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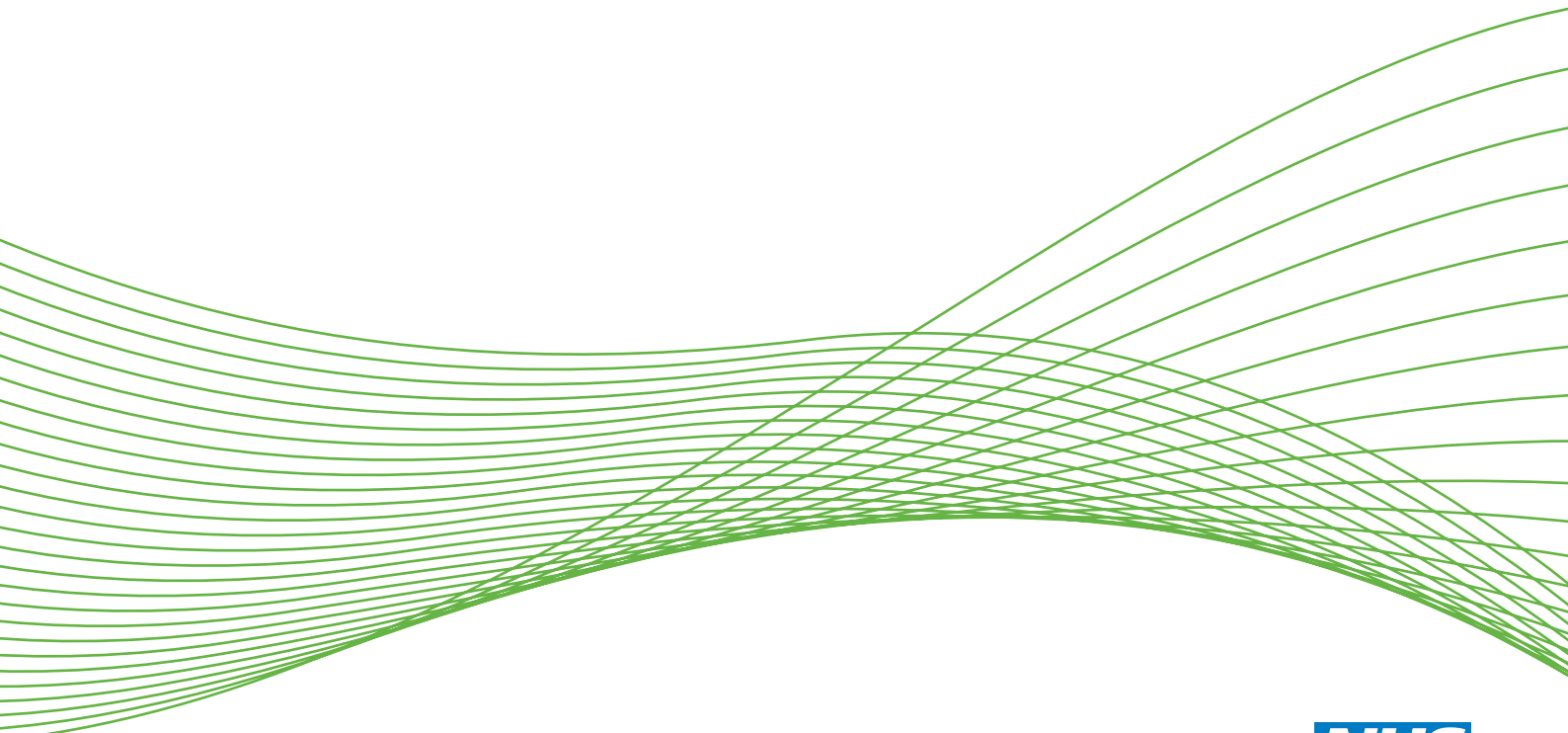
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## Contrast-enhanced ultrasound using SonoVue® (sulphur hexafluoride microbubbles) compared with contrast-enhanced computed tomography and contrast-enhanced magnetic resonance imaging for the characterisation of focal liver lesions and detection of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

*M Westwood, M Joore, J Grutters, K Redekop, N Armstrong, K Lee, V Gloy, H Raatz, K Misso, J Severens and J Kleijnen*



**National Institute for  
Health Research**



# **Contrast-enhanced ultrasound using SonoVue<sup>®</sup> (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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# Abstract

## 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

M Westwood,<sup>1\*</sup> M Joore,<sup>2</sup> J Grutters,<sup>3</sup> K Redekop,<sup>4</sup> N Armstrong,<sup>1</sup> K Lee,<sup>1</sup> V Gloy,<sup>5</sup> H Raatz,<sup>5</sup> K Misso,<sup>1</sup> J Severens<sup>6</sup> and J Kleijnen<sup>7</sup>

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**Background:** Medical imaging techniques are important in the management of many patients with liver disease. Unenhanced ultrasound examinations sometimes identify focal abnormalities in the liver that may require further investigation, primarily to distinguish liver cancers from benign abnormalities. One important factor in selecting an imaging test is the ability to provide a rapid diagnosis. Options for additional imaging investigations include computed tomography (CT) and/or magnetic resonance imaging (MRI) and biopsy when the diagnosis remains uncertain. CT and MRI usually require referral with associated waiting time and are sometimes contraindicated. The use of contrast agents may improve the ability of ultrasound to distinguish between liver cancer and benign abnormalities and, because it can be performed at the same appointment as unenhanced ultrasound, more rapid diagnoses may be possible.

**Objective:** To compare the clinical effectiveness and cost-effectiveness of contrast-enhanced ultrasound (CEUS) using SonoVue® with that of contrast-enhanced computed tomography (CECT) and contrast-enhanced magnetic resonance imaging (CEMRI) for the assessment of adults with focal liver lesions (FLLs) in whom previous liver imaging is inconclusive.

**Data sources:** 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.

**Review methods:** Systematic review methods followed published guidance. Risk of bias was assessed using a modified version of the QUADAS-2 tool. Results were stratified by clinical indication for imaging (characterisation of FLLs detected on ultrasound surveillance of cirrhosis patients, detection of liver

metastases, characterisation of incidentally detected FLLs, assessment of treatment response). For incidental FLLs, pooled estimates of sensitivity and specificity, with 95% CIs, were calculated using a random-effects model. For other clinical indications a narrative summary was used. The cost-effectiveness of CEUS was modelled separately for the three main clinical applications considered [characterisation of FLLs detected on ultrasound surveillance of cirrhosis patients, detection of liver metastases in patients with colorectal cancer (CRC), characterisation of incidentally detected FLLs].

**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 diagnostic test accuracy studies. Studies in cirrhosis patients reported varying estimates of test performance. There was no consistent evidence of a significant difference in performance between imaging modalities. It was unclear whether or not CEUS alone is adequate to rule out hepatocellular carcinoma (HCC) for FLLs of <30 mm; one study indicated that CEUS may be better at ruling out HCC for FLLs of 11–30 mm [very small FLLs (<10 mm) excluded]. There was no consistent evidence of a difference in test performance between imaging modalities for the detection of metastases; CEUS alone may be adequate to rule out liver metastases in colorectal cancer. In patients with incidentally detected FLLs, the pooled estimates of sensitivity for any malignancy using CEUS and CECT were 95.1% and 94.6%, respectively, and the corresponding specificity estimates were 93.8% and 93.1% respectively. One study comparing CEUS with CEMRI reported similar sensitivity and lower specificity for both modalities. In the surveillance of cirrhosis, CEUS was as effective as but £379 less costly than CECT. CEMRI was £1063 more costly than CEUS and gained 0.022 QALYs. In the detection of liver metastases from CRC, CEUS cost £1 more than CECT, and at a lifetime time horizon they yielded equal QALYs. CEMRI was dominated by CECT. In the characterisation of incidentally detected FLLs, CEUS was slightly more effective than CECT and CEMRI (by 0.0002 QALYs and 0.0026 QALYs respectively) and less costly (by £52 and £131 respectively).

**Limitations:** There were a number of methodological issues specific to the studies included in this review. The main indication for liver imaging in the populations considered is likely to be to rule out primary liver cancer or metastases. Therefore, patient-level analyses of test performance are of particular interest. Some of the studies included in this review reported per-patient analyses; however, no study clearly stated how results were defined (e.g. was the presence of any positive lesion regarded as a positive test for the whole patient). In addition, a number of studies reported data for one lesion per patient (treated as per-patient data in this assessment). These studies generally selected the largest lesion or the lesion 'most suspicious for malignancy' for inclusion in analyses, with the consequence that estimates of test performance may have been exaggerated. The applicability of studies included in this review may be limited, as the majority of imaging studies were interpreted by multiple, experienced operators and the prevalence of malignancy in included studies appeared higher than might be expected in clinical practice. The cost-effectiveness analyses did not take into account the potential benefits of reduced anxiety that may arise from potentially shorter waiting times associated with SonoVue CEUS.

**Conclusions:** SonoVue CEUS could provide similar diagnostic performance to other imaging modalities (CECT and CEMRI) for the assessment of FLLs. Economic analyses indicated that CEUS was a cost-effective replacement for CEMRI. 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. Further research is needed to compare the effects of different imaging modalities (SonoVue CEUS, CECT, CEMRI) on therapeutic planning, treatment and clinical outcomes. Future test accuracy studies should provide standardised definitions of a positive imaging test, and compare all three imaging modalities in the same patient group.

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# Glossary

**Cholangiocarcinoma** Cancer of the bile ducts, which drain bile from the liver into the small intestine.

**Cirrhosis** A consequence of liver disease, most commonly alcoholism, hepatitis B and C, or fatty liver disease. It is characterised by replacement of liver tissue with fibrosis and scar tissue, leading to loss of liver function.

**Computed tomography** A medical imaging technique using tomography created by computer processing to generate a three-dimensional internal image from a series of two-dimensional radiographic images.

**Contrast-enhanced ultrasound** The application of a contrast agent to conventional ultrasonography. Ultrasound contrast agents rely on the different ways that sound waves are reflected from interfaces between substances, for example microbubbles and human tissue. The difference in echogenicity (ability to reflect ultrasound waves) between microbubbles and surrounding tissues is very high and intravenous contrast injection can be used to visualise blood perfusion and to distinguish between benign and malignant tissue.

**Cost-effectiveness analysis** An economic analysis that converts effects into health terms and describes the costs for additional health gain.

**Decision modelling** A theoretical construct that allows the comparison of the relationship between costs and outcomes of alternative health-care interventions.

**False-negative** Incorrect negative test result – number of diseased persons with a negative test result.

**False-positive** Incorrect positive test result – number of non-diseased persons with a positive test result.

**Focal nodular hyperplasia** A benign, usually asymptomatic tumour of the liver, which rarely grows or bleeds and has no malignant potential. It is often characterised by a central stellate scar.

**Haemangioma** The most common benign tumour of the liver, usually of mesenchymal origin and comprising masses of atypical blood vessels.

**Hepatocellular carcinoma** The most common type of liver cancer, usually secondary to scarring of the liver (cirrhosis) or hepatitide viral infection (hepatitis B or C).

**Incremental cost-effectiveness ratio** The difference in the mean costs of two interventions in the population of interest divided by the difference in the mean outcomes in the population of interest.

**Index test** The test whose performance is being evaluated.

**Magnetic resonance imaging** A medical imaging technique that uses nuclear magnetic resonance to image the nuclei of atoms inside the body. It provides good contrast between the different tissues of the body and can be useful in distinguishing malignant from benign tumours.

**Markov model** An analytical method particularly suited to modelling repeated events or the progression of a chronic disease over time.

**Meta-analysis** Statistical techniques used to combine the results of two or more studies and obtain a combined estimate of effect.

**Meta-regression** Statistical technique used to explore the relationship between study characteristics and study results.

**Metastasis** The spread of a disease from one organ or part to another non-adjacent organ or part.

**Opportunity cost** The cost of forgone outcomes that could have been achieved through alternative investments.

**Publication bias** Bias arising from the preferential publication of studies with statistically significant results.

**Quality of life** An individual's emotional, social and physical well-being and his or her ability to perform the ordinary tasks of living.

**Quality-adjusted life-year** A measure of health gain used in economic evaluations in which survival duration is weighted or adjusted by the patient's quality of life during the survival period.

**Radiofrequency ablation** A medical procedure in which tumour tissue is ablated using the heat generated from the high-frequency alternating current.

**Receiver operating characteristic curve** A graph that illustrates the trade-offs between sensitivity and specificity that result from varying the diagnostic threshold.

**Reference standard** The best currently available diagnostic test against which the index test is compared.

**Sensitivity** Proportion of people with the target disorder who have a positive test result.

**Specificity** Proportion of people without the target disorder who have a negative test result.

**Transarterial chemoembolisation** A minimally invasive medical procedure to restrict blood flow to the tumour; frequently used to treat hepatocellular carcinoma.

**True-negative** Correct negative test result – number of non-diseased persons with a negative test result.

**True-positive** Correct positive test result – number of diseased persons with a positive test result.

## List of abbreviations

AASLD	American Association for the Study of Liver Diseases	HBV	hepatitis B virus
AFP	alpha-fetoprotein	HCC	hepatocellular carcinoma
ALD	alcoholic liver disease	HCV	hepatitis C virus
CCC	cholangiocarcinoma	HTA	Health Technology Assessment
CEA	carcinoembryonic antigen	ICER	incremental cost-effectiveness ratio
CECT	contrast-enhanced computed tomography	MDCT	multidetector computed tomography
CEMRI	contrast-enhanced magnetic resonance imaging	MRI	magnetic resonance imaging
CEUS	contrast-enhanced ultrasound	NHS EED	NHS Economic Evaluation Database
CI	confidence interval	NICE	National Institute for Health and Care Excellence
CRC	colorectal carcinoma	NIHR	National Institute for Health Research
CRD	Centre for Reviews and Dissemination	OR	odds ratio
CT	computed tomography	PEI	percutaneous ethanol injection
DARE	Database of Abstracts of Reviews of Effects	PenTAG	Peninsula Technology Assessment Group
DTA	diagnostic test accuracy	PRESS EBC	Peer Review of Electronic Search Strategies Evidence-Based Checklist
EASL	European Association for the Study of the Liver	QALY	quality-adjusted life-year
EFSUMB	European Federation of Societies for Ultrasound in Medicine and Biology	RFA	radiofrequency ablation
FDG-PET	fluorodeoxyglucose positron emission tomography	ROC	receiver operating characteristic
FLL	focal liver lesion	RON	Romanian new leu
FNB	fine-needle biopsy	SCI	Science Citation Index
Gd-CEMRI	gadolinium contrast-enhanced magnetic resonance imaging	SPIO-CEMRI	superparamagnetic iron oxide contrast-enhanced magnetic resonance imaging
Gd-EOB-DTPA	gadolinium ethoxybenzyl diethylenetriamine penta-acetic acid	SROC	summary receiver operating characteristic



## LIST OF ABBREVIATIONS

TAE	transarterial embolisation	TNM	tumour, lymph node, metastases
TACE	transarterial chemoembolisation	US	ultrasound

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

# 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](http://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](http://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 FLLs.

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.

## Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.



# Chapter 1 Objective

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





## Chapter 2 Background and definition of the decision problem

### Conditions and aetiologies

The indication for this assessment is the characterisation of FLLs and detection of liver metastases in adults and the target conditions are malignancies of the liver [primary hepatocellular carcinoma (HCC) or liver metastases].

In the context of this assessment, the term 'focal lesion in the liver' refers to any focal area of perceived difference seen on an imaging study and occurring in one specific area of the liver. FLLs can be broadly classified as benign (e.g. haemangioma, focal nodular hyperplasia, focal fatty infiltration or sparing and adenoma) or malignant [e.g. primary HCC, cholangiocarcinoma (CCC) or liver metastases], with the identification or exclusion of malignancy being the primary aim of diagnostic imaging. The distinction between benign and malignant determines the individual's prognosis and the subsequent treatment strategy. Benign, asymptomatic FLLs usually do not require any treatment. Depending on the specific type of lesion, the individual may be monitored and the lesion rescanned in 6–12 months. Once a malignant lesion is identified it is important to distinguish between primary and secondary cancers as this is likely to impact on how the individual is managed. Malignant lesions may be treated by a range of interventions including chemotherapy, liver resection (surgery) and local ablative therapy. The treatment of primary HCC has been addressed in published guidelines<sup>1,2</sup> and the National Institute for Health and Care Excellence (NICE) has issued guidance on a number of individual interventions for primary HCC and liver metastases (see *Appendix 6*). However, expert opinion suggests that practice within the NHS may vary significantly across regions based on clinician preference.

Although liver cancer is rare in the UK (age-standardised rates are 4.7 per 100,000 men and 2.9 per 100,000 women),<sup>3</sup> it is the second most rapidly increasing cancer in men and the third in women (increases of 38% and 28%, respectively, in the last decade).<sup>4</sup> However, as 70–75% of FLLs assessed in the NHS may be benign, one possible benefit of CEUS may be the rapid rule-out of malignancy with an associated reduction in anxiety for patients and families. The current practice of referring patients with inconclusive unenhanced ultrasound (US) for CEMRI and/or CECT may result in a wait of up to several months.

Because SonoVue CEUS should be used only when unenhanced US is inconclusive, we consider its primary application to be for the characterisation of lesions (benign or malignant) in patients with known FLLs; most patients who have already undergone unenhanced US and who have proceeded to CEUS are likely to have FLLs (seen at unenhanced US), the nature of which remains uncertain. Detection of FLLs at unenhanced US may be 'incidental' (FLLs detected in patients undergoing abdominal US for symptoms and/or biochemistry suggestive of possible liver disease or for other reasons unrelated to possible liver disease) or the result of routine surveillance of patients with cirrhosis. CEUS may also identify additional FLLs over and above those detected on unenhanced US. Other relevant applications include the detection of specific types of malignant FLLs [e.g. liver metastases from colorectal carcinoma (CRC), recurrent or residual disease following treatment of a known malignancy]. A recent systematic review reported ranges for the sensitivity and specificity of SonoVue CEUS for the detection of liver metastases from CRC of 79–100% and 95–100%, respectively,<sup>5</sup> but this review did not provide any comparison with the accuracy of other imaging techniques.

## Description of technologies under assessment (SonoVue)

SonoVue is a second-generation contrast agent that uses sulphur hexafluoride microbubbles for CEUS imaging in adults. It is used to enhance the echogenicity of the blood and can thus improve the signal-to-noise ratio in US. SonoVue should be used only in patients for whom unenhanced US is inconclusive.<sup>6</sup> Low solubility gas contrast agents such as SonoVue allow imaging at low mechanical index, which in turn leads to effective tissue signal suppression.<sup>6</sup> First-generation agents have now been superseded by second-generation agents and are no longer available in Europe.

The SonoVue product information lists its applications as:

- echocardiography – provision of opacification of cardiac chambers and enhancement of left ventricular echocardial border delineation in patients with suspected or known cardiovascular disease
- Doppler US of the macrovasculature – detection or exclusion of abnormalities in the cerebral arteries, extracranial carotid arteries or peripheral arteries
- Doppler US of the microvasculature – visualising the vascularity of liver and breast lesions for lesion characterisation.

The focus of this assessment was CEUS of the liver.

SonoVue consists of a kit containing a vial of sulphur hexafluoride gas and phospholipid powder, a prefilled syringe of solvent (sodium chloride solution) and a transfer and a separate delivery system. The saline is introduced into the vial by the delivery system and, once reconstituted, microbubbles are formed. These microbubbles are the contrast agent, which is injected into a peripheral vein at the antecubital fossa. When the US probe is placed on the abdomen, US waves cause the microbubbles to resonate so that a signal is picked up by a transducer and an image is formed on a screen.

As this contrast agent is a pure blood pool agent it remains within the patient's blood vessels and, depending on the type of lesion, it shows a pattern of uptake similar to that of computed tomography (CT) or magnetic resonance imaging (MRI) vascular contrast agents. The contrast agent is broken down by the body after a few minutes and the sulphur hexafluoride gas is exhaled through the lungs and the phospholipid component of the microbubble shell is metabolised (re-entering the endogenous phospholipid metabolic pathway). The adverse event rate associated with the use of SonoVue for liver imaging is likely to be similar to or lower than that associated with other imaging modalities (CECT or CEMRI). A post-marketing study, published in 2006, included 23,188 abdominal investigations and reported adverse events in 29 cases, of which only two were graded as serious.<sup>7</sup>

The dual blood supply of liver tissue from the hepatic artery (25–30%) and the portal vein (70–75%) means that three vascular phases can be visualised using CEUS: the hepatic arterial phase (starting approximately 10–20 seconds after injection of the contrast agent into a peripheral vein and lasting for approximately 10–15 seconds); the portal venous phase (following the hepatic arterial phase and lasting until approximately 2 minutes after the initial injection); and the late phase (following the portal venous phase and lasting until clearance of the contrast agent from the hepatic parenchyma, up to 4–6 minutes after the initial injection). The arterial phase provides information on the extent and pattern of vascularity in the lesion, and the portal venous and late phases provide information on the washout of the contrast agent from the lesion compared with that of normal liver tissue.<sup>6</sup>

The European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) produced guidelines and good clinical practice recommendations for CEUS in 2004. The latest version of the guidelines was published in 2008 and is currently being updated.<sup>6</sup> The 2008 EFSUMB guidelines recommend the use of CEUS for the characterisation of FLLs in the following indications:

- in patients with incidental findings on routine US

- for the investigation of lesions or suspected lesions in chronic hepatitis or liver cirrhosis
- for the investigation of lesions or suspected lesions in patients with a history of malignancy
- in patients with inconclusive MRI/CT or cytology/histology results
- for the characterisation of portal vein thrombosis.

The guidelines recommend the use of CEUS for the detection of FLLs in the following indications:

- to rule out liver metastases
- in selected cases, when clinically relevant for treatment planning and as a complement to CECT and/or CEMRI, to assess the number and location of liver metastases
- for the surveillance of patients with known malignancy
- in suspected CCC, when other imaging is inconclusive
- in suspected liver trauma (in some situations).

The EFSUMB guidelines provide information on the typical enhancement patterns associated with various types of benign and malignant liver lesions;<sup>6</sup> *Table 1* shows the typical enhancement patterns described for the malignant lesions considered in this assessment.

When considering the post-treatment assessment of patients who have undergone percutaneous ablation therapies, CEUS can potentially provide useful information when unenhanced US cannot. This is because assessment of vascularisation and tissue perfusion is essential to enable differentiation of tissue necrosis from residual tumour.<sup>6</sup>

Other similar US contrast agents (e.g. Luminity<sup>®</sup>, Lantheus Medical Imaging, and Optison<sup>®</sup>, GE Healthcare) are indicated for use in echocardiography only. Therefore, no equivalent alternative technologies were considered in this assessment.

## Comparators

Patients with inconclusive unenhanced US are currently referred for CECT and/or CEMRI. The comparators for this assessment are therefore CECT and CEMRI. Contrast-enhanced MRI generally uses gadolinium-based vascular contrast agents, which can differentiate between benign and malignant FLLs based on vascular enhancement patterns in a similar way to CECT and CEUS. However, CEMRI of the liver can also use hepatocyte-specific contrast agents such as superparamagnetic iron oxide (SPIO). Hepatocyte-specific contrast agents are taken up by Kupffer cells in the normal liver and benign lesions and may therefore aid the identification of malignant lesions, which are generally deficient in Kupffer cells, particularly when such lesions are hypervascular.<sup>8,9</sup> 'Combined' vascular and hepatocyte-specific contrast agents such as gadolinium ethoxybenzyl diethylenetriamine penta-acetic acid (Gd-EOB-DTPA) can also be used.<sup>10</sup> A recent systematic review compared the accuracy of SonoVue CEUS, CECT and CEMRI for the differentiation of malignant and benign liver lesions. The reported sensitivities were 88% (95% CI 87% to 90%),

**TABLE 1** Typical enhancement patterns of malignant FLLs

	Arterial phase	Portal venous phase	Late phase
HCC in cirrhosis	Hyper-enhancing, complete Non-enhancing areas	Iso-enhancing Non-enhancing areas	Hypo-/iso-enhancing
HCC in non-cirrhotic liver	Hyper-enhancing	Hypo-/non-enhancing	Hypo-/non-enhancing
Liver metastases (hypovascular)	Rim enhancement	Hypo-enhancing	Hypo-/non-enhancing
Liver metastases (hypervascular)	Hyper-enhancing, complete	Hypo-enhancing	Hypo-/non-enhancing

90% (95% CI 88% to 92%) and 86% (95% CI 83% to 88%), respectively, and corresponding specificities were 81% (95% CI 79% to 84%), 77% (95% CI 71% to 82%) and 81% (95% CI 76% to 85%).<sup>11</sup> However, these data were based on indirect comparisons, and estimates for CEMRI combined studies using vascular contrast agent with studies using hepatocyte-specific contrast agent.

Contrast-enhanced ultrasound could be included in the diagnostic pathway as a replacement for CECT/CEMRI (Figure 1) or as a triage step to reduce the use of CECT/CEMRI (Figure 2).

Expert opinion indicated that biopsy would not be performed on the basis of unenhanced US examination alone; therefore, biopsy was not considered a relevant comparator for CEUS.

### Care pathways/current practice

Focal liver lesions found on unenhanced US may be ‘incidental’ (FLLs detected in patients undergoing abdominal US for symptoms and/or biochemistry suggestive of possible liver disease or for other reasons unrelated to possible liver disease) or appear as the result of routine surveillance of patients with cirrhosis. In both cases investigation is focused upon characterisation of lesions, primarily to determine whether they are benign or malignant. Other relevant applications include the detection of specific types of malignant FLL such as liver metastases from CRC. The care pathways for each of these applications are described below.

In general, care pathways for patients with liver malignancy are guided by prognosis. Prognosis depends on both the stage of the tumour and underlying liver function. For any care pathway, survival time of the patient is the key variable of interest. Improvements in survival by any therapeutic option are largely dependent on the disease stage at diagnosis. The earlier the diagnosis, the greater the chance of a successful treatment.

### Incidentally detected focal liver lesions

A focal lesion in the liver refers to any tissue abnormality occurring in one specific area of the liver. FLLs can be classified into two main categories, namely benign or malignant. Benign FLLs include haemangioma,

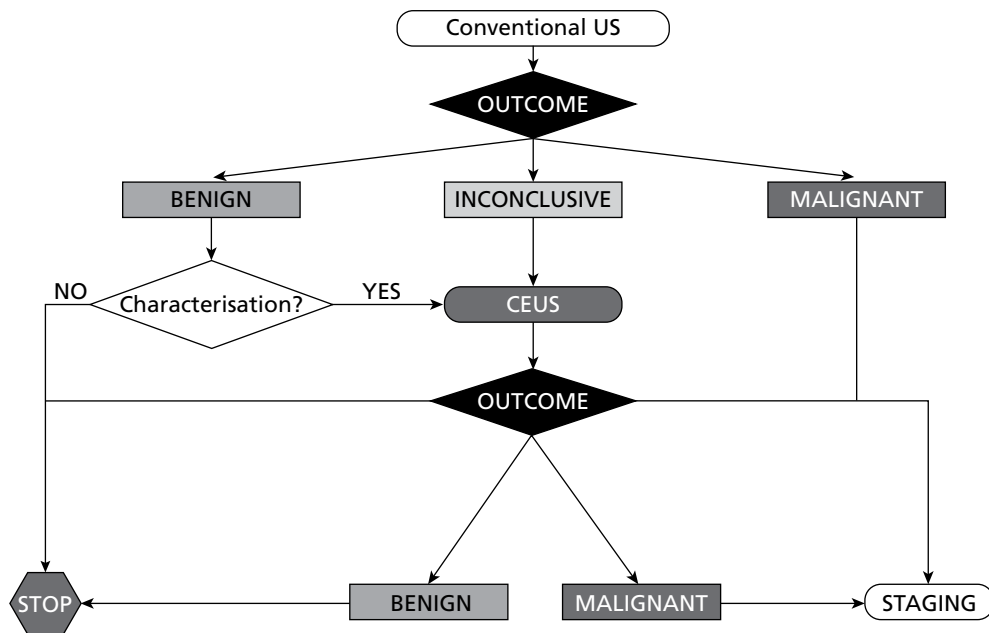
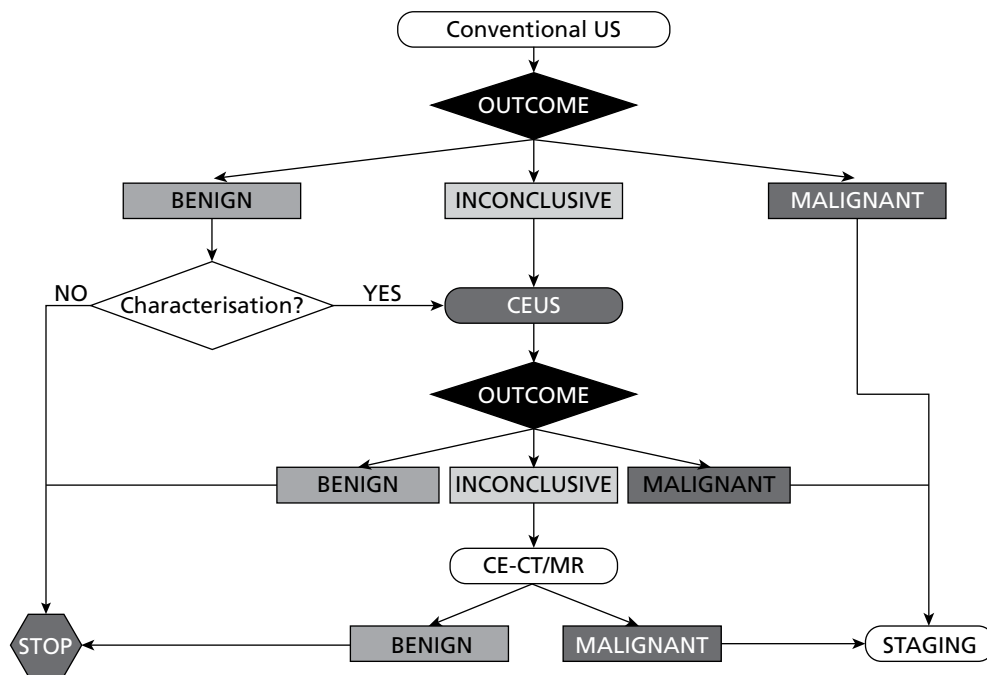


FIGURE 1 Diagnostic algorithm for liver imaging: CEUS as a replacement test for CECT/CEMRI.



**FIGURE 2** Diagnostic algorithm for liver imaging: CEUS as a triage test to reduce the use of CECT/CEMRI.

focal nodular hyperplasia, focal fatty sparing and adenoma. Malignant FLLs include primary cancer of the liver, known as HCC, and secondary cancers of the liver (metastases) resulting from primary cancers occurring elsewhere in the body (e.g. CRC, breast cancer, lung cancer and pancreatic cancer).

Once a lesion has been incidentally detected in an individual the foremost concern is to differentiate between benign and malignant lesions. This distinction determines the individual's prognosis and the subsequent treatment strategy. Benign liver lesions, because of their asymptomatic nature, often require no treatment. In such cases it is common for the individual to be monitored and the lesion rescanned in 6–12 months. Once a malignant lesion is identified it is important to distinguish between primary and secondary cancers, as this is likely to impact how the individual is managed. Malignant lesions may be treated by a range of interventions including chemotherapy, liver resection (surgery), radiofrequency ablation (RFA) and transarterial therapies such as selective internal radiation therapy for metastatic lesions secondary to CRC. A fine needle aspiration biopsy to assist in the diagnosis is not always needed and involves the risk of bleeding and the seeding of neoplastic cells (along the needle tract). It has been argued that the biopsy provides little additional information beyond what can be established from a patient history, medical examination, laboratory testing and imaging.<sup>12</sup>

### Cirrhosis surveillance

Guidelines from the UK Hepatocellular Group advise that, for all patients with cirrhosis who might be suitable candidates for treatment for HCC, surveillance using abdominal US and alpha-fetoprotein (AFP) estimation should be considered.<sup>2</sup> If surveillance is offered it should involve abdominal US assessments in combination with serum AFP estimation at 6-month intervals. US is used for surveillance because it is low risk, non-invasive and has good acceptance by patients. However, fibrous septa and regenerative nodules characteristic of cirrhosis produce a coarse US pattern that can inhibit detection of small HCCs.<sup>13</sup> If the US is inconclusive, confirmatory testing will take place using CECT or CEMRI. The decision about whether to use CEMRI or CECT as the next imaging modality following the initial US scan is highly dependent on clinician preferences and local availability. Although CEMRI in general has a better sensitivity and specificity than CECT for the detection and characterisation of FLLs, the main disadvantage of MRI is the often long waiting times; it can sometimes take up to 6 months for the presence or absence of a FLL to be confirmed. A focal lesion in the liver of a patient with cirrhosis is highly likely to be HCC.<sup>2</sup> Biopsy is

rarely required for diagnosis as this can usually be established radiologically, and seeding of tumour in the needle tract occurs in 1–3% of cases. Therefore, it is advised to avoid biopsy of potentially operable lesions when possible. Clinical practice guidelines from the European Association for the Study of the Liver (EASL) state that non-invasive diagnostic criteria for HCC (hypervascular in the arterial phase with washout in the portal venous or delayed phases) can be applied in cirrhotic patients; one imaging technique is needed for lesions of >1 cm diameter while two techniques are recommended in suboptimal settings and biopsy is recommended only when a diagnosis cannot be reached using non-invasive criteria.<sup>13</sup> HCC can be curatively treated with surgery, either hepatic resection or liver transplantation.<sup>2</sup> Palliative treatments include percutaneous ethanol injection (PEI), RFA and transarterial chemoembolisation (TACE).

Surgical resection is the treatment of choice for HCC in non-cirrhotic patients. Cirrhotic patients need to be carefully selected for resection because they are especially prone to postoperative liver failure and increased risk of death. Survival after resection improves if the disease is diagnosed during the very early stages when liver function is preserved, the patient is asymptomatic and the nodule size is small (single, <2 cm); it can then exceed 50% at 5 years. Taking liver function into account can help to identify patients in whom the resection could lead to decompensation of the liver and death, when resection might not be the treatment of choice. In contrast, more advanced liver tumours preclude resection. Commonly, the indication for resection is limited to patients with single tumours in the liver, without signs of vascular invasion and dissemination by the tumour. Benefits from other treatment options, such as adjuvant chemotherapy, are uncertain. Recurrence of HCC is very frequent and exceeds 70% at 5 years. Repeated resection is possible if intrahepatic dissemination of the tumour has not occurred. Liver transplantation is an option for early-stage HCC (<5 cm or with up to three nodules <3 cm) but is not recommended for more advanced stages. If resection or transplantation is not appropriate, percutaneous ablation (local tumour cell destruction by chemicals or temperature) can be applied to patients with early-stage HCC.

Non-curative (palliative) treatment options may be considered when disease has progressed to medium or more advanced stages and surgery or percutaneous ablation is not considered appropriate. During tumour growth the tumour becomes highly arterialised, meaning that most blood that supplies the tumour is from the hepatic artery. During transarterial embolisation (TAE), acute arterial obstruction is provoked, which causes ischaemic tumour necrosis. If TAE is combined with a chemotherapeutic agent, which is injected into the hepatic artery prior to the procedure, the procedure is called TACE. TACE is indicated if the tumour has multiple nodules, without affecting blood vessels or dissemination outside the liver. Complete necrosis of the tumour is rarely achieved after one treatment, thus treatment needs to be repeated several times. Response to treatment improves survival, which varies from 20% to 60% at 2 years depending on tumour stage, liver function and general health status. Systemic chemotherapy in treating HCC is sometimes used although it is not recommended by the American Association for the Study of Liver Diseases (AASLD).<sup>1</sup> EASL clinical practice guidelines recommend sorafenib (Nexavar®, Bayer Schering) as the standard systemic therapy in patients with well-preserved liver function (Child–Pugh class A), advanced HCC or tumours progressing after locoregional therapies.<sup>13</sup>

Patients at an advanced stage of the disease, characterised by failure of liver function, tumour growth and dissemination or physical impairment, will not benefit from the above treatments and might therefore be enrolled in trials of new agents. In the terminal stage symptomatic treatment is appropriate.<sup>1</sup>

### **Liver metastases for colorectal cancer**

For cancers of both the colon and the rectum, surgical resection is the mainstay of definitive treatment.<sup>14</sup> After surgical resection, patients may present with metastases. Metastases often first occur in the liver and this may be the only site of spread in 30–40% of patients with advanced disease.<sup>15</sup> For a patient discovered to have isolated liver metastases, CT of the chest, abdomen and pelvis should be performed to determine whether or not metastases at multiple sites are present. Isolated liver metastases of colorectal origin are commonly resected, with or without preoperative chemotherapy. In cases of small liver metastases, colon and liver resection might be combined in one surgery. Metastases at multiple sites may also be resected, with or without chemotherapy, or will be palliatively treated. If resection is not appropriate, systemic

treatments such as chemotherapy in combination with other medication may be used; however, response to treatment is generally poor. Ablative therapy may also be considered; however, this is recommended only in the context of randomised controlled trials. As with HCC, recurrence of metastases after liver resection occurs in up to 60% of patients.<sup>15</sup>

Patients without metastases are advised to undergo regular surveillance with a minimum of two CTs of the chest, abdomen and pelvis in the first 3 years and regular serum carcinoembryonic antigen (CEA) tests (at least every 6 months in the first 3 years).<sup>14</sup> Follow-up after liver resection is very dependent on local protocols but may include CT of the chest and liver and CEA testing for 5 years.





## Chapter 3 Assessment of clinical effectiveness

A systematic review was conducted to summarise the evidence on the clinical-effectiveness of SonoVue CEUS for the assessment of FLLs in adults with previously inconclusive liver imaging. Systematic review methods followed the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care,<sup>16</sup> the NICE Diagnostic Assessment Programme interim methods statement<sup>17</sup> and the Cochrane *Handbook for DTA Reviews*.<sup>18</sup>

### Inclusion and exclusion criteria

#### Participants

Study populations eligible for inclusion were adults ( $\geq 18$  years) in whom previous liver imaging has been inconclusive, including patients being assessed for:

- suspected primary HCC
- suspected secondary malignancy (liver metastases)
- response to treatment/recurrence of known liver malignancy.

#### Setting

Relevant settings were secondary or tertiary care.

#### Interventions

The intervention (index test) was SonoVue CEUS.

#### Comparators

Comparator tests eligible for inclusion were:

- CECT
- CEMRI.

#### Reference standard

Studies reporting the diagnostic accuracy of SonoVue CEUS for the characterisation of FLLs (identification of liver malignancy) or the detection of liver metastases were required to use histology, following biopsy or surgical excision, to confirm the diagnosis in patients with positive index test results. Patients who test negative on the index test will generally not undergo biopsy or surgical treatment; clinical/radiological follow-up for a minimum of 6 months was therefore considered an acceptable reference standard in these patients.

#### Protocol modification

The reference standard criteria were extended for studies on the characterisation of FLLs only (suspected HCC) to include studies that use EASL/AASLD non-invasive diagnostic criteria (two concordant imaging test results) as the reference standard.<sup>1,13</sup> This modification does not apply to test accuracy studies on the detection of liver metastases. This extension of the inclusion criteria was made because clinical opinion indicated that biopsy of small, test-positive lesions may be considered unethical in this population and that the original criterion (biopsy for imaging test-positive patients/lesions and 6-month follow-up for imaging test-negative patients/lesions) may result in important studies being excluded.

## Outcomes

Studies reporting the following outcomes were considered relevant:

- effect of testing on treatment plan (e.g. surgical or medical management, or palliative care), when information on the appropriateness of the final treatment plan is also reported
- effect of pretreatment testing on clinical outcome (e.g. overall survival, progression-free survival)
- prognosis – the ability of the test result to predict clinical outcome (e.g. overall survival, progression-free survival, response to treatment)
- test accuracy and number of patients/lesions classified as non-diagnostic by SonoVue CEUS.

For included studies reporting any of the above outcome measures, the following outcomes were considered, if reported:

- the acceptability of tests to patients or surrogate measures of acceptability (e.g. waiting time and associated anxiety)
- adverse events associated with testing (e.g. claustrophobia, reaction to contrast media)
- additional FLLs detected by CEUS, over and above those seen on unenhanced US.

Radiation exposure was not considered a relevant outcome as the population is mostly older adults in whom additional incident cancers due to imaging-related radiation are likely to be minimal. In addition, a previous technology assessment (new-generation CT for cardiac imaging) showed that including radiation exposure in modelling did not influence the results of cost-effectiveness analyses.<sup>19</sup>

## Study design

The following study designs were eligible for inclusion:

- Randomised or non-randomised controlled trials in which participants are assigned to the intervention or comparator test, for treatment planning, and outcomes are compared at follow-up.
- Observational studies that report the results of multivariable regression modelling, with clinical outcome (e.g. survival, response to treatment) as the dependent variable and the index test result as an independent variable. Included studies should control adequately for potential confounders (e.g. age, tumour stage, previous treatment, results of other imaging).
- Test accuracy studies in which the index test is compared with one or more of the comparators and the reference standard. Test accuracy studies of the index test alone were included when these were conducted in patients who had previously undergone one or more of the comparator tests (e.g. a study of the accuracy of SonoVue for the diagnosis of HCC in patients with inconclusive findings on CECT).

Included test accuracy studies were required to report the absolute numbers of true-positive, false-negative, false-positive and true-negative index test results or sufficient information to allow their calculation.

The following study/publication types were excluded:

- preclinical and animal studies
- reviews, editorials and opinion pieces
- case reports
- studies reporting only technical aspects of the test or image quality
- studies with < 10 participants.

## Search strategy

Search strategies were based on target condition and intervention, as recommended in the CRD's *Guidance for Undertaking Reviews in Health Care* and the *Cochrane Handbook for DTA Reviews*.<sup>16,18,20</sup>

The following databases were searched for relevant studies from 2000 to September/October 2011:

- MEDLINE (2000–September 2011 Week 4) (OvidSP)
- MEDLINE In-Process & Other Non-Indexed Citations and Daily Update (2000–5 October 2011) (OvidSP)
- EMBASE (2000–2011 Week 39) (OvidSP)
- Cochrane Database of Systematic Reviews (CDSR) (The Cochrane Library Issue 10, 2011) (Wiley)
- Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 4, 2011) (Wiley)
- Database of Abstracts of Reviews of Effects (DARE) (2000–6 October 2011) (via The Cochrane Library)
- Health Technology Assessment (HTA) database (2000–6 October 2011) (via The Cochrane Library)
- DARE (1 January 2011–6 October 2011) (CRD website)
- HTA database (1 January 2011–6 October 2011) (CRD website)
- Science Citation Index (SCI) (2000–6 October 2011) (Web of Science)
- National Institute for Health Research (NIHR) HTA database (2000–2011) (internet).

Supplementary searches were undertaken on the following resources to identify grey literature and completed and ongoing trials:

- National Institutes of Health ClinicalTrials.gov (2000–7 October 2011) ([www.clinicaltrials.gov/](http://www.clinicaltrials.gov/))
- Current Controlled Trials (2000–7 October 2011) ([www.controlled-trials.com/](http://www.controlled-trials.com/))
- World Health Organization International Clinical Trials Registry Platform (ICTRP) (2000–7 October 2011) ([www.who.int/ictcp/en/](http://www.who.int/ictcp/en/))
- EU Clinical Trials Register (EU CTR) (2000–8 October 2011) ([www.clinicaltrialsregister.eu/](http://www.clinicaltrialsregister.eu/)).

Searches were undertaken to identify studies of SonoVue/sulphur hexafluoride CEUS in the diagnosis of liver cancer (primary and metastases). The main EMBASE strategy for each set of searches was independently peer reviewed by a second information specialist using the PRESS EBC (Peer Review of Electronic Search Strategies Evidence-Based Checklist).<sup>21</sup> Search strategies were developed specifically for each database and the keywords associated with liver cancer (primary and metastases) were adapted according to the configuration of each database. Searches took into account generic and other product names for the intervention. No restrictions on language or publication status were applied. Limits were applied to remove animal studies. Full search strategies are reported in *Appendix 1*.

Electronic searches were undertaken on the following conference abstracts:

- EFSUMB (EUROSON):
  - 2011: [www.wfumb2011.org/index.php?pid=70](http://www.wfumb2011.org/index.php?pid=70)
  - 2008: [www.thieme-connect.com/ejournals/toc/ultraschall/33697/grouping/54161](http://www.thieme-connect.com/ejournals/toc/ultraschall/33697/grouping/54161)
  - 2007: [www.interplan.de/pages/euroson2007/front\\_content.php?idcat=82](http://www.interplan.de/pages/euroson2007/front_content.php?idcat=82)
- Radiological Society of North America (RSNA)
  - 2010: <http://rsna2010.rsna.org/search/search.cfm>
  - 2009: <http://rsna2009.rsna.org/search/search.cfm>
  - 2008: <http://rsna2008.rsna.org/program.cfm>
  - 2007: <http://rsna2007.rsna.org/rsna2007/v2007/conference/track.cvn>
  - 2006: <http://rsna2006.rsna.org/rsna2006/v2006/conference/track.cvn>
- European Congress of Radiology (ESR)
  - 2011: [www.myesr.org/cms/website.php?id=/en/past\\_congresses/ecr\\_2011/ecr\\_2011\\_book\\_of\\_abstracts.htm](http://www.myesr.org/cms/website.php?id=/en/past_congresses/ecr_2011/ecr_2011_book_of_abstracts.htm)
  - 2010: [www.myesr.org/cms/website.php?id=/en/ecr\\_2010/book\\_of\\_abstracts.htm](http://www.myesr.org/cms/website.php?id=/en/ecr_2010/book_of_abstracts.htm)

- 2009: [www.myesr.org/cms/website.php?id=/en/ecr\\_2009/ecr\\_2009\\_book\\_of\\_abstracts.htm](http://www.myesr.org/cms/website.php?id=/en/ecr_2009/ecr_2009_book_of_abstracts.htm)
- 2008: [www.abstractsonline.com/viewer/?mkey={9AF35541-5128-444B-9D15-447022358A3F}](http://www.abstractsonline.com/viewer/?mkey={9AF35541-5128-444B-9D15-447022358A3F})
- 2007: [www.abstractsonline.com/viewer/?mkey={9A26688A-5BBE-4366-AE14-5AC99DF8F8E4}](http://www.abstractsonline.com/viewer/?mkey={9A26688A-5BBE-4366-AE14-5AC99DF8F8E4})
- 2006: [www.abstractsonline.com/viewer/?mkey={6748FA35-D7A5-44B0-B8D4-4E2E51850B06}](http://www.abstractsonline.com/viewer/?mkey={6748FA35-D7A5-44B0-B8D4-4E2E51850B06}).

