies comparing all three imaging modalities could provide a useful vehicle for the collection of information on patients' preferences. Further investigation of the potential role of CEMRI, using newer 'combined' vascular and hepatocyte-specific contrast agents, may also be warranted. The practicality and effectiveness of SonoVue CEUS in the assessment of multiple lesions in both lobes of the liver should also be considered.

## Study registration

This study is registered as PROSPERO: CRD42011001694.

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