We planned to search the British Medical Ultrasound Society (BMUS) conference abstracts (2006–11) but these were not available online.

Identified references were downloaded into EndNote X4 software (Thomson Reuters, CA, USA) for further assessment and handling.

References in retrieved articles were checked for additional studies.

## Inclusion screening and data extraction

Two reviewers (MW and VG) independently screened the titles and abstracts of all reports identified by searches and any discrepancies were discussed and resolved by consensus. Full copies of all studies deemed potentially relevant were obtained and the same two reviewers independently assessed these for inclusion; any disagreements were resolved by consensus. Details of studies excluded at the full-paper screening stage are presented in *Appendix 5*.

Studies listed in submissions from the manufacturer of SonoVue, Bracco UK Ltd, were first checked against the project reference database in EndNote X4; any studies not already identified by our searches were screened for inclusion following the process described above. Studies referenced by the manufacturer and excluded at the full-paper screening stage are noted in *Appendix 5*. *Appendix 5* also includes a list of studies referenced by the manufacturer that were excluded at title and abstract screening.

When there was insufficient information for full inclusion assessment, study authors were contacted for clarification.

Data were extracted on study details (study design, participant recruitment, setting, funding, stated objective and clinical indication for testing relevant to this assessment for which data were reported), study participants (total number of participants and total number of FLLs, study inclusion criteria, study exclusion criteria, participant age and gender distribution, participant characteristics relevant to liver cancer risk, lesion size and final diagnoses), details of the index test, comparator(s) and reference standard (technical details of the test, details of who interpreted tests and how, threshold used to define a positive test) and study results. All but one of the studies included in the review were diagnostic test accuracy (DTA) studies and the results extracted from these studies were unit of analysis (patient or lesion); numbers of true-positive, false-negative, false-positive and true-negative test results; numbers of patients or lesions classified as non-diagnostic by SonoVue CEUS and/or comparator(s). The remaining study was a controlled trial that compared assessment with conventional imaging (CECT or CEMRI) plus unenhanced US with assessment with conventional imaging (CECT or CEMRI) plus SonoVue CEUS prior to RFA; data were extracted from this study to calculate odds ratios (ORs) and mean differences for dichotomous and continuous patient-relevant outcomes respectively. Data were extracted by one reviewer using a piloted, standard data extraction form and checked by a second (MW and VG); any disagreements were resolved by consensus. Chinese-language studies were extracted by one reviewer (MW) working with a native speaker (KL) and the only German language study was extracted by one reviewer and checked by a second (VG and HR) Full data extraction tables are provided in *Appendix 4*.

## Quality assessment

The evidence-based QUADAS tool<sup>22-24</sup> is recommended for assessing the methodological quality of test accuracy studies.<sup>16,18</sup> A revised version of QUADAS (QUADAS-2) has recently been published<sup>25</sup> (www.QUADAS.org). QUADAS-2 more closely resembles the approach and structure of the Cochrane risk of bias tool. It is divided into four key domains covering participant selection, index test, reference standard and the flow of patients through the study (including the timing of tests). Each domain is rated for risk of bias (low, high or unclear) and the tool provides signalling questions in each domain to aid reviewers in reaching a judgement. The participant selection, index test and reference standard domains are also separately rated for concerns regarding the applicability of the study to the review question (low, high or unclear). Thus, QUADAS-2 separates bias from external validity (applicability) and does not include any items that assess only reporting quality. The QUADAS-2 tool does not currently include domains specific to the assessment of studies comparing multiple index tests, such as those included in this assessment. Further development of QUADAS-2 in this area is planned. A modified version of the QUADAS-2 tool, which includes an additional domain for the comparator test and additional signalling questions in the flow and timing domain, has been used in this assessment. Review-specific guidance was produced for the use of the modified version of QUADAS-2 and is reported in *Appendix 2*.

The results of the quality assessment are summarised and presented in tables and graphs in the results section of the systematic review and are presented in full, by study, in *Appendix 3*. No diagnostic accuracy data set included in this assessment was of sufficient size to allow statistical exploration of between-study heterogeneity based on aspects of risk of bias. The findings of the quality assessment were used to inform recommendations for future research.

The risk of bias in the controlled clinical trial was assessed using a table based on The Cochrane Collaboration's tool for assessing risk of bias.<sup>26</sup>

## Methods of analysis/synthesis

The results of the DTA studies included in this review were summarised by clinical indication for imaging (characterisation of FLLs detected on routine surveillance of cirrhosis patients using unenhanced US, detection of liver metastases in patients with known primary malignancy, characterisation of incidentally detected FLLs visualised on unenhanced US, assessment of response to treatment in known liver malignancy) and further stratified by target condition (HCC, liver metastases or 'any liver malignancy') and/or comparator test(s) (CECT, CEMRI, both), as appropriate. For all included studies the absolute numbers of true-positive, false-negative, false-positive and true-negative test results, as well as sensitivity and specificity values, with 95% confidence intervals (CIs) were presented in results tables for index test, comparator and target condition reported. When multiple data sets were reported (e.g. for per-patient and per-lesion data, different diagnostic criteria, different lesion sizes) these were extracted in full. Data on the number of non-diagnostic tests were also included in the results tables and described in text summaries. No study reported data on patient preferences and one study reported absence of index test-associated adverse events; the latter was recorded in the relevant results table.

When groups of similar studies (comparable clinical indication, index test and comparator, target condition and diagnostic criteria) included four or more data sets, we planned to construct summary receiver operating characteristic (SROC) curves and calculate summary estimates of sensitivity and specificity with 95% CIs using the bivariate modelling approach;<sup>27-29</sup> four data sets are the minimum requirement to fit models of this type. However, the review included only one group of four similar studies and this group included one study that used a suboptimal reference standard (as described in the protocol modification noted in *Inclusion and exclusion criteria*). Pooled estimates of sensitivity and specificity with 95% CIs were therefore calculated using a random-effects model and forest plots were constructed showing the sensitivity and specificity estimates from each study together with pooled estimates. A

sensitivity analysis was undertaken to assess the effect of excluding the large study that used a suboptimal reference standard; these analyses were conducted using MetaDiSc 1.4 ([www.hrc.es/investigacion/metadisc\\_en.htm](http://www.hrc.es/investigacion/metadisc_en.htm)).<sup>30</sup>

Between-study clinical heterogeneity was assessed qualitatively. Statistical heterogeneity was assessed for the one meta-analysis undertaken using the chi-squared test and inconsistency was quantified using the  $I^2$  statistic,<sup>31</sup> although these measures are of limited value given the small number of studies involved. There were no data sets of sufficient size (minimum 10) to allow statistical exploration of sources of heterogeneity by including additional covariables in the SROC model.

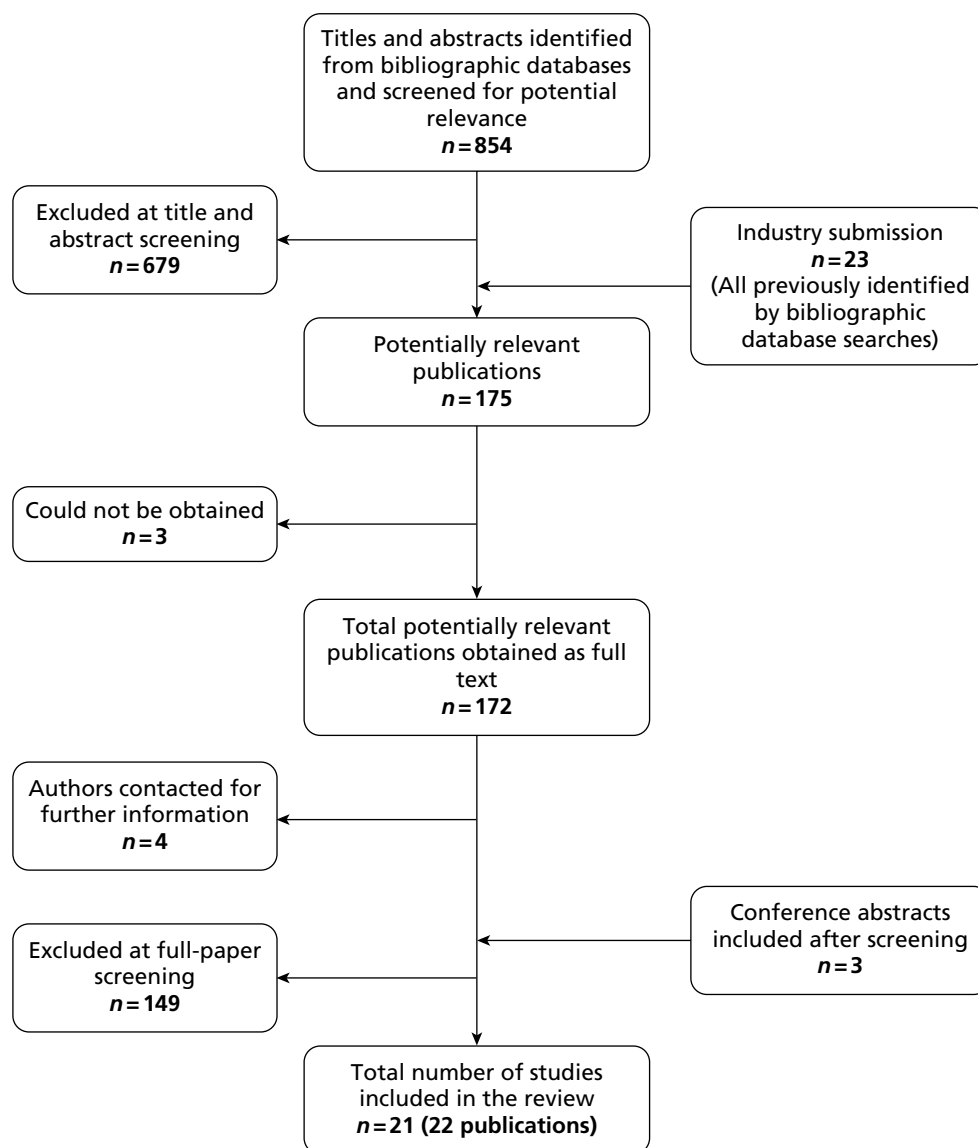
Where meta-analysis was considered unsuitable for the data identified (e.g. because of heterogeneity and/or small number of studies), studies were summarised using a narrative synthesis. Text and tables were stratified by clinical indication and target condition, as described above. Where appropriate, the results of individual studies were plotted in the receiver operating characteristic (ROC) plane.

## Results of the assessment of clinical effectiveness

The literature searches of bibliographic databases identified 854 references. After initial screening of titles and abstracts, 175 were considered to be potentially relevant and ordered for full-paper screening. No additional papers were ordered based on screening of the industry submission; all studies submitted had already been identified by the bibliographic database searches. No additional studies were identified from searches of clinical trials registries. Of the 175 publications considered potentially relevant, three<sup>32-34</sup> could not be obtained within the time scale of this assessment; these were held in British Library stacks that are currently closed for asbestos removal or were not held by the British Library. Four studies, reported as conference abstracts, did not contain sufficient information to complete inclusion assessment and authors were contacted for additional information;<sup>35-38</sup> one response was received and all four studies were finally excluded. *Figure 3* shows the flow of studies through the review process and *Appendix 5* provides details of all publications excluded at the full-paper screening stage with reasons for exclusion.

Based on the searches and inclusion screening described above, 19 publications of 18 studies were included in the review. Hand searching of conference proceedings resulted in the inclusion of a further three studies, which were published in abstract form only.<sup>39-41</sup> A total of 21 studies in 22 publications were therefore included in the review.

All but one of the included studies were test accuracy studies; of the 20 test accuracy studies, seven concerned the use of SonoVue CEUS for the characterisation of FLLs detected at routine surveillance of patients with cirrhosis,<sup>42-48</sup> four assessed the performance of SonoVue CEUS for the detection of liver metastases in patients with known primary cancers (CRC),<sup>39,49-51</sup> six concerned the use of SonoVue CEUS for the characterisation of incidentally detected FLLs<sup>41,52-56</sup> and three considered the use of SonoVue CEUS to assess response to treatment in patients with liver cancer.<sup>40,57,58</sup> The remaining study was a controlled trial that compared assessment with conventional imaging (CECT or CEMRI) plus unenhanced US with assessment with conventional imaging (CECT or CEMRI) plus SonoVue CEUS prior to RFA.<sup>59</sup> This study reported the following patient-relevant outcomes: successful ablation, tumour progression, incidence of new HCC, incidence of repeat RFA, local progression-free survival, new tumour-free survival and post-therapy complications.



**FIGURE 3** Flow of studies through the review process.

All included studies were published in 2006 or later. Sixteen of the 21 included studies were conducted in Europe (the majority in Italy or Spain) and the remaining five studies were conducted in China (including two Chinese-language publications). Two studies reported funding from the manufacturer of SonoVue<sup>55,56</sup> and 13 studies did not report any information on funding sources.

Table 2 shows the details of the included studies, the clinical indication for imaging for which they reported data and the target conditions (primary HCC, liver metastases, 'any liver malignancy' or response to treatment) and comparator tests assessed. Further details of the characteristics of study participants and the technical details of the conduct of the index test (SonoVue CEUS), comparator test(s) and reference standard (where applicable) and their interpretation are reported in the data extraction tables presented in Appendix 4.



TABLE 2 Included studies

Study ID	Study design	Objective	US (CCTs and RCTs only)	Combined imaging
Blondin 2011 <sup>48</sup>	Retrospective analysis based on a search of the radiological information system between January 2007 and March 2009	To compare the diagnostic accuracy of CEUS and hepatobiliary contrast-enhanced MRI of the liver in evaluating FLLs in patients with liver cirrhosis		
Catala 2007 <sup>52</sup>	Prospective cohort of adult patients (≥18 years) with FLLs detected on US December 2002–August 2003 Single centre, Spain One author supported in part by a grant from the Carolina Foundation	To compare the diagnostic accuracy of real-time evaluation by CEUS using SonoVue vs SCT in the characterisation of FLLs and to determine the degree of correlation between the two techniques		✓
Chen 2007 <sup>59</sup> Related publication <sup>60</sup> excluded as duplicate	Prospective CCT of patients with HCC who were being assessed before RFA treatment July 2002–March 2005 Single centre, China Funding NR	To evaluate the use of CEUS in assessing patients for RFA and to compare the efficacy of RFA after CEUS with the efficacy of RFA after US	✓	
Clevert 2009 <sup>51</sup>	Prospective cohort of consecutive patients with suspected liver malignancy <sup>a</sup> Recruitment dates NR Two centre, Germany Funding NR	To assess the diagnostic performance of CHI with SonoVue compared with biphasic multislice CECT for the detection of malignant liver lesions		
Dai 2008 <sup>43</sup>	Prospective cohort of consecutive patients with confirmed cirrhosis, without extrahepatic malignancy, who had indeterminate liver nodules on surveillance US March 2004–March 2005 Single centre, China Funding NR	To investigate the diagnostic value for indeterminate small (1–2 cm) hepatic nodules detected by surveillance US in patients with cirrhosis using CEUS compared with helical CECT		
Feng 2007 <sup>57</sup> (Chinese language)	Prospective cohort of patients with known liver malignancy (21 HCC, 3 metastases), undergoing cryosurgery November 2004–February 2006 Single centre, China Funding NR	To evaluate the role of CEUS in assessing the short-term therapeutic response of hepatic carcinoma with cryosurgery		✓
Flor 2009 <sup>39</sup> (abstract only)	Prospective cohort of patients with known primary cancer and indeterminate liver lesions on MDCT Recruitment dates NR Single centre, Italy Funding NR	To evaluate the role of plain US and CEUS in characterising small indeterminate MDCT-detected FLLs in patients with known primary cancer		

Comparator CECT	Comparator CEMRI	Any liver malignancy	Primary HCC	Metastases	Treatment success	Study design and outcome extracted
	✓		✓			DTA Accuracy data (characterisation of FLLs detected at cirrhosis surveillance): HCC vs benign
✓		✓	✓	✓		DTA Accuracy data (characterisation of incidentally detected FLLs): separate data for HCC, liver metastases and any liver malignancy
			✓		✓	CCT
✓		✓ <sup>a</sup>				DTA Accuracy data (detection of liver metastases)
✓			✓			DTA Accuracy data (characterisation of FLLs detected at cirrhosis surveillance): HCC vs benign
					✓	DTA Accuracy data (detection of treatment success)
				✓		DTA Accuracy data (detection of liver metastases)

continued

TABLE 2 Included studies (continued)

Study ID	Study design	Objective	US (CCTs and RCTs only)	Combined imaging
Fornier 2008 <sup>44</sup>	Prospective cohort of asymptomatic patients with Child–Pugh A/B cirrhosis and no history of HCC, with a new liver nodule detected on surveillance US November 2003–August 2006 Two centre, Spain and USA Supported by grants from Instituto de Salud Carlos III, Spain; BBVA Foundation; Fundación Científica de la Asociación Española de Ayuda contra el Cáncer, Spain, grant nos PI 05/150, 06/132 and 05/645; NIH-NIDDK grant no. 1R01DK076986–0	To evaluate the accuracy of CEUS and dynamic MRI for the diagnosis of nodules of $\leq 20$ mm detected during US surveillance		
Gierbliński 2008 <sup>53</sup>	Prospective cohort of patients with incidentally detected solid liver lesions, referred for biopsy June 2005–March 2006 Single centre, Poland Funding NR	To determine whether or not CEUS is an accurate method to differentiate FLLs and reduce the need for fine-needle biopsy		
Giorgio 2007 <sup>45</sup>	Prospective study of consecutive patients with cirrhosis and a single liver nodule of $\leq 30$ mm identified on surveillance US September 2003–June 2004 Single centre, Italy Funding NR	To evaluate the role of low mechanical index CEUS for the characterisation of small HCC in cirrhotic patients compared with ultrafast gadolinium-enhanced MRI		
Jonas 2011 <sup>50</sup> (abstract only)	Prospective study of consecutive patients with CRC metastases who were considered candidates for curative surgery and who underwent complete preoperative workup 2005–7 Single centre, Sweden Funding NR	To assess the sensitivity and specificity of four imaging modalities (CEUS, CECT, CEMRI and FDG-PET) in detecting liver metastases in patients with CRC		
Leoni 2010 <sup>42</sup>	Retrospective analysis of a study of consecutive patients with cirrhosis with one to three liver nodules (1–3 cm) detected at surveillance US September 2003–November 2005 Single centre, Italy No financial support	To assess the diagnostic contribution of vascular contrast-enhanced techniques and the possible additional contribution of SPIO MRI for the diagnosis of HCC in cirrhosis		

Comparator CECT	Comparator CEMRI	Any liver malignancy	Primary HCC	Metastases	Treatment success	Study design and outcome extracted
	✓		✓			DTA Accuracy data (characterisation of FLLs detected at cirrhosis surveillance): HCC vs benign
		✓				DTA Accuracy data (characterisation of incidentally detected FLLs): any malignancy vs benign
	✓		✓			DTA Accuracy data (characterisation of FLLs detected at cirrhosis surveillance): HCC vs benign
✓	✓			✓		DTA Accuracy data (detection of liver metastases)
✓	✓		✓			DTA Accuracy data (characterisation of FLLs detected at cirrhosis surveillance): HCC vs benign

continued

TABLE 2 Included studies (*continued*)

Study ID	Study design	Objective	US (CCTs and RCTs only)	Combined imaging
Li 2007 <sup>54</sup>	Prospective study of patients with FLLs detected at US and unenhanced CT Recruitment dates NR Single centre, China Supported by the Clinical New Technology Foundation of Southwest Hospital (SWH2005A004)	To compare the efficacy of contrast-enhanced pulse-inversion harmonic sonography for the characterisation of FLLs with that of contrast-enhanced helical CT		
Lüttich 2006 <sup>40</sup> (abstract only)	Cohort of patients with HCC undergoing RFA treatment Recruitment dates NR Single centre, Spain Funding NR			
Mainenti 2010 <sup>49</sup>	Prospective study of consecutive patients with histologically proven CRC who were scheduled for surgery July 2005–March 2007 Single centre, Italy Funding NR	To compare CEUS, MDCT, MRI with extracellular contrast agent (Gd-CEMRI), MRI with intracellular contrast agent (SPIO-CEMRI) and PET/CT in the detection of hepatic metastases from CRC		
Quaia 2009 <sup>46</sup>	Prospective study of patients with cirrhosis who had at least one hepatocellular nodule detected on surveillance US Recruitment dates NR Two centre, Italy Funding NR	To assess the added diagnostic value of CEUS combined with 64-row MDCT in the assessment of hepatocellular nodule vascularity in patients with liver cirrhosis		✓
Sangiovanni 2010 <sup>47,61</sup>	Prospective study of patients with cirrhosis who had at least one hepatocellular nodule detected on surveillance US April 2006 to NR Single centre, Italy Funded by grant no. PUR 2008, University of Milan and a personal donation (Dr Aldo Antognozzi)	To assess the sensitivity, specificity and economic impact of all possible sequential combinations of contrast imaging techniques in patients with cirrhosis with 1- to 2-cm liver nodules undergoing US surveillance		✓

Comparator CECT	Comparator CEMRI	Any liver malignancy	Primary HCC	Metastases	Treatment success	Study design and outcome extracted
✓		✓				DTA Accuracy data (characterisation of incidentally detected FLLs): any malignancy vs benign
	✓				✓	DTA Accuracy data (detection of treatment success)
✓	✓			✓		DTA Accuracy data (detection of liver metastases)
✓			✓			DTA Accuracy data (characterisation of FLLs detected at cirrhosis surveillance): HCC vs benign
✓	✓		✓			DTA Accuracy data (characterisation of FLLs detected at cirrhosis surveillance): HCC vs benign

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continued

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TABLE 2 Included studies (*continued*)

Study ID	Study design	Objective	US (CCTs and RCTs only)	Combined imaging
Seitz 2009 <sup>55</sup> (linked to Seitz 2010 <sup>56</sup> )	Cohort of 267 patients who underwent SCT from a prospective study of 1349 consecutive patients with newly detected solid liver mass visible during routine US. Data extracted for the subgroup of patients (158) in whom diagnosis was histologically confirmed (2×2 data could not be extracted for the remaining patients) May 2004–December 2006 Multicentre, Germany, Austria and Switzerland Funded by Bracco Research (Konstanz, Germany) for the online data forms, quality control, calculations and statistical analyses	To evaluate the diagnostic value of CEUS for the characterisation of FLLs in a prospective multicentre study in clinical practice. For this purpose CEUS was compared with SCT, the standard radiological method		
Seitz 2010 <sup>56</sup> (linked to Seitz 2009 <sup>55</sup> )	Cohort of 269 patients who underwent MRI from a prospective study of 1349 consecutive patients with newly detected FLLs identified on US. Data extracted for the subgroup of patients (84) in whom diagnosis was histologically confirmed (2×2 data could not be extracted for the remaining patients) May 2004–December 2006 Multicentre, Germany Funding by Bracco Research (Konstanz, Germany) for the online data forms, quality control, calculations and statistical analyses	To assess the diagnostic performance of CEUS (compared with MRI) in a large patient cohort with FLLs recently discovered by US but not yet characterised		
Solbiati 2006 <sup>41</sup> (abstract only)	Retrospective analysis of data from patients with incidentally detected FLLs 5-year experience, dates not specified Single centre, Italy Funding NR	To assess the diagnostic performance and cost-effectiveness of CEUS in the characterisation of FLLs		
Zhou 2007 <sup>58</sup> (Chinese language)	Retrospective analysis of data from patients undergoing non-surgical treatment for HCC June 2005–June 2006 Single centre, China Funding NR	To investigate the value of CEUS for non-surgical treatment response in HCC		

CCT, controlled clinical trial; CHI, contrast-enhanced harmonic imaging; FDG-PET, fluorodeoxyglucose positron emission tomography; Gd-CEMRI, gadolinium contrast-enhanced magnetic resonance imaging; MDCT, multidetector computed tomography; NR, not reported; PET, positron emission tomography; SCT, spiral computed tomography; US, unenhanced ultrasound.

a 52 of the 59 positive diagnoses were liver metastases; therefore, this study was classified as 'detection of metastases'.

Comparator CECT	Comparator CEMRI	Any liver malignancy	Primary HCC	Metastases	Treatment success	Study design and outcome extracted
✓			✓	✓		DTA Accuracy data (characterisation of incidentally detected FLLs): separate data for HCC, liver metastases and any liver malignancy
	✓		✓	✓		DTA Accuracy data (characterisation of incidentally detected FLLs): separate data for HCC, liver metastases and any liver malignancy
✓		✓				DTA Accuracy data (characterisation of incidentally detected FLLs): any malignancy vs benign
✓					✓	DTA Accuracy data (detection of treatment success)



### **Accuracy of SonoVue contrast-enhanced ultrasound for the characterisation of focal liver lesions detected on surveillance of patients with cirrhosis**

Seven studies reported comparisons of SonoVue CEUS with other imaging techniques for the characterisation of FLLs detected on unenhanced US surveillance of patients with known cirrhosis.<sup>42–48</sup> One study, by Sangiovanni *et al.*, was reported as both a full paper<sup>47</sup> and a conference abstract.<sup>61</sup> All of the studies in this section reported accuracy data for the differentiation of HCC from other liver lesions only and one study<sup>45</sup> reported that there were no imaging-related adverse events. In total, the seven studies in this section reported 369 diagnoses of malignant liver lesions, of which 366 were HCC; the remaining lesions comprised two CCC and one liver metastasis. All studies in this section reported per-lesion data; three studies reported data for one lesion per patient, equivalent to per-patient test performance.<sup>44,45,47</sup> Studies generally focused on the characterisation of small to medium FLLs. Four studies prespecified the size of FLLs considered:  $\leq 30$  mm<sup>42,45,46</sup> or  $\leq 20$  mm.<sup>47</sup> In two studies the mean size was  $15 \pm 3$  mm<sup>43</sup> and 14 mm (range 7–20 mm).<sup>44</sup> The remaining study did not specify lesion size as an inclusion criterion or report mean lesion size.<sup>48</sup> Two studies explicitly excluded lesions of  $< 10$  mm<sup>42,47</sup> and one study reported stratified data for different lesion sizes ( $\leq 10$  mm and 11–30 mm).<sup>45</sup> Two studies compared SonoVue CEUS with CECT,<sup>43,46</sup> three studies compared SonoVue CEUS with CEMRI<sup>45,48,62</sup> and the remaining two studies compared SonoVue CEUS with both CECT and CEMRI.<sup>42,47</sup> One study included in this section explicitly reported that patients had an uncertain diagnosis following unenhanced US.<sup>43</sup> Five studies had previous unenhanced US examination as an inclusion criterion, and the ‘concern regarding applicability’ criterion for quality assessment was rated ‘unclear’ for these studies (see *Table 3*).<sup>42,44–47</sup> The remaining study was a retrospective analysis of information derived from a radiology database; inclusion criteria specified only that patients should have received both CEUS and CEMRI and histological confirmation of diagnosis (examinations prior to contrast-enhanced imaging were not specified), and the ‘concern regarding applicability’ criterion was therefore rated ‘high’ risk of bias for this study.<sup>48</sup> Comparators and imaging criteria used to define a positive test for HCC varied across studies and no meta-analyses were therefore undertaken. All but one<sup>42</sup> of the studies in this section used histological confirmation in all patients or histological confirmation of imaging-positive patients and follow-up of imaging-negative patients as the reference standard.

All studies in this section were rated as ‘low’ or ‘unclear’ risk of bias for the ‘index test’ and ‘comparator test’ domains of the quality assessment tool. Two studies recruited consecutive samples of patients without inappropriate exclusions and were rated as ‘low’ risk of bias for ‘patient selection’.<sup>43,45</sup> Four studies were rated as ‘high’ risk of bias for the ‘patient selection’ domain because of the retrospective study design<sup>48</sup> or inappropriate exclusions.<sup>42,46,47</sup> Two studies excluded very small lesions ( $< 10$  mm);<sup>42,47</sup> as these lesions may be more difficult to characterise, their exclusion may result in overestimations of test performance. One study excluded lesions with peripheral enhancement on CECT, which was considered to be indicative of a high probability of haemangioma.<sup>46</sup> Two of the three studies were also rated as ‘high’ risk of bias for the ‘flow and timing domain’ of the assessment, in one case because the reference standard used was not independent of the imaging test results<sup>42</sup> and in the other because a high proportion of lesions (approximately 40%) were excluded because a histopathological reference standard was not performed.<sup>46</sup> One study was also rated as ‘high’ risk of bias for the ‘reference standard’ domain because a suboptimal reference standard (concordance between at least two imaging test results) was used in the majority of cases.<sup>42</sup>

The two studies that compared CEUS and CECT had slightly differing definitions of a positive imaging test (hyperenhancement in the arterial phase followed by portal venous washout<sup>43</sup> and hyperenhancement in the arterial phase with or without portal venous washout).<sup>46</sup> Neither study reported a significant difference in performance between imaging modalities for the differentiation of HCC from other liver lesions and neither study specified exclusion of very small FLLs. However, no data for very small FLLs were reported; in one study 46% of lesions were 10–15 mm and 54% were 16–20 mm<sup>43</sup> and in the other study all lesions were in the range 10–30 mm.<sup>46</sup> The study by Dai *et al.*<sup>43</sup> reported slightly higher estimates of

test performance, particularly for CECT specificity (see *Table 4*). The sensitivity estimates for CEUS and CECT were 91.1% (95% CI 80.4% to 97.0%) and 80.4% (95% CI 67.6% to 89.8%), respectively, and the corresponding specificities were 87.2% (95% CI 74.3% to 95.2%) and 97.9 (95% CI 88.7% to 99.9%).<sup>43</sup> The definition of HCC used by this study corresponded most closely with that reported in the EFSUMB guidelines on the use of CEUS.<sup>6</sup> *Table 1* summarises the typical enhancement patterns seen in various malignant FLLs. Quiaia *et al.*<sup>46</sup> reported sufficient data to allow calculation of sensitivity and specificity for the combination of CEUS and CECT, with a positive finding on either imaging technique treated as 'test positive'; they reported an increase in sensitivity for combined imaging compared with either CEUS or CECT alone with no change in specificity.

Three studies compared CEUS and CEMRI; two used gadolinium contrast-enhanced magnetic resonance imaging (Gd-CEMRI)<sup>44,45</sup> and one used Gd-EOB-DTPA-CEMRI,<sup>48</sup> a 'combined' vascular and hepatocyte-specific contrast agent. The two studies that compared CEUS and Gd-CEMRI used different definitions of a positive imaging test result and only Forner *et al.*<sup>44</sup> reported data for a definition of HCC, which corresponded with that given in the EFSUMB guidelines,<sup>6</sup> which they described as 'conclusive' HCC. Forner *et al.*<sup>44</sup> also reported data for a definition of 'suspicious' HCC (hyperenhancement in the arterial phase without portal venous washout). Sensitivity and specificity were similar for CEUS and Gd-CEMRI using either criterion. Specificity tended to increase and sensitivity to decrease for both imaging modalities when the stricter 'conclusive' definition of HCC was used. This study did not stratify data by lesion size; however, very small lesions ( $\leq 10$  mm) were included (15% of lesions were  $< 10$  mm, 49% were 10–15 mm and 36% were 16–20 mm). The authors also stated that use of the AASLD criteria (concordant, 'conclusive' findings on CEUS and CEMRI) resulted in 100% specificity but low sensitivity (33%) (data not reported). Giorgio *et al.*<sup>45</sup> used (arterial phase) hypervascularity as the definition of a positive test and stratified data by lesion size. There was no significant difference in the performance of CEUS and Gd-CEMRI for the differentiation of HCC from benign lesions, for FLLs between 11 and 30 mm, and both techniques had sensitivity and specificity values  $> 85\%$  (see *Table 4*). For very small FLLs ( $\leq 10$  mm), the sensitivity of CEUS was lower than that of CEMRI (27% vs 73%); for both imaging techniques, sensitivity was poor when the analysis was restricted to very small FLLs.<sup>45</sup> Imaging test performance estimates were similar for the 'all lesion' data set from Giorgio *et al.*<sup>45</sup> and the 'suspicious' diagnostic criteria data set from Forner *et al.*;<sup>44</sup> these data sets were similar in terms of diagnostic criteria and distribution of lesion size. The study that used Gd-EOB-DTPA-CEMRI did not report any information on lesion size.<sup>48</sup> The criteria used to define a positive imaging test result matched the definition of HCC given in the EFSUMB guidelines.<sup>6</sup> Sensitivity estimates were similar and high ( $> 90\%$ ) for both CEUS and Gd-EOB-DTPA-CEMRI (see *Table 4*). Specificity appeared lower for CEUS than for Gd-EOB-DTPA-CEMRI; however, the small number of patients with benign lesions in this study resulted in high imprecision in specificity estimates: 50% (95% CI 42% to 88%) for CEUS and 83% (95% CI 36% to 100%) for Gd-EOB-DTPA-CEMRI.

The two studies that assessed all three imaging modalities<sup>42,47</sup> both reported data using a definition of HCC that broadly corresponded to that given in the EFSUMB guidelines,<sup>6</sup> although Leoni *et al.*<sup>42</sup> stated 'typical enhancement pattern' without specifying portal venous/late phase washout and Sangiovanni *et al.*<sup>47</sup> also reported data using arterial hyperenhancement and portal venous washout separately as the definitions of HCC. Both studies assessed Gd-CEMRI and one study also assessed CEMRI using SPIO, a contrast agent that is selectively taken up by Kupffer cells in the normal liver and benign lesions and can therefore be used to identify HCCs, which are generally deficient in Kupffer cells.<sup>47</sup> When the EFSUMB-consistent definition of HCC was used, the two studies reported similar specificity estimates for all imaging modalities and for both MRI contrast agents; however, Leoni *et al.*<sup>42</sup> tended to report higher estimates of sensitivity. Sensitivity estimates from these studies were generally lower than those from studies with an EFSUMB-consistent definition of HCC that compared only CECT with CEUS<sup>43</sup> or CEMRI with CEUS.<sup>44,48</sup> Leoni *et al.*<sup>42</sup> reported that Gd-CEMRI had the highest sensitivity of the imaging modalities assessed [81.8% (95% CI 69.1% to 90.9%)]. Both studies reported sufficient data to allow calculation of sensitivity and specificity estimates, with a positive result on any of the three imaging modalities treated as index test positive. Data from Leoni *et al.*<sup>42</sup> indicated that combining the three imaging modalities in this way could increase sensitivity [98.2%

(95% CI 90.3% to 100%)] and decrease specificity [75.0% (95% CI 50.9% to 91.3%)] relative to any of the three imaging modalities alone. By contrast, combined imaging modality data from Sangiovanni *et al.*<sup>47</sup> did not appear to indicate significant improvements in sensitivity.

*Table 3* provides a summary of the QUADAS-2 assessments for studies in this section and *Table 4* summarises individual study results.

TABLE 3 QUADAS-2 results for studies on the accuracy of SonoVue CEUS for the characterisation of FLLs detected on surveillance of patients with cirrhosis

Study ID	Risk of bias			Applicability concerns		
	Patient selection	Index test	Comparator test	Reference standard	Flow and timing	Patient selection
Blondin 2011 <sup>48</sup>	⊗	?	?	⊗	⊗	⊗
Dai 2008 <sup>43</sup>	⊗	⊗	⊗	?	⊗	⊗
Forner 2008 <sup>44</sup>	?	?	⊗	?	?	?
Giorgio 2007 <sup>45</sup>	⊗	⊗	⊗	⊗	⊗	?
Leoni 2010 <sup>42</sup>	⊗	⊗	⊗	⊗	⊗	?
Quaia 2009 <sup>46</sup>	⊗	⊗	⊗	?	⊗	?
Sangiovanni <sup>47,61</sup>	⊗	?	?	⊗	⊗	?

⊗, low risk; ⊗, high risk; ?, unclear risk.

**TABLE 4** Accuracy of SonoVue CEUS compared with other imaging techniques for the characterisation of FFLs detected during routine surveillance of patients with known cirrhosis

Study ID	Patient or lesion data	Index test or comparator	Reference standard	TP	FN	FP
<b>HCC</b>						
<b>SonoVue CEUS compared with CECT</b>						
Dai 2008 <sup>43</sup>	<i>n</i> = 103 FFLs in 72 patients (per-lesion data)	CEUS SonoVue HCC = positive <sup>b</sup>	Histopathology following biopsy, with negative biopsy confirmed by a minimum of 6 months' follow-up	51	5	6
		CECT with Somatom Plus 4 (Siemens Medical Systems, Erlangen, Germany) HCC = positive <sup>b</sup>		45	11	1
Quaia 2009 <sup>46</sup>	<i>n</i> = 121 FFLs (≤30 mm) in 106 patients (per-lesion data)	CEUS sulphur hexafluoride-filled microbubbles HCC = positive <sup>c</sup> (readers 1 and 2)	FNB in all lesions	64	8	15
				63	9	18
		CECT with Aquilion (Toshiba Medical Systems, Tochigi-ken, Japan) or Brilliance (Philips, Cleveland, OH, USA) HCC = positive <sup>c</sup> (readers 1&2)		53	19	14
				51	21	14
		CEUS + CECT HCC = either test positive (readers 1 and 2)		70	2	14
		70	2	15		
<b>SonoVue CEUS compared with CEMRI</b>						
Blondin 2011 <sup>48</sup>	<i>n</i> = 47 FFLs in 33 patients	CEUS SonoVue HCC = positive <sup>b</sup>	Histology (surgery or biopsy) in all lesions	38	3	3
		Gd-EOB-DTPA CEMRI with MAGNETOM Avanto (Siemens) HCC = positive <sup>b</sup>		37	4	1
Forner 2008 <sup>44</sup>	<i>n</i> = 89 patients (one lesion per patient)	CEUS SonoVue HCC suspicious <sup>d</sup> or conclusive <sup>b</sup> = positive	FNB for test positive, imaging follow-up for test negative	47	13	4
		CEUS SonoVue HCC conclusive <sup>b</sup> = positive		31	29	2
		Gd-CEMRI with Symphony system (Siemens) HCC suspicious <sup>d</sup> or conclusive <sup>b</sup> = positive		51	9	3
		Gd-CEMRI HCC conclusive <sup>b</sup> = positive		37	23	1

TN	Sensitivity (95% CI) (%) <sup>a</sup>	Specificity (95% CI) (%) <sup>a</sup>	Non-diagnostic	Adverse events	Acceptability to patients
41	91.1 (80.4 to 97.0)	87.2 (74.3 to 95.2)	None	NR	NR
46	80.4 (67.6 to 89.8)	97.9 (88.7 to 99.9)			
34	88.9 (79.3 to 95.1)	69.4 (54.6 to 81.7)	<i>n</i> = 4 inadequate CEUS examinations excluded from study	NR	NR
31	87.5 (77.6 to 94.1)	63.3 (48.3 to 76.6)			
35	73.6 (61.9 to 83.3)	71.4 (56.7 to 83.4)	<i>n</i> = 10 inadequate CECT examinations excluded from study		
35	70.8 (58.9 to 81.0)	71.4 (56.7 to 83.4)			
35	97.2 (90.3 to 99.7)	71.4 (56.7 to 83.4)	See above		
34	97.2 (90.3 to 99.7)	69.4 (54.6 to 81.7)			
3	93 (80 to 98)	50 (42 to 88)	None	NR	NR
5	90 (77 to 97)	83 (36 to 100)			
25	78.3 (65.8 to 87.9)	86.2 (68.3 to 96.1)			
27	51.7 (38.4 to 64.8)	93.1 (77.2 to 99.2)			
26	85.0 (73.4 to 92.9)	89.7 (72.6 to 97.8)			
28	61.7 (48.2 to 73.9)	96.6 (82.2 to 99.9)			

continued

**TABLE 4** Accuracy of SonoVue CEUS compared with other imaging techniques for the characterisation of FFLs detected during routine surveillance of patients with known cirrhosis (*continued*)

Study ID	Patient or lesion data	Index test or comparator	Reference standard	TP	FN	FP
Giorgio 2007 <sup>45</sup>	<i>n</i> = 73 FLLs (one lesion per patient)	CEUS SonoVue HCC = positive <sup>e</sup>	US-guided FNB in all patients	37	11	1
	<i>n</i> = 21 FLLs (≤10 mm)			3	8	0
	<i>n</i> = 52 FLLs (11–30 mm)			34	3	1
	<i>n</i> = 73 FLLs (one lesion per patient)	Gd-CEMRI with Symphony system HCC = positive <sup>f</sup>		43	5	3
	<i>n</i> = 21 FLLs (≤10 mm)			8	3	1
	<i>n</i> = 52 FLLs (11–30 mm)			35	2	2
<b>SonoVue CEUS compared with CECT and CEMRI</b>						
Leoni 2010 <sup>42</sup>	<i>n</i> = 75 FLLs in 60 patients (10–30 mm)	CEUS SonoVue HCC = positive <sup>g</sup>	Two or more concordant imaging results ( <i>n</i> = 44), FNB ( <i>n</i> = 14) or follow-up at 3-month intervals ( <i>n</i> = 1) for positive test	37	18	2
		CECT with Emotion 6 (Siemens) HCC = positive <sup>g</sup>	FNB ( <i>n</i> = 7) or follow-up at 3-month intervals ( <i>n</i> = 9) for test negative	37	18	2
		Gd-CEMRI with Signa (GE Medical Systems, WI, USA) HCC = positive <sup>g</sup>		45	10	1
	<i>n</i> = 68 FLLs (10–30 mm)	SPIO-CEMRI with Signa HCC = positive <sup>g</sup>		35	15	1
	<i>n</i> = 75 FLLs (10–30 mm)	CEUS + CECT + CEMRI HCC = any test positive		54	1	5
Sangiovanni 2010 <sup>47,61</sup>	<i>n</i> = 55 FLLs selected from 67 FLLs in 64 patients (10–20 mm)	CEUS SonoVue HCC = positive <sup>b</sup>	FNB in all lesions	9	25	0
		CEUS SonoVue HCC = positive <sup>h</sup>		23	11	5
		CEUS SonoVue HCC = positive <sup>i</sup>		13	21	1
		CECT with Definition system (Siemens) HCC = positive <sup>b</sup>		16	18	0
		CECT HCC = positive <sup>h</sup>		22	12	4
		CECT HCC = positive <sup>i</sup>		18	16	0

TN	Sensitivity (95% CI) (%) <sup>a</sup>	Specificity (95% CI) (%) <sup>a</sup>	Non-diagnostic	Adverse events	Acceptability to patients
24	77.1 (62.7 to 88.0)	96.0 (79.6 to 99.9)	None	No side effects observed in any patients	NR
10	27.3 (6.0 to 61.0)	100 (69.2 to 100)			
14	91.9 (78.1 to 98.3)	93.3 (68.1 to 99.8)			
22	89.6 (77.3 to 96.5)	88.0 (68.8 to 97.5)		NR	
9	72.7 (39.0 to 94.0)	90.0 (55.5 to 99.7)			
13	94.6 (81.8 to 99.3)	86.7 (59.5 to 98.3)			
18	67.3 (53.3 to 79.3)	90.0 (68.3 to 98.8)	None	NR	NR
18	67.3 (53.3 to 79.3)	90.0 (68.3 to 98.8)			
19	81.8 (69.1 to 90.9)	95.0 (75.1 to 99.9)			
17	70.0 (55.4 to 82.1)	94.4 (72.7 to 99.9)	Seven FLLs not assessed with SPIO-MRI		
15	98.2 (90.3 to 100)	75.0 (50.9 to 91.3)	None		
21	26.5 (12.9 to 44.4)	100 (83.9 to 100)	None	NR	NR
16	67.6 (49.5 to 82.6)	76.2 (52.8 to 91.8)			
20	38.2 (22.2 to 56.4)	95.2 (76.2 to 99.9)			
21	47.1 (29.8 to 64.9)	100 (83.9 to 100)			
17	64.7 (46.5 to 80.3)	81.0 (58.1 to 94.6)			
21	52.9 (35.1 to 70.2)	100 (83.9 to 100)			
					continued



**TABLE 4** Accuracy of SonoVue CEUS compared with other imaging techniques for the characterisation of FFLs detected during routine surveillance of patients with known cirrhosis (*continued*)

Study ID	Patient or lesion data	Index test or comparator	Reference standard	TP	FN	FP
	<i>n</i> = 53 <sup>i</sup> FFLs (10–20 mm)	Gd-CEMRI with Avanto system (Siemens)		14	18	0
		HCC = positive <sup>b</sup>				
		Gd-CEMRI		21	11	8
		HCC = positive <sup>h</sup>				
		Gd-CEMRI		19	13	1
		HCC = positive <sup>i</sup>				
		CEUS + CECT + CEMRI		22	12	0
		HCC = at least one test positive <sup>b</sup>				

**Liver metastases**

No studies identified

**Any malignancy**

No studies identified

FN, false-negative; FNB, fine-needle biopsy; FP, false-positive; ND, non-diagnostic; NR, not reported; TN, true-negative; TP, true-positive.

a Calculated values.

b Hyperenhancement in the arterial phase and hypoenhancement in the portal venous and late phases (portal venous washout).

c Hyperenhancement in the arterial phase and iso- or hyperenhancement in the portal venous and late phases with evidence of peripheral rim-like enhancement, or hyperenhancement in the arterial phase and hypoenhancement in the portal venous and late phases with or without peripheral vascular rim.

d Hyperenhancement in the arterial phase without washout in the venous phase.

e Hyper-echogenicity related to hypervascularity on US.

f Typical pattern of round area of hypervascularity and lack of portal supply.

g Hyperenhancement in the arterial phase, 'typical enhancement pattern for HCC'.

h Arterial hypervascularity.

i Portal venous washout.

j Two patients were excluded from analyses because they could not undergo CEMRI.

TN	Sensitivity (95% CI) (%) <sup>a</sup>	Specificity (95% CI) (%) <sup>a</sup>	Non-diagnostic	Adverse events	Acceptability to patients
21	43.8 (26.4 to 62.3)	100 (83.9 to 100)			
13	65.6 (46.8 to 81.4)	61.9 (38.4 to 81.9)			
20	59.4 (40.6 to 76.3)	95.2 (76.2 to 99.9)			
21	64.7 (46.5 to 80.3)	100 (83.9 to 100)			

### **Accuracy of SonoVue contrast-enhanced ultrasound for the detection of liver metastases in patients with known primary malignancy**

Two studies compared SonoVue CEUS with both CECT and CEMRI (SPIO-CEMRI in one study and both SPIO-CEMRI and Gd-CEMRI in the other study) for the detection of liver metastases in patients with known CRC.<sup>49,50</sup> Both studies reported per-lesion accuracy data and one study<sup>49</sup> also reported per-patient data. These two studies reported a total of 46 diagnoses of metastatic liver lesions. One of these studies included only patients with known liver metastases who were being considered for curative surgery and was therefore rated as having 'high' concerns regarding applicability.<sup>50</sup> One study, which compared CEUS and CECT and reported data on the detection of any liver malignancy, was included in this section because the diagnostic status of participants at baseline was unclear and 52 of the 59 positive final diagnoses were liver metastases (primary tumours: colon 43, breast 5, neuroendocrine 2, renal 2); this study was rated 'unclear' for concerns regarding applicability.<sup>51</sup> One further study, which did not include a comparator test, was included in this section.<sup>39</sup> This study was included in the review because it reported an inclusion criterion of 'indeterminate MDCT [multidetector computed tomography]-detected FLLs in patients with known primary cancers' (various locations) and could therefore provide information on how SonoVue CEUS performs in patients who have had previous imaging other than US and in whom the diagnosis remains uncertain. All studies in this section used histological confirmation in all patients or histological confirmation of imaging-positive patients and follow-up of imaging-negative patients as the reference standard.

Two of the four studies included in this section were reported only as conference abstracts,<sup>39,50</sup> resulting in a frequent judgement of 'unclear' risk of bias on quality assessment domains (see *Table 5*). Of the two full papers in this section,<sup>49,51</sup> Clevert *et al.*<sup>51</sup> was rated 'high' risk of bias for the 'flow and timing' domain of QUADAS-2 because 21% of participants were excluded from the CECT analysis; both studies were judged to be at 'low' or 'unclear' risk of bias for all other domains. The study by Jonas *et al.*<sup>50</sup> was rated as 'high' risk of bias for the 'patient selection' domain because it aimed to assess the ability of imaging modalities to detect liver metastases while including only patients with known liver metastases.

When definitions of a positive imaging test were reported, studies that assessed imaging tests using vascular contrast media (CEUS, CECT and Gd-CEMRI) gave various descriptions of peripheral rim enhancement as the criteria for liver metastases. In addition, two studies reported data for CEMRI using the hepatocyte-specific contrast agent SPIO.<sup>49,50</sup> Jonas *et al.*<sup>50</sup> reported 100% specificity and, similarly, high (83–97%) estimates of sensitivity for all three imaging modalities (CEUS, CECT and SPIO-CEMRI). Mainenti *et al.*<sup>49</sup> also reported high (83–100%) specificity values for all imaging modalities and for both per-lesion and per-patient data. Per-patient sensitivity estimates were also consistent across all imaging modalities (83% in all cases);<sup>49</sup> however, for both CEUS and CECT, the sensitivity estimates appeared lower for per-lesion data (50% and 69% respectively) than for per-patient data.<sup>49</sup> For both CEMRI methods, the per-lesion estimate of sensitivity (81%) was similar to the per-patient estimate.<sup>49</sup> By contrast, Clevert *et al.*<sup>51</sup> reported per-patient data and found similarly high (>95%) estimates of sensitivity for both CEUS and CECT; however, specificity appeared lower for CECT than for CEUS [71.4% (95% CI 47.8% to 88.7%) and 97.6% (95% CI 87.1% to 99.9%) respectively] and images were non-diagnostic in approximately 15% of CT examinations.

*Table 5* provides a summary of the QUADAS-2 assessments for studies in this section and *Table 6* summarises individual study results.

TABLE 5 QUADAS-2 results for studies of the accuracy of SonoVue CEUS for the detection of liver metastases in patients with known primary malignancy

Study ID	Risk of bias			Applicability concerns		
	Patient selection	Index test	Comparator test	Reference standard	Flow and timing	Patient selection
Clevert 2009 <sup>51</sup>	☺	☺	☺	?	☹	?
Flor 2009 <sup>39</sup> (abstract only)	?	?	NA	?	?	☹
Jonas 2011 <sup>50</sup> (abstract only)	☹	?	?	?	?	☹
Mainenti 2010 <sup>49</sup>	☺	☺	☺	?	☺	?

☺, low risk; ☹, high risk; ?, unclear risk; NA, not applicable (no comparator test).

**TABLE 6** Accuracy of SonoVue CEUS compared with other imaging techniques for the detection of liver metastases in patients with known primary malignancy

Study ID	Patient or lesion data	Index test or comparator	Reference standard	TP	FN	FP	TN	Sensitivity (95% CI) <sup>a</sup>	Specificity (95% CI) <sup>a</sup>	Non-diagnostic (n patients/ lesions)	Adverse events	Acceptability to patients
<b>CRC</b>												
<b>SonoVue CEUS compared with CECT and CEMRI</b>												
Jonas 2011 <sup>50</sup> (abstract only)	n = 48 FLLs in 20 patients (by lesion data)	CEUS SonoVue M = positive	Histology in all resected test-positive lesions	26	4	0	18	86.7 (69.3 to 96.2)	100 (81.5 to 100)	NR	NR	NR
		SPIO-CEMRI (no further details reported)	All patients followed up for at least 36 months	29	1	0	18	96.7 (82.8 to 99.9)	100 (81.5 to 100)			
		M = positive		25	5	0	18	83.3 (65.3 to 94.4)	100 (81.5 to 100)			
		CECT (no further details reported)										
		M = positive										
Mainenti 2010 <sup>49</sup>	n = 34 patients	CEUS SonoVue	FNB for imaging test positive	5	1	4	24	83.3 (35.9 to 99.6)	85.7 (67.3 to 96.0)	None	NR	NR
	n = 57 FLLs	M = positive <sup>b</sup>		8	8	5	36	50.0 (24.7 to 75.3)	87.8 (73.8 to 95.9)			
	n = 34 patients	CECT with Aquilion 4 (Toshiba)	12 months' follow-up for imaging test negative	5	1	1	27	83.3 (35.9 to 99.6)	96.4 (81.7 to 99.9)			
	n = 57 FLLs	M = positive <sup>c</sup>		11	5	7	34	68.8 (41.3 to 89.0)	82.9 (67.9 to 92.8)			
	n = 34 patients	Gd-CEMRI (Gyroscan Intera 1.5T, Philips Medical Systems, Best, the Netherlands)		5	1	0	28	83.3 (35.9 to 99.6)	100 (87.7 to 100)			
	n = 57 FLLs	M = positive <sup>d</sup>		13	3	0	41	81.3 (54.4 to 96.0)	100 (91.4 to 100)			
	n = 34 patients	SPIO-CEMRI		5	1	1	27	83.3 (35.9 to 99.6)	96.4 (81.7 to 99.9)			
	n = 57 FLLs	M = positive <sup>e</sup>		13	3	1	40	81.3 (54.4 to 96.0)	97.6 (87.1 to 99.9)			

Study ID	Patient or lesion data	Index test or comparator	Reference standard	TP	FN	FP	TN	Sensitivity (95% CI) (%) <sup>a</sup>	Specificity (95% CI) (%) <sup>a</sup>	Non-diagnostic (n patients/ lesions)	Adverse events	Acceptability to patients
<b>Other primary tumours</b>												
<b>SonoVue CEUS compared with CECT</b>												
Clevert 2009 <sup>51</sup>	n = 100 patients (maximum five lesions per patient)	CHI SonoVue Any liver malignancy = positive <sup>f</sup>	Histology for all FLLs	58	1	1	40	98.3 (90.9 to 100)	97.6 (87.1 to 99.9)	None	NR	NR
	n = 92 <sup>g</sup> patients (maximum five lesions per patient)	CECT, Somatom Sensation 16 or 64 (Siemens) Any liver malignancy = positive <sup>f</sup>		56	2	6	15	96.6 (88.1 to 99.6)	71.4 (47.8 to 88.7)	13 (excluded from analysis)	NR	NR
<b>SonoVue CEUS following inconclusive CECT/CEMRI</b>												
Flor 2009 <sup>39</sup> (abstract only)	n = 26 FLLs	CEUS SonoVue M = positive	FNB or 3- to 6-month follow-up	4	1	0	21	80.0 (28.4 to 99.5)	100 (83.9 to 100)	None	NR	NR

CHI, contrast-enhanced harmonic imaging; FN, false-negative; FNB, fine-needle biopsy; FP, false-positive; M, metastases; ND, non-diagnostic; NR, not reported; TN, true-negative; TP, true-positive.

a Calculated values.

b Lesion with a wide echogenic spectrum, poorly defined margins and hypoperfused or with peripheral enhancement.

c Hypodense lesion with poorly defined margins, appearing hypoperfused or with irregular peripheral enhancement.

d Lesion with moderate hypointensity on T1-weighted image and hyperintensity on T2-weighted image, or isointense in both, which appeared hypoperfused or with irregular peripheral enhancement.

e Lesion with moderate hypointensity on T1-weighted image and hyperintensity on T2-weighted image, or isointense in both, which did not concentrate intracellular contrast agent.

f The majority of malignant liver lesions (52/59) were metastases.

g Eight patients did not receive CT.

### **Accuracy of SonoVue contrast-enhanced ultrasound for the characterisation of incidentally detected focal liver lesions**

Five studies reported comparisons of SonoVue CEUS with other imaging techniques for the characterisation of incidentally detected liver lesions identified by unenhanced US.<sup>41,52,54–56</sup> All of these studies reported accuracy data for the differentiation of malignant from benign liver lesions and three studies also provided stratified data for the identification of HCC and the identification of liver metastases.<sup>52,55,56</sup> All but one of the studies in this section reported data on one lesion per patient and the remaining study<sup>41</sup> reported per-lesion data for 694 lesions in 686 patients. Therefore, although data are reported per lesion, all results reported in this section can be considered equivalent to per-patient test performance. Four studies compared SonoVue CEUS with CECT<sup>41,52,54,55</sup> and one of these<sup>52</sup> also reported data on the combined performance of SonoVue CEUS and CECT, with a positive result on either test treated as positive. One study compared SonoVue CEUS with CEMRI.<sup>55</sup> No study reported comparative accuracy data for all three imaging modalities. None of the comparative accuracy studies described in this section explicitly stated that patients had an uncertain diagnosis following unenhanced US, although all patients had a prior unenhanced US examination and therefore the applicability criterion for the quality assessment was rated 'unclear' in all cases.

One further study, which did not include a comparator test, was included in this section.<sup>53</sup> This study was included in the review because it reported an inclusion criterion of 'previous US and/or CT that had suggested the possibility of malignant liver lesions (not sufficiently proven benignancy)' and could therefore provide information on how SonoVue CEUS performs in patients who have had previous imaging other than US and in whom the diagnosis remains uncertain. Altogether, the six studies included in this section reported 805 diagnoses of malignant liver lesions; these included 459 HCC, 333 liver metastases and 13 CCC. It should be noted that overlap between the study populations of Seitz *et al.*<sup>55</sup> and Seitz *et al.*<sup>56</sup> is highly likely as these two publications by the same group reported a very similar study design and identical recruitment periods; Seitz *et al.*<sup>55</sup> reported a comparison of SonoVue CEUS with CECT and Seitz *et al.*<sup>56</sup> reported a comparison of SonoVue CEUS with CEMRI in a smaller group of patients. All but one<sup>41</sup> of the studies in this section used histological confirmation in all patients or histological confirmation of imaging-positive patients and follow-up of imaging-negative patients as the reference standard.

Studies were generally poorly reported, resulting in a judgement of 'unclear' risk of bias for many of the QUADAS-2 domain assessments. No study in this section reported recruiting a consecutive or random sample of participants and the 'patient selection' domain of QUADAS-2 was consequently rated 'high' or 'unclear' risk of bias in all cases. In addition, one study<sup>53</sup> excluded patients who were unable to undergo biopsy and both Seitz *et al.* studies<sup>55,56</sup> divided participants into two subgroups based on probable diagnoses after unenhanced US ('suspected benign' and 'suspected malignant'). For the Seitz *et al.* studies, accuracy data could be extracted only for the 'suspected malignant' subgroup; this may have resulted in a higher than usual prevalence of malignancy and possible overestimation of test performance. Two studies were also rated as 'high' risk of bias for the 'flow and timing' domain, in one case<sup>52</sup> because more than half of the participants initially recruited were excluded from the analyses (either because more than 1 month had elapsed between SonoVue CEUS and CECT or because positive lesions could not be confirmed by pathology) and in the second case<sup>41</sup> because the reference standard used was not independent of the index test results. This study was also rated 'high' risk of bias for the 'reference standard' domain because a suboptimal reference standard (concordance between at least two imaging modalities) was used in the majority of cases.

All of the comparative accuracy studies in this section reported no significant difference in the accuracy of CEUS and CECT or CEMRI for the characterisation of focal FLLs.<sup>41,52,54–56</sup> The primary analysis in all studies was for the differentiation of malignant from benign lesions. Studies used similar criteria to define HCC (hyperenhancement in the arterial phase followed by portal venous/late phase washout) and liver metastases (peripheral rim enhancement in the arterial phase, decreasing in the portal venous and late phases). These criteria are consistent with the typical enhancement patterns described in the EFSUMB guideline on the use of CEUS<sup>6</sup> (see *Table 1*). Pooled estimates of test performance for distinguishing malignant from benign FLLs, derived from the four studies that compared CEUS with CECT,<sup>41,52,54–56</sup>

indicated that sensitivity and specificity were similar for the two imaging modalities. The pooled estimates for the sensitivity of CEUS and CECT were 95.1% (95% CI 93.3% to 96.6%) and 94.6% (95% CI 92.7% to 96.1%) respectively. The pooled estimates for the specificity of CEUS and CECT were 93.8% (95% CI 90.4% to 96.3%) and 93.1% (95% CI 89.6% to 95.8%) respectively.  $I^2$  values were moderate (50–75%) for CEUS and high (>75%) for CECT. *Figures 4 and 5* illustrate the sensitivity and specificity values for each study comparing CEUS and CT, with pooled estimates. Sensitivity analyses excluding the study that used a suboptimal reference standard<sup>41</sup> showed a trend towards lower estimates of test performance and reduced heterogeneity ( $I^2$  values were low, <50%, in all cases). The new pooled estimates for the sensitivity of CEUS and CECT were 92.3% (95% CI 88.2% to 95.3%) and 87.4% (95% CI 82.7% to 91.3%), respectively, and the new pooled estimates for specificity were 88.2% (95% CI 79.8% to 93.9%) and 82.8% (95% CI 73.6% to 89.8%) respectively. It should be noted that exclusion of the study by Solbiati<sup>41</sup> resulted in a large reduction in sample size (694 FLLs from a total sample size of 1038 FLLs) and hence greater imprecision (wider CIs) in the estimates of sensitivity and specificity.

The single study that compared CEUS with CEMRI found no significant difference between the performance of the two imaging modalities for the differentiation of malignant from benign FLLs. The reported sensitivities were 90.0% (95% CI 80.0% to 97.0%) and 81.8% (95% CI 69.1% to 90.9%), respectively, and the reported specificities were 66.7% (95% CI 46.3% to 83.5%) and 63.0% (95% CI 42.4% to 80.6%) respectively. This study used gadolinium-enhanced MRI in all patients, with the addition of SPIO-MRI in an unspecified number of patients.

One study reported sufficient data to allow calculation of sensitivity and specificity for the combination of CEUS and CECT, with a positive finding on either imaging technique treated as 'test positive'.<sup>52</sup> These data indicated that the addition of CECT to the imaging workup would not increase the accuracy of diagnosis over that obtained by CEUS alone; the sensitivity and specificity of CEUS for differentiating malignant from benign lesions were 91.1% (95% CI 78.8% to 97.5%) and 93.8% (95% CI 79.2% to 99.2%), respectively, and for CEUS and CECT combined were 93.3% (95% CI 81.7% to 98.6%) and 93.8% (95% CI 79.2% to 99.2%) respectively. Three studies reported sufficient data to derive estimates of test performance by lesion type (HCC and liver metastases), two comparing CEUS and CECT<sup>52,55</sup> and one comparing CEUS and CEMRI.<sup>56</sup> The sensitivity and specificity of CEUS and CECT were similar for the characterisation of HCC; however, one study indicated that CEUS may be more sensitive than CECT for the characterisation of metastases [92.9% (95% CI 82.7% to 98.0%) compared with 67.9% (95% CI 54.0% to 79.7%)].<sup>55</sup> The sensitivity and specificity of CEUS and CEMRI were similar for both HCC and liver metastases.<sup>56</sup>

*Table 7* provides a summary of the QUADAS-2 assessments for studies in this section and *Table 8* summarises individual study results. *Figure 6* shows the results for differentiation of malignant from benign FLLs for all studies in this section, plotted in the ROC plane.

**TABLE 7** QUADAS-2 results for studies of the accuracy of SonoVue CEUS for the characterisation of incidentally detected FLLs

Study ID	Risk of bias					Applicability concerns
	Patient selection	Index test	Comparator test	Reference standard	Flow and timing	Patient selection
Catala 2007 <sup>52</sup>	⊗	⊙	⊙	?	⊗	?
Gierbliński 2008 <sup>53</sup>	⊗	?	NA	⊙	?	?
Li 2007 <sup>54</sup>	?	⊙	⊙	?	⊙	?
Seitz 2009 <sup>55</sup>	⊗	?	?	?	?	?
Seitz 2010 <sup>56</sup>	⊗	?	?	?	?	?
Solbiati 2006 <sup>41</sup> (abstract only)	⊗	?	?	⊗	⊗	?

⊙, low risk; ⊗, high risk; ?, unclear risk; NA, not applicable (no comparator test).



**TABLE 8** Accuracy of SonoVue CEUS compared with other imaging techniques for the characterisation of incidentally detected FLLs

Study ID	Patient or lesion data	Index test or comparator	Reference standard
<b>HCC</b>			
<i>SonoVue CEUS compared with CECT</i>			
Catala 2007 <sup>52</sup>	<i>n</i> = 77 patients (one lesion per patient)	CEUS SonoVue HCC = positive <sup>b</sup>  CECT with Somatom Plus 4 (Siemens) HCC = positive <sup>b</sup>  CEUS + CECT HCC = either test positive	Histology following biopsy or surgery for test positive, MRI and follow-up ≥ 12 months for test negative
Seitz 2009 <sup>55</sup> (related publication Seitz 2010 <sup>56</sup> )	Subgroup B (suspected malignant lesion) <sup>c</sup> <i>n</i> = 158 FLLs (one lesion per patient)	CEUS SonoVue HCC = positive  CECT (device not specified) HCC = positive	FNB <i>n</i> = 154 (remaining four lesions excluded)
<i>SonoVue CEUS compared with CEMRI</i>			
Seitz 2010 <sup>56</sup> (related publication Seitz 2009 <sup>55</sup> )	Subgroup B (suspected malignant lesion) <sup>c</sup> <i>n</i> = 84 FLLs (one lesion per patient)	CEUS SonoVue HCC = positive  Gd-CEMRI and SPIO-CEMRI in some cases (number unspecified) (device not specified) HCC = positive	FNB <i>n</i> = 82 (two lesions excluded)
<i>SonoVue CEUS following inconclusive CECT/CEMRI</i>			
Gierbliński 2008 <sup>53</sup>	<i>n</i> = 100 patients (one lesion per patient)	CEUS SonoVue HCC = positive <sup>b</sup>	FNB with clinical and imaging follow-up for biopsy-negative patients
<b>Liver metastases</b>			
<i>SonoVue CEUS compared with CECT</i>			
Catala 2007 <sup>52</sup>	<i>n</i> = 77 patients (one lesion per patient)	CEUS SonoVue M = positive <sup>d</sup>  CECT with Somatom Plus 4 (Siemens) M = positive <sup>d</sup> pattern  CEUS + CECT M = either test positive	Histology following biopsy or surgery for test positive, MRI and follow-up ≥ 12 months for test negative
Seitz 2009 <sup>55</sup> (related publication Seitz 2010 <sup>56</sup> )	Subgroup B (suspected malignant lesion) <sup>c</sup> <i>n</i> = 158 FLLs (one lesion per patient)	CEUS SonoVue M = positive  CECT (device not specified) M = positive	FNB <i>n</i> = 154 (four lesions excluded)

TP	FN	FP	TN	Sensitivity (95% CI) (%) <sup>a</sup>	Specificity (95% CI) (%) <sup>a</sup>	Non-diagnostic	Adverse events	Acceptability to patients
41	4	2	30	91.1 (78.8 to 97.5)	93.8 (79.2 to 99.2)	None	NR	NR
39	6	2	30	86.7 (73.2 to 94.9)	93.8 (79.2 to 99.2)			
42	3	2	30	93.3 (81.7 to 98.6)	93.8 (79.2 to 99.2)			
34	6	4	110	85.0 (70.2 to 94.3)	96.5 (91.3 to 99.0)	None	NR	NR
28	12	6	108	70.0 (53.5 to 83.4)	94.7 (88.9 to 98.0)			
23	6	11	42	79.3 (60.3 to 92.0)	79.2 (65.9 to 89.2)	NR	NR	NR
24	5	13	40	82.8 (64.2 to 94.2)	75.5 (61.7 to 86.2)			
7	2	1	90	77.8 (40.0 to 97.2)	98.9 (94.0 to 100)	None	NR	NR
11	1	0	65	91.7 (61.5 to 99.8)	100 (94.5 to 100)	None	NR	NR
11	1	0	65	91.7 (61.5 to 99.8)	100 (94.5 to 100)			
11	1	0	65	91.7 (61.5 to 99.8)	100 (94.5 to 100)			
52	4	17	81	92.9 (82.7 to 98.0)	82.7 (73.7 to 89.6)	None	NR	NR
38	18	23	75	67.9 (54.0 to 79.7)	76.5 (66.9 to 84.5)			

continued

**TABLE 8** Accuracy of SonoVue CEUS compared with other imaging techniques for the characterisation of incidentally detected FLLs (*continued*)

Study ID	Patient or lesion data	Index test or comparator	Reference standard
<b>SonoVue CEUS compared with CEMRI</b>			
Seitz 2010 <sup>56</sup> (related publication Seitz 2009 <sup>55</sup> )	Subgroup B (suspected malignant lesion) <sup>c</sup> <i>n</i> = 84 FLLs (one lesion per patient)	CEUS SonoVue M = positive  Gd-CEMRI and SPIO-CEMRI in some cases (number unspecified) (device not specified)  HCC = positive	FNB <i>n</i> = 82 (two lesions excluded)
<b>SonoVue CEUS following inconclusive CECT/CEMRI</b>			
Gierbliński 2008 <sup>53</sup>	<i>n</i> = 100 patients (one lesion per patient)	CEUS SonoVue M = positive <sup>e</sup>	FNB with clinical and imaging follow-up for biopsy-negative patients
<b>Any malignancy</b>			
<b>SonoVue CEUS compared with CECT</b>			
Catala 2007 <sup>52</sup>	<i>n</i> = 77 patients (one lesion per patient)	CEUS SonoVue Any malignancy (HCC <sup>b</sup> or M <sup>d</sup> ) = positive  CECT with Somatom Plus 4 (Siemens) Any malignancy (HCC <sup>b</sup> or M <sup>d</sup> ) = positive  CEUS + CECT Either test positive = positive	Histology following biopsy or surgery for index test positive, MRI and follow-up ≥ 12 months for index test negative
Li 2007 <sup>54</sup>	<i>n</i> = 109 patients (one lesion per patient)	CEUS SonoVue Any malignancy (HCC, <sup>f</sup> CCC, <sup>g</sup> M <sup>h</sup> ) = positive    CECT with Somatom Sensation (Siemens) Any malignancy (HCC, CCC, M) = positive	Histopathology following surgical resection or FNB
Seitz 2009 <sup>55</sup> (related publication Seitz 2010 <sup>56</sup> )	Subgroup B (suspected malignant lesion) <sup>c</sup> <i>n</i> = 158 FLLs (one lesion per patient)	CEUS SonoVue Any malignancy = positive <sup>i</sup>  CECT (device not specified) Any malignancy = positive	FNB <i>n</i> = 154 (four lesions excluded)

TP	FN	FP	TN	Sensitivity (95% CI) (%) <sup>a</sup>	Specificity (95% CI) (%) <sup>a</sup>	Non-diagnostic	Adverse events	Acceptability to patients
17	5	15	45	77.3 (54.6 to 92.2)	75.0 (62.1 to 85.3)	NR	NR	NR
14	8	14	46	63.6 (40.7 to 82.8)	76.7 (64.0 to 86.6)			
13	1	2	84	92.9 (66.1 to 99.8)	97.7 (91.9 to 99.7)	None	NR	NR
52	5	2	18	91.2 (80.7 to 97.1)	90.0 (68.3 to 98.8)	None	NR	NR
50	7	2	18	87.7 (76.3 to 94.9)	90.0 (68.3 to 98.8)			
53	4	2	18	93.0 (83.0 to 98.1)	90.0 (68.3 to 98.8)			
72	9	2	26	88.9 (80.0 to 94.8)	92.9 (76.5 to 99.1)	Three lesions not visualised. All were malignant and are classified as FN	NR	NR
67	14	6	22	82.7 (72.7 to 90.2)	78.6 (59.0 to 91.7)	Seven lesions not visualised. Five were malignant and are classified as FN; two were benign and are classified as TN		
104	5	7	38	95.4 (89.6 to 98.5)	84.4 (70.5 to 93.5)	None	NR	NR
99	10	8	37	90.8 (83.8 to 95.5)	82.2 (67.9 to 92.0)			

continued

**TABLE 8** Accuracy of SonoVue CEUS compared with other imaging techniques for the characterisation of incidentally detected FLLs (*continued*)

Study ID	Patient or lesion data	Index test or comparator	Reference standard
Solbiati 2006 <sup>41</sup> (abstract only)	<i>n</i> = 694 FLLs in 686 patients, one lesion missing from analysis (per-lesion data)	CEUS SonoVue Any malignancy (HCC, M, CCC) = positive  CECT (device not specified) Any malignancy (HCC, M, CCC) = positive	Concordant CEUS and CT result ( <i>n</i> = 656) or FNB when results were discordant ( <i>n</i> = 38)
<b><i>SonoVue CEUS compared with CEMRI</i></b>			
Seitz 2010 <sup>56</sup> (related publication Seitz 2009 <sup>55</sup> )	Subgroup B (suspected malignant lesion) <sup>c</sup> <i>n</i> = 84 FLLs (one lesion per patient)	CEUS SonoVue Any malignancy = positive <sup>e</sup>  Gd-CEMRI and SPIO-CEMRI in some cases (number unspecified) (device not specified) HCC = positive	FNB <i>n</i> = 82 (two lesions excluded)
<b><i>SonoVue CEUS following inconclusive CECT/CEMRI</i></b>			
Gierbliński 2008 <sup>53</sup>	<i>n</i> = 100 patients (one lesion per patient)	CEUS SonoVue Any malignancy (HCC <sup>b</sup> or M <sup>g</sup> ) = positive	FNB with clinical and imaging follow-up for biopsy-negative patients

FN, false-negative; FNB, fine-needle biopsy; FP, false-positive; M, metastases; ND, non-diagnostic; NR, not reported; SCT, spiral computed tomography; TN, true-negative; TP, true-positive.

a Calculated values.

b Hyperenhancement in the arterial phase and hypo- or iso-enhancement in the portal venous and late phases.

c Subgroup A (suspected benign lesions) excluded.

d Hypo- to high enhancement in the arterial phase; hypoenhancement, quick washout or rim-like enhancement in the portal venous phase; hypoenhancement in the late phase.

e Rim-like enhancement in the arterial phase and hypoenhancement in the portal venous and late phases.

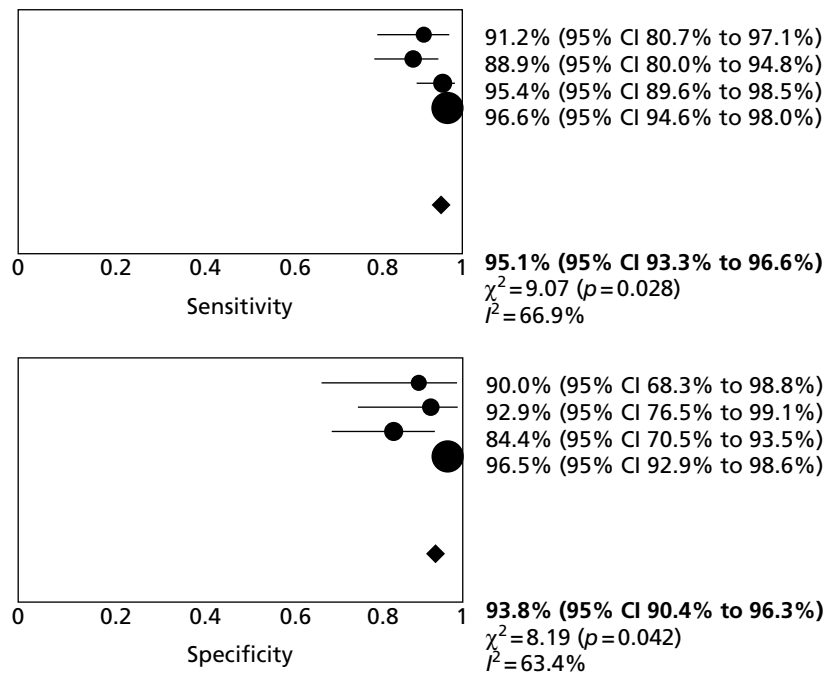
f Tortuous intratumoural vessels and diffuse enhancement in the arterial phase, decreasing in the portal venous and late phases.

g Variable intratumoural vessels and heterogeneous peripheral enhancement in the arterial phase, decreasing in the portal venous and late phases. Dilatation of the bile ducts near the tumour may be accentuated after enhancement.

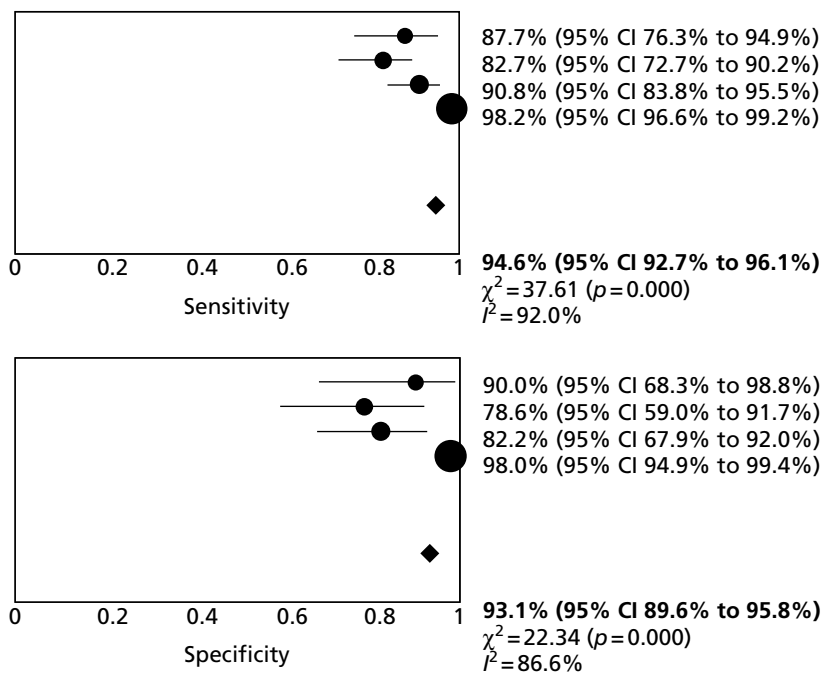
h Enhancing peripheral rim, variable intratumoural enhancement in the arterial phase, decreasing in the portal venous and late phases.

i Hypoenhancement in the late phase.

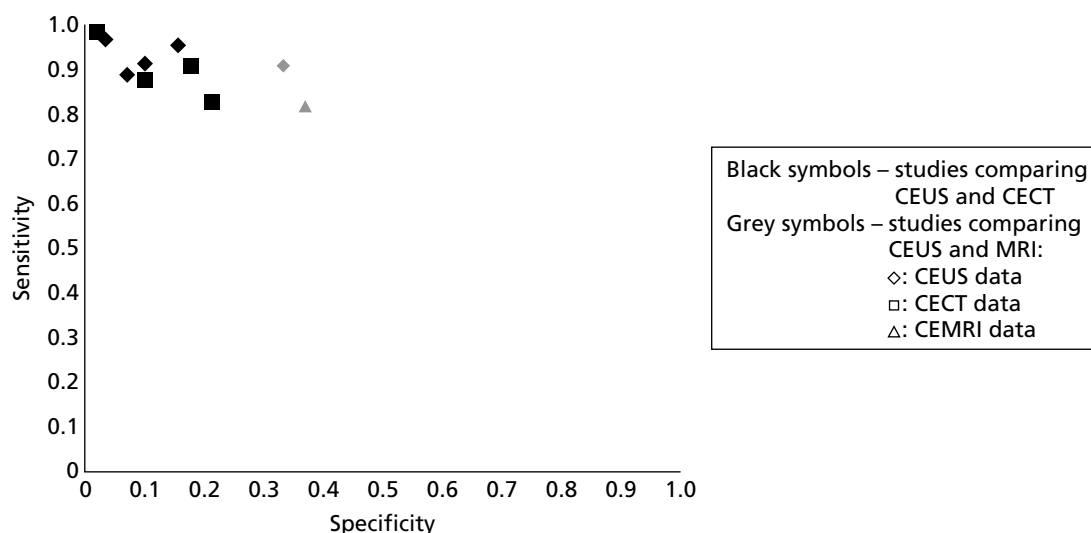
TP	FN	FP	TN	Sensitivity (95% CI) (%) <sup>a</sup>	Specificity (95% CI) (%) <sup>a</sup>	Non-diagnostic	Adverse events	Acceptability to patients
478	17	7	191	96.6 (94.6 to 98.0)	96.5 (92.9 to 98.6)	One (results missing for one lesion)	NR	NR
486	9	4	194	98.2 (96.6 to 99.2)	98.0 (94.9 to 99.4)			
50	5	9	18	90.9 (80.0 to 97.0)	66.7 (46.3 to 83.5)	Nine lesions (six benign and three malignant); these were classified as FP and FN respectively	NR	NR
45	10	10	17	81.8 (69.1 to 90.9)	63.0 (42.4 to 80.6)	Nine lesions (three benign and six malignant); these were classified as FP and FN respectively		
21	2	3	74	91.3 (72.0 to 98.9)	96.1 (89.0 to 99.2)	None	NR	NR



**FIGURE 4** Forest plot of sensitivity and specificity of CEUS for the identification of any liver malignancy in patients with incidentally detected FLLs.



**FIGURE 5** Forest plot of sensitivity and specificity of CECT for the identification of any liver malignancy in patients with incidentally detected FLLs.



**FIGURE 6** Receiver operating characteristic plane plot comparing performance of imaging tests for the differentiation of malignant from benign lesions in patients with incidentally detected FLLs.

### Accuracy of SonoVue contrast-enhanced ultrasound for the determination of treatment success in patients with known liver malignancy

Three studies reported comparisons of SonoVue CEUS with other imaging modalities for the assessment of treatment success (complete response) in patients with malignant liver lesions (mainly HCC).<sup>40,57,58</sup> Two were Chinese-language publications<sup>57,58</sup> and the other was published only as a conference abstract.<sup>40</sup> The two Chinese studies reported per-lesion data, with one<sup>57</sup> reporting only one lesion per patient, and the remaining study reported only per-patient data.<sup>40</sup> The studies assessed patients following cryosurgery,<sup>57</sup> RFA<sup>40</sup> and 'non-surgical treatment'.<sup>58</sup> Sample sizes were small: in total, studies reported data for 105 lesions (102 HCC and three liver metastases) in 97 patients. All three studies included only patients who were undergoing treatment for known liver malignancies and all studies were therefore rated as having 'low' concerns regarding applicability.

Studies were generally poorly reported and all QUADAS-2 risk of bias domains were rated 'unclear'.

One of the two Chinese studies compared CEUS with CECT or CEMRI (numbers of patients receiving CECT and CEMRI, respectively, were not specified)<sup>57</sup> and the other compared CEUS with CECT.<sup>58</sup> Both studies reported similar, high sensitivity (95.5–100%) and specificity (83.3–100%) for all imaging modalities, although small sample sizes resulted in wide CIs. One study reported sufficient data to allow the calculation of sensitivity and specificity for the combination of CEUS and CECT, with a negative finding on either imaging technique treated as 'test negative' for complete response.<sup>58</sup> These data indicated that the addition of CECT would not increase the accuracy of the assessment of response to treatment over that obtainable by CEUS alone; the sensitivity and specificity of CEUS for detecting complete response were 97.8% (95% CI 88.5% to 99.9%) and 94.4% (95% CI 72.7% to 99.9%), respectively, and for CEUS and CECT combined were 97.8% (95% CI 88.5% to 99.9%) and 100% (95% CI 81.5% to 100%) respectively. The remaining study compared CEUS with Gd-CEMRI and included only 15 patients undergoing RFA, with five final diagnoses of 'complete ablation'.<sup>40</sup> The results of the two techniques were identical; sensitivity for the detection of complete ablation was 80% (95% CI 28.4% to 99.5%) and there were nine false-positives, resulting in a very low estimate of specificity [10.0% (95% CI 3.0% to 44.5%)].

Table 9 provides a summary of the QUADAS-2 assessments for studies in this section and Table 10 summarises individual study results.



**TABLE 9** QUADAS-2 results for studies of the accuracy of SonoVue CEUS for the determination of treatment success in patients with known liver malignancy

Study ID	Risk of bias					Applicability concerns
	Patient selection	Index test	Comparator test	Reference standard	Flow and timing	Patient selection
Feng 2007 <sup>57</sup>	?	?	?	?	?	☹
Lüttich 2006 <sup>40</sup> (abstract only)	?	?	?	?	?	☹
Zhou 2007 <sup>58</sup>	?	?	?	?	?	☹

☹, low risk; ☹, high risk; ?, unclear risk.

**TABLE 10** Accuracy of SonoVue CEUS compared with other imaging techniques for the assessment of treatment response in patients with known liver malignancy

Study ID	Patient or lesion data	Index test or comparator	Reference standard	TP	FN	FP	TN	Sensitivity (95% CI) (%) <sup>a</sup>	Specificity (95% CI) (%) <sup>a</sup>	Non-diagnostic	Adverse events	Acceptability to patients
Feng 2007 <sup>57</sup> (Chinese language)	n = 26 malignant (23 HCC, 3 M) lesions in 23 patients treated with cryosurgery	CEUS SonoVue Test positive = complete response to treatment	Histopathological diagnosis	20	1	0	5	100 (83.2 to 100)	83.3 (35.9 to 99.6)	None	NR	NR
Lüttich 2006 <sup>40</sup> (abstract only)	n = 15 patients treated with RFA	CECT or CEMRI (no details reported) Test positive = complete response to treatment	Biopsy	4	1	9	1	80.0 (28.4 to 99.5)	10.0 (3.0 to 44.5)	None	NR	NR
Zhou 2007 <sup>58</sup> (Chinese language)	n = 64 HCC lesions in 56 patients who had undergone non-surgical treatment	CEUS SonoVue Test positive = complete response to treatment (no enhancement) CECT, Somatom Balance, (Siemens) Test positive = response to treatment (no enhancement)	Positive imaging test (no enhancement) confirmed by imaging follow-up at 3 months Negative imaging test (partial enhancement) confirmed by FNB	45	1	1	17	97.8 (88.5 to 99.9)	94.4 (72.7 to 99.9)	None	NR	NR
		CEUS + CECT Either test negative (partial enhancement) = negative		45	1	0	18	97.8 (88.5 to 99.9)	100 (81.5 to 100)			

FN, false-negative; FNB, fine-needle biopsy; FP, false-positive; M, metastases; NR, not reported; TN, true-negative; TP, true-positive.  
<sup>a</sup> Calculated values.

### **Effectiveness of SonoVue contrast-enhanced ultrasound for treatment planning in patients with known liver malignancy**

One controlled clinical trial compared SonoVue CEUS with unenhanced US (control) when added to routine imaging (CECT or CEMRI) for pretreatment assessment of patients undergoing RFA for HCC.<sup>59</sup> This study assessed the effect of CEUS on treatment effectiveness (successful ablation) as the primary outcome measure. Secondary outcomes were incidence of tumour progression, new HCC, repeat RFA and post-therapy complications, and duration of local progression-free survival and new tumour-free survival. The CEUS and control groups were similar at baseline in terms of age, gender distribution, numbers who had CECT and numbers who had CEMRI, TNM (tumour, lymph node, metastases) stage, tumour size and number, and numbers who had Child–Pugh class A cirrhosis.

This non-randomised study was considered to have ‘risk of bias’ in a number of areas. Alternate allocation of patients to the CEUS and control groups means that clinicians could predict patient allocation before recruitment. The nature of the study precluded the blinding of patients, and the blinding of assessors and/or clinicians planning RFA protocols was not clear. Finally, 14 patients who were considered unsuitable for RFA after imaging assessment (nine in the CEUS group and five in the control group) were excluded from the analyses.

There were no significant differences in the rates of successful ablation (primary outcome) or post-therapy complications between the CEUS group and the control group. Use of CEUS in the pretreatment imaging protocol was found to significantly reduce incidence of tumour progression, new HCC and repeat RFA over a 2-year follow-up period; ORs were 0.35 (95% CI 0.13 to 0.95), 0.34 (95% CI 0.16 to 0.72) and 0.33 (95% CI 0.17 to 0.66) respectively. The use of CEUS also increased local progression-free survival [mean difference 7.2 months (95% CI 6.6 months to 7.8 months)] and new tumour-free survival [mean difference 11.7 months (95% CI 11.1 months to 12.3 months)].

Table 11 provides a summary of the risk of bias assessment for this study and Table 12 summarises the results.

**TABLE 11** Risk of bias assessment for studies of the effectiveness of SonoVue CEUS for treatment planning in patients with known liver malignancy

Item	Judgement	Description
Adequate sequence generation?	Yes	Alternate allocation
Allocation concealment?	No	Alternate allocation means that assignment of an individual patient to a test group can be easily predicted
Blinding?	No	Patients could not be blinded to the tests being undertaken and it was not clear whether or not those assessing the efficacy of treatment were aware of test allocations. It was not clear if those who designed the RFA protocol knew the results of CEUS and US or of only one of the tests
Were patient characteristics comparable at baseline?	Yes	
Incomplete outcome data addressed?	Yes	All outcomes assessed appear to be reported for all patients
Free of selective reporting?	Yes	All outcomes assessed appear to be reported for all patients
Free of other bias?	No	Patients in both groups who were judged to be unsuitable for RFA were excluded from the analyses

TABLE 12 Effectiveness of SonoVue CEUS compared with unenhanced US for treatment planning in patients with known liver malignancy

Study ID	Population	Intervention	Comparator	Outcome <sup>a</sup>	n with outcome (I)	n with outcome (C)	OR (95% CI) <sup>b</sup>	Mean $\pm$ SD (I)	Mean $\pm$ SD (C)	Mean difference (95% CI) <sup>a</sup>
Chen 2007 <sup>59</sup> (related publication <sup>60</sup> )	Patients with HCC, undergoing RFA treatment	CEUS SonoVue and CECT or CEMRI before treatment (83 patients, 114 tumours)	US and CECT or CEMRI before treatment (82 patients, 107 tumours)	Primary treatment effectiveness (successful ablation)	77	71	1.99 (95% CI 0.70 to 5.66)	NA	NA	NA
				Tumour progression	6	15	0.35 (95% CI 0.13 to 0.95)	NA	NA	NA
				New HCC	13	29	0.34 (95% CI 0.16 to 0.72)	NA	NA	NA
				Repeat RFA	17	36	0.33 (95% CI 0.17 to 0.66)	NA	NA	NA
				Local progression-free survival	NA	NA	NA	40.5 $\pm$ 1.9 months	33.3 $\pm$ 2.2 months	7.2 (95% CI 6.6 to 7.8)
				New tumour-free survival	NA	NA	NA	38.1 $\pm$ 2.0 months	26.4 $\pm$ 2.0 months	11.7 (95% CI 11.1 to 12.3)
				Post-therapy complications	1	3	0.32 (95% CI 0.03 to 3.15)	NA	NA	NA

C, comparator (US); I, intervention (CEUS); NA, not applicable.

a Outcomes were determined by imaging follow-up 1 month after RFA and every following 2–3 months in the first year and 4–6 months in the second year. RFA was considered successful if there was no contrast enhancement in or around the tumour, the margins of the ablation zone were clear and smooth and the ablation zone extended beyond the tumour borders.

b Calculated values.

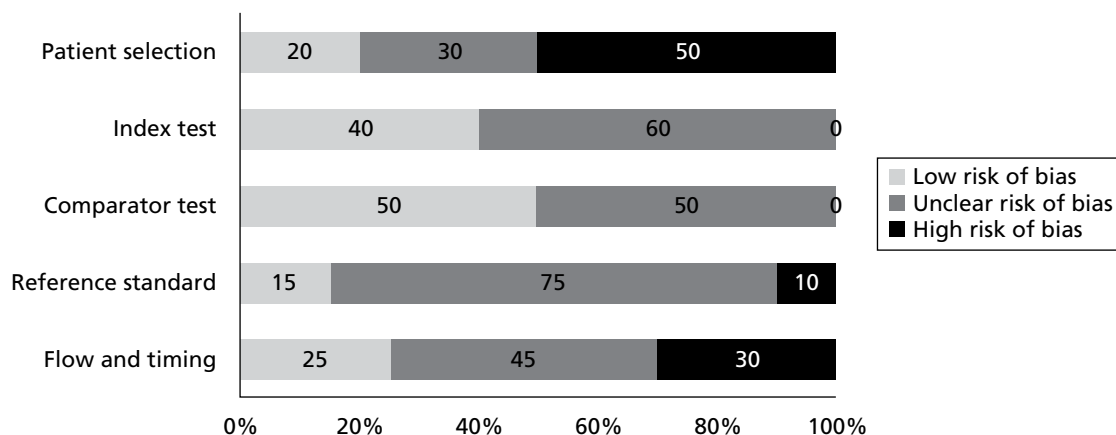
## Summary of clinical effectiveness results

Twenty of the 21 studies included in the systematic review were DTA studies: seven compared the performance of imaging modalities for the characterisation of FLLs detected on surveillance of cirrhosis patients using unenhanced US; four compared the performance of imaging modalities for the detection of liver metastases in patients with known primary cancer (CRC); six compared the performance of imaging modalities for the characterisation of incidentally detected FLLs identified by unenhanced US; and three compared the performance of imaging modalities for the determination of treatment response in patients with liver cancer.

The majority of included test accuracy studies were judged to be at 'low' or 'unclear' risk of bias with respect to the 'index test', 'comparator test' and 'reference standard' domains. 'Unclear' ratings for these domains most frequently arose from insufficient detail in the reporting of how tests were interpreted, particularly blinding of interpreters to other test results. Reporting quality was generally poor and a number of studies were reported only as conference abstracts, resulting in a high proportion of 'unclear' risk of bias ratings across domains (*Figure 7*). 'High' risk of bias ratings for the 'patient selection' domain arose from the use of a retrospective study design or from inappropriate exclusions of particular patient groups (e.g. exclusion of patients with a low probability of malignancy). 'High' risk of bias ratings for the 'flow and timing' domain arose from exclusion of > 10% of patients from analyses or, in two cases, from incorporation of index test results in the reference standard. The last two studies were also rated as 'high' risk of bias for the 'reference standard' domain.

Studies varied in terms of target condition (HCC, liver metastases or 'any malignancy'), definitions of a positive imaging test in studies of the same target condition, and lesion size assessed. Overall, there was no clear indication that any of the imaging modalities (CEUS, CECT or CEMRI) or contrast media considered offered superior performance for any of the clinical applications assessed.

Studies conducted in cirrhosis patients undergoing routine surveillance all concerned the differentiation of HCC from other lesion types in small to medium (<30 mm) FLLs. The definition of a positive test for HCC varied, including arterial enhancement followed by portal venous washout, arterial enhancement alone and portal venous washout alone. There was no consistent evidence for any significant difference in test performance between the three imaging modalities and three MRI contrast media assessed. Results were inconsistent for the studies that reported an EFSUMB-consistent definition of HCC (arterial phase enhancement followed by portal venous/late phase washout). One study comparing CEUS and CECT reported high per-lesion sensitivity (91% and 80% respectively) and specificity (87% and 98% respectively) estimates; all lesions in this study were between 10 and 20 mm. Two studies comparing CEUS and Gd-CEMRI reported inconsistent sensitivity estimates for CEUS (93% and 52%), with the lower



**FIGURE 7** Summary of QUADAS-2 assessments.

sensitivity estimate arising from a study that included very small ( $\leq 10$  mm) FLLs. Two studies comparing all three imaging modalities reported similar, high specificity estimates ( $>90\%$  in most cases) for all imaging modalities; however, sensitivity estimates were inconsistent between the two studies. Sensitivity estimates were 67% and 27% for CEUS; 67% and 47% for CECT; and 82% and 44% for Gd-CEMRI. Sensitivity estimates from these two studies were generally lower than those in studies that compared only two imaging modalities using a similar definition of HCC and similar lesion size. There was some evidence from one study comparing CEUS and Gd-CEMRI that these techniques may be better at ruling out HCC in FLLs between 11 and 30 mm (sensitivities for CEUS and CEMRI were 92% and 95% respectively) than in small FLLs of  $\leq 10$  mm (sensitivities 27% and 73% respectively); however, this study did not use an EFSUMB-consistent definition of HCC. There was also some evidence from two studies that combined imaging using CEUS and CECT or all three imaging modalities, in which any positive imaging result was treated as 'test positive', that combined imaging may increase sensitivity. Overall, inconsistent estimates of sensitivity mean that it is unclear whether or not CEUS alone is adequate to rule out HCC for FLLs  $<30$  mm in this population; CEUS alone may be adequate to rule out HCC for FLLs 11–30 mm, with very small FLLs ( $<10$  mm) not considered.

Studies of the diagnosis of liver metastases using imaging with vascular contrast media (CEUS, CECT and Gd-CEMRI) in which definitions of a positive imaging test were reported gave various descriptions of peripheral rim enhancement as the criterion for liver metastases. Two studies reported data for SPIO-CEMRI. There was no consistent evidence for any significant difference in test performance between the three imaging modalities assessed and different MRI contrast media assessed. Both per-patient and per-lesion sensitivity estimates were generally high in all studies [ $>83\%$  for all imaging modalities and both MRI contrast agents in two studies of patients with CRC and  $>95\%$  for both CEUS and CECT in a third study of patients with various primary cancers (majority CRC)]. The limited data available indicate that CEUS alone may be adequate to rule out liver metastases in patients with known primary malignancies.

The primary outcome measure reported by studies conducted in patients with incidentally detected FLLs was test accuracy for the differentiation of malignant from benign liver lesions. Studies used arterial enhancement followed by portal venous washout to define a positive test for primary liver cancer (HCC) and peripheral rim enhancement to define a positive test for liver metastases; these criteria are consistent with those defined in the EFSUMB guidelines on the use of CEUS<sup>6</sup> (see *Table 1*). All studies reported no significant difference in the accuracy of CEUS and CECT or CEMRI for the characterisation of focal FLLs. All but one study reported data for one lesion per patient and the remaining study reported data for 694 lesions in 686 patients; data were therefore treated as per patient. The pooled estimates of sensitivity for the detection of 'any liver malignancy' were approximately 95% for both CEUS and CECT and the pooled estimates of specificity were 94% and 93%, respectively, based on data from four studies. The single study comparing CEUS with CEMRI used Gd-CEMRI in all patients, with the addition of SPIO-CEMRI in an unspecified number of cases, and reported sensitivity estimates of 91% and 82%, respectively, and specificity estimates of 67% and 63% respectively. Data from one study indicated that combined imaging using both CEUS and CECT, in which a positive result on either modality was treated as 'test positive', did not increase sensitivity. High estimates of sensitivity indicate that CEUS alone may be adequate to rule out liver malignancy in this population.

Two Chinese-language studies compared imaging modalities for the assessment of response to treatment (cryosurgery and non-surgical treatment) in patients with HCC. One study compared CEUS and CECT in the same patients and the other compared CEUS and CECT or CEMRI. All sensitivity estimates were  $>95\%$  and all specificity estimates were  $>80\%$ . These very limited data indicate that CEUS may provide information on response in patients treated for HCC. However, these data are very limited and may not be directly applicable to UK clinical practice; further studies, ideally conducted in a UK setting, are required to confirm findings.

One controlled clinical trial indicated that the inclusion of CEUS in pretreatment imaging protocols for patients undergoing RFA for HCC may result in reduced incidence of disease progression, new HCC and repeat RFA, and increased local progression- and new tumour-free survival compared with unenhanced US. However, no difference was found in the primary outcome, successful ablation. High-quality RCTs are needed to determine the relative effectiveness of different imaging strategies for treatment planning.

## Chapter 4 Assessment of cost-effectiveness

### Search strategy

Searches were undertaken to identify cost-effectiveness studies of US, MRI and CT in the diagnosis of liver cancer. As with the clinical effectiveness searching, the main EMBASE strategy for each set of searches was independently peer reviewed by a second information specialist using the PRESS EBC checklist.<sup>21</sup> Search strategies were developed specifically for each database and searches took into account generic and other product names for the intervention. No restrictions on language or publication status were applied. Limits were applied to remove animal studies. Full search strategies are reported in *Appendix 1*.

The following databases were searched for relevant studies from 2000 to October/November 2011:

- MEDLINE (2000–September 2011 Week 4) (OvidSP)
- MEDLINE In-Process & Other Non-Indexed Citations and Daily Update (2000–10 October 2011) (OvidSP)
- EMBASE (2000–11 Week 40) (OvidSP)
- NHS Economic Evaluation Database (NHS EED) (2000–11) (via The Cochrane Library)
- NHS EED (1 January 2011–12 October 2011) (CRD website)
- Health Economic Evaluations Database (HEED) (2000–12 October 2011) (Wiley) (<http://onlinelibrary.wiley.com/book/10.1002/9780470510933>)
- SCI (2000–7 October 2011) (Web of Science).

Supplementary searches on FLLs and liver cancers were undertaken on the following resources to identify guidelines and guidance:

- National Guidelines Clearinghouse (NGC) (2005–10 November 2011) ([www.guideline.gov/](http://www.guideline.gov/))
- Guidelines International Network (GIN) (2005–10 November 2011) ([www.g-i-n.net](http://www.g-i-n.net))
- NICE guidance (up to 10 November 2011) (<http://guidance.nice.org.uk/>)
- TRIP database (limited to guidelines) (2005–10 November 2011) ([www.tripdatabase.com/](http://www.tripdatabase.com/))
- HTA database (2005–10 November 2011) (CRD website).

Identified references were downloaded in EndNote X4 software for further assessment and handling.

References in retrieved articles were checked for additional studies.

### Review of economic analyses of SonoVue

A total of 1194 titles and abstracts were screened from which 40 papers were selected. After full-paper screening 36 studies were excluded and four that met the inclusion criteria were included. A summary of each of these studies is provided in *Table 13*, with a quality checklist based on Drummond and Jefferson<sup>63</sup> provided in *Table 14*.

Faccioli *et al.*<sup>64</sup> developed a decision model to assess the costs of testing for benign FLLs after the introduction of CEUS. In total, 398 benign FLL patients (angiomas, focal nodular hyperplasias and pseudolesions) with suspicious lesions at baseline US from the radiology department of a hospital in Italy between 2002 and 2005 were reviewed and entered into the model. All lesions underwent CEUS and 98 also underwent CT. The average follow-up was 22 months and none of the CEUS diagnoses changed during the follow-up.



TABLE 13 Summary of economic studies

Study details	Faccioli 2007 <sup>64</sup>	Romanini 2007 <sup>66</sup>	Sangiovanni 2010 <sup>47</sup>	Şirli 2010 <sup>67</sup>	Zaim 2011 <sup>68</sup>
Time horizon	NA	NA	NA	NA	24 months
Objective	To perform a cost analysis of CEUS in the study of benign FLLs with intermediate appearance on US	To evaluate the clinical and economic consequences of the introduction of CEUS into the diagnostic clinical algorithm for the characterisation of incidental FLLs	To assess the sensitivity, specificity, diagnostic accuracy and economic impact of all possible sequential combinations of contrast imaging techniques in patients with cirrhosis with 1- to 2-cm liver nodules undergoing US surveillance	To evaluate if CEUS is a cost-efficient method for the first-line examination for FLL characterisation	To evaluate the cost-effectiveness of the application of CEUS as a diagnostic imaging technique in the first-line characterisation of FLLs in the Netherlands
Source of effectiveness information/testing accuracy data	398 benign FLL patients between 2002 and 2005	Consecutive patients with FLLs presenting from January 2002 to October 2005 (575 FLLs)	64 patients with 67 de novo liver nodules	316 FLLs were included in the CEUS evaluation performed during a 6-month period	170 prospectively enrolled patients > 18 years were included in a single-centre study at EMC
Comparators	<ul style="list-style-type: none"> <li>US → CEUS → (when inconclusive) MRI/CT</li> </ul>	<ul style="list-style-type: none"> <li>US → CEUS → (if inconclusive) CECT/CEMRI</li> <li>US → CECT/CEMRI → (if inconclusive) CEMRI</li> </ul>	<p>AASLD approach:</p> <ul style="list-style-type: none"> <li>CEUS and CT → (when inconclusive) MRI → (if required) FNB</li> <li>CEUS and MRI → (when inconclusive) CT → (if required) FNB</li> <li>CT and MRI → (when inconclusive) CEUS → (if required) FNB</li> </ul> <p>Study criteria approach:</p> <ul style="list-style-type: none"> <li>CEUS → (when inconclusive) CT → (when inconclusive) MRI → (if required) FNB</li> <li>CEUS → (when inconclusive) MRI → (when inconclusive) CT → (if required) FNB</li> <li>CT → (when inconclusive) CEUS → (when inconclusive) MRI → (if required) FNB</li> <li>CT → (when inconclusive) MRI → (when inconclusive) CEUS → (if required) FNB</li> <li>MRI → (when inconclusive) CEUS → (when inconclusive) CT → (if required) FNB</li> </ul>	<ul style="list-style-type: none"> <li>CEUS → CECT (if the result is inconclusive)</li> <li>CEUS → CEMRI (if the result is inconclusive)</li> <li>CECT</li> <li>CEMRI</li> </ul>	<ul style="list-style-type: none"> <li>CEUS</li> <li>CEMRI</li> <li>CECT</li> <li>Reference standard</li> </ul>
Reference standard	NA	CECT/CEMRI	Histology following FNB	NA	Imaging (MRI/CT), biopsy/surgical specimens and clinical judgement

Study details	Faccioli 2007 <sup>64</sup>	Romanini 2007 <sup>66</sup>	Sangiovanni 2010 <sup>47</sup>	Şirli 2010 <sup>67</sup>	Zaim 2011 <sup>68</sup>
Unit costs	Source: Hospital administrative office, SIRM publication, <sup>65</sup> resource management service of this hospital	Source: NHS Italy and hospitals	Italian NHS	Source: Mean costs practised in Timisoara	Source: CVZ, Dutch tariffs and EMC <sup>69</sup> [all costs reported in 2009 were inflated to 2010 values using the Centraal Bureau voor de Statistiek (CBS) website: www.cbs.nl]
Measure of benefit	Measured by the amount of money saved	Measured by the amount of money saved	Measured by the amount of money saved	Measured by the amount of money saved	Life-year gained
Study type	Cost analysis	Cost analysis	Cost analysis	Cost comparison study (prospective study)	Cost-effectiveness study
Model assumptions	NA	NA	NA	NA	The costs and effectiveness calculation for metastatic patients does not include secondary sites Patients belonging to the benign group assumed to have the same life expectancy It was assumed that the time horizon does not capture patients undergoing liver transplantation; only screening for liver transplantation was included in the analysis All treatment, follow-up and non-follow-up costs and probabilities were assumed based on the reference standard
Perspective	Radiology department of this hospital	NHS and hospitals in Italy	Italian NHS	NA	Hospital in the Netherlands
Discount rate	NA	NA	NA	NA	Costs 4%, effects 1.5%
Uncertainty around cost-effectiveness ratio expressed	NA	NA	NA	NA	CEUS strategy was cost-effective at a threshold of 20,000 euros per life-year in 90% of the simulation; MRI/CT strategy was cost-effective at a threshold of 20,000 euros per life-year in 10% of the simulation

continued

TABLE 13 Summary of economic studies (continued)

Study details	Faccioli 2007 <sup>64</sup>	Romanini 2007 <sup>66</sup>	Sangiovanni 2010 <sup>47</sup>	Şirdi 2010 <sup>67</sup>	Zaim 2011 <sup>68</sup>
Sensitivity analysis	NA	NA	NA	NA	Resource use and unit cost data were tested by varying the costs by ±30% of the mean
Outcome (cost and life-years per QALY) per comparator	Total cost saving from 2002 to 2005: 47,055.33 euros	<p>NHS:</p> <ul style="list-style-type: none"> <li>US → CT/MRI: 134,576.60 euros</li> <li>US → CEUS: 55,674.30 euros</li> </ul> <p>Hospitals:</p> <ul style="list-style-type: none"> <li>US → CT/MRI: 147,045 euros</li> <li>US → CEUS: 61,979 euros</li> </ul>	<p>AASLD approach:</p> <ul style="list-style-type: none"> <li>CEUS and CT → (when inconclusive) MRI → (if required) FNB: 26,440 euros (479 euros per patient)</li> <li>CEUS and MRI → (when inconclusive) CT → (if required) FNB: 30,922 euros (558 euros per patient)</li> <li>CT and MRI → (when inconclusive) CEUS → (if required) FNB: 33,898 euros (623 euros per patient)</li> </ul> <p>Study criteria approach:</p> <ul style="list-style-type: none"> <li>CEUS → (when inconclusive) CT → (when inconclusive) MRI → (if required) FNB: 28,667 euros (535 euros per patient)</li> <li>CEUS → (when inconclusive) MRI → (when inconclusive) CT → (if required) FNB: 30,215 euros (545 euros per patient)</li> <li>CT → (when inconclusive) CEUS → (when inconclusive) MRI → (if required) FNB: 28,909 euros (544 euros per patient)</li> <li>CT → (when inconclusive) MRI → (when inconclusive) CEUS → (if required) FNB: 29,346 euros (553 euros per patient)</li> <li>MRI → (when inconclusive) CEUS → (when inconclusive) CT → (if required) FNB: 30,970 euros (580 euros per patient)</li> <li>MRI → (when inconclusive) CT → (when inconclusive) CEUS → (if required) FNB: 30,607 euros (577 euros per patient)</li> </ul>	<p>NA</p> <ul style="list-style-type: none"> <li>CEUS first line + CT second line = 75,690 RON</li> <li>CEUS first line + MRI second line = 99,780 RON</li> <li>CT first line: 90,060 RON</li> <li>MRI first line: 205,400 RON</li> </ul>	<ul style="list-style-type: none"> <li>Total discounted per-patient cost of CEUS: 8309 euros</li> <li>Total discounted per-patient costs with MRI/CT = 8761 euros</li> <li>Total discounted per-patient life-years for CEUS: 1.538</li> <li>Total discounted per-patient life-years for MRI/CT: 1.536</li> </ul>

Study details	Faccioli 2007 <sup>64</sup>	Romanini 2007 <sup>66</sup>	Sangiovanni 2010 <sup>47</sup>	Şirli 2010 <sup>67</sup>	Zaim 2011 <sup>68</sup>
Summary of incremental analysis	Equivalent to 118.23 euros saving per person	Total saving for the NHS: 78,902 euros (162.70 euros per patient) Total saving for hospitals: 85,065.96 euros (175.39 euros per patient)			Incremental per-patient cost for CEUS was estimated to be -452 euros (-160 euros for the diagnostic phase and -292 euros for the treatment phase)
NA, not available; QALY, quality-adjusted life-year.					

TABLE 14 Economic study quality checklist

	Faccioli 2007 <sup>64</sup>	Romanini 2007 <sup>66</sup>	Sangiovanni 2011 <sup>47</sup>	Şirli 2010 <sup>67</sup>	Zaim 2011 <sup>68</sup>
<b>Study design</b>					
The research question is stated	✓	✓	✓	✓	✓
The economic importance of the research question is stated	✓	✓	✓	✓	✓
The viewpoint(s) of the analysis are clearly stated and justified	✗	✓	✓	✗	✓
The rationale for choosing alternative programmes or interventions compared is stated	✓	✓	✓	✓	✓
The alternatives being compared are clearly described	✓	✓	✓	✓	✓
The form of economic evaluation used is stated	✓	✓	✓	✓	✓
The choice of form of economic evaluation is justified in relation to the questions addressed	✓	✓	✓	✓	✓
<b>Data collection</b>					
The source(s) of effectiveness estimates used are stated	✓	✓	✓	✓	✗
Details of the design and results of the effectiveness study are given (if based on a single study)	✓	✓	✓	✓	✗
Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies)	NA	NA	NA	NA	NA
The primary outcome measure(s) for the economic evaluation are clearly stated	✓	✓	✓	✓	✓
Methods-to-value benefits are stated	✓	✓	✓	✓	✗
Details of the subjects from whom valuations were obtained are given	✓	✓	✓	✓	✓
Productivity changes (if included) are reported separately	NA	NA	NA	NA	NA
The relevance of productivity changes to the study question is discussed	✗	✗	✗	✗	✗
Quantities of resource use are reported separately from their unit costs	✓	✗	✓	✓	✗
Methods for the estimation of quantities and unit costs are described	✓	✗	✓	✗	✗
Currency and price data are recorded	✓	✓	✓	✓	✓
Details of currency of price adjustments for inflation or currency conversion are given	✗	✗	✗	✗	✓
Details of any model used are given	NA	NA	NA	NA	NA
The choice of model used and the key parameters on which it is based are justified	✓	✓	✓	✓	✓
<b>Analysis and interpretation of results</b>					
Time horizon of costs and benefits is stated	✓	✓	✓	✓	✓
The discount rate(s) is stated	✗	✗	✗	✗	✓
The choice of discount rate(s) is justified	✗	✗	✗	✗	✓
An explanation is given if costs and benefits are not discounted	✗	✗	✗	✗	NA

TABLE 14 Economic study quality checklist (continued)

	Faccioli 2007 <sup>64</sup>	Romanini 2007 <sup>66</sup>	Sangiovanni 2011 <sup>47</sup>	Şirli 2010 <sup>67</sup>	Zaim 2011 <sup>68</sup>
Details of statistical tests and CIs are given for stochastic data	✘	✘	✓	✘	✘
The approach to sensitivity analysis is given	NA	NA	NA	NA	✓
The choice of variables for sensitivity analysis is justified	NA	NA	NA	NA	✘
The ranges over which the variables are varied are justified	NA	NA	NA	NA	✘
Relevant alternatives are compared	✓	✓	✓	✓	✓
Incremental analysis is reported	✓	✓	✘	✓	✓
Major outcomes are presented in a disaggregated as well as aggregated form	✓	✓	✓	✓	✓
The answer to the study question is given	✓	✓	✓	✓	✓
Conclusions follow from the data reported	✓	✓	✓	✓	✓
Conclusions are accompanied by the appropriate caveats	✓	✓	✓	✓	✓

✓, yes; ✘, no; NA, not available.

Equipment costs (purchase and service contract costs), agents and related costs (contrast agents, saline solution, medical supplies and films) and human resource costs (radiologists, technicians, nurses and administrative staff) were evaluated within the model. The calculation of equipment costs was based on utilisation time per examination, considering both purchase price and depreciation; these were all obtained from the hospital administrative office with a constant annual depreciation rate. The costs of all medical staff and administrators (per minute) were derived from the Società Italiana di Radiologia Medica (SIRM) publication.<sup>65</sup> The formula for the 'total saving' calculation was  $CT \times n - [(CEUS - US) \times n]$ , with  $n$  representing the number of examinations. The cost year was 2006.

For each US examination, the total cost was 46.36 euros and disaggregated costs were 8.43 euros for equipment, 5.96 euros for agents and related costs and 31.97 euros for human resource costs. In each CEUS examination, equipment costs were 8.43 euros, agents and related costs were 43.04 euros and human resources were 50.04 euros, giving a total cost of 101.51 euros. For each CECT examination, the aggregate cost was 211.48 euros, calculated by summing 68.27 euros for equipment costs, 62.96 euros for agents and related costs and 80.25 euros for human resource costs. The total saving from replacing CEUS as the second-line diagnostic procedure for the 398 patients modelled was 47,055.33 euros.

Romanini *et al.*<sup>66</sup> conducted a multicentre prospective study to evaluate the economic and clinical outcomes after the introduction of CEUS in diagnostic procedures for incidentally detected FLLs. A total of 485 patients presenting with uncharacterised FLLs, without liver cirrhosis, were recruited into the study from January 2002 to October 2005. All patients underwent two diagnostic strategies, that is, patients were their own control group:

- US → CEUS → (if inconclusive) CECT/CEMRI
- US → CECT/CEMRI → (if inconclusive) CEMRI.

Cost items included diagnostic examinations, health-care professional time, pharmaceuticals, laboratory tests, medical devices and material for imaging. Reimbursement for baseline US was 51.13 euros, for CEUS was 76.13 euros, for CT with or without contrast agent was 164.75 euros and for MRI with or without contrast agent was 259.70 euros, according to a regional reimbursement price list. Other variable hospital costs were obtained from hospitals joining the study. From the Italian NHS perspective, the

conventional diagnostic pathway with CECT and CEMRI cost a total of 134,576.60 euros. A total saving of 78,902 euros could be made by adopting the CEUS strategy, that is, 162.70 euros per patient. From the hospitals' perspective, the total expenditure incurred by the conventional approach was 147,045 euros, compared with 61,979 euros using the CEUS strategy. The reimbursement to the hospital per person for the conventional strategy was 277 euros, 26 euros less than the original spending by the hospital; for the CEUS strategy the reimbursement agency paid only 114.79 euros to the hospital, 13 euros less than the original spending by the hospital.

Şirli *et al.*<sup>67</sup> conducted a prospective study in the Department of Gastroenterology and Hepatology in a hospital in Romania to evaluate the cost differences when CEUS replaced CECT/CEMRI as the first-line examination for FLL characterisation. All of the CEUS liver evaluations performed from September 2009 to March 2010 were included in the study. The cost of a CEUS positive diagnosis was compared with the cost of a CECT and/or CEMRI positive diagnosis. The cost of a CECT/CEUS examination was added when the CEUS result was inconclusive:

- CEUS → (when inconclusive) CECT
- CEUS → (when inconclusive) CEMRI
- CECT
- CEMRI.

Contrast-enhanced ultrasound provided a conclusive diagnosis for 250 of 316 FLLs; the remaining 66 required further imaging (CECT or CEMRI). Therefore, the total examination cost for CEUS followed by CECT when necessary was 75,690 Romanian new leu (RON) [180 RON (cost for single CEUS examination) × 316 + 285 RON (cost for single CECT examination) × 66]. The total cost following the second strategy was 99,780 RON [180 RON (cost for single CEUS examination) × 316 + 650 RON (cost for single CEMRI examination) × 66]. When using CECT only the total cost was 90,060 RON and when using CEMRI only the total cost was 205,400 RON. To sum up, by adopting CEUS for first-line FLL characterisation, the cost saving per person was 45.5 RON compared with CT as first line and 334.2 RON compared with MRI as first line.

Sangiovanni *et al.*<sup>47</sup> conducted a study to assess the diagnostic accuracy and also the economic impact of all possible diagnostic strategy combinations in characterising FLLs (including only 1- to 2-cm lesions) in Italy. Compensated cirrhosis patients diagnosed with liver nodules under US surveillance were included in this study. All possible examinations [CT, MRI, CEUS and US-guided fine-needle biopsy (FNB)] were performed until a final diagnosis was obtained. The study assessed costs using two approaches. The first was in accordance with AASLD guidelines, with the final diagnosis of HCC needing concordant results from at least two imaging techniques; a third examination was recommended only when the previous two were discordant. FNB was performed only when the vascular pattern observed was different in the first two diagnostic procedures. The second approach was to perform a single scan and then perform subsequent scans if the result was inconclusive; although not stated, it appeared that FNB was performed only if all three scans were inconclusive.

The AASLD approach implied three possible permutations, that is:

- CEUS and CT → (when inconclusive) MRI → (if required) FNB
- CEUS and MRI → (when inconclusive) CT → (if required) FNB
- CT and MRI → (when inconclusive) CEUS → (if required) FNB.

The study criteria approach implied six possible permutations, that is:

- CEUS → (when inconclusive) CT → (when inconclusive) MRI → (if required) FNB
- CEUS → (when inconclusive) MRI → (when inconclusive) CT → (if required) FNB

- CT → (when inconclusive) CEUS → (when inconclusive) MRI → (if required) FNB
- CT → (when inconclusive) MRI → (when inconclusive) CEUS → (if required) FNB
- MRI → (when inconclusive) CEUS → (when inconclusive) CT → (if required) FNB
- MRI → (when inconclusive) CT → (when inconclusive) CEUS → (if required) FNB.

Following the AASLD guideline approach, CEUS + CT with MRI and FNB when required was considered the cheapest combination, with a total aggregate cost of 26,440 euros, equivalent to 479 euros per person. This strategy was 79 euros cheaper per person than CEUS + MRI → CT → FNB and 144 euros cheaper per person than CT + MRI → CEUS → FNB. The most inexpensive strategy using the study criteria approach was CEUS → CT → MRI → FNB: 535 euros per person, within the range of 9–45 euros cheaper than the rest of the strategies.

The study conducted by Zaim *et al.*<sup>68</sup> assessed cost-effectiveness when CEUS was applied as the second-line imaging technique in FLL characterisation. Patients with a FLL diagnosis were recruited between January 2009 and June 2010 in a medical centre in the Netherlands. All participants had at least one baseline US and received both the conventional imaging strategy, which was US, followed by MRI or CT, and CEUS. Those diagnosed with benign lesions underwent a minimum of 6 months of follow-up. Those with malignant lesions underwent curative or palliative treatments. Costs included costs of diagnostic techniques (US, CEUS, CT, MRI, laboratory tests and liver biopsy), surgical resection, intensive care stays, hospitalisation, outpatient visits and various treatment strategies (RFA, TACE, chemotherapy, palliative care and liver transplantation). All unit prices were based on Farmacotherapeutisch Kompas (CVZ) and Dutch tariffs and Erasmus Medical Centre (EMC) data at the 2010 rate.<sup>69</sup> The time horizon was 24 months with a 1.5% discount rate for health outcomes and 4% for costs. Deterministic and probabilistic sensitivity analyses were performed in the study. The discounted cost per patient undergoing CEUS was 8309 euros; this was less than that for patients following the conventional strategy, which was 8761 euros per person. The aggregate cost saving was 452 euros per person, of which 160 euros constituted the diagnostic phase and 292 euros the treatment phase. Total discounted life-years gained per patient were 1.538 for the CEUS strategy and 1.536 for the conventional strategy. The results of the probabilistic sensitivity analyses indicated that, when the cost-effectiveness threshold was 20,000 euros per life-year, the CEUS strategy was cost-effective in 90% of the simulation and the MRI/CT strategy was cost-effective in only 10% of the simulation.

Although all of the studies were of reasonably good quality, they did not fully address our research question. Limitations included restricted information about disease management and progression, choice of equipment and administrative procedures in different settings, inclusion of costing elements in the calculation and health outcomes. Zaim *et al.*<sup>68</sup> was the only paper that modelled disease management and reported relevant health outcomes; however, the follow-up lasted only 24 months.

## Model structure and methodology

The aim of the health economic analysis was to investigate the cost-effectiveness of CEUS using the contrast agent SonoVue for the assessment of adults with FFLs in whom unenhanced US or other liver imaging is inconclusive. In the analysis we focused on the clinical applications for which the most data on test performance were available (see previous chapters) and for which we are most likely to see a clinical benefit from the use of CEUS. Therefore, the health economic analysis assessed 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 FLLs.



The comparators included the following liver imaging techniques:

- CECT
- Gd-CEMRI
- SPIO-CEMRI.

Three separate models were used to assess the cost-effectiveness of CEUS using the contrast agent SonoVue in the populations specified above:

- a cirrhosis surveillance model
- a liver metastases of CRC model
- an incidentally detected FLL model.

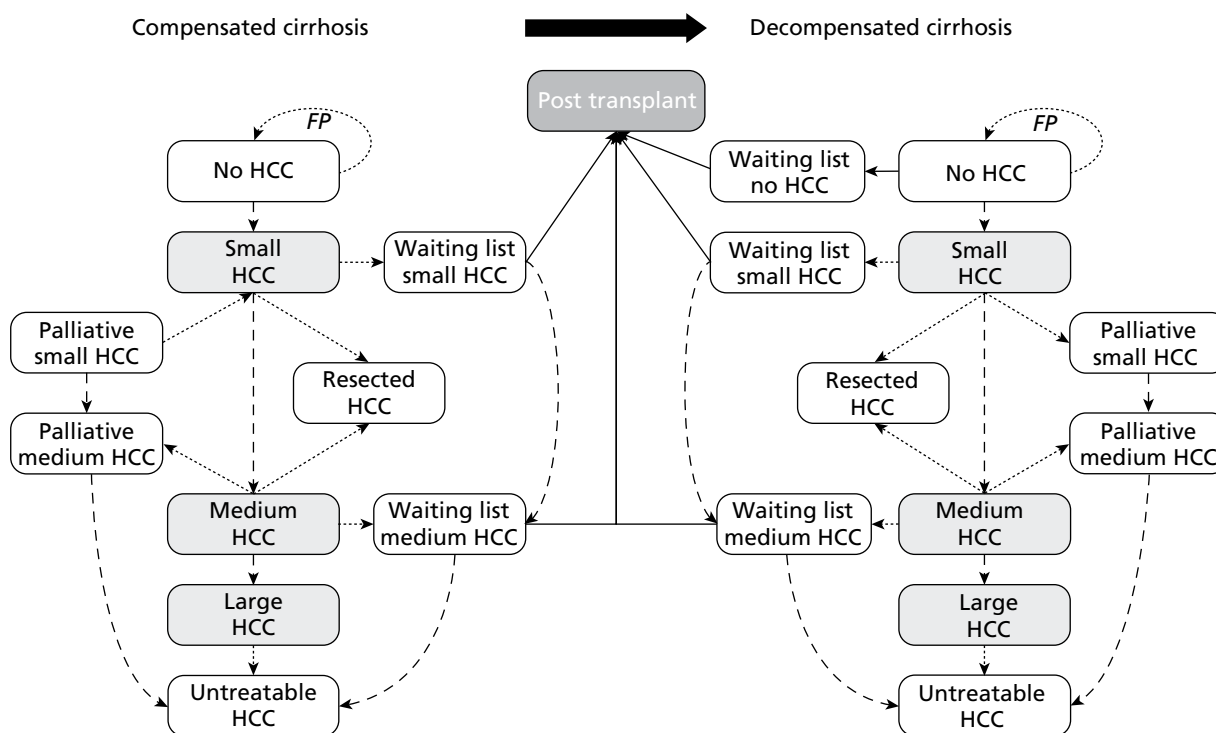
In all models the mean costs and life-years and quality-adjusted life-years (QALYs) gained per patient were calculated for each comparator. Costs and benefits were discounted at 3.5%. The three models are described in detail in the following sections.

### *Cirrhosis surveillance model*

The cirrhosis surveillance model is 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).<sup>70</sup> This model was developed to assess the cost-effectiveness of several surveillance strategies in cirrhotic patients to identify HCC, using periodic serum AFP testing and/or liver US examination with CT as a confirmatory imaging technique, followed by treatment with liver transplantation or resection when appropriate. One of the research recommendations made by the authors was to assess the value of CEUS in surveillance strategies for cirrhotic patients. For the assessment of the value of CEUS in cirrhosis surveillance, this model required adaptation, because it did not allow for a confirmatory test with less than perfect accuracy. Also, the original model did not allow the comparison of different confirmatory tests.

The population of interest in the cirrhosis surveillance model in this assessment consisted of those with a diagnosis of compensated cirrhosis deemed eligible to enter a surveillance programme [aged  $\leq 70$  years with no pre-existing medical conditions that would preclude treatment with a liver transplant or hepatic resection (including current alcohol or intravenous drug abuse)]. The model allowed separate analysis of each of three cirrhosis aetiologies: alcoholic liver disease (ALD), hepatitis B virus (HBV) and hepatitis C virus (HCV). In the base-case analysis, results were produced for a mixed cohort weighted according to the following proportions: 57.6% ALD, 7.3% HBV and 35.1% HCV (expert opinion; as in the PenTAG model<sup>70</sup>). A probabilistic state transition (Markov) cohort model, constructed using Excel (Microsoft Corporation, Redmond, WA, USA), was used. The time horizon was lifetime and the cycle duration was 1 month.

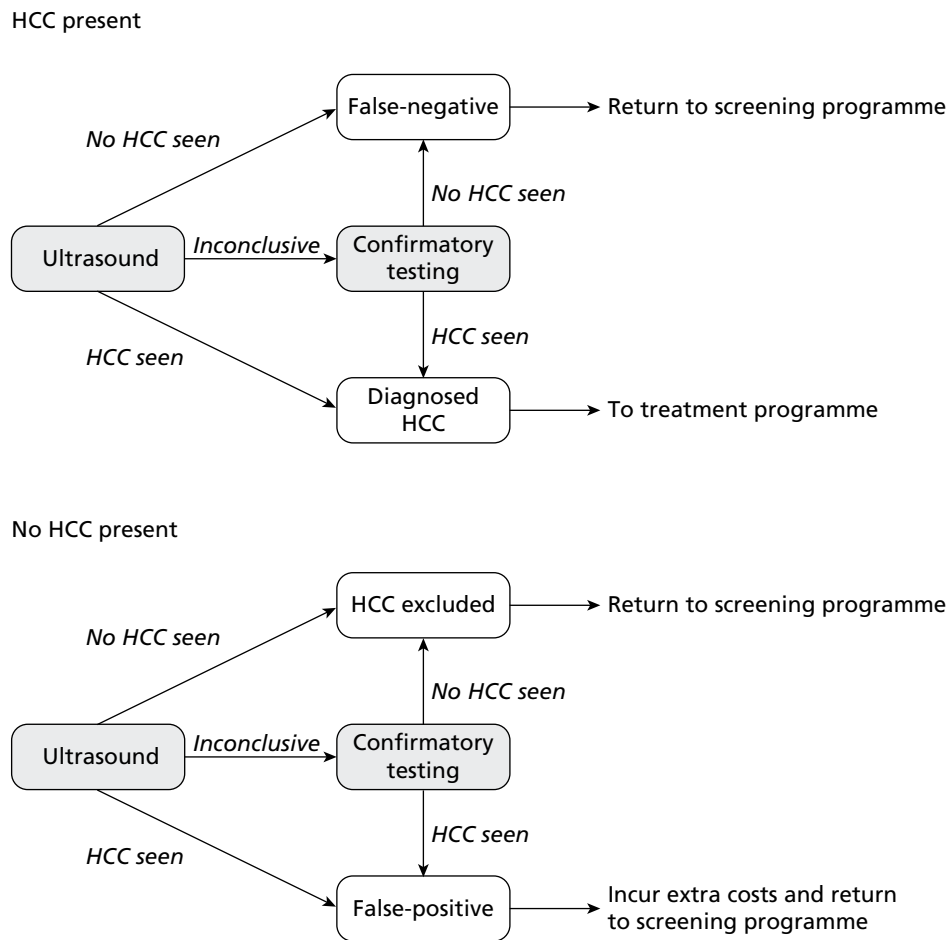
The model diagram is shown in *Figure 8*. States are shown as boxes and allowable state transitions are shown as arrows. The basis of the model was the disease process or 'natural history' of cirrhosis. Within the natural history model, a distinction was made between those with compensated and those with decompensated cirrhosis. Those with compensated cirrhosis can progress to decompensated cirrhosis, which is irreversible and associated with excess mortality, costs and quality of life decrements. The rate of incidence of HCC is the same in those with compensated and decompensated cirrhosis. HCC can be either diagnosed or occult. Three classes of tumours were distinguished: small tumours (<2 cm), medium tumours (2–5 cm) and large tumours (>5 cm). Tumour size was used as a surrogate measure of all characteristics of tumour progression. Hence, tumour progression was modelled by a tumour growth rate. Both test performance in identifying tumours and treatability of the tumour are dependent on the tumour size. For example, for larger tumours there is a greater likelihood of identification. Incidental/symptomatic presentation of HCC is possible for those with both compensated and decompensated cirrhosis, for all tumour sizes, although with significantly lower probabilities for small and medium-sized tumours.



**FIGURE 8** Model diagram for cirrhosis surveillance, based on Thomson Coon *et al.*<sup>70</sup> Each cycle all patients who are alive can stay in the same health state, die from non-HCC related causes, or move according to the shown transitions. Patients with compensated cirrhosis can decompensate, by moving to the corresponding decompensated cirrhosis health state. Patients who are palliative or untreatable can die from HCC. Light grey states represent occur HCC. Dotted lines represent detection of HCC after screening or showing symptoms; stacked lines represent tumour growth; solid lines represent transplant.

The surveillance programme and treatment components are superimposed onto the disease process. The technical performance of each testing strategy was modelled using decision trees. The testing strategies consisted of unenhanced US followed by CEUS, CECT, Gd-CEMRI or SPIO-CEMRI as a confirmatory imaging test. In the base-case analysis surveillance was every 6 months and stopped for people who reached the age of 70 years. It was also assumed that compliance was 100%. The decision trees are shown in *Figure 9*.

The treatments considered in the model are liver transplantation and liver resection. People can enter the transplant waiting list following diagnosis of either surgically treatable HCC or decompensated cirrhosis. There is no prioritisation of people waiting for a transplant. During the time on the waiting list people are subject to the same natural history process as during prelisting. There is no waiting list for liver resection for HCC. Some people are deemed unsuitable for surgical treatment, including those whose tumours are large or whose tumours become large while on the transplant waiting list. Small tumours are deemed more amenable to surgical treatment than medium-sized tumours. People who undergo successful liver transplant or resection enter a simplified disease process in which post-transplant or post-resection mortality, costs and utilities are taken into account. People with small and medium-sized tumours that are deemed to be surgically untreatable enter a series of states to model palliative care. Palliative care includes PEI, RFA and TACE and supportive care. Once people progress to untreatable large HCC, an excess mortality and associated costs and utilities are applied to reflect the palliation provided by TACE for a proportion of these people. An overview of the key structural assumptions is provided in the following section. A more detailed description of the model structure can be found in Thompson Coon *et al.*<sup>70</sup>



**FIGURE 9** Decision tree structure for the cirrhosis model. Note: The confirmatory tests are the comparators in this analysis: CEUS, CECT, Gd-CEMRI and SPIO-CEMRI.

### Summary of structural assumptions (adapted from Thompson Coon *et al.*<sup>70</sup>)

- All tumours are uninodular, with diameter used as a surrogate index of all characteristics of tumour progression.
- Progression from compensated to decompensated cirrhosis is irreversible.
- The rate of incidence of HCC is the same in compensated and decompensated livers.
- The presence of a HCC tumour has no direct effect on mortality until it becomes 'large', at which point it becomes symptomatic and is associated with an additional mortality rate.
- Incidental/symptomatic diagnosis is possible alongside all interventions, including 'no surveillance'.
- The ceiling age for surveillance is 70 years.
- In the base case there is 100% compliance with the surveillance programme.
- There is a small rate of false-positive diagnoses as a result of surveillance, all of which are assumed to be rapidly discovered before treatment, as both resection and transplant involve further diagnostic workup.
- There is no waiting list for liver resection.
- There is no prioritisation of people on the transplant waiting list.
- No ablative therapies are applied to patients on the transplant waiting list.
- Some people are deemed to have surgically untreatable tumours at the time of diagnosis of HCC.

### Liver metastases of colorectal cancer model

The CRC metastases model is a modified version of the metastatic model developed by Brush *et al.*<sup>71</sup> This model was developed to assess the cost-effectiveness of fluorodeoxyglucose positron emission tomography

(FDG-PET)/CT as an add-on device in detecting metastatic cancer compared with conventional imaging (CT). The model was adapted to assess the cost-effectiveness of CEUS compared with CECT, Gd-CEMRI and SPIO-CEMRI in detecting metastases from CRC after an inconclusive unenhanced US scan. In addition to changing the comparators in the model, we added the cost of a whole-body CT scan for all patients with a positive test to detect whether or not metastases at extra sites are present. We also changed the way that false-positives were handled, and changed the watch and wait strategy to correspond with latest guidance. The watch and wait strategy was given not only to patients without metastases but also to those patients treated and still alive. A final addition was that we assigned false-negatives poorer survival in the first year because they are not treated immediately. These adaptations are described in more detail below. A decision tree combined with a probabilistic state transition (Markov) cohort model, constructed using Excel, was used. The time horizon was lifetime and the cycle duration was 1 year.

Figure 10 depicts the decision tree structure used for the metastases model. Patients who had previously had surgical treatment for primary CRC and in a routine follow-up assessment (involving a clinical examination and CEA testing) were found to have rising CEA levels and were identified as potentially having a metastatic recurrence received an unenhanced abdominal US scan. When this US scan was deemed inconclusive, the patient entered the decision tree and could receive CEUS, CECT, Gd-CEMRI or SPIO-CEMRI. Similar to the Brush *et al.* model,<sup>71</sup> the decision tree splits the patient population according to true disease status (metastatic recurrence or no metastatic recurrence) before applying the DTA estimates, so that accurate and inaccurate diagnoses can be identified.

In this model, imaging (CEUS, CECT, Gd-CEMRI or SPIO-CEMR) will identify either metastases (test positive) or no metastases (test negative). After a positive test, patients receive a whole-body CECT scan to identify whether there are metastases at one site or at multiple sites. In the base case it was assumed that all patients in the model receive a biopsy to confirm the metastases before treatment, and it was assumed that biopsy is 100% accurate. Thus, in contrast to the Brush *et al.* model,<sup>71</sup> patients with a false-positive test result will not receive treatment. Patients with a positive biopsy (true-positives) receive treatment. In line with Brush *et al.*<sup>71</sup> it was assumed that all patients with metastases at a single site will receive preoperative chemotherapy and surgery for metastases, and that patients with metastases at multiple sites are assumed to be non-curable and will receive either preoperative chemotherapy followed by surgery and palliative care, or chemotherapy and palliative care. In line with the Brush *et al.* model, patients with a negative test result are followed up in a watch and wait strategy for 3 years. Also in line with the Brush *et al.* model, for patients who are inaccurately diagnosed as having no metastases (false-negatives), the true diagnosis is assumed to be identified within a year if the patient is still alive. These metastases can be detected during scans in the watch and wait strategy or because the patient becomes symptomatic. This delayed detection involves a second scan (CEUS, CECT, Gd-CEMRI or SPIO-CEMRI, depending on the comparator), a whole-body CT and a biopsy.

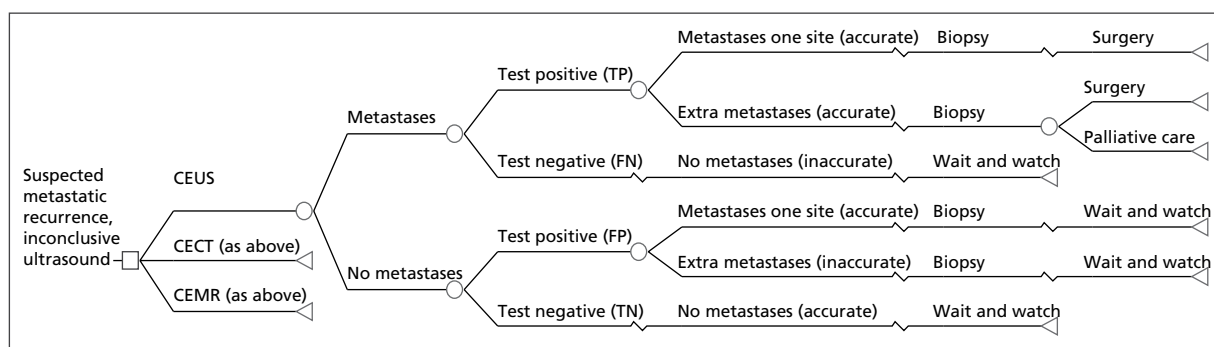


FIGURE 10 Decision tree structure for the liver metastases from CRC model.

After the decision tree phase, a state transition (Markov) model was used to follow up the patients (*Figure 11*). After the second year, when every patient is correctly diagnosed, patients can either stay in their health state or die. In the first 3 years, patients without metastases and those who were treated were assumed to be followed up using the watch and wait strategy.

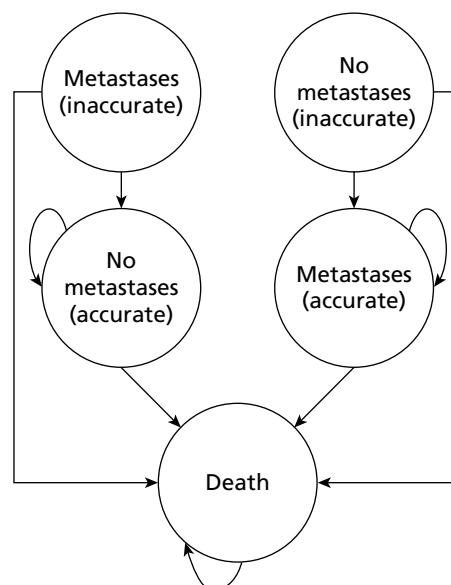
### Summary of structural assumptions

- For patients who are inaccurately diagnosed as having no metastases, the true diagnosis is identified within a year if the patient is still alive, either through regular tests in the watch and wait strategy or because the metastases become symptomatic.
- All patients with a positive test result receive a whole-body CT scan to identify whether or not metastases are present at multiple sites. This scan does not detect inaccuracies of the previous (positive) test.
- Patients who are inaccurately diagnosed as having metastases receive a biopsy and are therefore not treated for their metastases.
- All patients with metastases at a single site will receive preoperative chemotherapy and metastatic surgery.
- Patients with both hepatic and extrahepatic metastases are assumed to be non-curable and will receive one of two treatment options: preoperative chemotherapy followed by metastatic surgery and palliative care or chemotherapy and palliative care.
- All patients identified as having no metastatic recurrence, as well as patients who have been treated for their metastases, would be treated with a watch and wait strategy in which they would be followed up annually for 3 years.
- If there are no metastases at baseline, metastases will not occur. The watch and wait strategy is used to detect local recurrences and these are not incorporated in the model.

### *Incidentally detected focal liver lesion model*

Patients with incidentally detected FLLs can have a variety of diseases, ranging from malignant lesions such as HCC and metastases to different types of benign lesions. *Figure 12* illustrates the different combinations of test results and lesion types. The choice of lesion categories was based on similarities and differences in treatments, costs and prognosis.

The prognosis, costs and QALYs seen among patients diagnosed with HCC were modelled using the cirrhosis model, whereas the prognosis, costs and QALYs among patients with liver metastases were

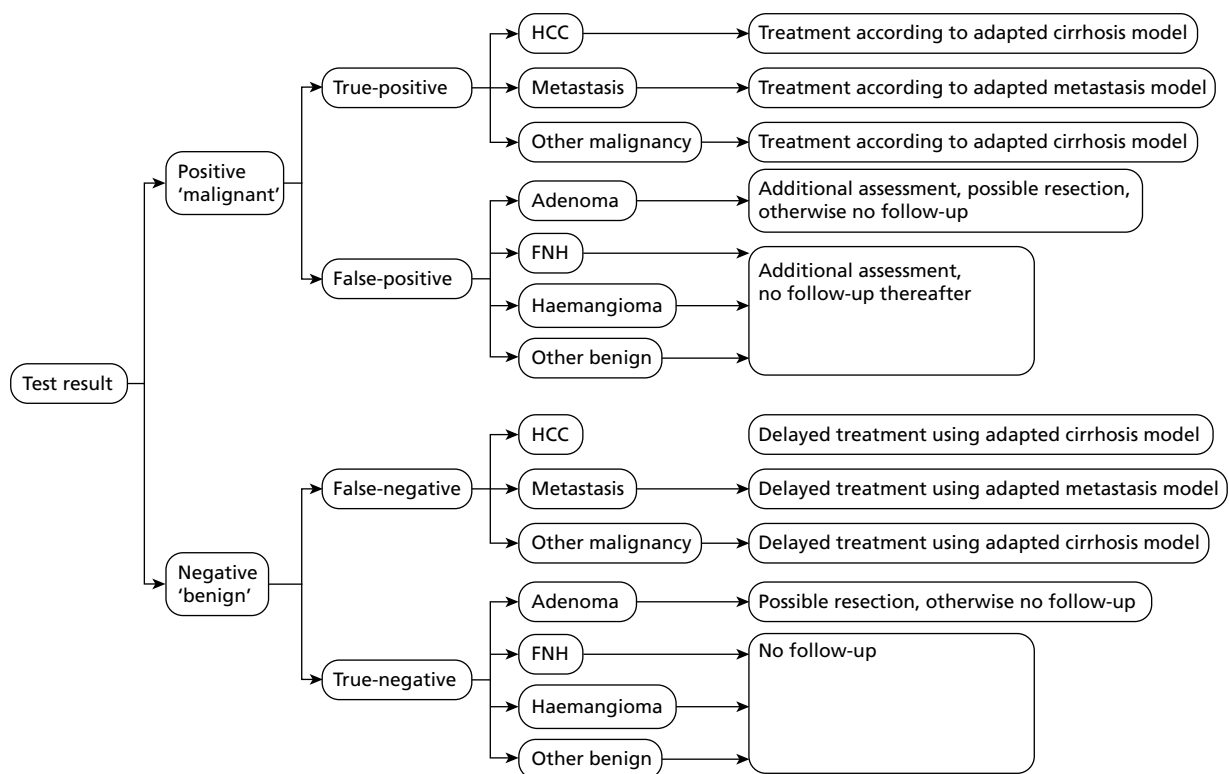


**FIGURE 11** Simplified schematic diagram of the Markov model for follow-up of patients in the CRC metastases model.

modelled using the liver metastases model. The incidentally detected FLL model therefore incorporated elements of the cirrhosis model and elements of the liver metastases model as well as some new elements. The cirrhosis model required adjustments before it could be incorporated into these analyses. One important issue related to when HCC is diagnosed. In particular, although none of the patients in the cirrhosis surveillance model has HCC at the start of the simulation, all HCC patients in the incidentally detected FLL model will have HCC at the start of the simulation.

The economic and health consequences of false-positive and false-negative results were modelled in the following ways. First, it was assumed that patients with HCC who were not correctly identified at baseline would be correctly diagnosed within several months, as essentially all of these patients will have important risk factors (e.g. alcohol misuse, newly diagnosed cirrhosis or hepatitis) that are identified at baseline. Patients with a false-positive diagnosis (in particular, patients with a benign tumour that was misclassified as a malignant tumour) were assumed to undergo one additional follow-up consult as a result of this misclassification. This was viewed as a conservative assumption that would bias the assessment against CEUS and in favour of the comparators (CECT, CEMRI), as a false-positive result might lead to even greater costs than the cost of simply one extra visit and as CEUS was found to have a lower rate of false-positives in the DTA studies.

The costs, life-years and QALYs for patients having a malignancy other than HCC or metastases were assumed to be equal to those for HCC patients (see *Figure 12*). These other types of malignant lesions (e.g. lymphoma) were infrequently seen among patients with an incidentally detected FLL and the studies comparing CEUS with CECT or CEMRI provided little information about these lesions. Given the heterogeneity in costs and QALYs within this group (and even among patients with the same malignancy), we chose to set the base-case values to the costs and QALYs seen with HCC patients and emphasise that this was an assumption. However, it was known in advance that the costs and QALYs of these patients would have a limited effect on the cost-effectiveness of CEUS compared with the comparators for two reasons: the values for the sensitivity of CEUS and the comparators were very similar and the prior



**FIGURE 12** Description of patient categories and their treatments used in the incidentally detected FLL model.

probability of other malignancies was small. In fact, the only possible way in which the values for costs and QALYs of other malignancies could have any effect on the overall cost-effectiveness was if the costs and QALYs changed dramatically if the malignancy were to be incorrectly classified as a benign lesion (i.e. a false-negative test result). The impact of this false-negative effect was therefore examined using sensitivity analysis.

### Summary of structural assumptions made in the incidentally detected focal liver lesion model

- Patients with HCC have a small HCC lesion and compensated cirrhosis at the time of assessment. The cirrhosis surveillance model made it possible to explore the impact of assuming that these patients have a medium lesion and compensated cirrhosis at the time of assessment, and the costs and QALYs associated with this alternative were used in a sensitivity analysis.
- Patients with HCC who are incorrectly diagnosed at baseline will be correctly diagnosed later (within several months). This is assumed because these patients will be followed up because of the presence of some of the risk factors known to result in HCC (e.g. history of alcohol misuse, hepatitis B or C).
- Patients diagnosed with an apparently benign lesion do not undergo treatment unless they have a (hepatic) adenoma, in which case they may undergo a resection.
- The mean costs and health outcomes of patients with incidentally detected FLLs that are metastatic can be estimated using the model for liver metastases from CRC, because the highest proportion of liver metastases will originate from CRC. For example, Catala *et al.*<sup>52</sup> reported that 7 of the 12 patients with metastases in their study had CRC, and this corresponds with findings elsewhere in the literature as well as frequencies reported by one of the clinicians queried during this study.

## Model parameters

### Cirrhosis surveillance model

#### Test performance

It was assumed that the surveillance strategy started with unenhanced US. The test performance of US used in the model was based on the study by Bennett *et al.*,<sup>72</sup> as used in the HTA report by Thompson Coon *et al.*<sup>70</sup> (Table 15). This study was preferred over other studies because it distinguished between small, medium and large tumours and had a relatively large sample size ( $n = 200$ ).

Additional imaging takes place following an inconclusive unenhanced US scan. The percentage of unenhanced US examinations that are inconclusive was estimated to be 43%, based on information provided by the manufacturer of SonoVue during the scoping phase of this assessment.

**TABLE 15** Test performance of US used in the decision trees for the cirrhosis surveillance model

Parameter		Value	Distribution <sup>a</sup>	TP	FN	FP	TN
Sensitivity for identifying tumours	Small	0.11	Dirichlet	3	25	6	118
	Medium	0.29	Dirichlet	2	5	0	2
	Large	0.75	Dirichlet	3	1	0	0
False-positive rate	US	0.04	Dirichlet	See data used to model sensitivity			

FN, false-negative; FP, false-positive; TN, true-negative; TP, true-positive.

a The Dirichlet distribution is the multivariate generalisation of the beta distribution. The parameters of the distribution are the observed test results (TP, FP, FN, TN), presented in the table.

Source: based on Bennett *et al.*<sup>72</sup>

In the systematic review seven studies<sup>42,43–46,48,61</sup> that compared CEUS with at least one of the comparators (CECT, Gd-CEMRI or SPIO-CEMR) for the characterisation of FLLs detected during routine surveillance of cirrhotic patients were identified. In the base-case analysis the probability of identifying a HCC, as well as the proportion of people with a false-positive test result, was taken from the study by Leoni *et al.*<sup>42</sup> (Table 16). The main reason for using this study was that it used diagnostic criteria matching the EFSUMB guidance on the use of CEUS,<sup>6</sup> and reported data on the performance of CEUS, CECT and Gd-CEMRI in the same population, whereas most other studies compared CEUS with either CECT or CEMRI. A potential disadvantage of the Leoni *et al.* study was that it used a suboptimal reference standard (concordance between at least two imaging test results) for the majority of patients. Leoni *et al.* also reported accuracy data for SPIO-CEMRI, which were not incorporated in the base-case analysis. The study included patients with liver lesions between 1 and 3 cm; therefore, in the base case we used these results to model the diagnostic accuracy for both small (<2 cm) and medium-sized (2–5 cm) tumours. The sensitivity for the identification of large HCCs was assumed to be 100% for all confirmatory imaging tests and this assumption was agreed by the clinical experts.

### Transition probabilities

The transition probabilities were all taken from the cirrhosis surveillance model reported in Thompson Coon *et al.*<sup>70</sup> A detailed description of the estimates of the transition probabilities can be found in this HTA report. An overview of the parameters used in the model that affect transition probabilities is provided in Table 17.

### Costs

The cost of CEUS (in addition to unenhanced US) was based on expert opinion, both from clinicians and the manufacturer. The cost of the contrast was assumed to be £48.70 (estimate supplied by the manufacturer and agreed by clinicians). This cost includes the cost of cannulation. In addition, we expected CEUS to take more time than the unenhanced US scan. Therefore, we used the difference between the reference cost of an US scan of <20 minutes (£55) and the reference cost of an US scan of >20 minutes (£71) as the additional time cost of CEUS.<sup>84</sup> The total additional costs of CEUS were therefore estimated to be £65. This implies that CEUS is performed in the same appointment as the unenhanced US scan. The costs of the other diagnostic tests, outpatient appointments, orthotopic liver transplantation (OLT) and resection were based on NHS reference costs (NHSRC).<sup>84</sup>

All other cost inputs were based on Thompson Coon *et al.*,<sup>70</sup> recalculated to the 2011 price level.<sup>85</sup> A detailed description of these costs can be found in this HTA report.<sup>70</sup> The parameters used in the model affecting costs are listed in Table 18.

**TABLE 16** Test performance of confirmatory imaging used in the decision tree for the cirrhosis surveillance model

Parameter		Value	Distribution <sup>a</sup>	TP	FN	FP	TN
Sensitivity for identifying small and medium tumours	CEUS	0.67	Dirichlet	37	18	2	18
	CECT	0.67	Dirichlet	37	18	2	18
	Gd CEMRI	0.82	Dirichlet	45	10	1	19
False-positive rate	CEUS	0.03	Dirichlet	See data used to model sensitivity			
	CECT	0.03	Dirichlet	See data used to model sensitivity			
	Gd CEMRI	0.01	Dirichlet	See data used to model sensitivity			

FN, false-negative; FP, false-positive; TN, true-negative; TP, true-positive.

a The Dirichlet distribution is the multivariate generalisation of the beta distribution. The parameters of the distribution are the observed test results (TP, FP, FN, TN), presented in the table.

Source: based on Leoni *et al.*<sup>42</sup>



TABLE 17 Parameters used in the cirrhosis surveillance model: transition probabilities

Parameter	Value	Source	Distribution	Range of values used in sensitivity analysis	
				Lower	Upper
Mean age at start (years)	53.3	Roberts <i>et al.</i> <sup>73</sup>	Normal	43.3	63.3
				SE = 0.1789	
HBV	44.0	Fattovich <i>et al.</i> <sup>74</sup>	Normal	34.0	54.0
				SE = 0.1789	
HCV	54.0	Fattovich <i>et al.</i> <sup>75</sup>	Normal	44.0	64.0
				SE = 0.1789	
% male	67.1	ONS <sup>76</sup>	Beta	50.0	90.2
				$\alpha = 211, \beta = 90$	
HBV	86.5	Fattovich <i>et al.</i> <sup>74</sup>	Beta	82.6	89.7
				$\alpha = 302, \beta = 47$	
HCV	58.1	Fattovich <i>et al.</i> <sup>75</sup>	Beta	53.1	62.9
				$\alpha = 223, \beta = 161$	
Upper age limit for surveillance (years)	70	AA <sup>a</sup>	Log-normal	60	80
				Mean of logs = 4.249, $\sigma = 0.006$	
Composition of mixed aetiology cohort (%)	57.6	EO <sup>b</sup>	Fixed	-	-
HBV	7.3		Fixed	-	-
HCV	35.1		Fixed	-	-
Annual incidence of cirrhosis decomposition (%)	3.3	Assumed same as HBV	Beta	-	-
				$\alpha = 5, \beta = 156$	
HBV	3.3	Fattovich <i>et al.</i> <sup>77</sup>	Beta	-	-
				$\alpha = 5, \beta = 156$	
HCV	5.3		Beta	-	-
				$\alpha = 7, \beta = 129$	
Annual incidence of HCC (%)	1.7	Fattovich <i>et al.</i> <sup>78</sup>	Beta	-	-
				$\alpha = 10, \beta = 574$	
HBV	2.2		Beta	-	-
				$\alpha = 9, \beta = 392$	
HCV	3.7		Beta	-	-
				$\alpha = 47, \beta = 1237$	
Probability that tumour increases in size	0.056	Taouli <i>et al.</i> <sup>79</sup>	Beta PERT <sup>c</sup>	0.036	0.089
				$\lambda = 4$	
Medium to large tumours	0.036		Beta PERT <sup>c</sup>	0.023	0.056
				$\lambda = 4$	
Annual symptomatic/incidental presentation rate for HCC (%)	1.6	Rates calibrated to be in line with Trevisani <i>et al.</i> <sup>80</sup>	Beta	0	16.2
Small tumours	12.1		Beta	0%	30.3
Medium tumours	50		Beta	0	100
Large tumours				$\alpha = 500, \beta = 500$	

Parameter	Value	Source	Distribution	Range of values used in sensitivity analysis	
				Lower	Upper
Proportion with decompensated cirrhosis who are listed for OLT (%)	90	AA <sup>a</sup>	Beta PERT <sup>c</sup>	$\lambda = 4$	100
Proportion with HCC who receive resection (%)	20	AA <sup>a</sup>	Beta PERT <sup>c</sup>	$\lambda = 4$	30
Proportion with HCC who are listed for OLT (%)	5	AA <sup>a</sup>	Beta PERT <sup>c</sup>	$\lambda = 4$	10
Proportion with HCC who are deemed surgically untreatable (%)	75	AA <sup>a</sup>	Beta PERT <sup>c</sup>	$\lambda = 4$	85
Monthly probability of receiving OLT once on waiting list	85	AA <sup>a</sup>	Beta PERT <sup>c</sup>	$\lambda = 4$	88
Annual mortality rate due to decompensated cirrhosis (%)	5	AA <sup>a</sup>	Fixed	–	–
Annual mortality rate due to decompensated cirrhosis (%)	10	AA <sup>a</sup>	Fixed	–	–
Annual mortality rate due to decompensated cirrhosis (%)	0.2541	UK Transplant <sup>b1</sup>	Beta	$\alpha = 577, \beta = 1694$	–
Annual mortality rate due to decompensated cirrhosis (%)	0	AA <sup>a</sup>	Fixed	–	–
Annual mortality rate due to decompensated cirrhosis (%)	17.7	Average HBV and HCV	Beta	$\alpha = 17, \beta = 81$	12.7
Annual mortality rate due to decompensated cirrhosis (%)	22.5	Fattovich <i>et al.</i> <sup>77</sup>	Beta	$\alpha = 7, \beta = 26$	18.9
Annual mortality rate due to decompensated cirrhosis (%)	12.9	Fattovich <i>et al.</i> <sup>75</sup>	Beta	$\alpha = 8, \beta = 57$	12.7
90-day mortality rate for patients undergoing OLT (%)	6.0	UK Transplant <sup>b1</sup>	Beta PERT <sup>c</sup>	$\lambda = 4$	0.0
90-day mortality rate for patients undergoing OLT (%)	15.0	UK Transplant <sup>b1</sup>	Beta PERT <sup>c</sup>	$\lambda = 4$	4.7
90-day mortality rate for patients undergoing OLT (%)	7.4	UK Transplant <sup>b1</sup>	Beta PERT <sup>c</sup>	$\lambda = 4$	3.0
Proportion of patients surviving 1 year following OLT (%)	92.0	UK Transplant <sup>b1</sup>	Beta PERT <sup>c</sup>	$\lambda = 4$	84.5
Proportion of patients surviving 1 year following OLT (%)	78.0	UK Transplant <sup>b1</sup>	Beta PERT <sup>c</sup>	$\lambda = 4$	65.9
Proportion of patients surviving 1 year following OLT (%)	87.6	UK Transplant <sup>b1</sup>	Beta PERT <sup>c</sup>	$\lambda = 4$	81.9

continued

TABLE 17 Parameters used in the cirrhosis surveillance model: transition probabilities (continued)

Parameter	Value	Source	Distribution	Range of values used in sensitivity analysis	
				Lower	Upper
Proportion of patients surviving 5 years following OLT (%)	54.7	UK Transplant <sup>a1</sup>	Beta PERT <sup>c</sup>	38.2	71.3
	68.5		Beta PERT <sup>c</sup>	54.3	82.8
90-day mortality rate for patients undergoing resection (%)	55.8		Beta PERT <sup>c</sup>	41.0	70.6
	3.9	Llovet <i>et al.</i> <sup>a2</sup>	Beta PERT <sup>c</sup>	1.3	10.8
Proportion of patients surviving 1 year following resection (%)	85.0		Beta PERT <sup>c</sup>	79.0	88.0
	62.0	Llovet <i>et al.</i> <sup>a2</sup>	Beta PERT <sup>c</sup>	54.0	76.0
Proportion of patients surviving 3 years following resection (%)	51.0		Beta PERT <sup>c</sup>	36.0	58.0
	72.9	Llovet <i>et al.</i> <sup>a2</sup>	Beta PERT <sup>c</sup>	34.6	97.3
Annual mortality rate associated with occult large HCC (%)	64.4	Greten <i>et al.</i> <sup>a3</sup>	Beta PERT <sup>c</sup>	33.6	84.8
			Beta PERT <sup>c</sup>		

OLT, orthotopic liver transplantation; ONS, Office for National Statistics.

a Author assumption in Thompson Coon *et al.*<sup>70</sup>

b Expert opinion in Thompson Coon *et al.*<sup>70</sup>

c In the beta PERT distribution,  $\lambda$  is the scale parameter that scales the height of the distribution. If the scale parameter equals 4, the distribution approximates the normal distribution.

TABLE 18 Parameters used in the cirrhosis surveillance model: costs

Parameter	Cost (£)		Source	Distribution	Range of values used in sensitivity analysis	
					Lower	Upper
<b>Unit costs</b>						
US scan	55	Per scan	NHSRC <sup>84</sup>	Beta PERT <sup>a</sup>	40	65
SonoVue contrast agent	49	Per scan	Expert opinion	Beta PERT <sup>a</sup>	40	60
Additional time for CEUS	16	Per scan	NHSRC <sup>84</sup>	Beta PERT <sup>a</sup>	0	39
CECT (one area)	116	Per scan		Beta PERT <sup>a</sup>	88	126
Gd-CEMRI (one area)	189	Per scan		Beta PERT <sup>a</sup>	137	226
SPIO-CEMRI (one area)	189	Per scan		Beta PERT <sup>a</sup>	137	226
Outpatient appointment	150	Per appointment		Beta PERT <sup>a</sup>	72	228
OLT	26,329	Per operation		Beta PERT <sup>a</sup>	20,169	38,406
Resection	6521	Per operation		Beta PERT <sup>a</sup>	1812	7246
<b>State costs</b>						
All compensated cirrhosis states	1394	Per year	Thompson Coon <i>et al.</i> , <sup>70</sup> updated to 2011	Beta PERT <sup>a</sup>	867	1961
All decompensated cirrhosis states	11,335	Per year		Beta PERT <sup>a</sup>	7738	14,931
All known HCC states	1486	Per year <sup>b</sup>		Beta PERT <sup>a</sup>	743	2971
Post OLT (year 1)	11,923	Per patient per year		Beta PERT <sup>a</sup>	5835	18,021
Post OLT (year 2 onwards)	1889	Per patient per year		Beta PERT <sup>a</sup>	992	2796
Post resection	4266	Per patient per year		Beta PERT <sup>a</sup>	2824	5752
Palliative care (small and medium tumours)	1955	Per year <sup>b</sup>		Beta PERT <sup>a</sup>	977	3909
Palliative care (large tumours)	214			Beta PERT <sup>a</sup>	106	428
<b>Event costs</b>						
False-positive diagnosis	618	Per false-positive diagnosis	Thompson Coon <i>et al.</i> , <sup>70</sup> updated to 2011	Beta PERT <sup>a</sup>	419	961
Symptomatic/incidental diagnosis	198	Per diagnosis		Beta PERT <sup>a</sup>	94	287

a In the beta PERT distributions,  $\lambda$  (the scale parameter that scales the height of the distribution) equals 4, which means that the distribution approximates the normal distribution.

b In addition to the costs of the underlying cirrhosis.

**TABLE 19** Parameters used in the cirrhosis surveillance model: utilities

Parameter	Value	Source	Distribution	Range of values used in sensitivity analysis	
				Lower	Upper
Compensated cirrhosis	0.75	Chong <i>et al.</i> <sup>86</sup>	Beta PERT <sup>b</sup>	0.66	0.83
Decompensated cirrhosis	0.66	Chong <i>et al.</i> <sup>86</sup>	Beta PERT <sup>b</sup>	0.46	0.86
Untreatable HCC	0.64	Chong <i>et al.</i> <sup>86</sup>	Beta PERT <sup>b</sup>	0.44	0.86
Month of OLT	0.50	AA <sup>a</sup>	Beta PERT <sup>b</sup>	0.30	0.60
Post OLT (year 1)	0.69	Ratcliffe <i>et al.</i> <sup>87</sup>	Beta PERT <sup>b</sup>	0.64	0.74
Post OLT (year 2 onwards)	0.73	Ratcliffe <i>et al.</i> <sup>87</sup>	Beta PERT <sup>b</sup>	0.67	0.78
Month of resection	0.50	AA <sup>a</sup>	Beta PERT <sup>b</sup>	0.30	0.60

a Author assumption as reported in Thompson Coon *et al.*<sup>70</sup>

b In the beta PERT distributions,  $\lambda$  (the scale parameter that scales the height of the distribution) equals 4, which means that the distribution approximates the normal distribution.

## Utilities

Utilities were taken from the HTA report by Thompson Coon *et al.*<sup>70</sup> (Table 19)

## Liver metastases of colorectal cancer model

### Test performance

Chapter 3 reports the results of two studies identified that assessed the accuracy of CEUS compared with CECT and/or Gd-CEMRI and/or SPIO-CEMRI in detecting liver metastases in CRC patients after inconclusive unenhanced US.<sup>49,50</sup> The test performance found in the Mainenti *et al.* study<sup>49</sup> was used in the base case as this study compared all three alternative tests (CECT, Gd-CEMRI, SPIO-CEMRI) with CEUS. In this study, based on a total of 34 patients, sensitivity was 83% for all comparators. Specificity was lowest for CEUS (86%), followed by CECT (96%), SPIO-CEMRI (96%) and Gd-CEMRI (100%). An overview of the test performance is presented in Table 20. A Dirichlet distribution based on the observed counts was used to assess the uncertainty surrounding these results.

### Transition probabilities

All transition probabilities used in the model are listed in Table 21 and are in line with the probabilities used in the Brush *et al.* model.<sup>71</sup> The probability of having metastases after CRC is expected to be 40%.<sup>88</sup> Even though the population modelled in the present analysis has already had an inconclusive US scan and may therefore be a slightly different population, we expected this figure to also apply to our population. Of those patients with metastases, approximately 30% have them at one site.<sup>89</sup>

In line with Brush *et al.*<sup>71</sup> we assumed that all patients with metastases at a single site receive preoperative chemotherapy and metastatic surgery. Patients with extra metastases receive either preoperative chemotherapy followed by metastatic surgery and palliative care (20%) or chemotherapy and palliative care. All patients without a metastatic recurrence are followed up using a watch and wait strategy.

Five-year overall survival rates were extracted from Brush *et al.*<sup>71</sup> Patients who were inaccurately classified as having no metastases and who therefore failed to receive treatment in the first year were expected to have a higher probability of dying in this first year than those who were immediately treated for their metastases. Therefore, in the first year patients who had undetected metastases at one site had the probability of dying of those who were treated for extra metastases with surgery. Similarly, patients who had undetected metastases at multiple sites who could have been treated with surgery were assumed

**TABLE 20** Test performance of imaging used in the decision tree for the metastases model

Parameter	Value	Distribution <sup>a</sup>	Observed counts ( <i>n</i> = 34)				
			TP	FN	FP	TN	
Sensitivity	CEUS	0.83	Dirichlet	5	1		
	CECT	0.83	Dirichlet	5	1		
	Gd-CEMRI	0.83	Dirichlet	5	1		
	SPIO-CEMRI	0.83	Dirichlet	5	1		
Specificity	CEUS	0.86	Dirichlet			4	24
	CECT	0.96	Dirichlet			1	27
	Gd-CEMRI	0.96	Dirichlet			0	28
	SPIO-CEMRI	1.00	Dirichlet			1	27

FN, false-negative; FP, false-positive; TN, true-negative; TP, true-positive.

a The Dirichlet distribution is the multivariate generalisation of the beta distribution. The parameters of the distribution are the observed test results (TP, FP, FN, TN), presented in the table.

Source: based on Mainenti *et al.*<sup>49</sup>

**TABLE 21** Parameters used in the metastases model: transition probabilities

Parameter	Value	Source	Distribution	
<b>Cancer prevalence</b>				
Probability of having metastases	0.40	Saunders <i>et al.</i> <sup>88</sup>	Beta	SE = 0.1
Probability of having metastases at one site	0.30	Lejeune <i>et al.</i> <sup>89</sup>	Beta	SE = 0.1
<b>Treatments</b>				
Metastases: preoperative chemotherapy and metastatic surgery	1.00	Assumption based on Brush <i>et al.</i> <sup>71</sup>	Fixed	
Extra metastases: preoperative chemotherapy and metastatic surgery	0.20	MSAC <sup>90</sup>	Beta	SE = 0.04
Watch and wait	1.00	Assumption based on Brush <i>et al.</i> <sup>71</sup>	Fixed	
<b>5-year overall survival</b>				
No metastases	0.85	American Cancer Society <sup>91</sup>	Beta	SE = 0.01
Metastases: surgery for cure	0.24	AJCC <sup>92</sup>	Beta	SE = 0.03
Extra metastases: metastatic surgery and palliative care	0.12	AJCC <sup>92</sup>	Beta	SE = 0.04
Extra metastases: palliative care	0.06	AJCC <sup>92</sup>	Beta	SE = 0.04

AJCC, American Joint Committee on Cancer; MSAC, Medical Services Advisory Committee.

Source: based on Brush *et al.*<sup>71</sup>

to have the probability of dying of those patients who received palliative care. Patients with undetected metastases at multiple sites who would have received palliative care were assumed not to experience increased mortality. After 1 year, all patients were assigned the mortality rate that belonged to their type of metastases and treatment. The survival rates were converted to yearly probabilities and extrapolated to 10 years, after which patients were assumed to have survived their disease and returned to the average

mortality rate for their age.<sup>93</sup> To inform this mortality rate, the model assumed a starting age of 50 years and a male-to-female ratio of 55:45.<sup>94</sup>

### Costs

Both the costs of the imaging techniques and the costs of subsequent treatment were taken into account (Table 22). The costs of CEUS were similar to those in the cirrhosis surveillance model. Because all patients already received an unenhanced US scan, the costs of CEUS consisted of the cost of the extra time used for CEUS as opposed to an unenhanced US scan (£16) and the cost of the contrast (£48.70). CECT was assumed to scan three areas (chest, abdomen, pelvis) whereas CEMRI was assumed to scan two to three areas. The costs of biopsy, whole-body CT and the watch and wait strategy were based on NHSRC reference costs.<sup>84</sup> The watch and wait strategy consisted of two CECT scans over 3 years and a serum CEA test twice a year for 3 years.<sup>14</sup> Costs of treatment were based on the costs used by Brush *et al.*<sup>71</sup>

### Utilities

All utility scores used in the model were based on Brush *et al.*<sup>71</sup> and are presented in Table 23. Patients who were inaccurately diagnosed as having no metastatic recurrence and who therefore failed to receive treatment in the first year were assigned a disutility for that year to account for the negative impact on their quality of life. Likewise, patients without metastases who unnecessarily received treatment (in a sensitivity analysis) were assigned a lower utility score to account for the negative impact of this unnecessary treatment on their quality of life.

It was assumed that the average utility experienced by patients in a particular stage was constant for 5 years post diagnosis. Patients who were still alive 5 years post diagnosis were assigned age-specific utility weights based on UK population norms.<sup>102</sup>

**TABLE 22** Parameters used in the metastases model: costs

Parameter	Cost (£)	Source	Distribution	Range of values used in sensitivity analysis	
				Lower	Upper
SonoVue contrast agent	49	Expert opinion	Beta PERT <sup>a</sup> $\lambda = 4$	40	60
Additional time for CEUS	16	NHSRC <sup>84</sup>	Beta PERT <sup>a</sup> $\lambda = 4$	0	39
CECT (three areas)	162	NHSRC <sup>84</sup>	Beta PERT <sup>a</sup> $\lambda = 4$	120	192
Gd-CEMRI (two to three areas)	366	NHSRC <sup>84</sup>	Beta PERT <sup>a</sup> $\lambda = 4$	175	374
SPIO-CEMRI (two to three areas)	366	NHSRC <sup>84</sup>	Beta PERT <sup>a</sup> $\lambda = 4$	175	374
Biopsy	1437	NHSRC <sup>84</sup>	Beta PERT <sup>a</sup> $\lambda = 4$	989	1798
Whole-body CT	162	NHSRC <sup>84</sup>	Beta PERT <sup>a</sup> $\lambda = 4$	120	192
Chemotherapy	11,532	BNF 58, <sup>95</sup> ISD, <sup>96</sup> Cancer Research UK <sup>97</sup>	Fixed		
Surgery	9134	ISD <sup>96</sup>	Normal	SD = 1827	
Palliative care	2468	Guest <i>et al.</i> <sup>98</sup>	Normal	SD = 494	
Watch and wait	110	NHSRC, <sup>84</sup> NICE <sup>14</sup>	Beta PERT <sup>a</sup>	82	130

BNF, *British National Formulary*; ISD, *Information Services Division*.

a In the beta PERT distributions,  $\lambda$  (the scale parameter that scales the height of the distribution) equals 4, which means that the distribution approximates the normal distribution.

Source: based on Brush *et al.*<sup>71</sup>

**TABLE 23** Parameters used in the metastases model: utilities

Parameter	Value	Source	Distribution	
No metastases	0.91	Ramsey <i>et al.</i> <sup>99</sup>	Beta	SE = 0.11
Metastases at one site	0.84	Ramsey <i>et al.</i> <sup>99</sup>	Beta	SE = 0.12
Extra metastases: surgery for cure	0.74	Langenhoff <i>et al.</i> <sup>100</sup>	Beta	SE = 0.21
Extra metastases: palliative care	0.52	Tengs and Wallace <sup>101</sup>	Beta	SE = 0.08
Patients receiving unnecessary metastatic surgery	0.74	Langenhoff <i>et al.</i> <sup>100</sup>	Beta	SE = 0.14
Patients receiving unnecessary palliative care	0.61	Tengs and Wallace <sup>101</sup>	Beta	SE = 0.20
Disutility for patients who fail to receive surgery	0.30	Assumption based on Tengs and Wallace <sup>101</sup>	Gamma	SE = 0.08
Disutility for patients who fail to receive palliative care	0.20	Assumption based on Tengs and Wallace <sup>101</sup>	Gamma	SE = 0.08

Source: based on Brush *et al.*<sup>71</sup>

### *Incidentally detected focal liver lesion model*

#### Test performance

As noted earlier, different studies have compared CEUS with CECT and CEMRI in its ability to characterise incidentally FLLs. Three different types of diagnostic outcome have been studied: diagnosis of any malignancy, diagnosis of HCC and diagnosis of metastases. Of these three, the most common outcome has been any malignancy. In addition, most studies have compared CEUS with CECT; only one has compared CEUS with CEMRI. These two factors made it impossible to combine all results into one analysis without important assumptions (listed in *Incidentally detected FLL model*). This issue was resolved by utilising the test performance results in various ways.

The approach used in the base-case analysis was to take the results from the meta-analysis of four studies that compared CEUS with CECT in their ability to differentiate between malignant and benign lesions (described in *Chapter 3, Accuracy of SonoVue CEUS for the characterisation of incidentally detected FLLs*). The following results illustrate how similar the performance of CEUS and CECT are (*Table 24*). The CIs shown were calculated using the exact method.

In addition to using the sensitivity and specificity values from the meta-analysis, we also used the results from the individual studies (see *Chapter 3, Accuracy of SonoVue CEUS for the characterisation of incidentally detected FLLs* for details). Dirichlet distributions were applied when the results from these individual studies were used. Use of these distributions had no influence on the prior probability of the different diagnoses as test performance and prior probability were combined to calculate the post-test probability using Bayes' theorem.

In the past, only one study has compared the test accuracy of CEUS with MRI.<sup>56</sup> As noted in *Chapter 3* (see *Accuracy of SonoVue CEUS for the characterisation of incidentally detected FLLs*), this study reported that all patients in subgroup B underwent Gd-CEMRI, and that a subset of these patients also underwent SPIO-CEMRI. It is therefore difficult to refer to the accuracy of Gd-CEMRI or SPIO-CEMRI in the characterisation of incidentally detected FLL. For this reason, in the sections relating to the use of MRI in the characterisation of incidentally detected FLL, we refer to CEMRI.



**TABLE 24** Test performance of CEUS and CECT in their ability to characterise any malignancy: incidentally detected FLLs

	Estimate (%)	95% CI (exact method) (%)
Sensitivity of CEUS	95.1	93.3 to 96.6
Sensitivity of CECT	94.6	92.7 to 96.1
Specificity of CEUS	93.8	90.4 to 96.3
Specificity of CECT	93.1	89.6 to 95.8

As noted above, some studies examined the ability of imaging tests to correctly identify HCC and metastases. While modelling, we made it possible to use these results instead of the results based on malignancy compared with no malignancy.

With regard to the outcome of malignancy compared with no malignancy, we assumed that any mistakes in diagnosis were made at random and were not associated with any particular lesion type. For example, if a malignant lesion was incorrectly classified by CEUS as a benign lesion, the type of benign lesion in that instance was determined according to the relative frequencies of the different benign lesion types.

Nevertheless, a number of different probabilities were used in this model. The first set of probabilities related to the prior probabilities (or prevalence) of the different types of lesions at the time of assessment (*Table 25*). The prevalence of malignant lesions varied substantially between the diagnostic accuracy studies included in the systematic review. In one study the probability of any malignancy was 23%,<sup>53</sup> whereas in another it was 74%.<sup>52</sup> In the final protocol for this study it was stated that expert opinion had suggested that as many as 70–75% of FLLs assessed in the NHS may be benign. This percentage might be higher if the population in question were to be limited to incidentally detected FLLs. The clinicians surveyed during the present study were of the opinion that the chance of malignancy was rather low in this population. As a consequence, we used a low probability of malignancy in the base-case scenario. The values shown in *Table 25* were based on the results of Bartolotta *et al.*,<sup>103</sup> who reported a low probability of malignancy of 4.3%. As Bartolotta *et al.* reported no patients with HCC in their study, we increased this to 0.05 to introduce a small chance that a patient with HCC would appear on occasion in the analysis.

As noted above, care was taken to ensure that the estimates of test performance were kept separate from the prior probabilities of the different malignancies by combining prior probability, sensitivity and specificity using Bayes' theorem. This enabled us to vary the prior probability of malignancy in sensitivity analyses.

The incidentally detected FLL model was a decision-analytic model and not a Markov model and therefore did not directly involve the modelling of health states. The prognosis of patients following the initial diagnostic assessment was estimated using existing disease models and background mortality data (national vital statistics). The prognosis associated with the two most important types of malignant lesions (HCC and metastases) was estimated using the two other models applied in this HTA (i.e. the cirrhosis model and the liver metastases model). The following assumptions were made regarding the prognosis of patients with incidentally detected FLLs.

### Summary of assumptions made in the incidentally detected focal liver lesion model regarding probabilities

- Patients with HCC have a small HCC lesion and compensated cirrhosis at the time of assessment. The cirrhosis surveillance model made it possible to explore the impact of assuming that these patients have a medium-sized lesion and compensated cirrhosis at the time of assessment, and the costs and QALYs associated with this alternative were used in a sensitivity analysis.
- Patients with HCC who are incorrectly diagnosed at baseline will be correctly diagnosed later (within several months). This is assumed because these patients will be followed up because of the presence

**TABLE 25** Probabilities of the different types of lesions at time of assessment: incidental FLL model

Type of lesion	Prior probability	Distribution	Alpha	Beta
Metastases	0.0211	Beta	3	139
HCC	0.0004	Beta	0.05	141.95
CCC	0.0070	Beta	1	141
Other malignancy	0.0004	Beta	0.05	141.95
Haemangioma	0.4993	Beta	70.9	71.1
Focal nodular hyperplasia	0.3169	Beta	45	97
Hepatocellular adenoma	0.0141	Beta	2	140
Focal fatty sparing	0.0704	Beta	10	132
Other benign lesion	0.0704	Beta	10	132
Probability of malignant lesion	0.0289	Beta	NA	NA
Probability of benign lesion	0.9711	Beta	NA	NA

NA, not applicable.

of one or more risk factors for HCC, such as newly diagnosed cirrhosis and hepatitis. The impact of delayed treatment is 1 less life-year, 1 less QALY and 5% extra costs. The impact of delayed treatment was varied in sensitivity analyses.

- Patients diagnosed with an apparent benign lesion do not undergo treatment unless they have a (hepatic) adenoma, in which case they may undergo a resection [base-case chance of resection: 50% (but varied in sensitivity analyses)].

### Costs

The costs of diagnostic tests, outpatient appointments, biopsy, OLT and resection were taken from the NHSRC.<sup>84</sup> Many of the values used in the incidentally detected FLL analyses were similar to those used in the cirrhosis analyses (*Table 26*). All other cost inputs were based on Thompson Coon *et al.*,<sup>70</sup> recalculated to the 2011 price level using the Personal and Social Services Research Unit (PSSRU) unit costs.<sup>85</sup>

The costs of treating HCC and metastases were based on the calculations in the cirrhosis surveillance and liver metastases models (see *Table 26*). However, adaptations of the cirrhosis model were needed before the results could be used for these analyses. In particular, it was assumed that a small tumour was found at diagnosis. Therefore, the total costs shown here cannot be compared with the total costs reported for cirrhosis surveillance. In contrast, the estimated costs of liver metastases treatment were based directly on the base-case results for liver metastases reported later in this chapter. Although it could be argued that some cost components (such as the costs of the initial diagnostic assessment) should be removed as they are not relevant for the incidentally detected FLL model, we chose to leave the total costs unchanged to allow the reader to trace the origin of these cost estimates. Moreover, these costs are greatly overshadowed by the other treatment-related costs and the standard error.

### Utilities

Patients with an incidentally detected lesion that is benign are expected to lead a normal life in the future. For this reason it was assumed that their life expectancy and quality of life would not be different from those of the general population. In contrast, patients with a malignant lesion can have a poorer quality of life. The impact of disease on health utilities was based on the results of the cirrhosis and liver metastases models, as HCC and liver metastases are two important types of malignant lesion that may be identified. More information about the impact that these have on utilities is provided in the other sections of this chapter.

**TABLE 26** Parameters used in the incidentally detected FLL model: costs

	Cost (£)	Lower (£)	Upper (£)	Distribution
Imaging				
US	16	0	39	Beta PERT
Contrast	48.70	40	60	Beta PERT
CEUS	65			
CECT	116	88.21	126.33	Beta PERT
CEMRI <sup>a</sup>	189	137.27	225.89	Beta PERT
	Mean cost (£)	Standard error (£)		Distribution
HCC (correctly diagnosed)	24,645	3980		Normal
HCC (incorrectly diagnosed)	25,877	3980		Normal
Metastasis (correctly diagnosed)	7518	1808		Normal
Metastasis (incorrectly diagnosed)	7894	1808		Normal
Follow-up (total)	150	(min.–max.) 144–156		Beta PERT (when varied)
Resection	6521	(min.–max.) 1812–7246		Beta PERT

max., maximum; min., minimum.

<sup>a</sup> Type of contrast used in CEMRI not indicated here as both types were used in test accuracy studies.

One factor not included in the analysis was the extent of disutility resulting from the anxiety caused by an incorrect diagnosis. Another type of disutility not explicitly included in the analysis related to the possible disutility from any delay before undergoing the test. Differences in waiting time between CEUS, CECT and CEMRI are expected, as CEUS can be performed right after the unenhanced US, as part of the same examination. However, it is uncertain how much disutility may be caused by differences in waiting time.

### Summary of assumptions made in the incidentally detected focal liver lesion model regarding utilities

- Patients with HCC who are incorrectly diagnosed at baseline will be correctly diagnosed later (within several months). This is assumed because these patients will be followed up because of other risk factors, such as newly diagnosed cirrhosis and hepatitis. The impact of delayed treatment is 1 fewer QALY.
- Patients diagnosed with an apparent benign lesion will have a life expectancy and quality of life equal to those seen among people in the general population of the same age and sex.

### Additional analyses

First, one-way sensitivity analyses were performed for all key parameters, especially for parameters in the models that were based on expert opinion. Next, probabilistic sensitivity analyses were performed using parameter distributions instead of fixed values. The chosen distributions are presented for each input parameter in *Tables 25* and *26*. Decision uncertainty regarding mutually exclusive alternatives is reflected using cost-effectiveness planes and cost-effectiveness acceptability curves. Specific additional analyses (including one-way sensitivity analyses) are listed in the following sections for each model.

### **Cirrhosis surveillance model**

The proportion of patients receiving confirmatory imaging (the proportion of patients with an inconclusive unenhanced US scan: 43%) was an uncertain parameter in the model. Therefore, we performed a sensitivity analysis in which CEUS, CECT and Gd-CEMRI were used for a proportion of patients equal to the proportion of patients with a positive unenhanced US scan (as a minimum estimate of the patients requiring confirmatory imaging). Second, we reduced the proportion of inconclusive unenhanced US scans considerably (20% instead of 43%). Next, we conducted sensitivity analyses on the age limit of surveillance (90 years instead of 70 years), the frequency of screening (every year instead of every 6 months) and the tumour sizes for which the accuracy data were applied (small only instead of small and medium-sized).

Finally, scenario analyses were conducted using other sources for the accuracy of the tests. As alternative sources we used the articles by Dai *et al.*,<sup>43</sup> Quaia *et al.*,<sup>46</sup> Blondin *et al.*<sup>48</sup> and Giorgio *et al.*<sup>45</sup> (using data for 11- to 30-mm lesions). Dai *et al.* and Blondin *et al.* were included as other examples of studies that used a standard (EFSUMB guidelines<sup>6</sup>) definition of HCC, and Giorgio *et al.* and Quaia *et al.* were included to explore the effects of using other definitions of HCC. The study by Forner *et al.*<sup>44</sup> was not used because it included a significant proportion of patients with very small (<10 mm) FLLs and the study by Sangiovanni *et al.*<sup>47</sup> was not used because it was considered to be an 'outlier' (accuracy results differed substantially from those of other, apparently similar studies).

### **Liver metastases from colorectal cancer model**

First, we analysed the impact of not having a biopsy before treatment on the expected costs and effects. This would imply that patients who were inaccurately detected as having metastases would receive treatment, as was assumed in the Brush *et al.* model.<sup>71</sup> Second, we examined the impact of a 80% instead of a 40% probability of having metastases. We did this because our population of patients who have already received an unenhanced US scan may be slightly different from the population in Brush *et al.*<sup>71</sup> and may consist of more patients with metastases.

Next, we performed scenario analyses using other sources as input for the accuracy of the tests. Although the results refer to lesions instead of patients, we used the sensitivity and specificity reported in Jonas *et al.*<sup>50</sup> to assess the impact on the expected costs and effects. We also used the sensitivity and specificity reported in Clevert *et al.*;<sup>51</sup> this study included some patients with primary cancers other than CRC, but the majority (>80%) of metastases diagnosed were from CRC.

### **Incidentally detected focal liver lesion model**

A number of different parameters were varied to investigate their impact on the cost-effectiveness of CEUS. First, we increased the probability of a malignant lesion. We also examined the impact of basing the values for the sensitivity and specificity of CEUS and CECT on individual studies rather than on the meta-analysis. We then examined whether or not assuming that all patients with HCC had medium-sized lesions instead of small lesions would have an effect on the results. Lastly, we analysed the impact of changing the costs and health loss from an incorrect diagnosis of HCC or metastasis.

## **Results**

### **Cirrhosis surveillance model**

#### **Effectiveness of surveillance**

In the base case we compared CEUS, CECT and Gd-CEMRI (*Table 27*). Based on the accuracy data, as found by Leoni *et al.*,<sup>42</sup> we found that the proportion of patients dying from HCC was slightly higher for CEUS (17%) and CECT (17%) than for Gd-CEMRI (16%). This resulted in a slightly higher number of expected discounted life-years (13.76) and QALYs (10.18) gained by Gd-CEMRI than by CEUS and CECT (13.73 and 10.15 respectively).

**TABLE 27** Effectiveness of cirrhosis surveillance (discounted)

	CEUS	CECT	Gd-CEMRI
Proportion dying from HCC (%)	17	17	16
Proportion dead by age 75 (%)	54	54	53
Number of total life-years	13.730	13.730	13.764
Number of total QALYs	10.153	10.153	10.175

**TABLE 28** Breakdown of discounted costs of cirrhosis surveillance (£)

	CEUS	CECT	Gd-CEMRI
Surveillance	1559	1939	2420
Imaging	1436	1816	2359
False-positive	123	123	61
Maintenance	23,631	23,631	23,687
Symptomatic detection	12	12	11
Compensated cirrhosis	13,043	13,043	13,014
Decompensated cirrhosis	2119	2119	2092
Known HCC	380	380	379
Post transplant	7822	7822	7931
Post resection	3	3	56
Palliative	57	57	59
Transplant waiting list	195	195	198
Treatment	10,554	10,554	10,700
Transplantation	10,504	10,504	10,644
Resection	50	50	56
Total	35,744	36,124	36,807

### Costs of surveillance

The total discounted costs were lowest for CEUS (£35,744), followed by CECT (£36,124) and Gd-CEMRI (£36,807) (*Table 28*). The main cost difference was in the imaging costs. Because Gd-CEMRI had a higher sensitivity than CEUS and CECT, HCC was identified at an earlier stage, improving the options for treatment. This also resulted in higher maintenance and treatment costs for CEMRI compared with CEUS and CECT.

### Cost-effectiveness of surveillance

Contrast-enhanced ultrasound was found to have the lowest discounted lifetime cost per patient (£35,744), followed by CECT (£36,124) and Gd-CEMRI (£36,807) (*Table 29*). Compared with CEUS, CECT was as effective and more costly and was thus considered to be dominated by CEUS. Gd-CEMRI was £1063 (95% CI £449 to £1492) more expensive than CEUS per patient, but also yielded 0.022 (95% CI -0.002 to 0.050) more QALYs, resulting in an incremental cost-effectiveness ratio (ICER) of £48,454 per QALY gained. As this is above the typical willingness-to-pay threshold of £30,000 per QALY gained, Gd-CEMRI was not deemed cost-effective compared with CEUS.

**TABLE 29** Base-case cost-effectiveness results for cirrhosis surveillance

Strategy	Cost (£)	QALYs	Compared with CEUS		Compared with next most cost-effective strategy					
			Incremental cost (£)	Incremental QALYs	Incremental cost per QALY (£)	Comparator	Incremental cost (£)	Incremental QALYs	Incremental cost per QALY (£)	
CEUS	35,744	10.153								
CECT	36,124	10.153	379	0.000	Dominated	CEUS	379	0.000		Dominated
Gd-CEMRI	36,807	10.175	1063	0.022	48,454	CEUS	1063	0.022		48,454

**TABLE 30** Results of sensitivity analysis for cirrhosis surveillance: imaging used as confirmatory after all positive non-enhanced US examinations

Strategy	Cost (£)	QALYs	Compared with CEUS		Compared with next most cost-effective strategy					
			Incremental cost (£)	Incremental QALYs	Incremental cost per QALY (£)	Comparator	Incremental cost (£)	Incremental QALYs	Incremental cost per QALY (£)	
CEUS	35,828	10.220								
CECT	35,867	10.220	39	0.000	Dominated	CEUS	39	0.000		Dominated
Gd-CEMRI	36,148	10.245	321	0.025	12,806	CEUS	321	0.025		12,806

## Additional analyses for surveillance

### *Sensitivity analyses*

First, we analysed the impact of using CEUS, CECT and CEMRI as confirmatory imaging for a proportion of patients equal to the proportion of patients with a positive unenhanced US scan (*Table 30*). In line with the base-case analysis, CEUS was as effective and less costly than CECT. Gd-CEMRI was also more costly (£321) and more effective (0.025 QALYs) than CEUS, resulting in an ICER of £12,806 per QALY gained. Based on a willingness-to-pay threshold of £20,000–30,000, this indicated that Gd-CEMRI was cost-effective compared with CEUS in this analysis.

Second, we changed the proportion of inconclusive US scans from 43% to 20% (*Table 31*), the age limit of surveillance to 90 years instead of 70 years (*Table 32*), the frequency of screening to every year instead of every 6 months (*Table 33*) and the accuracy data to use only those that applied to small tumours instead of small and medium-sized tumours (*Table 34*). Only when changing the proportion of inconclusive US scans was Gd-CEMRI cost-effective compared with CEUS, with an ICER of £16,121 per QALY gained. In all other sensitivity analyses CEUS dominated CECT and was cost-effective compared with Gd-CEMRI.

### *Scenario analyses*

Scenario analyses were conducted using other sources for data on the accuracy of the tests. As alternative sources we first used the articles by Dai *et al.*<sup>43</sup> and Quaia *et al.*<sup>46</sup> These studies both compared CEUS and CECT. Dai *et al.* used a definition of a positive test for HCC which was comparable with that used in the EFSUMB guidelines,<sup>6</sup> whereas Quaia *et al.* did not. Using data from either study, CEUS was found to be less costly and more effective than CECT (*Tables 35 and 36*).

Next, we used Blondin *et al.*<sup>48</sup> and Giorgio *et al.*<sup>45</sup> as sources for input for the accuracy of CEUS and Gd-CEMRI (*Tables 37 and 38* respectively). Blondin *et al.* used a definition of a positive test for HCC which was comparable with that used in the EFSUMB guidelines,<sup>6</sup> whereas Giorgio *et al.* did not. Based on Blondin *et al.*, Gd-CEMRI was found to be more costly and less effective than CEUS. Based on Giorgio *et al.*, using only data for lesions between 11 and 30 mm, Gd-CEMRI was found to be more costly, but also more effective than CEUS. However, the resulting ICER of £297,695 was very high.

### *Probabilistic sensitivity analysis*

Over 5000 replications, CEUS has the highest probability of being cost-effective for thresholds < £55,000 (*Figure 13*). Above this threshold, Gd-CEMRI has the highest probability of being cost-effective. At a threshold of £20,000–30,000, the probability that CEUS, CECT or Gd-CEMRI is cost-effective is 99%, 0% and 1% respectively.

*Table 39* provides an overview of the results of all of the sensitivity and scenario analyses.

## *Liver metastases of colorectal cancer model*

### **Effectiveness of diagnosing liver metastases**

As indicated previously, Mainenti *et al.*<sup>49</sup> found that the sensitivities of CEUS, CECT, Gd-CEMRI and SPIO-CEMRI were equal. This resulted in an equal number of cases incorrectly diagnosed without metastases (false-negatives) in the base-case analysis. Because of a lower specificity, the number of cases incorrectly diagnosed with metastases (false-positives) was highest for CEUS, followed by CECT, SPIO-CEMRI and Gd-CEMRI. Because false-positive results were assumed to be detected with a biopsy before treatment, differences in specificity did not affect the expected life-years and QALYs (*Table 40*).

### **Costs of diagnosing liver metastases**

An overview of the total discounted costs in the different cost categories per test strategy is given in *Table 41*. Although CEUS is less costly than CECT, the total diagnostic cost in the CEUS strategy is higher than that in the CECT strategy. This is because all patients with a positive test result receive a whole-body

**TABLE 31** Results of sensitivity analysis for cirrhosis surveillance: proportion of inconclusive US scans 20%

Strategy	Cost (£)	QALYs	Compared with CEUS			Compared with next most cost-effective strategy			
			Incremental cost (£)	Incremental QALYs	Incremental cost per QALY (£)	Comparator	Incremental cost (£)	Incremental QALYs	Incremental cost per QALY (£)
CEUS	35,784	10.192							
CECT	35,959	10.192	176	0.000	Dominated	CEUS	176	0.000	Dominated
Gd-CEMRI	36,408	10.216	624	0.024	16,121	CEUS	624	0.024	16,121

**TABLE 32** Results of sensitivity analysis for cirrhosis surveillance: age limit for screening 90 years

Strategy	Cost (£)	QALYs	Compared with CEUS			Compared with next most cost-effective strategy			
			Incremental cost (£)	Incremental QALYs	Incremental cost per QALY (£)	Comparator	Incremental cost (£)	Incremental QALYs	Incremental cost per QALY (£)
CEUS	36,163	10.164							
CECT	36,593	10.164	430	0.000	Dominated	CEUS	430	0.00	Dominated
Gd-CEMRI	37,367	10.188	1204	0.023	51,619	CEUS	1204	0.023	51,619



TABLE 33 Results of sensitivity analysis for cirrhosis surveillance: annual screening

Strategy	Cost (£)	QALYs	Compared with CEUS		Compared with next most cost-effective strategy		
			Incremental cost (£)	Incremental QALYs	Incremental cost (£)	Incremental QALYs	Incremental cost per QALY (£)
CEUS	34,431	10.093					
CECT	34,629	10.093	198	0.000	198	0.000	Dominated
Gd-CEMRI	35,025	10.109	594	0.016	594	0.016	37,619

TABLE 34 Results of sensitivity analysis for cirrhosis surveillance: accuracy data for small tumours only

Strategy	Cost (£)	QALYs	Compared with CEUS		Compared with next most cost-effective strategy		
			Incremental cost (£)	Incremental QALYs	Incremental cost (£)	Incremental QALYs	Incremental cost per QALY (£)
CEUS	36,054	10.191					
CECT	36,432	10.191	378	0.000	378	0.000	Dominated
Gd-CEMRI	36,966	10.195	913	0.004	913	0.004	244,840

**TABLE 35** Results of scenario analysis for cirrhosis surveillance: Dai *et al.*<sup>43</sup> used as source for accuracy data

Strategy	Cost (£)	QALYs	Compared with CEUS		
			Incremental cost (£)	Incremental QALYs	Incremental cost per QALY (£)
CEUS	36,203	10.188			
CECT	36,332	10.184	129	-0.004	Dominated

**TABLE 36** Results of scenario analysis for cirrhosis surveillance: Quaia *et al.*<sup>46</sup> used as source for accuracy data

Strategy	Cost (£)	QALYs	Compared with CEUS		
			Incremental cost (£)	Incremental QALYs	Incremental cost per QALY (£)
CEUS	36,479	10.185			
CECT	36,767	10.180	288	-0.005	Dominated

**TABLE 37** Results of scenario analysis for cirrhosis surveillance: Blondin *et al.*<sup>48</sup> used as source for accuracy data

Strategy	Cost (£)	QALYs	Compared with CEUS		
			Incremental cost (£)	Incremental QALYs	Incremental cost per QALY (£)
CEUS	36,248	10.190			
Gd-CEMRI	36,948	10.187	700	-0.003	Dominated

**TABLE 38** Results of scenario analysis for cirrhosis surveillance: Giorgio *et al.*<sup>45</sup> used as source for accuracy data

Strategy	Cost (£)	QALYs	Compared with CEUS		
			Incremental cost (£)	Incremental QALYs	Incremental cost per QALY (£)
CEUS	36,034	10.189			
Gd-CEMRI	37,078	10.192	1044	0.004	297,695

CT and biopsy, and in the CEUS strategy more patients have a positive test result. This implies that in the CEUS strategy, unnecessary additional diagnostic tests are performed. Because patients without metastases are not treated, and all metastases are eventually detected, costs of treatment are similar. Because of the higher total diagnostic cost, the average total discounted cost of CEUS (£7547) per patient is slightly higher than that for CECT (£7545). The average total discounted costs per patient for both Gd-CEMRI (£7724) and SPIO-CEMRI (£7758) are higher than those for CEUS and CECT, with SPIO-CEMRI having the highest cost because of unnecessary whole-body scans and biopsies.

### Cost-effectiveness of diagnosing liver metastases

In the base-case analysis, the different imaging techniques to detect liver metastases from CRC resulted in equal expected lifetime QALYs (8.364). CECT was found to be the least costly test, with expected costs of £7510 per patient. The expected lifetime cost per patient of CEUS was only slightly more than that for CECT (£7511). Gd-CEMRI (£7688) and SPIO-CEMRI (£7722) were both more costly than, and thus dominated by, CECT and CEUS. Although technically speaking CECT dominates CEUS, their effectiveness is equal and their expected costs are extremely close (*Table 42*).

TABLE 39 Overview of the sensitivity and scenario analyses for cirrhosis surveillance

Analysis	Comparator	Compared with CEUS		
		Incremental cost (£)	Incremental QALYs	Incremental cost per QALY (£)
<b>Base-case analysis</b>				
	CECT	379	0.000	Dominated
	Gd-CEMRI	1063	0.022	48,454
<b>Sensitivity analyses</b>				
Imaging used as confirmatory after all positive non-enhanced US examinations	CECT	39	0.000	Dominated
	Gd-CEMRI	321	0.025	12,806
Proportion of inconclusive US scans 20% instead of 43%	CECT	176	0.000	Dominated
	Gd-CEMRI	624	0.024	16,121
Age limit for screening 90 years instead of 70 years	CECT	430	0.000	Dominated
	Gd-CEMRI	1204	0.023	51,619
Annual screening instead of every 6 months	CECT	198	0.000	Dominated
	Gd-CEMRI	594	0.016	37,619
Accuracy data for small tumours only instead of for small and medium-sized tumours	CECT	378	0.000	Dominated
	Gd-CEMRI	913	0.004	244,840
<b>Scenario analyses</b>				
Dai <i>et al.</i> <sup>43</sup> used as source for accuracy data	CECT	129	-0.004	Dominated
Quaia <i>et al.</i> <sup>46</sup> used as source for accuracy data	CECT	288	-0.005	Dominated
Blondin <i>et al.</i> <sup>48</sup> used as source for accuracy data	Gd-CEMRI	700	-0.003	Dominated
Giorgio <i>et al.</i> <sup>45</sup> used as source for accuracy data	Gd-CEMRI	1044	0.004	297,695

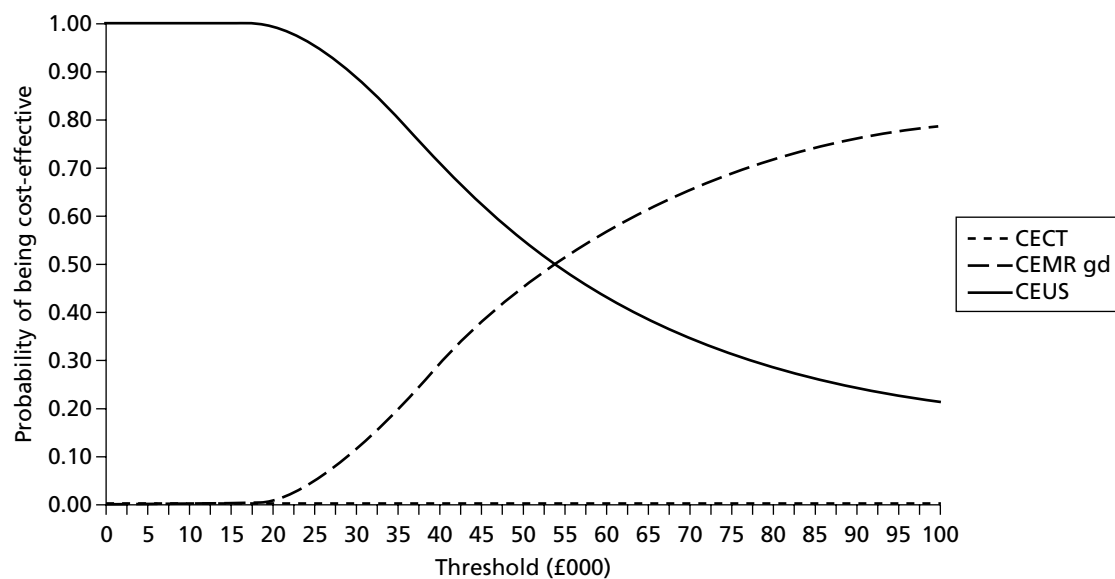


FIGURE 13 Cost-effectiveness acceptability curves: cirrhosis surveillance (effects are QALYs; both costs and effects are discounted).

**TABLE 40** Life-years and QALYs for metastases of CRC model

	CEUS	CECT	Gd-CEMR	SPIO-CEMRI
Number of discounted total life-years	10.40	10.40	10.40	10.40
Number of discounted total QALYs	8.36	8.36	8.36	8.36

**TABLE 41** Breakdown of discounted costs (£): metastases of CRC model

	CEUS	CECT	Gd-CEMRI	SPIO-CEMRI
Diagnostics	795	793	971	1006
Initial imaging	67	169	381	381
Whole-body scan	75	64	61	64
Biopsy	653	560	529	560
Treatment	6716	6716	6716	6716
Surgery/chemotherapy	3583	3583	3583	3583
Palliative care	2901	2901	2901	2901
Watch and wait	232	232	232	232
Total	7511	7510	7688	7722

## Additional analyses for diagnosing liver metastases

### *Sensitivity analyses*

When it is assumed that patients with a positive test do not undergo biopsy but are treated for their disease, implying that patients without metastases can receive unnecessary treatment, the lower specificity of CEUS leads to a loss in QALYs (*Table 43*). CEUS now yields the lowest number of QALYs (8.343) and is most expensive (£8335), while Gd-CEMRI, which is the most accurate, yields the highest number of QALYs (8.364) and is the least expensive (£7158). In this sensitivity analysis, Gd-CEMRI dominates the other tests because of its better accuracy.

If CEUS is combined with biopsy (see *Table 42*), and CECT, Gd-CEMRI and SPIO-CEMRI are not followed by biopsy (see *Table 43*), then CEUS and Gd-CEMRI are most effective, both yielding 8.364 QALYs. However, CEUS is more costly than, and is thus dominated by, Gd-CEMRI. CECT and SPIO-CEMRI are now dominated by Gd-CEMRI.

If it is assumed that, instead of 40%, 80% of the initial population has metastases, the expected number of QALYs is 4.078 for all tests (*Table 44*). CEUS is now the least costly strategy, being £71 less costly than CECT. Because there is no difference between the tests in QALYs, the least costly test, CEUS, dominates all other tests.

### *Scenario analyses*

We examined the expected costs and effects using different sources for the accuracy of the tests. First, we incorporated the accuracy data of Jonas *et al.*<sup>50</sup> (*Table 45*). This study compared CEUS, CECT and SPIO-CEMRI and found perfect specificity for all tests, with sensitivities of 87%, 83% and 97% respectively. CECT was slightly more costly (£7) and slightly less effective (0.005 QALYs) than CEUS and thus was dominated by CEUS. SPIO-CEMRI was more costly and more effective than CEUS, resulting in an ICER of £43,318 per QALY gained.

The slightly lower sensitivity and specificity of CECT compared with CEUS found by Clevert *et al.*<sup>51</sup> resulted in CEUS being £300 less costly and yielding 0.002 more QALYs than CECT (*Table 46*).

TABLE 42 Costs, effects and cost-effectiveness results for detection of metastases from CRC

Strategy	Cost (£)	QALYs	Compared with CEUS		Compared with next most cost-effective strategy		
			Incremental cost (£)	Incremental QALYs	Incremental cost (£)	Incremental QALYs	Incremental cost per QALY (£)
CEUS	7511	8.364					
CECT	7510	8.364	-1	0.000	-1	0.000	Dominant
Gd-CEMRI	7688	8.364	177	0.000	178	0.000	Dominated
SPIO-CEMRI	7722	8.364	211	0.000	212	0.000	Dominated

TABLE 43 Results of sensitivity analysis for metastases from CRC model: no biopsy if test is positive

Strategy	Cost (£)	QALYs	Compared with CEUS		Compared with next most cost-effective strategy		
			Incremental cost (£)	Incremental QALYs	Incremental cost (£)	Incremental QALYs	Incremental cost per QALY (£)
CEUS	8335	8.343					
CECT	7321	8.359	-1015	0.016	-1015	0.016	Dominant
Gd-CEMRI	7158	8.364	-1177	0.021	-162	0.005	Dominant
SPIO-CEMRI	7537	8.359	-798	0.016	-379	0.005	Dominated

TABLE 44 Results of sensitivity analysis for metastases from CRC model: proportion of patients having metastases = 80%

Strategy	Compared with CEUS			Compared with next most cost-effective strategy			
	Cost (£)	QALYs	Incremental cost (£)	Incremental QALYs	Incremental cost (£)	Incremental QALYs	Incremental cost per QALY (£)
CEUS	14,419	4.078					
CECT	14,490	4.078	71	0.000	71	0.000	Dominated
Gd-CEMRI	14,700	4.078	281	0.000	281	0.000	Dominated
SPIO-CEMRI	14,711	4.078	292	0.000	292	0.000	Dominated

TABLE 45 Results of scenario analysis for metastases from CRC model: Jonas et al.<sup>50</sup> used as source for accuracy data

Strategy	Compared with CEUS			Compared with next most cost-effective strategy			
	Cost (£)	QALYs	Incremental cost (£)	Incremental QALYs	Incremental cost (£)	Incremental QALYs	Incremental cost per QALY (£)
CEUS	7468	8.369					
CECT	7475	8.364	7	-0.005			Dominated
SPIO-CEMRI	8055	8.382	587	0.014	587	0.014	43,318

TABLE 46 Results of scenario analysis for metastases from CRC model: Clevert et al.<sup>51</sup> used as source for accuracy data

Strategy	Compared with CEUS			Compared with next most cost-effective strategy			
	Cost (£)	QALYs	Incremental cost (£)	Incremental QALYs	Incremental cost (£)	Incremental QALYs	Incremental cost per QALY (£)
CEUS	7821	8.384					
CECT	8121	8.382	300	-0.002	300	-0.002	Dominated

### Probabilistic sensitivity analyses

Based on the probabilistic sensitivity analysis with 5000 replications, we found that CEUS and CECT have a similar probability of being cost-effective across all willingness-to-pay thresholds (*Figure 14*). CEUS has a slightly higher probability of being cost-effective up to a threshold of £20,000, after which CECT has a somewhat higher probability of being cost-effective. At a threshold of £20,000 per QALY, CECT has the highest probability of being cost-effective (48%), followed by CEUS (47%), Gd-CEMRI (3%) and SPIO-CEMRI (2%).

### Incidentally detected focal liver lesion model

#### Effectiveness

*Table 47* shows the effectiveness results from the base-case analysis. Two pairs of results are shown here: the first pair shows the results of CEUS compared with CECT, and the second pair shows the results of CEUS compared with CEMRI. The two sets are kept separate because four studies compared CEUS with CECT whereas one study compared CEUS with CEMRI. Very small differences in effectiveness (life-years and QALYs) were seen between CEUS and the two comparators. This was to be expected as the test performance results of the tests were not very different.

#### Costs

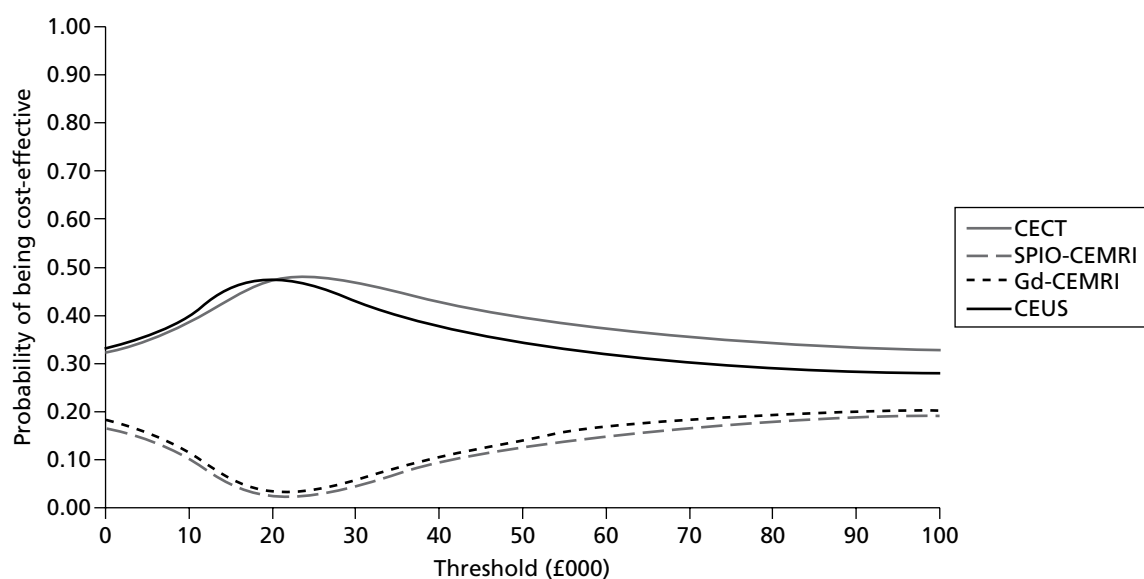
As with the effectiveness results, the small differences in test performance results resulted in small differences in overall costs (*Table 48*). The critical factor for any difference in costs is simply the cost of the initial test.

#### Cost-effectiveness

The following results were seen in the base-case analysis (*Table 49*). As expected, the lower costs of CEUS combined with the slightly better test performance meant that CEUS dominated both CECT and CEMRI. The main factor in these calculations was the cost of the tests.

#### Additional analyses

Additional analyses changed the absolute costs and effectiveness of the different strategies; however, this did not lead to any dramatic changes in the incremental costs and effectiveness of CEUS compared with CECT or CEMRI. The most critical factor in the analyses related to the costs of the tests. The impact of any



**FIGURE 14** Cost-effectiveness acceptability curves: liver metastases from CRC (effects are QALYs; both costs and effects are discounted).

**TABLE 47** Base-case effectiveness results (discounted) for characterisation of incidentally detected FLLs

Comparisons	Life-years	QALYs
CEUS (vs CECT)	17.205	13.330
CECT	17.205	13.330
CEUS (vs CEMRI)	17.204	13.329
CEMRI	17.201	13.327

**TABLE 48** Base-case cost results (£) for the incidentally detected FLL model

	CEUS (vs CECT)	CECT	CEUS (vs CEMRI)	CEMRI
Initial assessment	73.5	125	112.6	242
Initial imaging	64.7	116	64.7	189
False-positive costs	8.9	9.9	47.9	53
Treatment	397	397	398	400
Metastases	159	159	160	160
HCC	9	9	9	9
Other malignancies	183	183	183	184
Adenoma	46	46	47	47
Total	471	522	511	642

**TABLE 49** Base-case cost-effectiveness results for the incidentally detected FLL model

Comparison	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
CEUS vs CECT	-52	0.0002	Dominant
CEUS vs CEMRI	-131	0.0026	Dominant

other elements (e.g. prior probabilities of a particular diagnosis, costs of treatment) was minimal because the accuracies of the tests were so similar.

### Sensitivity analyses

The first sensitivity analysis involved varying the prior probability of malignancy to a value much higher than that used in the base-case scenario. In this analysis, the prior probability was raised from the base-case value of 2.89% to 94% [based on the highest percentages for HCC and metastasis reported in the individual studies (58% of patients with HCC<sup>52</sup> and 36% of patients with metastases)].<sup>55</sup> Although this exceptionally high probability of malignancy was not viewed as realistic in daily practice, it was seen as a way to explore the degree of robustness of the results. As expected, the higher probability of malignancy reduced the absolute number of QALYs and increased the costs (*Table 50*). However, it increased the incremental QALYs only slightly and had no effect on incremental costs and therefore essentially had no effect on the cost-effectiveness of CEUS compared with CECT or 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.



**TABLE 50** Results of sensitivity analysis for the incidentally detected FLL model: prior probability of malignancy increased to the maximum observed frequencies of HCC and metastasis (any type)

Comparison	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	Incremental cost per QALY (£)
CEUS (vs CECT)	6.654	17,121	0.005	-56	Dominant
CECT	6.649	17,177			
CEUS (vs CEMRI)	6.614	17,160	0.086	-202	Dominant
CEMRI	6.529	17,362			

We also examined the effect on the results of assuming that all patients with HCC had medium-sized lesions instead of small lesions. When we applied this in the model and also increased the risk of HCC to the highest value seen in the DTA studies (58% of patients with HCC<sup>52</sup>), there was no effect on the cost-effectiveness of CEUS compared with CECT or CEMRI.

When the consequences of an incorrectly diagnosed malignant lesion were made more severe (i.e. by reducing QALYs or increasing costs), this improved the cost-effectiveness of CEUS compared with CECT or CEMRI. For example, if an incorrect diagnosis of HCC and metastases led to a doubling of the costs (compared with the costs following a correct diagnosis) and the QALYs were set to zero, CEUS remained the dominant strategy. *Table 51* shows the results of this analysis.

As expected, when an incorrect diagnosis of HCC or metastases did not result in any health or economic consequences, there was no difference in effectiveness between CEUS, CECT and CEMRI. However, because a difference in costs was still observed, this could be viewed as a situation of extended dominance in both comparisons (*Table 52*).

### **Probabilistic sensitivity analyses**

Probabilistic sensitivity analyses revealed that there was no uncertainty about the cost savings of CEUS compared with CECT (mean difference -£52, 95% CI -£81 to -£22) but some uncertainty about their differences in effectiveness (mean difference 0.00014, 95% CI -0.00100 to 0.00130). Note that these CIs were based on symmetrical beta PERT distributions for the cost parameters. When the original beta PERT distributions were used, a mean difference of -£46 (95% CI -£71 to -£21) was found.

*Figure 15* shows the cost-effectiveness acceptability curve comparing CEUS with CECT. This curve shows that the probability of CEUS being cost-effective compared with CECT is >95% at willingness-to-pay thresholds of up to £20,000.

When the differences in costs and effects between CEUS and CEMRI are visualised on the cost-effectiveness plane, it is clear that there is little doubt about the cost savings of CEUS compared with CEMRI, but some uncertainty about their differences in effectiveness.

The results of probabilistic sensitivity analyses comparing CEUS with CEMRI were similar to those shown above for CEUS compared with CECT. There was less certainty about the expected amount of cost savings of CEUS compared with CEMRI (mean difference -£131, 95% CI -£194 to -£69) and some uncertainty about their differences in effectiveness (mean difference 0.0039, 95% CI -0.0058 to 0.0135). Once again, these calculations were made using symmetrical beta PERT distributions for cost parameters to ensure that the point estimate for the cost difference would correspond with the point estimate based on the deterministic analysis. When the original beta PERT distributions were used, a mean difference of -£125 (95% CI -£183 to -£67) was found.

**TABLE 51** Results of sensitivity analysis for the incidentally detected FLL model: more severe consequences of an incorrect diagnosis of HCC and metastases

Comparison	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	Incremental cost per QALY (£)
CEUS (vs CECT)	13.321	486	0.001	-54	Dominant
CECT	13.320	540			
CEUS (vs CEMRI)	13.312	541	0.020	-162	Dominant
CEMRI	13.293	702			

**TABLE 52** Results of sensitivity analysis for the incidentally detected FLL model: less severe consequences of an incorrect diagnosis of HCC and metastases

Comparison	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	Incremental cost per QALY (£)
CEUS (vs CECT)	13.332	469	0.000	-52	Extended dominance
CECT	13.332	521			
CEUS (vs CEMRI)	13.332	509	0.000	-130	Extended dominance
CEMRI	13.332	639			

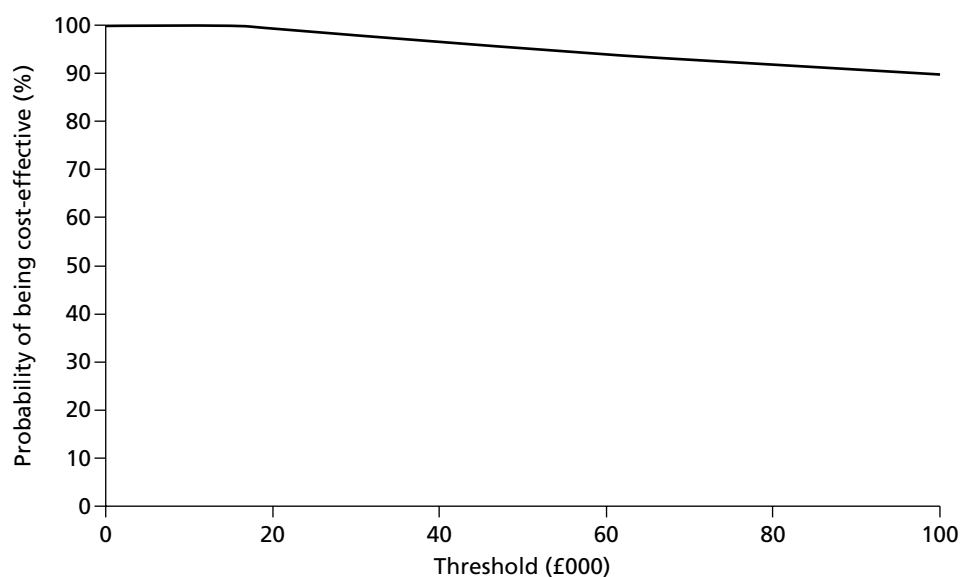
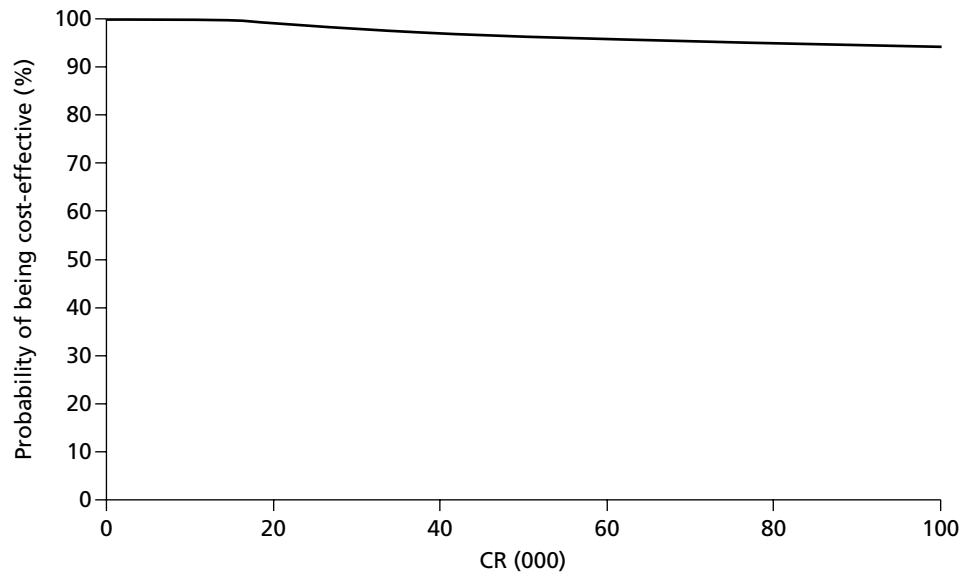
**FIGURE 15** Cost-effectiveness acceptability curve comparing CEUS with CECT: incidentally detected FLL model (effects are QALYs; both costs and effects are discounted).

Figure 16 shows the cost-effectiveness acceptability curve comparing CEUS with CEMRI. Here we see that the probability of CEUS being cost-effective compared with CEMRI is >95% at all willingness-to-pay thresholds between £0 and £20,000.



**FIGURE 16** Cost-effectiveness acceptability curve comparing CEUS with CEMRI: incidentally detected FLL model (effects are QALYs; both costs and effects are discounted).

# Chapter 5 Discussion

## Statement of principal findings

### *Clinical effectiveness*

Twenty of the 21 studies included in the systematic review were DTA studies: seven compared the performance of imaging modalities for the characterisation of FLLs detected on surveillance of cirrhosis patients using unenhanced US; four compared the performance of imaging modalities for the detection of liver metastases in patients with known primary cancers; six compared the performance of imaging modalities for the characterisation of incidentally detected FLLs identified by unenhanced US; and three compared the performance of imaging modalities for the determination of treatment response in patients with liver cancers.

The only controlled clinical trial identified indicated that the inclusion of CEUS in pretreatment imaging protocols for patients undergoing RFA for HCC may result in a reduced incidence of disease progression, new HCC and repeat RFA, and increased local progression-free and new tumour-free survival, compared with unenhanced US. However, this was a small non-randomised study that had a number of methodological weaknesses and no difference was found in the primary outcome of successful ablation. High-quality RCTs are needed to determine the relative effectiveness of different imaging strategies for treatment planning.

Test accuracy studies varied in terms of target condition (HCC, liver metastases or 'any malignancy'), definitions of a positive imaging test used by studies of the same target condition, 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 clinical indications assessed. This is consistent with two other recently published systematic reviews, which found no significant difference in the performance of CEUS, CECT and CEMRI for the characterisation of FLLs.<sup>11,104</sup> Neither of these two reviews reported details of the clinical application of imaging in the included studies (i.e. were FLLs incidentally detected, detected on surveillance or detected during the assessment for liver metastases in patients with known primary cancers) or of the target conditions (e.g. HCC, liver metastases or 'any liver malignancy'), and one review<sup>104</sup> did not specify the use of SonoVue as the contrast agent for CEUS.

The majority of included test accuracy studies were judged to be at 'low' or 'unclear' risk of bias with respect to the 'index test', 'comparator test' and 'reference standard' domains. 'Unclear' ratings for these domains most frequently arose from insufficient detail in the reporting of how tests were interpreted, particularly blinding of interpreters to other test results. Reporting quality was generally poor and a number of studies were reported only as conference abstracts, resulting in a high proportion of 'unclear' risk of bias ratings across QUADAS-2 domains (see *Figure 7*). 'High' risk of bias ratings for the 'patient selection' domain arose from the use of a retrospective study design or from inappropriate exclusions of particular patient groups (e.g. exclusion of patients with a low probability of malignancy); exclusion of patients with a low probability of disease might result in underestimations of test accuracy, although this was not apparent from the results observed. 'High' risk of bias ratings for the 'flow and timing' domain arose from exclusion of >10% of patients from analyses or, in two cases, from incorporation of index test results in the reference standard. The last two studies were also rated as 'high' risk of bias for the 'reference standard' domain.

Test accuracy studies included in this review were grouped by clinical application: characterisation of FLLs detected on routine unenhanced US surveillance of patients with known cirrhosis, detection of liver metastases in patients with known primary tumours (CRC), characterisation of FLLs in patients with incidentally detected lesions and assessment of response in patients treated for liver malignancy.

Studies conducted in cirrhosis patients undergoing routine surveillance all concerned the differentiation of HCC from other lesion types in small to medium-sized (<30 mm) FLLs. The definition of a positive test for HCC varied across studies. Studies assessing CEMRI used three contrast agents: gadolinium, a vascular contrast agent; SPIO, a hepatocyte-specific contrast agent which is taken up by Kupffer cells in the normal liver and benign lesions and may therefore aid identification of HCC, which are generally deficient in Kupffer cells, particularly when such lesions are hypervascular;<sup>8,9</sup> and Gd-EOB-DTPA-CEMRI, a 'combined' vascular and hepatocyte-specific contrast agent.<sup>10</sup> There was no consistent evidence for any significant difference in test performance between the three imaging modalities and three MRI contrast media assessed. When a definition of HCC consistent with that given in the EFSUMB guidelines<sup>6</sup> (arterial phase enhancement followed by portal venous/late phase washout) was used, estimates of the sensitivity and specificity of each of the imaging modalities assessed varied across studies. There was some evidence from one study that compared CEUS and Gd-CEMRI that these imaging techniques may be better at ruling out HCC in FLLs of between 11 and 30 mm (sensitivities for CEUS and Gd-CEMRI were 92% and 95% respectively) than in small FLLs of  $\leq 10$  mm (sensitivities of 27% and 73% respectively), although this study did not use an EFSUMB-consistent definition of HCC. It is therefore possible that some of the variation in sensitivity estimates seen across studies of FLLs of <30 mm may be due to differences in the size distribution of FLLs included. There was also some evidence from two studies that combined imaging using CEUS and CECT or all three imaging modalities, in which any positive imaging result was treated as 'test positive', that combined imaging may increase sensitivity. Inconsistent estimates of sensitivity mean that it is unclear whether or not CEUS alone is adequate to rule out HCC for FLLs of <30 mm in this population; CEUS alone may be adequate to rule out HCC for FLLs of 11–30 mm, with very small FLLs (<10 mm) not considered.

Studies of the diagnosis of liver metastases using imaging with vascular contrast media (CEUS, CECT and Gd-CEMRI) in which definitions of a positive imaging test were reported gave various descriptions of peripheral rim enhancement as the criteria for liver metastases. Two studies also reported data for SPIO-CEMRI. There was no consistent evidence for any difference in test performance between the three imaging modalities and the different contrast media assessed. Per-patient sensitivity estimates from two studies were generally high [83% for all imaging modalities and both MRI contrast agents in one study of patients with CRC and >95% for both CEUS and CECT in a second study of patients with various primary cancers (majority CRC)]. The only previous systematic review identified, which assessed SonoVue CEUS for the diagnosis of liver metastases, did not include any comparator tests and reported sensitivities for CEUS ranging from 79% to 100%. The limited data available indicate that CEUS alone may be adequate to rule out liver metastases in patients with known primary malignancies.

The primary outcome measure reported by studies conducted in patients with incidentally detected FLLs was test accuracy for the differentiation of malignant from benign liver lesions. Studies consistently used definitions of the imaging criteria for HCC and liver metastases that were similar to those reported in the EFSUMB guidelines on the use of CEUS.<sup>6</sup> All studies reported no significant difference in the accuracy of CEUS and CECT or CEMRI for the characterisation of FLLs. All but one study reported data for one lesion per patient and the remaining study reported data for 694 lesions in 686 patients; data were therefore treated as per patient. The pooled estimates of sensitivity for the identification of 'any liver malignancy' were approximately 95% for both CEUS and CECT and the pooled estimates of specificity were 94% and 93%, respectively, based on data from four studies. The single study comparing CEUS with CEMRI used Gd-CEMRI in all patients, with the addition of SPIO-CEMRI in an unspecified number of cases, and reported sensitivity estimates of 91% and 82%, respectively, and corresponding specificity estimates of 67% and 63%. Data from one study indicated that combined imaging using both CEUS and CECT, in which a positive result on either modality was treated as 'test positive', did not increase sensitivity. This, combined with the high estimates of sensitivity, indicates that CEUS alone may be adequate to rule out liver malignancy in this population.

Two Chinese-language studies comparing imaging modalities for the assessment of response to treatment (cryosurgery and non-surgical treatment) in patients with HCC reported per-lesion sensitivity estimates of >95% and specificity estimates of >80% for complete response, using CEUS, CECT and CECT or Gd-CEMRI.

These data indicate that CEUS may provide information on response in patients treated for HCC. However, these data are very limited and may not be directly applicable to UK clinical practice; further studies, ideally conducted in a UK setting, are required to confirm findings. The possibility of the rapid detection of residual tumour tissue using CEUS has the potential to allow the immediate extension of interstitial therapy; however, no data were identified on any therapeutic consequences of using CEUS to assess response to initial treatment.

### Cost-effectiveness

The cost-effectiveness analysis of the use of CEUS in patients with an inconclusive unenhanced US test indicated that the use of CEUS instead of CEMRI was considered 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, whereas the two techniques were similar in terms of costs and effects in the detection of liver metastases from CRC.

In the surveillance of cirrhosis, CEUS was found to be as effective as but £379 less costly than CECT. This indicates that CEUS dominates CECT. Gd-CEMRI was found to be £1063 more costly than CEUS and gained 0.022 more QALYs. This resulted in an ICER of £48,545 per QALY gained. This ICER is deemed unacceptable given the currently used willingness-to-pay thresholds of £20,000 and £30,000 per additional QALY. CEUS can therefore be considered the most cost-effective option after inconclusive unenhanced US. These base-case results were based on one source for accuracy, the study by Leoni *et al.*<sup>42</sup> Using the two other studies that compared CEUS and CECT corroborated the dominance of CEUS over CECT, showing even lower effectiveness for CECT. Compared with Gd-CEMRI, CEUS was cost-effective in most sensitivity analyses, except when all positive unenhanced US examinations were subject to confirmatory testing instead of the inconclusive US examinations, and when the proportion of patients having an inconclusive US scan was considerably lower (20% instead of 43%). These two analyses resulted in acceptable ICERs for Gd-CEMRI compared with CEUS of £12,806 and £16,121 respectively.

In the diagnosis of liver metastases from CRC, CEUS was found to have similar costs and effects to those of CECT. Using a lifetime time horizon the two techniques yielded equal QALYs per patient, with CEUS costing £1 more than CECT. Both Gd-CEMRI and SPIO-CEMRI were dominated by CECT in this population because they were more costly and equally as effective. However, in the base-case analysis it was assumed that patients who were incorrectly diagnosed with liver metastases would receive a biopsy before they were treated and that this mistake would be discovered. If this is not assumed and patients could receive unnecessary treatment, the lower specificity of CEUS had larger consequences. Under this assumption, CEUS is both the most costly and the least effective option, and Gd-CEMRI dominates all other tests. However, it is questionable whether or not this would occur in practice. If the proportion of patients having metastases were higher, CEUS would dominate the other tests. Based on the two other studies that reported accuracy data in this population,<sup>50,51</sup> CEUS was found to dominate CECT. Gd-CEMRI yielded 0.014 more QALYs but was also £587 more costly than CEUS, resulting in an ICER of £43,318 per QALY gained. As this is above the willingness-to-pay threshold of £30,000 per QALY, Gd-CEMRI is deemed not cost-effective compared with CEUS.

The final evaluation involved the comparison of CEUS with CECT and CEMRI in the characterisation of incidentally detected FLLs. In the base-case analysis, no large differences in effectiveness were found between the three imaging strategies (incremental QALYs: CEUS vs CECT: 0.00016; CEUS vs CEMRI: 0.0026). However, a difference in costs was found (CEUS vs CECT: -£52; CEUS vs CEMRI: -£131) and this resulted in a situation of dominance. Probabilistic sensitivity analysis revealed that there was little uncertainty about the cost-effectiveness of CEUS compared with the other two tests. Additional analyses changed the absolute costs and effectiveness of the different strategies but did not lead to dramatic changes in the incremental costs and effectiveness of CEUS compared with CECT or CEMRI. One critical factor in the analyses related to the costs of the tests. This could mean that local conditions may play a role in deciding which test is preferable, assuming that the costs of these tests can be influenced by local conditions.

## Strengths and limitations of the assessment

### *Clinical effectiveness*

Extensive literature searches were conducted in an attempt to maximise retrieval of relevant studies. These included electronic searches of a variety of bibliographic databases, as well as screening of clinical trials registers and conference abstracts to identify unpublished studies. Because of the known difficulties in identifying test accuracy studies using study design-related search terms,<sup>20</sup> search strategies were developed to maximise sensitivity at the expense of reduced specificity. Thus, large numbers of citations were identified and screened, many of which did not meet the inclusion criteria of the review.

The possibility of publication bias remains a potential problem for all systematic reviews. Considerations may differ for systematic reviews of test accuracy studies. It is relatively simple to define a positive result for studies of treatment, for example a significant difference between the treatment and control groups that favours treatment. This is not the case for test accuracy studies, which measure agreement between index test and reference standard. It would seem likely that studies finding greater agreement (high estimates of sensitivity and specificity) will be published more often. In addition, test accuracy data are often collected as part of routine clinical practice, or by retrospective review of records; test accuracy studies are not subject to the formal registration procedures applied to RCTs and are therefore more easily discarded when results appear unfavourable. The extent to which publication bias occurs in studies of test accuracy remains unclear; however, simulation studies have indicated that the effect of publication bias on meta-analytic estimates of test accuracy is minimal.<sup>105</sup> Formal assessment of publication bias in systematic reviews of test accuracy studies remains problematic and reliability is limited.<sup>105</sup> We did not undertake a statistical assessment of publication bias in this review; however, our search strategy included a variety of routes to identify unpublished studies and resulted in the inclusion of a number of conference abstracts.

Clear inclusion criteria were specified in the protocol for this review and the one protocol modification that occurred during the assessment has been documented in *Chapter 3* of this report (see *Inclusion and exclusion criteria*). The eligibility of studies for inclusion is therefore transparent. In addition, we have provided specific reasons for excluding all of the studies considered potentially relevant at initial citation screening (see *Appendix 5*). The review process followed recommended methods to minimise the potential for error and/or bias.<sup>16</sup> Studies were independently screened for inclusion by two reviewers and data extraction and quality assessment were carried out by one reviewer and checked by a second (MW and VG). Any disagreements were resolved by consensus. Chinese-language studies were extracted by one reviewer (MW) working with a native speaker (KL) and the only German-language study was extracted by one reviewer (VG).

With one exception, all studies included in the review were test accuracy studies. The methodological quality of these studies was assessed using a modification of the QUADAS-2 tool.<sup>25</sup> The QUADAS tool has been recommended for assessing the methodological quality of test accuracy studies<sup>16,18</sup> and has been widely adopted by researchers and key organisations such as The Cochrane Collaboration, NICE and the Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) in Germany. It has been mentioned in more than 200 abstracts in the DARE database and has been cited more than 500 times. The revised version of QUADAS (QUADAS-2) has recently been published.<sup>25</sup> QUADAS-2 more closely resembles the approach and structure of the Cochrane risk of bias tool. It is structured into four key domains covering participant selection, index test, reference standard and the flow of patients through the study (including the timing of tests). Each domain is rated for risk of bias (low, high or unclear) and the tool provides signalling questions in each domain to help reviewers in reaching a judgement. The participant selection, index test and reference standard domains are also separately rated for concerns regarding the applicability of the study to the review question (low, high or unclear). However, the QUADAS-2 tool does not currently include domains specific to the assessment of studies comparing multiple index tests; further development of QUADAS-2 in this area is planned. This assessment used a modified version of the QUADAS-2 tool that includes an additional domain for the comparator test and additional signalling questions in the flow and timing domain. It should be noted, however, that these components of the tool

were not developed using the same rigorous evidence-based approach as for the core QUADAS-2 tool. The inclusion criteria for this review were considered to largely match the review question and questions of applicability were therefore relevant only to the patient selection domain. The review-specific guidance used in our QUADAS-2 assessment is reported in *Appendix 2*. The results of the risk of bias assessment are reported in full for all included studies in *Appendix 3* and in summary in *Chapter 3* (see *Results of the assessment of clinical effectiveness*). However, the usefulness of this assessment was limited by poor reporting of primary study methods, particularly with respect to how the index and comparator tests and the reference standard were applied. This issue was exacerbated because four of the 20 test accuracy studies (20%) were reported only as conference abstracts.

The systematic review conducted for this assessment represents an improvement on previously published systematic reviews<sup>11,104,106</sup> in that it focuses on studies that directly compared the performance of SonoVue CEUS with at least one other imaging modality, as well as clearly distinguishing between both the clinical application and the target condition of imaging.

Hierarchical or bivariate models are considered the optimal methods for estimating SROC curves and pooled estimates of sensitivity and specificity.<sup>16,27</sup> The bivariate model analyses sensitivity and specificity jointly, retaining the paired nature of the original data, and has been shown to produce equivalent results to the hierarchical SROC model in the absence of other study-level covariates.<sup>28</sup> However, the fitting of this model requires a minimum of four data sets. There was only one group of four studies in this assessment for which meta-analytic pooling was considered potentially appropriate (similar clinical application, target condition and comparator test). One of these studies used a suboptimal reference standard and a sensitivity analysis was used to investigate the influence of this study upon the overall estimate of test performance, reducing the data set to three studies; for this reason, a random-effects model was used to generate pooled estimates of sensitivity and specificity, with 95% CIs.

In addition to the limited potential for meta-analysis and the general methodological quality issues outlined above, there were a number of reporting/methodological problems specific to this review. Of particular concern for this assessment was the way in which data were reported in terms of the unit of analysis. The main reason for undertaking liver imaging in the populations considered is likely to be to rule out primary liver cancer or liver metastases. Therefore, patient-level analyses of test performance are of particular interest. Some of the studies included in this review reported per-patient analyses; however, no study clearly stated how per-patient test results were defined (e.g. was the presence of any positive lesion regarded as a positive test for the whole patient). Some of the included studies reported per-lesion data (multiple lesions per patient). These type of within-patient 'clustered' data are a common feature of test accuracy studies and are likely to result in a correlation between results within each patient, which should be accounted for in any statistical analysis.<sup>107</sup> Uncorrected estimates of sensitivity and specificity derived from such data are likely to be accurate, but imprecision will be underestimated.<sup>107</sup> Of greater concern are those studies that reported data for one lesion per patient (treated as per-patient data in this assessment) but in which multiple lesions per patient were present, as was the case for the majority of studies evaluating SonoVue CEUS for the characterisation of incidentally detected FLLs.<sup>52,54-56</sup> These studies generally selected the largest lesion or the lesion 'most suspicious for malignancy' for inclusion in analyses, with the result that estimates of test performance may have been exaggerated. It might be argued that, when considering the ability of a test to rule out malignancy, performance for the characterisation of smaller ambiguous lesions is an important consideration.

All assessments of diagnostic accuracy are underpinned by the assumption that the reference standard, against which the index and comparator tests are evaluated, is 100% sensitive and 100% specific. The inclusion criteria specified by the protocol for this assessment allowed the use of different reference standards for test-positive and test-negative patients (histology and clinical follow-up respectively). This approach was used because it may be considered unethical to perform biopsy of test-negative patients or lesions. However, delayed verification, as represented by clinical follow-up, is inherently flawed in that follow-up must be of sufficient duration for any false-positive or false-negative test results to become



apparent, but prolonged follow-up may also result in changes in disease state and hence misclassification of test results. In addition, a protocol modification allowed the inclusion of studies on the characterisation of FLLs (suspected HCC) that used EASL/AASLD non-invasive diagnostic criteria (two concordant imaging test results) as the reference standard. Two additional studies were included in the review as a result of this protocol modification.<sup>42,41</sup> Studies using this type of reference standard may be subject to incorporation bias. However, the implications of this are unclear; the review of sources of variation and bias in test accuracy studies, conducted as part of the development of QUADAS, found no evidence on the effects of incorporation bias,<sup>23</sup> and the update of this review, conducted during the development of QUADAS-2, found two contradictory studies, one reporting no effect of incorporation bias on accuracy and one reporting increased sensitivity and reduced specificity in the presence of incorporation bias (unpublished data).

The clinical applicability of accuracy data included in this review may have some limitations. The inclusion criteria for this assessment specified that SonoVue CEUS should be used for the characterisation of FLLs when unenhanced US examination was considered inconclusive. Although all study participants had imaging-detected FLLs before undergoing SonoVue CEUS, only one study<sup>43</sup> explicitly stated that unenhanced US was inconclusive. Perhaps more importantly, the prevalence of malignancy appeared high in studies assessing the accuracy of CEUS and other imaging modalities for the characterisation of incidentally detected FLLs; these study populations may not be representative of the population with incidental FLLs seen in clinical practice. When any information on the interpretation of CEUS was reported (see *Appendix 4*), the majority of DTA studies included in this review reported consensus interpretation by multiple experienced operators (experience ranging from >2 years to 20 years). It should be noted that operator training and experience may have important effects on the diagnostic performance of CEUS, but insufficient data are currently available to explore these potential effects.

The majority of included studies reported no information on funding; two studies reported funding from the manufacturer of SonoVue.<sup>55,56</sup>

### Cost-effectiveness

In this study we built three separate models for the three different potential uses of CEUS: surveillance of cirrhosis, detection of liver metastases from CRC and characterisation of incidentally detected FLLs. All three models were based on existing models that had previously informed NICE guidance.<sup>70,71</sup> When necessary we updated and improved these models. The model for incidentally detected FLLs was a combination of the two updated and improved models.

In each of the three analyses we used evidence to inform parameters that was relevant for the UK and as up-to-date and of as high a quality as possible. When evidence was not available from published studies or databases, we used the most likely and plausible ranges based on expert opinion.

As expected, the main driver of the models was the accuracy of the different tests. There was only one group of four studies in this assessment for which meta-analytic pooling was considered potentially appropriate (similar clinical application, target condition and comparator test): the use of CEUS to characterise incidentally detected FLLs. As a consequence, the estimated cost-effectiveness of CEUS for the surveillance of cirrhosis and the diagnosis of liver metastases from CRC had to be based on single studies. Scenario analyses were performed using other available studies and these analyses showed that in general the source for accuracy influences the costs and effects of the different tests. However, the use of different sources resulted in similar conclusions. CEUS was found to be the most cost-effective test for the surveillance of cirrhosis, and the two alternative sources for the liver metastases model produced favourable results for CEUS.

In general, the studies used to estimate test accuracy appeared to involve different types of patient populations. The studies used for the incidentally detected FLL model, for example, defined incidentally detected FLLs in different ways. Interestingly, regardless of the variation in composition of the patient

populations, there was never an instance when the test accuracy results of CEUS and CECT were very different. All studies concluded that the two tests were comparable in performance.

Another main driver was the clinical pathway of incorrectly diagnosed patients. Although the pathway may be straightforward for false-negative patients, as their disease may be correctly diagnosed at a later stage of the initial workup, it is not as clear for false-positive patients. In the liver metastases from CRC model we assumed that patients who are inaccurately diagnosed as having metastases would receive biopsy before treatment. This implies that patients were not unnecessarily treated. However, it is unclear what happens to these patients in practice. Therefore, we performed a sensitivity analysis in which patients without metastases were treated if they were incorrectly diagnosed. In this sensitivity analysis CEUS was found to be the least effective and most costly option. Although we do not expect it to be realistic that patients without metastases will actually receive treatment, it is important to note this factor.

Besides being less costly, CEUS has the advantage compared with CECT and especially CEMRI that it is highly accessible. All patients already receive an unenhanced US examination and can be immediately diagnosed using CEUS as part of the same examination. A potential benefit of CEUS is therefore the reduction in anxiety in patients because a malignant lesion is ruled out sooner as a result of not having to wait too long for another test. This benefit was not taken into account in the analysis as little evidence is available on the effect of anxiety on quality of life. It might be expected that the effects of using CEUS are therefore underestimated. Although the length of wait associated with other imaging modalities is uncertain, the consideration of this anxiety factor would only further support the use of CEUS over CECT or CEMRI.

## Uncertainties

### Clinical effectiveness

None of the clinical applications of liver imaging considered in this review was evaluated by a large number of studies; the maximum was seven studies on the performance of imaging modalities for the characterisation of FLLs detected on surveillance of cirrhosis patients using unenhanced US. Although this review benefits from focusing on studies that directly compared the performance of SonoVue CEUS with that of other imaging modalities, as noted above in the strengths and limitations section, only two studies on the characterisation of FLLs detected on surveillance of cirrhosis patients<sup>42,47</sup> and two studies on the detection of liver metastases in patients with known primary cancers<sup>49,50</sup> compared all three imaging modalities under assessment (CEUS, CECT and CEMRI). Most studies that assessed CEMRI used gadolinium-based vascular contrast agent, which has a comparable mode of operation with that of CEUS and CECT. However, CEMRI of the liver can also be conducted using hepatocyte-specific contrast agents such as SPIO or 'combined' vascular and hepatocyte-specific agents such as Gd-EOB-DTPA; only four of the studies included in our systematic review reported data for these types of contrast agent.<sup>42,49,48,50</sup> Studies were generally small (15 of the 20 DTA studies included fewer than 100 participants) and, within clinical applications, studies varied in terms of target condition (HCC, liver metastases or 'any malignancy'), definitions of a positive imaging test used by studies of the same target condition, comparator imaging technologies and lesion size assessed. In addition, four of the 20 test accuracy studies were reported only as conference abstracts,<sup>39-41,50</sup> which further limited the available data. These factors meant that, as detailed above in the statement of principal findings for the clinical effectiveness assessment, only one meta-analysis was undertaken (studies comparing CEUS with CECT for the characterisation of incidentally detected FLLs). Based on the available data, SonoVue CEUS appeared to offer similar diagnostic performance to that of other imaging modalities (CECT and CEMRI) for all clinical applications considered, but data were generally insufficient to support firm conclusions.

SonoVue CEUS is generally used for the characterisation or detection of liver lesions in patients for whom unenhanced US examination has proved inconclusive. In addition to test accuracy, it is therefore particularly important to assess the proportion of patients in whom US examination remains inconclusive

even after contrast-enhancement compared with the proportion in whom comparator imaging technologies are inconclusive. Four of the 20 DTA studies included in this review explicitly reported the numbers of participants in whom imaging was inconclusive; three studies indicated that SonoVue CEUS was inconclusive in slightly fewer patients than CECT (0%,<sup>51</sup> 3%<sup>46</sup> and 3%<sup>54</sup> for SonoVue CEUS compared with 14%,<sup>51</sup> 8%<sup>46</sup> and 6%<sup>54</sup> for CECT). One study reported 11% inconclusive imaging results for both SonoVue CEUS and CEMRI.<sup>56</sup> Although not explicitly stated, all other included studies appeared to report complete data sets and hence may be inferred to have had no inconclusive imaging examinations.

When diagnostic accuracy is comparable across imaging modalities, comparison of adverse event rates associated with the different imaging options, as well as consideration of patients' preferences, are also of particular importance. Only one of the DTA studies included in this review reported any information on adverse events related to testing; the authors of this study stated that there were no adverse events associated with SonoVue CEUS but did not report any information about the comparator technology Gd-CEMRI.<sup>45</sup> A large, retrospective safety study of SonoVue CEUS in abdominal applications, which did not meet the inclusion criteria for this review, reported data from 23,188 investigations in 29 centres in Italy.<sup>7</sup> This study found 29 cases of adverse events, of which two were graded as serious, one as severe, three as moderate and 23 as mild. There were no fatal adverse events. One of the serious adverse events occurred in a patient with prostate cancer who was being investigated to characterise a liver lesion suspected of metastases; this patient complained of dyspnoea with signs of bronchoplasm, slight hypotension and bradycardia within 1 minute after injection of SonoVue. The majority of non-serious adverse events resolved without intervention and included itching, mild dizziness, moderate hypotension, headache, sensation of warmth and nausea and vomiting. None of the studies identified reported any information on patient preferences.

Acceptability to patients and the potential for reduced anxiety provided by the ability to conduct CEUS at the same appointment as the initial US examination are also likely to be important factors in the choice of imaging modality; however, no studies were identified that reported these outcome measures.

It should be further noted that, although this review provides some evidence on the accuracy of SonoVue CEUS for the characterisation of FLLs and the detection of liver metastases and response to treatment of liver cancers, only one study<sup>59</sup> was identified that reported the effects of imaging with SonoVue on patient outcomes; the ultimate aim of any research on clinical tests should be to determine impact on patient management and clinical outcomes. As described earlier in the statement of principal findings for the clinical effectiveness assessment, this study indicated that the inclusion of CEUS in pretreatment imaging protocols for patients undergoing RFA for HCC may result in some improved outcomes compared with unenhanced US. Overall, the effects, if any, of imaging with SonoVue CEUS on management and outcome of patients with FLLs remain uncertain.

### Cost-effectiveness

Many studies emphasised that the participating clinicians had years of experience in the use of CEUS. It is possible that the diagnostic accuracy of CEUS may be poorer if the user has little experience. However, widespread implementation of CEUS might also improve the experience with CEUS and ultimately improve accuracy.

The main uncertainty surrounding the cost-effectiveness of CEUS is how patients who are incorrectly diagnosed are managed. Arguably, this is very different across locations. In the cirrhosis surveillance model, patients are screened twice a year and it is expected that a lesion, although it may have grown and therefore be potentially less treatable, will be detected eventually. In the liver metastases from CRC model, patients with metastases will have associated symptoms and it is therefore justifiable to assume that metastases will be detected within a year. Patients with incidentally detected lesions also often have associated risk factors or evidence of liver disease, which may have been the indication for initial testing with unenhanced US or which may have been identified at this examination; hence, it is expected that their complaints will worsen and that their lesions will be detected within several months. How patients

with a false-positive test result are managed might be more complex. We assumed that, in all models, these patients would receive additional costs of unnecessary additional diagnostic tests but would not undergo inappropriate treatment as the correct diagnosis would be determined after additional diagnostic workup. In the liver metastases of CRC model we examined the extreme situation in which all patients who were incorrectly diagnosed with metastases would receive treatment for these metastases. As this involves the costs of the treatment as well as reduced quality of life, this has a considerable impact on the results.

In the cirrhosis surveillance model, the actual use of CEUS impacted the results. If CEUS were used after all positive instead of after all inconclusive unenhanced US examinations, or if the proportion of inconclusive unenhanced US tests were lower, Gd-CEMRI would be cost-effective compared with CEUS.



# Chapter 6 Conclusions

## Implications for service provision

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 surveillance of cirrhosis patients using unenhanced US, detection of liver metastases in patients with known primary cancers (CRC) and characterisation of incidentally detected FLLs identified by unenhanced US. 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 used by studies of the same target condition, comparator imaging technologies and lesion size assessed. Available data were insufficient to draw firm conclusions of the effectiveness of CEUS in treatment planning and the determination of treatment response.

The cost-effectiveness analysis of the use of CEUS in patients with an inconclusive unenhanced US test indicated that the use of CEUS instead of CEMRI was considered 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, whereas the two techniques were similar in terms of costs and effects in the detection of liver metastases from CRC. Although these conclusions can be very dependent on the actual management of incorrectly diagnosed lesions, it is expected that the use of CEUS can reduce costs without reducing quality of life and survival. It should be noted that experience with using CEUS can have an important impact on diagnostic accuracy.

If the main use of liver imaging in these populations 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 when unenhanced US is inconclusive. A potential advantage of using SonoVue CEUS would be the option of completing the assessment at the same time as the initial unenhanced US examination. 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 (e.g. by avoiding the administration costs of scheduling new appointments).

## Suggested research priorities

All but one of the studies included in our systematic review were DTA studies of liver imaging for the clinical applications specified in our protocol: characterisation of FLLs detected on surveillance of cirrhosis patients using unenhanced US, detection of liver metastases in patients with known primary cancers (CRC), characterisation of incidentally detected FLLs identified by unenhanced US and determination of treatment response in patients with liver cancers. The test accuracy study design compares the results of a new test (index test) with those of the reference standard (which are assumed always to be correct); it is therefore inherently not capable of comparing tests in terms of their ultimate impact on patient outcome. The only study included in this review that reported data on patient outcomes considered the impact on clinical outcomes following treatment of using SonoVue CEUS for pretreatment assessment. This study had a number of methodological limitations and found significant effects of SonoVue CEUS only on secondary outcomes. 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); evaluation in more than one centre is preferred to minimise performance bias. Long-term observational studies assessing the

clinical consequences of incorrect initial diagnoses may also provide an important source of information for future cost-effectiveness analyses. Other potentially important factors that may affect decision-making in the NHS and for which information is currently lacking include patient preferences and the acceptability of different imaging modalities, the potential effects of reduced anxiety arising from a more rapid diagnosis and the potential effects of operator experience on the diagnostic performance of CEUS.

Test accuracy data identified in this assessment were relatively sparse and studies were heterogeneous with respect to the target condition (HCC, liver metastases or 'any malignancy'), definitions of a positive imaging test used by studies of the same target condition, comparator imaging technologies and lesion size assessed. Standardisation of the definition of a positive imaging test for each target condition followed by further high-quality DTA studies are therefore needed to confirm our findings. Future DTA studies should ideally compare the performance of all three imaging modalities (SonoVue CEUS, CECT and CEMRI) in the same patient group and should also report the numbers of patients in whom imaging with each modality is non-diagnostic as well as any 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 QUADAS-2 assessment highlighted limitations in the reporting of many studies included in our review; future studies should follow the STARD (STAndards for the Reporting of Diagnostic accuracy studies) guidelines for reporting test accuracy studies.<sup>108,109</sup>

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## Contribution of authors

Marie Westwood, Viktoria Gloy and Heike Raatz planned and performed the systematic review and interpretation of evidence. Manuela Joore, Janneke Grutters and Ken Redekop planned and performed the cost-effectiveness analyses and interpreted the results. Nigel Armstrong and Kelly Lee contributed to the planning and interpretation of the cost-effectiveness analyses and acquisition of input data for modelling. Kate Misso devised and performed the literature searches and provided information support to the project. Jos Kleijnen and Johan Severens provided senior advice and support to the systematic review and cost-effectiveness analyses respectively. All parties were involved in drafting and/or commenting on the report.





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# Appendix 1 Literature search strategies

## Clinical effectiveness search strategies

### EMBASE (OvidSP): 2000–11 Week 39

Searched 6 October 2011.

1. metastasis/ (154,939)
2. (Metasta\$ or meta-sta\$).ti,ab,ot,hw. (394,219)
3. or/1-2 (394,219)
4. (liver or hepato\$ or hepatic\$).ti,ab,ot,hw. (999,970)
5. 3 and 4 (64,975)
6. exp liver tumor/ (134,843)
7. FLL.ti,ab,ot. (104)
8. FLLs.ti,ab,ot. (41)
9. bile duct carcinoma/ (9888)
10. ((liver\$ or hepat\$) adj3 (cancer\$ or met\$ or malignan\$ or carcinoma\$ or tumo?r\$ or neoplas\$ or adeno\$ or angiom\$ or sarcoma\$ or angiosarcoma\$)).ti,ab,ot,hw. (210,520)
11. (hepatoma\$ or h?emangiosarcoma\$ or h?emangio-sarcoma\$).ti,ab,ot,hw. (24,960)
12. (Focal liver lesion\$ and (cancer\$ or met or mets or metasta\$ or malignan\$ or carcinoma\$ or tumo?r\$ or neoplas\$ or adeno\$ or angiom\$ or sarcoma\$ or angiosarcoma\$)).ti,ab,ot,hw. (845)
13. (BFLL or BFLLS).ti,ab,ot. (5)
14. (HCC or HCCs).ti,ab,ot. (25,130)
15. (Cholangiocarcinoma\$ or Cholangio-carcinoma\$).ti,ab,ot,hw. (6557)
16. (Bile duct\$ adj3 (cancer\$ or met\$ or malignan\$ or lesion\$ or carcinoma\$ or tumo?r\$ or neoplas\$ or adeno\$ or angiom\$ or sarcoma\$)).ti,ab,ot,hw. (18,232)
17. or/5-16 (252,012)
18. Echography/ or Echotomography/ (186,679)
19. ((ultrasonic\$ or ultra-sonic\$) adj4 (scan or imag\$ or echogram\$ or sonogra\$ or detect\$ or diagnos\$ or exam\$)).ti,ot,ab,hw. (7362)
20. (ultraso\$ or ultra-so\$ or sonogra\$ or Echotomogra\$ or Echo-tomogra\$ or echoscope\$ or echosound\$ or Echogra\$ or echogra\$ or tomo-echogra\$ or tomoechogra\$).ti,ot,ab,hw. (413,388)
21. or/18-20 (413,388)
22. Sulfur hexafluoride/ (1199)
23. (hexafluoruro-sulfurico or SF6 or SF-6 or sulphur hexa-fluoride\$ or sulphur hexafluoride\$ or sulfur hexa-fluoride\$ or sulfur hexafluoride\$).af. (2094)
24. or/22-23 (2094)
25. 21 and 24 (328)
26. Sonovist/ or Sonovue/ (1350)
27. (Sonovue or sono-vue or Sonavoid or Sonogen or sonagen or Sonavist).af. (1507)
28. (CE-US or CEUS).ti,ab,ot. (900)
29. ((Sulfur or Sulphur) adj2 (hexafluoride\$ or hexa-fluoride\$) adj4 (US or ultraso\$ or ultra-so\$ or sonogra\$ or Echotomogra\$ or Echo-tomogra\$ or echoscope\$ or echosound\$ or Echogra\$ or tomo-echogra\$ or tomoechogra\$ or imag\$)).af. (30)
30. (SF6US or SF6-US or SF-6US or SF-6-US).af. (0)
31. ((SF6 or SF6 or sulfur hexafluoride\$ or sulfur hexafluoride\$ or sulphur hexafluoride\$ or sulphur hexafluoride\$) adj4 (bubbl\$ or microbubbl\$ or micro-bubbl\$ or micropartic\$ or micro-partic\$)).af. (153)
32. or/26-31 (2114)
33. 25 or 32 (2203)

34. 17 and 33 (676)
35. exp Liver Tumor/di (23,736)
36. bile duct carcinoma/di (2943)
37. metastasis/di (11,811)
38. or/35-37 (36,762)
39. 24 and 38 (40)
40. 34 or 39 (676)
41. limit 40 to yr="2000-Current" (668)
42. limit 41 to embase (613)
43. animal/ or animal experiment/ (3,084,529)
44. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).mp. (4,773,759)
45. or/43-44 (4,773,759)
46. exp human/ or human experiment/ (12,541,220)
47. 45 not (45 and 46) (3,833,028)
48. 42 not 47 (578)

### **MEDLINE (OvidSP): 2000–11 September Week 4**

Searched 6 October 2011.

1. neoplasm metastasis/ or neoplasm seeding/ or neoplasms, unknown primary/ (79,582)
2. (Metasta\$ or meta-sta\$).ti,ab,ot,hw. (311,666)
3. or/1-2 (313,877)
4. (liver or hepat\$ or hepatic\$).ti,ab,ot,hw. (871,423)
5. 3 and 4 (46,193)
6. exp Liver Neoplasms/ (112,995)
7. exp Bile Duct Neoplasms/ (11,958)
8. Carcinoma, Hepatocellular/ (51,056)
9. (FLL or FLLs).ti,ab,ot. (95)
10. Cholangiocarcinoma/ (4146)
11. ((liver\$ or hepat\$) adj3 (cancer\$ or met\$ or malignan\$ or carcinoma\$ or tumo?r\$ or neoplas\$ or adeno\$ or angiom\$ or sarcoma\$ or angiosarcoma\$)).ti,ab,ot,hw. (169,576)
12. (hepatoma\$ or h?emangiosarcoma\$ or h?emangio-sarcoma\$).ti,ab,ot,hw. (27,800)
13. (Focal liver lesion\$ and (cancer\$ or met or mets or metasta\$ or malignan\$ or carcinoma\$ or tumo?r\$ or neoplas\$ or adeno\$ or angiom\$ or sarcoma\$ or angiosarcoma\$)).ti,ab,ot,hw. (712)
14. (BFLL or BFLLS).ti,ab,ot. (3)
15. (HCC or HCCs).ti,ab,ot. (18,801)
16. (Cholangiocarcinoma\$ or Cholangio-carcinoma\$).ti,ab,ot,hw. (6205)
17. (Bile duct\$ adj3 (cancer\$ or met\$ or malignan\$ or lesion\$ or carcinoma\$ or tumo?r\$ or neoplas\$ or adeno\$ or angiom\$ or sarcoma\$)).ti,ab,ot,hw. (14,499)
18. or/5-17 (200,072)
19. ultrasonography/ or ultrasonography, doppler/ or exp ultrasonography, doppler, duplex/ or exp ultrasonography, doppler, pulsed/ (89,811)
20. ((ultrasonic\$ or ultra-sonic\$) adj4 (scan or imag\$ or echogram\$ or sonogra\$ or detect\$ or diagnos\$ or exam\$)).ti,ot,ab,hw. (6823)
21. (ultraso\$ or ultra-so\$ or sonogra\$ or Echotomogra\$ or Echo-tomogra\$ or echoscope\$ or echosound\$ or Echogra\$ or tomoechogra\$ or tomo-echogra\$).ti,ot,ab,hw. (276,299)
22. or/19-21 (280,667)
23. Sulfur Hexafluoride/ (1489)
24. (hexafluoruro-sulfurico or SF6 or SF-6 or sulphur hexa-fluoride\$ or sulphur hexafluoride\$ or sulfur hexa-fluoride\$ or sulfur hexafluoride\$).af. (2150)

25. or/23-24 (2150)
26. 22 and 25 (668)
27. (Sonovue or sono-vue or Sonavoid or Sonogen or sonagen or Sonavist).af. (505)
28. (CE-US or CEUS).ti,ab,ot. (524)
29. ((hexafluoruro-sulfurico or SF6 or SF-6) adj4 (US or ultraso\$ or ultra-so\$ or sonogra\$ or Echotomogra\$ or Echo-tomogra\$ or echoscop\$ or echosound\$ or Echogra\$ or tomoechogra\$ or tomo-echogra\$ or imag\$)).af. (7)
30. ((Sulfur or Sulphur) adj2 (hexafluoride\$ or hexa-fluoride\$) adj4 (US or ultraso\$ or ultra-so\$ or sonogra\$ or Echotomogra\$ or Echo-tomogra\$ or echoscop\$ or echosound\$ or Echogra\$ or tomoechogra\$ or tomo-echogra\$ or imag\$)).af. (28)
31. (SF6US or SF6-US or SF-6US or SF-6-US).af. (0)
32. ((SF6 or SF6 or sulphur hexafluoride\$ or sulphur hexa-fluoride\$ or sulfur hexafluoride\$ or sulfur hexa-fluoride\$) adj4 (bubbl\$ or microbubbl\$ or micro-bubbl\$ or micropartic\$ or micro-partic\$)).af. (213)
33. or/27-32 (1002)
34. 26 or 33 (1197)
35. 18 and 34 (367)
36. exp Liver Neoplasms/us (2714)
37. Carcinoma, Hepatocellular/us (1268)
38. exp Bile Duct Neoplasms/us (375)
39. Cholangiocarcinoma/us (137)
40. Neoplasm Metastasis/us (51)
41. Neoplasm Seeding/ra (1)
42. Neoplasms, Unknown Primary/us (21)
43. or/36-42 (3101)
44. 25 and 43 (163)
45. 35 or 44 (368)
46. limit 45 to yr="2000 -Current" (363)
47. animals/ not (animals/ and humans/) (3,606,824)
48. 46 not 47 (342)

### **MEDLINE In-Process & Other Non-Indexed Citations (OvidSP): 2000–5 October 2011**

#### **MEDLINE Daily Update (OvidSP): 2000–5 October 2011**

Searched 6 October 2011.

1. neoplasm metastasis/ or neoplasm seeding/ or neoplasms, unknown primary/ (66)
2. (Metasta\$ or meta-sta\$).ti,ab,ot,hw. (12,580)
3. or/1-2 (12,581)
4. (liver or hepato\$ or hepatic\$).ti,ab,ot,hw. (21,219)
5. 3 and 4 (1428)
6. exp Liver Neoplasms/ (134)
7. exp Bile Duct Neoplasms/ (6)
8. Carcinoma, Hepatocellular/ (99)
9. (FLL or FLLs).ti,ab,ot. (21)
10. Cholangiocarcinoma/ (7)
11. ((liver\$ or hepat\$) adj3 (cancer\$ or met\$ or malignan\$ or carcinoma\$ or tumor\$r\$ or neoplas\$ or adeno\$ or angioma\$ or sarcoma\$ or angiosarcoma\$)).ti,ab,ot,hw. (4928)
12. (hepatoma\$ or h?emangiosarcoma\$ or h?emangio-sarcoma\$).ti,ab,ot,hw. (482)
13. (Focal liver lesion\$ and (cancer\$ or met or mets or metasta\$ or malignan\$ or carcinoma\$ or tumor\$r\$ or neoplas\$ or adeno\$ or angioma\$ or sarcoma\$ or angiosarcoma\$)).ti,ab,ot,hw. (22)
14. (BFL or BFLS).ti,ab,ot. (0)
15. (HCC or HCCs).ti,ab,ot. (1356)

16. (Cholangiocarcinoma\$ or Cholangio-carcinoma\$).ti,ab,ot,hw. (319)
17. (Bile duct\$ adj3 (cancer\$ or met\$ or malignan\$ or lesion\$ or carcinoma\$ or tumor\$ or neoplas\$ or adeno\$ or angioma\$ or sarcoma\$)).ti,ab,ot,hw. (130)
18. or/5-17 (5956)
19. ultrasonography/ or ultrasonography, doppler/ or exp ultrasonography, doppler, duplex/ or exp ultrasonography, doppler, pulsed/ (57)
20. ((ultrasonic\$ or ultra-sonic\$) adj4 (scan or imag\$ or echogram\$ or sonogra\$ or detect\$ or diagnos\$ or exam\$)).ti,ot,ab,hw. (349)
21. (ultraso\$ or ultra-so\$ or sonogra\$ or Echotomogra\$ or Echo-tomogra\$ or echoscope\$ or echosound\$ or Echogra\$ or tomoechogra\$ or tomo-echogra\$).ti,ot,ab,hw. (11,431)
22. or/19-21 (11,432)
23. Sulfur Hexafluoride/ (0)
24. (hexafluoruro-sulfurico or SF6 or SF-6 or sulphur hexa-fluoride\$ or sulphur hexafluoride\$ or sulfur hexa-fluoride\$ or sulfur hexafluoride\$).af. (316)
25. or/23-24 (316)
26. 22 and 25 (3)
27. (Sonovue or sono-vue or Sonavoid or Sonogen or sonagen or Sonavist).af. (34)
28. (CE-US or CEUS).ti,ab,ot. (82)
29. ((hexafluoruro-sulfurico or SF6 or SF-6) adj4 (US or ultraso\$ or ultra-so\$ or sonogra\$ or Echotomogra\$ or Echo-tomogra\$ or echoscop\$ or echosound\$ or Echogra\$ or tomoechogra\$ or tomo-echogra\$ or imag\$)).af. (1)
30. ((Sulfur or Sulphur) adj2 (hexafluoride\$ or hexa-fluoride\$) adj4 (US or ultraso\$ or ultra-so\$ or sonogra\$ or Echotomogra\$ or Echo-tomogra\$ or echoscop\$ or echosound\$ or Echogra\$ or tomoechogra\$ or tomo-echogra\$ or imag\$)).af. (0)
31. (SF6US or SF6-US or SF-6US or SF-6-US).af. (0)
32. ((SF6 or SF6 or sulphur hexafluoride\$ or sulphur hexa-fluoride\$ or sulfur hexafluoride\$ or sulfur hexa-fluoride\$) adj4 (bubbl\$ or microbubbl\$ or micro-bubbl\$ or micropartic\$ or micro-partic\$)).af. (2)
33. or/27-32 (103)
34. 26 or 33 (104)
35. 18 and 34 (40)
36. exp Liver Neoplasms/us (2)
37. Carcinoma, Hepatocellular/us (1)
38. exp Bile Duct Neoplasms/us (0)
39. Cholangiocarcinoma/us (0)
40. Neoplasm Metastasis/us (0)
41. Neoplasm Seeding/ra (0)
42. Neoplasms, Unknown Primary/us (0)
43. or/36-42 (2)
44. 25 and 43 (0)
45. 35 or 44 (40)
46. limit 45 to yr="2000 -Current" (40)
47. animals/ not (animals/ and humans/) (2179)
48. 46 not 47 (40)

**Cochrane Database of Systematic Reviews (Wiley): Issue 10, 2011**  
**Cochrane Central Register of Controlled Trials (Wiley): Issue 4, 2011**

[www.thecochranelibrary.com/](http://www.thecochranelibrary.com/)

Search limited to 2000–11.

Searched 6 October 2011.

- #1 MeSH descriptor Neoplasm Metastasis, this term only (1725)
- #2 MeSH descriptor Neoplasm Seeding, this term only (25)
- #3 MeSH descriptor Neoplasms, Unknown Primary, this term only (32)

- #4 (Metasta\* or meta-sta\*):ti,ab,kw (10,876)
- #5 (#1 OR #2 OR #3 OR #4) (10,908)
- #6 (liver or hepato\* or hepatic\*):ti,ab,kw (30,235)
- #7 (#5 AND #6) (1342)
- #8 MeSH descriptor Liver Neoplasms explode all trees (1521)
- #9 MeSH descriptor Bile Duct Neoplasms explode all trees (128)
- #10 MeSH descriptor Carcinoma, Hepatocellular, this term only (769)
- #11 MeSH descriptor Cholangiocarcinoma, this term only (41)
- #12 (FLL or FLLs):ti,ab (0)
- #13 ((liver\* or hepat\*) near/3 (cancer\* or met\* or malignan\* or carcinoma\* or tumor\* or tumour\* or neoplas\* or adeno\* or angiom\* or sarcoma\* or angiosarcoma\*)):ti,ab,kw (5985)
- #14 (hepatoma\* or hemangiosarcoma\* or hemangio-sarcoma\* or haemangiosarcoma\* or haemangio-sarcoma\*):ti,ab,kw (71)
- #15 ((Focal NEXT liver NEXT lesion\*) and (cancer\* or met or mets or metasta\* or malignan\* or carcinoma\* or tumor\* or tumour\* or neoplas\* or adeno\* or angiom\* or sarcoma\* or angiosarcoma\*)):ti,ab,kw (20)
- #16 (BFL or BFLLS or HCC or HCCs):ti,ab (563)
- #17 (Cholangiocarcinoma\* or Cholangio-carcinoma\*):ti,ab,kw (70)
- #18 ((Bile NEXT duct\*) near/3 (cancer\* or met\* or malignan\* or lesion\* or carcinoma\* or tumor\* or tumour\* or neoplas\* or adeno\* or angiom\* or sarcoma\*)):ti,ab,kw (236)
- #19 (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18) (6625)
- #20 MeSH descriptor Ultrasonography, this term only (743)
- #21 MeSH descriptor Ultrasonography, Doppler, this term only (403)
- #22 MeSH descriptor Ultrasonography, Doppler, Duplex explode all trees (696)
- #23 MeSH descriptor Ultrasonography, Doppler, Pulsed explode all trees (120)
- #24 ((ultrasonic\* or ultra-sonic\*) near/4 (scan or imag\* or echogram\* or sonogra\* or detect\* or diagnos\* or exam\*)):ti,ab,kw (141)
- #25 (ultraso\* or ultra-so\* or sonogra\* or Echotomogra\* or Echo-tomogra\* or echoscope\* or echosound\* or Echogra\* or tomoechogra\* or tomo-echogra\*):ti,ab,kw (14,089)
- #26 (#20 OR #21 OR #22 OR #23 OR #24 OR #25) (14,122)
- #27 MeSH descriptor Sulfur Hexafluoride, this term only (54)
- #28 (hexafluoruro-sulfurico or SF6 or SF-6 or (sulphur NEXT hexafluoride\*) or (sulphur NEXT hexafluoride\*) or (sulfur NEXT hexafluoride\*) or (sulfur NEXT hexafluoride\*)) (125)
- #29 (#27 OR #28) (125)
- #30 (#26 AND #29) (39)
- #31 (Sonovue or sono-vue or Sonovoid or Sonogen or sonagen or Sonavist) (35)
- #32 (CE-US or CEUS):ti,ab (16)
- #33 ((hexafluoruro-sulfurico or SF6 or SF-6) near/4 (US or ultraso\* or ultra-so\* or sonogra\* or Echotomogra\* or Echo-tomogra\* or echoscop\* or echosound\* or Echogra\* or tomoechogra\* or tomo-echogra\* or imag\*)) (2)
- #34 ((Sulfur or Sulphur) near/2 (hexafluoride\* or hexa-fluoride\*) near/4 (US or ultraso\* or ultra-so\* or sonogra\* or Echotomogra\* or Echo-tomogra\* or echoscop\* or echosound\* or Echogra\* or tomoechogra\* or tomo-echogra\* or imag\*)) (11)
- #35 (SF6US or SF6-US or SF-6US or SF-6-US) (0)
- #36 ((SF6 or SF6 or (sulphur NEXT hexafluoride\*) or (sulphur NEXT hexa-fluoride\*) or (sulfur NEXT hexafluoride\*) or (sulfur NEXT hexa-fluoride\*)) near/4 (bubbl\* or microbubbl\* or micro-bubbl\* or micropartic\* or micro-partic\*)) (4)
- #37 (#31 OR #32 OR #33 OR #34 OR #35 OR #36) (56)
- #38 (#30 OR #37) (67)
- #39 (#19 AND #38) (15)
- #40 MeSH descriptor Liver Neoplasms explode all trees with qualifier: US (51)
- #41 MeSH descriptor Carcinoma, Hepatocellular, this term only with qualifier: US (23)

- #42 MeSH descriptor Bile Duct Neoplasms explode all trees with qualifier: US (4)
- #43 MeSH descriptor Cholangiocarcinoma explode all trees with qualifier: US (1)
- #44 MeSH descriptor Neoplasm Metastasis, this term only with qualifier: US (0)
- #45 MeSH descriptor Neoplasm Seeding, this term only with qualifier: US (0)
- #46 MeSH descriptor Neoplasms, Unknown Primary, this term only with qualifier: US (0)
- #47 (#40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46) (55)
- #48 (#39 OR #47), from 2000 to 2011 (40)

CDSR search retrieved 1 reference.

CENTRAL search retrieved 31 references.

**Database of Abstracts of Reviews of Effects via The Cochrane Library (Wiley): 2000–6 October 2011**

**Health Technology Assessment database via The Cochrane Library (Wiley): 2000–7 October 2011**

[www.thecochranelibrary.com/](http://www.thecochranelibrary.com/)

Search limited to 2000–11.

Searched 6 October 2011.

- #1 MeSH descriptor Neoplasm Metastasis, this term only (1725)
- #2 MeSH descriptor Neoplasm Seeding, this term only (25)
- #3 MeSH descriptor Neoplasms, Unknown Primary, this term only (32)
- #4 (Metasta\* or meta-sta\*):ti,ab,kw (10,876)
- #5 (#1 OR #2 OR #3 OR #4) (10,908)
- #6 (liver or hepato\* or hepatic\*):ti,ab,kw (30,235)
- #7 (#5 AND #6) (1342)
- #8 MeSH descriptor Liver Neoplasms explode all trees (1521)
- #9 MeSH descriptor Bile Duct Neoplasms explode all trees (128)
- #10 MeSH descriptor Carcinoma, Hepatocellular, this term only (769)
- #11 MeSH descriptor Cholangiocarcinoma, this term only (41)
- #12 (FLL or FLLs):ti,ab (0)
- #13 ((liver\* or hepat\*) near/3 (cancer\* or met\* or malignan\* or carcinoma\* or tumor\* or tumour\* or neoplas\* or adeno\* or angiom\* or sarcoma\* or angiosarcoma\*)):ti,ab,kw (5985)
- #14 (hepatoma\* or hemangiosarcoma\* or hemangio-sarcoma\* or haemangiosarcoma\* or haemangio-sarcoma\*):ti,ab,kw (71)
- #15 ((Focal NEXT liver NEXT lesion\*) and (cancer\* or met or mets or metasta\* or malignan\* or carcinoma\* or tumor\* or tumour\* or neoplas\* or adeno\* or angiom\* or sarcoma\* or angiosarcoma\*)):ti,ab,kw (20)
- #16 (BFLL or BFLLS or HCC or HCCs):ti,ab (563)
- #17 (Cholangiocarcinoma\* or Cholangio-carcinoma\*):ti,ab,kw (70)
- #18 ((Bile NEXT duct\*) near/3 (cancer\* or met\* or malignan\* or lesion\* or carcinoma\* or tumor\* or tumour\* or neoplas\* or adeno\* or angiom\* or sarcoma\*)):ti,ab,kw (236)
- #19 (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18) (6625)
- #20 MeSH descriptor Ultrasonography, this term only (743)
- #21 MeSH descriptor Ultrasonography, Doppler, this term only (403)
- #22 MeSH descriptor Ultrasonography, Doppler, Duplex explode all trees (696)
- #23 MeSH descriptor Ultrasonography, Doppler, Pulsed explode all trees (120)
- #24 ((ultrasonic\* or ultra-sonic\*) near/4 (scan or imag\* or echogram\* or sonogra\* or detect\* or diagnos\* or exam\*)):ti,ab,kw (141)
- #25 (ultraso\* or ultra-so\* or sonogra\* or Echotomogra\* or Echo-tomogra\* or echoscope\* or echosound\* or Echogra\* or tomoechogra\* or tomo-echogra\*):ti,ab,kw (14,089)
- #26 (#20 OR #21 OR #22 OR #23 OR #24 OR #25) (14,122)

- #27 MeSH descriptor Sulfur Hexafluoride, this term only (54)
- #28 (hexafluoruro-sulfurico or SF6 or SF-6 or (sulphur NEXT hexafluoride\*) or (sulphur NEXT hexafluoride\*) or (sulfur NEXT hexafluoride\*) or (sulfur NEXT hexafluoride\*)) (125)
- #29 (#27 OR #28) (125)
- #30 (#26 AND #29) (39)
- #31 (Sonovue or sono-vue or Sonavoid or Sonogen or sonagen or Sonavist) (35)
- #32 (CE-US or CEUS):ti,ab (16)
- #33 ((hexafluoruro-sulfurico or SF6 or SF-6) near/4 (US or ultraso\* or ultra-so\* or sonogra\* or Echotomogra\* or Echo-tomogra\* or echoscop\* or echosound\* or Echogra\* or tomoechogra\* or tomo-echogra\* or imag\*)) (2)
- #34 ((Sulfur or Sulphur) near/2 (hexafluoride\* or hexa-fluoride\*) near/4 (US or ultraso\* or ultra-so\* or sonogra\* or Echotomogra\* or Echo-tomogra\* or echoscop\* or echosound\* or Echogra\* or tomoechogra\* or tomo-echogra\* or imag\*)) (11)
- #35 (SF6US or SF6-US or SF-6US or SF-6-US) (0)
- #36 ((SF6 or SF6 or (sulphur NEXT hexafluoride\*) or (sulphur NEXT hexafluoride\*) or (sulfur NEXT hexafluoride\*) or (sulfur NEXT hexafluoride\*)) near/4 (bubbl\* or microbubbl\* or micro-bubbl\* or micropartic\* or micro-partic\*)) (4)
- #37 (#31 OR #32 OR #33 OR #34 OR #35 OR #36) (56)
- #38 (#30 OR #37) (67)
- #39 (#19 AND #38) (15)
- #40 MeSH descriptor Liver Neoplasms explode all trees with qualifier: US (51)
- #41 MeSH descriptor Carcinoma, Hepatocellular, this term only with qualifier: US (23)
- #42 MeSH descriptor Bile Duct Neoplasms explode all trees with qualifier: US (4)
- #43 MeSH descriptor Cholangiocarcinoma explode all trees with qualifier: US (1)
- #44 MeSH descriptor Neoplasm Metastasis, this term only with qualifier: US (0)
- #45 MeSH descriptor Neoplasm Seeding, this term only with qualifier: US (0)
- #46 MeSH descriptor Neoplasms, Unknown Primary, this term only with qualifier: US (0)
- #47 (#40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46) (55)
- #48 (#39 OR #47), from 2000 to 2011 (40)

DARE search retrieved 2 records.

HTA search retrieved 0 records.

### **Database of Abstracts of Reviews of Effects (Internet) (top-up search for currency)**

### **Health Technology Assessment database (Internet) (top-up search for currency)**

Records added to CRD databases between 1 January 2011 and 6 October 2011.

[www.york.ac.uk/inst/crd/](http://www.york.ac.uk/inst/crd/)

Searched 7 October 2011.

1. ((hexafluoruro-sulfurico or SF6 or SF-6) ) (414)
2. (US or ultraso\* or ultra-so\* or sonogra\* or Echotomogra\* or Echo-tomogra\* or echoscop\* or echosound\* or Echogra\* or tomoechogra\* or tomo-echogra\* or imag\*) (17,021)
3. #1 and #2 (155)
4. (CE-US or CEUS):ti,ab (188)
5. ((Sonovue or sono-vue or Sonavoid or Sonogen or sonagen or Sonavist)) (0)
6. (SF6US or SF6-US or SF-6US or SF-6-US) (0)
7. (Sulfur or Sulphur) AND (hexafluoride\* or hexa-fluoride\*) AND (US or ultraso\* or ultra-so\* or sonogra\* or Echotomogra\* or Echo-tomogra\* or echoscop\* or echosound\* or Echogra\* or tomoechogra\* or tomo-echogra\* or imag\*) (4)
8. (SF6 or SF6) AND (bubbl\* or microbubbl\* or micro-bubbl\* or micropartic\* or micro-partic\*) (0)



9. (sulphur NEXT hexafluoride\*) AND (bubbl\* or microbubbl\* or micro-bubbl\* or micropartic\* or micro-partic\*) (0)
10. (sulfur NEXT hexafluoride\*) AND (bubbl\* or microbubbl\* or micro-bubbl\* or micropartic\* or micro-partic\*) (0)
11. #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 (346)
12. (liver or hepato\* or hepatic\* or FLL or FLLs) (1877)
13. (hepatoma\* or hemangiosarcoma\* or hemangio-sarcoma\* or haemangiosarcoma\* or haemangio-sarcoma\*) (7)
14. (BFLL or BFLLS or HCC or HCCs) (70)
15. (Cholangiocarcinoma\* or Cholangio-carcinoma\*) (20)
16. (Bile NEXT duct\*) (140)
17. #12 OR #13 OR #14 OR #15 OR #16 (1965)
18. #11 AND #17 (19)
19. \* IN DARE WHERE PD FROM 01/01/2011 TO 07/10/2011 (3108)
20. **#18 AND #19 (2)**
21. \* IN HTA WHERE PD FROM 01/01/2011 TO 07/10/2011 (1418)
22. #18 AND #21 (0)

### Science Citation Index (Web of Science): 2000–11

Search limited to 2000–6 October 2011.

Searched 7 October 2011.

#25	416	#23 not #24
#24	1,035,565	TS=(cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamster or feline or ovine or canine or bovine or sheep)
#23	450	#9 AND #22
#22	1281	#21 OR #14
#21	1273	#20 OR #19 OR #18 OR #17 OR #16 OR #15
#20	144	TS=((SF6 or SF6 or (sulphur SAME hexafluoride*) or (sulphur SAME hexafluoride*) or (sulfur SAME hexafluoride*) or (sulfur SAME hexafluoride*)) SAME (bubbl* or microbubbl* or micro-bubbl* or micropartic* or micro-partic*))
#19	0	TS=(SF6US or SF6-US or SF-6US or SF-6-US)
#18	36	TS=((Sulfur or Sulphur) SAME (hexafluoride* or hexa-fluoride*) near/4 (US or ultraso* or ultra-so* or sonogra* or Echotomogra* or Echo-tomogra* or echoscop* or echosound* or Echogra* or tomoechogra* or tomo-echogra* or imag*))
#17	213	TS=((hexafluoruro-sulfurico or SF6 or SF-6) SAME (US or ultraso* or ultra-so* or sonogra* or Echotomogra* or Echo-tomogra* or echoscop* or echosound* or Echogra* or tomoechogra* or tomo-echogra* or imag*))
#16	576	TS=(CE-US or CEUS)
#15	546	TS=(Sonovue or sono-vue or Sonavoid or Sonogen or sonagen or Sonavist)
#14	135	#12 AND #13
#13	3932	TS=(hexafluoruro-sulfurico or SF6 or SF-6 or (sulphur SAME hexafluoride*) or (sulphur SAME hexa-fluoride*) or (sulfur SAME hexafluoride*) or (sulfur SAME hexa-fluoride*))
#12	166,385	#11 OR #10
#11	166,385	TS=(ultraso* or ultra-so* or sonogra* or Echotomogra* or Echo-tomogra* or echoscope* or echosound* or Echogra* or tomoechogra* or tomo-echogra*)
#10	14,050	TS=((ultrasonic* or ultra-sonic*) SAME (scan or imag* or echogram* or sonogra* or detect* or diagnos* or exam*))
#9	239,703	#8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
#8	9832	TS=((Bile SAME duct*) SAME (cancer* or met* or malignan* or lesion* or carcinoma* or tumor* or tumour* or neoplas* or adeno* or angiom* or sarcoma*))
#7	4831	TS=(Cholangiocarcinoma* or Cholangio-carcinoma*)

#6	1966	TI=(BFL or BFLLS or HCC or HCCs)
#5	1584	TS=((Focal SAME liver SAME lesion*) SAME (cancer* or met or mets or metasta* or malignan* or carcinoma* or tumor* or tumour* or neoplas* or adeno* or angiom* or sarcoma* or angiosarcoma*))
#4	10,317	TS=(hepatoma* or hemangiosarcoma* or hemangio-sarcoma* or haemangiosarcoma* or haemangio-sarcoma*)
#3	230,065	TS=((liver* or hepat*) SAME (cancer* or met* or malignan* or carcinoma* or tumor* or tumour* or neoplas* or adeno* or angiom* or sarcoma* or angiosarcoma*))
#2	224	TS=(FLL or FLLs)
#1	24,460	TS=((Metasta* or meta-sta*) AND (liver or hepato* or hepatic*))

### ClinicalTrials.gov (Internet)

<http://clinicaltrials.gov/ct2/search/advanced>

Searched 7 October 2011.

Advanced search option – search terms box

Search terms	Condition	Results
Sonovue OR sono-vue OR Sonavoid OR Sonogen OR sonagen OR Sonavist		22
CE-US OR CEUS		18
SF6US OR SF6-US OR SF-6US OR SF-6-US		0
(SF6 OR SF6) AND (liver OR hepato* OR hepatic* OR FLL OR FLLS OR BFLL OR BFLLS OR HCC OR HCCs OR hepatoma* OR hemangiosarcoma* OR hemangio-sarcoma* OR haemangiosarcoma* OR haemangio-sarcoma*)		0
SF6 OR SF6		0/11
(sulphur hexafluoride*) OR (sulphur hexafluoride*) OR (sulfur hexa-fluoride*) OR (sulfur hexa-fluoride*)		22
(hexafluoruro-sulfurico OR SF6 OR SF-6 OR (sulphur hexafluoride*) OR (sulphur hexafluoride*) OR (sulfur hexafluoride*) OR (sulfur hexafluoride*))	(liver OR hepato* OR hepatic* OR FLL OR FLLS OR BFLL OR BFLLS OR HCC OR HCCs OR hepatoma* OR hemangiosarcoma* OR hemangio-sarcoma* OR haemangiosarcoma* OR haemangio-sarcoma*)	8
Total		70

**metaRegister of Controlled Trials (Internet)**

[www.controlled-trials.com/](http://www.controlled-trials.com/)

Searched 7 October 2011.

Search terms	Results
CE-US OR CEUS	7
Sonovue OR sono-vue OR Sonavoid OR Sonogen OR sonagen OR Sonavist	4
(SF6US OR SF6-US OR SF-6US OR SF-6-US) and (liver or hepato or hepatic)	110
(SF6 OR SF6) AND (liver OR hepato OR hepatic OR FLL OR FLLS OR BFLL OR BFLLS OR HCC OR HCCs OR hepatoma* OR hemangiosarcoma OR hemangio-sarcoma OR haemangiosarcoma OR haemangio-sarcoma)	1
SF6 OR SF6	5
(sulphur hexafluoride) OR (sulphur hexafluoride) OR (sulfur hexa-fluoride) OR (sulfur hexa-fluoride)	2
hexafluoruro-sulfurico OR SF6 OR SF-6 OR (sulphur hexafluoride) OR (sulphur hexafluoride) OR (sulfur hexafluoride) OR (sulfur hexafluoride)	7
Total	136

**World Health Organization International Clinical Trials Registry Platform (Internet)**

[www.who.int/ictrp/en/](http://www.who.int/ictrp/en/)

Searched 7 October 2011.

Search terms	Results
CE-US OR CEUS	11
Sonovue OR sono-vue OR Sonavoid OR Sonogen OR sonagen OR Sonavist	7
SF6US OR SF6-US OR SF-6US OR SF-6-US	0
SF6 OR SF6	0
(sulphur hexafluoride) OR (sulphur hexafluoride) OR (sulfur hexa-fluoride) OR (sulfur hexa-fluoride)	0
hexafluoruro-sulfurico OR SF6 OR SF-6 OR (sulphur hexafluoride) OR (sulphur hexafluoride) OR (sulfur hexafluoride) OR (sulfur hexafluoride)	1
Total	19

**EU Clinical Trials Register (Internet)**

[www.clinicaltrialsregister.eu/ctr-search/](http://www.clinicaltrialsregister.eu/ctr-search/)

Searched 10 October 2011.

Search terms	Results
Sonovue OR sono-vue OR Sonavoid OR Sonogen OR sonagen OR Sonavist	21
SF6	3
SF-6	0
hexafluoruro-sulfurico	0
sulphur hexafluoride	5
sulfur hexafluoride	8
sulfur hexa-fluoride	0
sulphur hexa-fluoride	0
CE-US	2
CEUS	2
Total	41

*Conference abstract searches***EUROSON (European Federation of Ultrasound in Medicine and Biology) conference (Internet): 2007, 2008, 2011 only**

Searched 10 November 2011 (2011 abstracts); 21 November 2011 (2007–8 abstracts).

2011 = [www.wfumb2011.org/index.php?pid=70](http://www.wfumb2011.org/index.php?pid=70): searched title+abstract

2010 = Unable to access

2009 = Unable to access

2008 = [www.thieme-connect.com/ejournals/toc/ultraschall/33697/grouping/54161](http://www.thieme-connect.com/ejournals/toc/ultraschall/33697/grouping/54161): searched title

2007 = [www.interplan.de/pages/euroson2007/front\\_content.php?idcat=82](http://www.interplan.de/pages/euroson2007/front_content.php?idcat=82): searched title and abstract

2006 = Unable to access

Search terms	2011	2010	2009	2008	2007	2006
Sonovue or Sono-vue	35	–	–	0	41	–
Sonavoid	0	–	–	0	0	–
Sonogen	0	–	–	0	0	–
sonagen	0	–	–	0	0	–
Sonavist	0	–	–	0	0	–
SF6	0	–	–	0	0	–
hexafluoride	2	–	–	0	2	–
Sulphur	0	–	–	0	0	–
sulfur	3	–	–	0	2	–
CEUS	–	–	–	9	–	–
Liver	–	–	–	21	–	–
Hepat	–	–	–	27	–	–
Total by year	40	–	–	57	45	–
Total	142					

**European Congress of Radiology (internet): 2006–11**

Searched 10 November 2011.

2011 = [www.myesr.org/cms/website.php?id=/en/past\\_congresses/ecr\\_2011/ecr\\_2011\\_book\\_of\\_abstracts.htm](http://www.myesr.org/cms/website.php?id=/en/past_congresses/ecr_2011/ecr_2011_book_of_abstracts.htm)

2010 = [www.myesr.org/cms/website.php?id=/en/ecr\\_2010/book\\_of\\_abstracts.htm](http://www.myesr.org/cms/website.php?id=/en/ecr_2010/book_of_abstracts.htm)

2009 = [www.myesr.org/cms/website.php?id=/en/ecr\\_2009/ecr\\_2009\\_book\\_of\\_abstracts.htm](http://www.myesr.org/cms/website.php?id=/en/ecr_2009/ecr_2009_book_of_abstracts.htm)

2008 = [www.abstractsonline.com/viewer/?mkey={9AF35541-5128-444B-9D15-447022358A3F}](http://www.abstractsonline.com/viewer/?mkey={9AF35541-5128-444B-9D15-447022358A3F})

2007 = [www.abstractsonline.com/viewer/?mkey={9A26688A-5BBE-4366-AE14-5AC99DF8F8E4}](http://www.abstractsonline.com/viewer/?mkey={9A26688A-5BBE-4366-AE14-5AC99DF8F8E4})

2006 = [www.abstractsonline.com/viewer/?mkey={6748FA35-D7A5-44B0-B8D4-4E2E51850B06}](http://www.abstractsonline.com/viewer/?mkey={6748FA35-D7A5-44B0-B8D4-4E2E51850B06})

Search terms	2011	2010	2009	2008	2007	2006
Sonovue or Sono-vue	10	11	19	22	28	24
Sonavoid	0	0	0	0	0	0
Sonogen	0	0	0	0	0	0
sonagen	0	0	0	0	0	0
Sonavist	0	0	0	0	0	0
SF6	0	0	0	0	0	0
hexafluoride	1	0	1	3	3	4
Sulphur	1	0	1	0	1	2
sulfur	0	0	0	3	2	2
Total by year	12	11	21	28	34	32
Total	138					

## Radiological Society of North America conference (internet): 2006–10

Searched 10 November 2011.

2010 = <http://rsna2010.rsna.org/search/search.cfm>

2009 = <http://rsna2009.rsna.org/search/search.cfm>

2008 = <http://rsna2008.rsna.org/program.cfm>

2007 = <http://rsna2007.rsna.org/rsna2007/v2007/conference/track.cvn>

2006 = <http://rsna2006.rsna.org/rsna2006/v2006/conference/track.cvn>

Search terms	2010	2009	2008	2007	2006
Sonovue or Sono-vue	10	18	0	0	0
Sonavoid	0	0	0	0	0
Sonogen	0	0	0	0	0
sonagen	0	0	0	0	0
Sonavist	0	0	0	0	0
SF6	0	0	0	0	0
hexafluoride	4	1	0	0	0
Sulphur	2	1	0	0	0
sulfur	4	1	0	0	1
CEUS	–	–	6	3	2
Liver	–	–	84	76	87
Hepatic	–	–	34	49	34
Total by year	20	21	124	128	124
Total	417				

## Cost-effectiveness searches

### MEDLINE (OvidSP): 2000–11 September Week 2

Searched 11 October 2011.

1. neoplasm metastasis/ or neoplasm seeding/ or neoplasms, unknown primary/ (79,582)
2. (Metasta\$ or meta-sta\$).ti,ab,ot,hw. (311,666)
3. or/1-2 (313,877)
4. (liver or hepato\$ or hepatic\$).ti,ab,ot,hw. (871,423)
5. 3 and 4 (46,193)
6. exp Liver Neoplasms/ (112,995)
7. exp Bile Duct Neoplasms/ (11,958)
8. Carcinoma, Hepatocellular/ (51,056)
9. (FLL or FLLs).ti,ab,ot. (95)
10. Cholangiocarcinoma/ (4146)
11. ((liver\$ or hepat\$) adj3 (cancer\$ or met\$ or malignan\$ or carcinoma\$ or tumo?r\$ or neoplas\$ or adeno\$ or angiom\$ or sarcoma\$ or angiosarcoma\$)).ti,ab,ot,hw. (169,576)
12. (hepatoma\$ or h?emangiosarcoma\$ or h?emangio-sarcoma\$).ti,ab,ot,hw. (27,800)
13. (Focal liver lesion\$ and (cancer\$ or met or mets or metasta\$ or malignan\$ or carcinoma\$ or tumo?r\$ or neoplas\$ or adeno\$ or angiom\$ or sarcoma\$ or angiosarcoma\$)).ti,ab,ot,hw. (712)
14. (BFLL or BFLLS).ti,ab,ot. (3)

15. (HCC or HCCs).ti,ab,ot. (18,801)
16. (Cholangiocarcinoma\$ or Cholangio-carcinoma\$).ti,ab,ot,hw. (6205)
17. (Bile duct\$ adj3 (cancer\$ or met\$ or malignan\$ or lesion\$ or carcinoma\$ or tumo?r\$ or neoplas\$ or adeno\$ or angiom\$ or sarcoma\$)).ti,ab,ot,hw. (14,499)
18. or/5-17 (200,072)
19. tomography, emission-computed/ or exp tomography, x-ray computed/ (278,220)
20. exp Ultrasonography/ (220,625)
21. exp Tomography/ (530,496)
22. exp Magnetic Resonance Imaging/ (259,244)
23. exp Tomography, Emission-Computed/ (65,860)
24. Fluorodeoxyglucose F18/du (11,296)
25. (MSCT or MDST or MRI or FDGPET or FDG-PET or MDCT or IOUS or MRI or FMRI or NMRI or FNMRI).ti,ab,ot. (131,472)
26. (pet or petscan\$ or positron).ti,ot,ab,hw. (55,858)
27. (CAT or CTA or CT or cine-ct).ti,ab,ot. (241,703)
28. (3dcta or 3d-cta).ti,ab,ot. (189)
29. (64slice\$ or 64-slice\$ or 64row\$ or 64-row\$ or 64-detect\$).ti,ab,ot,hw. (1580)
30. ((nmr or comput\$ or mr) adj4 (scan\$ or imag\$ or tomogra\$ or angiogra\$ or angio-gra\$ or xray\$ or x-ray\$)).ti,ab,ot,hw. (473,823)
31. (electron beam adj4 (scan\$ or imag\$ or tomogra\$ or angiogra\$ or angio-gra\$ or xray\$ or x-ray\$)).ti,ab,ot,hw. (1499)
32. Chemical shift imag\$.ti,ot,ab,hw. (714)
33. ((ultrasonic\$ or ultra-sonic\$) adj4 (scan or imag\$ or tomogra\$ or echogram\$ or sonogra\$ or detect\$ or diagnos\$ or scintillat\$ or exam\$)).ti,ot,ab,hw. (7134)
34. MR imag\$.ti,ot,ab,hw. (36,261)
35. (ultraso\$ or ultra-so\$ or sonogra\$ or Echotomogra\$ or Echo-tomogra\$ or doptone or echoscope\$ or echosound\$ or tomogra\$ or Echogra\$ or zeugmatogra\$ or echogra\$ or tomoechogra\$ or tomodensitomet\$).ti,ot,ab,hw. (629,456)
36. "ultrasound without contrast".ti,ot,ab,hw. (1)
37. ("ultrasonography without contrast" or "ultrasonograph without contrast").ti,ot,ab,hw. (0)
38. ((Un-enhanced or Unenhanced) adj4 (sonogra\$ or ultra-so\$ or ultraso\$ or Echotomogra\$ or Echo-tomogra\$ or doptone or echoscope\$ or echosound\$ or tomogra\$ or Echogra\$ or zeugmatogra\$ or echogra\$ or tomoechogra\$ or tomodensitomet\$)).ti,ot,ab,hw. (367)
39. Positron emission tomogra\$.ti,ot,ab,hw. (38,028)
40. or/19-39 (1,087,651)
41. 18 and 40 (29,857)
42. exp Liver Neoplasms/us [Ultrasonography] (2714)
43. Carcinoma, Hepatocellular/us [Ultrasonography] (1268)
44. exp Bile Duct Neoplasms/us (375)
45. Cholangiocarcinoma/us [Ultrasonography] (137)
46. Neoplasm Metastasis/us [Ultrasonography] (51)
47. Neoplasm Seeding/ra [Radiography] (1)
48. Neoplasms, Unknown Primary/us [Ultrasonography] (21)
49. or/42-48 (3101)
50. 41 or 49 (30,149)
51. economics/ (26,431)
52. exp "costs and cost analysis"/ (160,527)
53. economics, dental/ (1886)
54. exp "economics, hospital"/ (17,621)
55. economics, medical/ (8758)
56. economics, nursing/ (3854)
57. economics, pharmaceutical/ (2288)



58. (economic\$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\$).ti,ab. (348,545)
59. (expenditure\$ not energy).ti,ab. (14,733)
60. (value adj1 money).ti,ab. (20)
61. budget\$.ti,ab. (14,850)
62. or/51-61 (463,424)
63. ((energy or oxygen) adj cost).ti,ab. (2377)
64. (metabolic adj cost).ti,ab. (624)
65. ((energy or oxygen) adj expenditure).ti,ab. (13,655)
66. or/63-65 (16,028)
67. 62 not 66 (459,787)
68. letter.pt. (728,700)
69. editorial.pt. (285,457)
70. historical article.pt. (282,970)
71. or/68-70 (1,283,982)
72. 67 not 71 (434,958)
73. animals/ not (animals/ and humans/) (3,606,824)
74. 72 not 73 (409,921)
75. 50 and 74 (506)
76. limit 75 to yr="2000 -Current" (293)

Economics filter: Centre for Reviews and Dissemination. *NHS EED economics filter: MEDLINE (Ovid) monthly search*. York: CRD; 2010. URL: [www.york.ac.uk/inst/crd/intertasc/nhs\\_eed\\_strategies.html](http://www.york.ac.uk/inst/crd/intertasc/nhs_eed_strategies.html) (accessed 28 September 2010).

### **MEDLINE In-Process & Other Non-Indexed Citations (OvidSP): 2000–10 October 2011**

#### **MEDLINE Daily Update (OvidSP): 2000–10 October 2011**

Searched 11 October 2011.

1. neoplasm metastasis/ or neoplasm seeding/ or neoplasms, unknown primary/ (84)
2. (Metasta\$ or meta-sta\$).ti,ab,ot,hw. (12,775)
3. or/1-2 (12,776)
4. (liver or hepato\$ or hepatic\$).ti,ab,ot,hw. (21,579)
5. 3 and 4 (1452)
6. exp Liver Neoplasms/ (174)
7. exp Bile Duct Neoplasms/ (7)
8. Carcinoma, Hepatocellular/ (125)
9. (FLL or FLLs).ti,ab,ot. (21)
10. Cholangiocarcinoma/ (8)
11. ((liver\$ or hepat\$) adj3 (cancer\$ or met\$ or malignan\$ or carcinoma\$ or tumo?r\$ or neoplas\$ or adeno\$ or angiom\$ or sarcoma\$ or angiosarcoma\$)).ti,ab,ot,hw. (5022)
12. (hepatoma\$ or h?emangiosarcoma\$ or h?emangio-sarcoma\$).ti,ab,ot,hw. (493)
13. (Focal liver lesion\$ and (cancer\$ or met or mets or metasta\$ or malignan\$ or carcinoma\$ or tumo?r\$ or neoplas\$ or adeno\$ or angiom\$ or sarcoma\$ or angiosarcoma\$)).ti,ab,ot,hw. (22)
14. (BFLL or BFLLS).ti,ab,ot. (0)
15. (HCC or HCCs).ti,ab,ot. (1380)
16. (Cholangiocarcinoma\$ or Cholangio-carcinoma\$).ti,ab,ot,hw. (322)
17. (Bile duct\$ adj3 (cancer\$ or met\$ or malignan\$ or lesion\$ or carcinoma\$ or tumo?r\$ or neoplas\$ or adeno\$ or angiom\$ or sarcoma\$)).ti,ab,ot,hw. (131)
18. or/5-17 (6064)
19. tomography, emission-computed/ or exp tomography, x-ray computed/ (339)
20. exp Ultrasonography/ (229)

21. exp Tomography/ (827)
22. exp Magnetic Resonance Imaging/ (433)
23. exp Tomography, Emission-Computed/ (109)
24. Fluorodeoxyglucose F18/du (25)
25. (MSCT or MDST or MRI or FDGPET or FDG-PET or MDCT or IOUS or MRI or FMRI or NMRI or FNMRI).ti,ab,ot. (7477)
26. (pet or petscan\$ or positron).ti,ot,ab,hw. (3355)
27. (CAT or CTA or CT or cine-ct).ti,ab,ot. (10,016)
28. (3dcta or 3d-cta).ti,ab,ot. (15)
29. (64slice\$ or 64-slice\$ or 64row\$ or 64-row\$ or 64-detect\$).ti,ab,ot,hw. (174)
30. ((nmr or comput\$ or mr) adj4 (scan\$ or imag\$ or tomogra\$ or angiogra\$ or angio-gra\$ or xray\$ or x-ray\$)).ti,ab,ot,hw. (10,787)
31. (electron beam adj4 (scan\$ or imag\$ or tomogra\$ or angiogra\$ or angio-gra\$ or xray\$ or x-ray\$)).ti,ab,ot,hw. (121)
32. Chemical shift imag\$.ti,ot,ab,hw. (33)
33. ((ultrasonic\$ or ultra-sonic\$) adj4 (scan or imag\$ or tomogra\$ or echogram\$ or sonogra\$ or detect\$ or diagnos\$ or scintillat\$ or exam\$)).ti,ot,ab,hw. (369)
34. MR imag\$.ti,ot,ab,hw. (1078)
35. (ultraso\$ or ultra-so\$ or sonogra\$ or Echotomogra\$ or Echo-tomogra\$ or doptone or echoscope\$ or echosound\$ or tomogra\$ or Echogra\$ or zeugmatogra\$ or echogra\$ or tomoechogra\$ or tomodensitomet\$).ti,ot,ab,hw. (21,818)
36. "ultrasound without contrast".ti,ot,ab,hw. (0)
37. ("ultrasonography without contrast" or "ultrasonograph without contrast").ti,ot,ab,hw. (1)
38. ((Un-enhanced or Unenhanced) adj4 (sonogra\$ or ultra-so\$ or ultraso\$ or Echotomogra\$ or Echo-tomogra\$ or doptone or echoscope\$ or echosound\$ or tomogra\$ or Echogra\$ or zeugmatogra\$ or echogra\$ or tomoechogra\$ or tomodensitomet\$)).ti,ot,ab,hw. (12)
39. Positron emission tomogra\$.ti,ot,ab,hw. (1414)
40. or/19-39 (38,105)
41. 18 and 40 (841)
42. exp Liver Neoplasms/us [Ultrasonography] (4)
43. Carcinoma, Hepatocellular/us [Ultrasonography] (3)
44. exp Bile Duct Neoplasms/us (0)
45. Cholangiocarcinoma/us [Ultrasonography] (0)
46. Neoplasm Metastasis/us [Ultrasonography] (0)
47. Neoplasm Seeding/ra [Radiography] (0)
48. Neoplasms, Unknown Primary/us [Ultrasonography] (0)
49. or/42-48 (4)
50. 41 or 49 (842)
51. economics/ (29)
52. exp "costs and cost analysis"/ (206)
53. economics, dental/ (0)
54. exp "economics, hospital"/ (43)
55. economics, medical/ (1)
56. economics, nursing/ (0)
57. economics, pharmaceutical/ (1)
58. (economic\$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\$).ti,ab. (24,833)
59. (expenditure\$ not energy).ti,ab. (706)
60. (value adj1 money).ti,ab. (2)
61. budget\$.ti,ab. (1368)
62. or/51-61 (26,315)
63. ((energy or oxygen) adj cost).ti,ab. (150)
64. (metabolic adj cost).ti,ab. (43)

65. ((energy or oxygen) adj expenditure).ti,ab. (582)
66. or/63-65 (752)
67. 62 not 66 (26,100)
68. letter.pt. (17,183)
69. editorial.pt. (10,629)
70. historical article.pt. (603)
71. or/68-70 (28,394)
72. 67 not 71 (25,702)
73. animals/ not (animals/ and humans/) (2838)
74. 72 not 73 (25,645)
75. 50 and 74 (7)
76. limit 75 to yr="2000 -Current" (7)

Economics filter: Centre for Reviews and Dissemination. *NHS EED economics filter: MEDLINE (Ovid) monthly search*. York: CRD; 2010. URL: [www.york.ac.uk/inst/crd/intertasc/nhs\\_eed\\_strategies.html](http://www.york.ac.uk/inst/crd/intertasc/nhs_eed_strategies.html) (accessed 28 September 2010).

### EMBASE (OvidSP): 2000–11 Week 40

Searched 12 October 2011.

1. metastasis/ (155,985)
2. (Metasta\$ or meta-sta\$).ti,ab,ot,hw. (396,806)
3. or/1-2 (396,806)
4. (liver or hepato\$ or hepatic\$).ti,ab,ot,hw. (1,004,150)
5. 3 and 4 (65,370)
6. exp liver tumor/ (135,580)
7. FLL.ti,ab,ot. (107)
8. FLLs.ti,ab,ot. (43)
9. bile duct carcinoma/ (9937)
10. ((liver\$ or hepat\$) adj3 (cancer\$ or met\$ or malignan\$ or carcinoma\$ or tumo?r\$ or neoplas\$ or adeno\$ or angiom\$ or sarcoma\$ or angiosarcoma\$)).ti,ab,ot,hw. (211,624)
11. (hepatoma\$ or h?emangiosarcoma\$ or h?emangio-sarcoma\$).ti,ab,ot,hw. (25,072)
12. (Focal liver lesion\$ and (cancer\$ or met or mets or metasta\$ or malignan\$ or carcinoma\$ or tumo?r\$ or neoplas\$ or adeno\$ or angiom\$ or sarcoma\$ or angiosarcoma\$)).ti,ab,ot,hw. (854)
13. (BFLL or BFLLS).ti,ab,ot. (5)
14. (HCC or HCCs).ti,ab,ot. (25,363)
15. (Cholangiocarcinoma\$ or Cholangio-carcinoma\$).ti,ab,ot,hw. (6601)
16. (Bile duct\$ adj3 (cancer\$ or met\$ or malignan\$ or lesion\$ or carcinoma\$ or tumo?r\$ or neoplas\$ or adeno\$ or angiom\$ or sarcoma\$)).ti,ab,ot,hw. (18,319)
17. or/5-16 (253,318)
18. exp Tomography/ (524,140)
19. exp Echography/ (399,873)
20. exp Nuclear-Magnetic-Resonance-Imaging/ (385,701)
21. Fluorodeoxyglucose-F-18/du (0)
22. (MSCT or MDST or MRI or FDGPET or FDG-PET or MDCT or IOUS or MRI or FMRI or NMRI or FNMRI).ti,ab,ot. (175,669)
23. (pet or petscan\$ or positron).ti,ot,ab,hw. (88,701)
24. (CAT or CTA or CT or cine-ct).ti,ab,ot. (295,625)
25. (3dcta or 3d-cta).ti,ab,ot. (261)
26. (64slice\$ or 64-slice\$ or 64row\$ or 64-row\$ or 64-detect\$).ti,ab,ot,hw. (2721)
27. ((nmr or comput\$ or mr) adj4 (scan\$ or imag\$ or tomogra\$ or angiogra\$ or angio-gra\$ or xray\$ or x-ray\$)).ti,ab,ot,hw. (554,605)

28. (electron beam adj4 (scan\$ or imag\$ or tomogra\$ or angiogra\$ or angio-gra\$ or xray\$ or x-ray\$)).  
ti,ab,ot,hw. (2528)
29. Chemical shift imag\$.ti,ot,ab,hw. (822)
30. ((ultrasonic\$ or ultra-sonic\$) adj4 (scan or imag\$ or tomogra\$ or echogram\$ or sonogra\$ or detect\$  
or diagnos\$ or scintillat\$ or exam\$)).ti,ot,ab,hw. (7723)
31. MR imag\$.ti,ot,ab,hw. (41,562)
32. (ultraso\$ or ultra-so\$ or sonogra\$ or Echotomogra\$ or Echo-tomogra\$ or doptone or echoscope\$  
or echosound\$ or tomogra\$ or Echogra\$ or zeugmatogra\$ or echogra\$ or tomoechogra\$ or  
tomodensitomet\$).ti,ot,ab,hw. (906,553)
33. "ultrasound without contrast".ti,ot,ab,hw. (2)
34. ("ultrasonography without contrast" or "ultrasonograph without contrast").ti,ot,ab,hw. (0)
35. ((Un-enhanced or Unenhanced) adj4 (sonogra\$ or ultra-so\$ or ultraso\$ or Echotomogra\$ or Echo-  
tomogra\$ or doptone or echoscope\$ or echosound\$ or tomogra\$ or Echogra\$ or zeugmatogra\$  
or echogra\$ or tomoechogra\$ or tomodensitomet\$)).ti,ot,ab,hw. (412)Positron emission tomogra\$.  
ti,ot,ab,hw. (67,261)
36. or/18-36 (1,418,654)
37. 17 and 37 (42,839)
38. health-economics/ (30,583)
39. exp economic-evaluation/ (172,264)
40. exp health-care-cost/ (165,499)
41. exp pharmacoeconomics/ (140,625)
42. or/39-42 (395,230)
43. (econom\$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\$).  
ti,ab. (448,361)
44. (expenditure\$ not energy).ti,ab. (17,805)
45. (value adj2 money).ti,ab. (974)
46. budget\$.ti,ab. (18,892)
47. or/44-47 (467,436)
48. 43 or 48 (700,900)
49. letter.pt. (742,741)
50. editorial.pt. (383,238)
51. note.pt. (452,797)
52. or/50-52 (1,578,776)
53. 49 not 53 (628,549)
54. (metabolic adj cost).ti,ab. (670)
55. ((energy or oxygen) adj cost).ti,ab. (2591)
56. ((energy or oxygen) adj expenditure).ti,ab. (15,505)
57. or/55-57 (18,084)
58. 54 not 58 (624,471)
59. exp animal/ (1,655,604)
60. exp animal-experiment/ (1,467,831)
61. nonhuman/ (3,718,682)
62. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or  
cats or bovine or sheep).ti,ab,sh. (4,119,669)
63. or/60-63 (5,951,308)
64. exp human/ (12,628,304)
65. exp human-experiment/ (293,772)
66. 65 or 66 (12,629,688)
67. 64 not (64 and 67) (4,686,921)
68. 59 not 68 (579,765)
69. 38 and 69 (895)

70. limit 70 to yr="2000 -Current" (667)

71. limit 71 to embase (604)

Economics filter: Centre for Reviews and Dissemination. NHS EED economics filter: EMBASE (Ovid) weekly search. York: CRD; 2010. URL: [www.york.ac.uk/inst/crd/intertasc/nhs\\_eed\\_strategies.html](http://www.york.ac.uk/inst/crd/intertasc/nhs_eed_strategies.html) (accessed 11 October 2011).

### **NHS Economic Evaluation Database (Wiley)**

Search limited to 2000–11.

Searched 12 October 2011.

- #1 MeSH descriptor Neoplasm Metastasis, this term only (1725)
- #2 MeSH descriptor Neoplasm Seeding, this term only (25)
- #3 MeSH descriptor Neoplasms, Unknown Primary, this term only (32)
- #4 (Metasta\* or meta-sta\*):ti,ab,kw (10,876)
- #5 (#1 OR #2 OR #3 OR #4) (10,908)
- #6 (liver or hepato\* or hepatic\*):ti,ab,kw (30,235)
- #7 (#5 AND #6) (1342)
- #8 MeSH descriptor Liver Neoplasms explode all trees (1521)
- #9 MeSH descriptor Bile Duct Neoplasms explode all trees (128)
- #10 MeSH descriptor Carcinoma, Hepatocellular, this term only (769)
- #11 MeSH descriptor Cholangiocarcinoma, this term only (41)
- #12 (FLL or FLLs):ti,ab (0)
- #13 ((liver\* or hepat\*) near/3 (cancer\* or met\* or malignan\* or carcinoma\* or tumor\* or tumour\* or neoplas\* or adeno\* or angiom\* or sarcoma\* or angiosarcoma\*)):ti,ab,kw (5985)
- #14 (hepatoma\* or hemangiosarcoma\* or hemangio-sarcoma\* or haemangiosarcoma\* or haemangio-sarcoma\*):ti,ab,kw (71)
- #15 ((Focal NEXT liver NEXT lesion\*) and (cancer\* or met or mets or metasta\* or malignan\* or carcinoma\* or tumor\* or tumour\* or neoplas\* or adeno\* or angiom\* or sarcoma\* or angiosarcoma\*)):ti,ab,kw (20)
- #16 (BFLL or BFLLS or HCC or HCCs):ti,ab (563)
- #17 (Cholangiocarcinoma\* or Cholangio-carcinoma\*):ti,ab,kw (70)
- #18 ((Bile NEXT duct\*) near/3 (cancer\* or met\* or malignan\* or lesion\* or carcinoma\* or tumor\* or tumour\* or neoplas\* or adeno\* or angiom\* or sarcoma\*)):ti,ab,kw (236)
- #19 (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18) (6625)
- #20 (#19), from 2000 to 2011 (85)
- #21 MeSH descriptor Tomography, Emission-Computed, this term only (660)
- #22 MeSH descriptor Tomography, X-Ray Computed explode all trees (2946)
- #23 MeSH descriptor Ultrasonography explode all trees (6398)
- #24 MeSH descriptor Tomography explode all trees (8806)
- #25 MeSH descriptor Magnetic Resonance Imaging explode all trees (4171)
- #26 MeSH descriptor Tomography, Emission-Computed explode all trees (2155)
- #27 MeSH descriptor Fluorodeoxyglucose F18, this term only with qualifier: DU (397)
- #28 (MSCT or MDST or MRI or FDGPET or FDG-PET or MDCT or IOUS or MRI or FMRI or NMRI or FNMRI):ti,ab (3437)
- #29 (pet or petscan\* or positron):ti,ab,kw (1958)
- #30 (CAT or CTA or CT or cine-ct):ti,ab (5318)
- #31 (3dcta or 3d-cta):ti,ab (4)
- #32 (64slice\* or 64-slice\* or 64row\* or 64-row\* or 64-detect\*):ti,ab,kw (52)
- #33 ((nmr or comput\* or mr) near/4 (scan\* or imag\* or tomogra\* or angiogra\* or angio-gra\* or xray\* or x-ray\*)):ti,ab,kw (8723)

- #34 ((electron NEXT beam) near/4 (scan\* or imag\* or tomogra\* or angiogra\* or angio-gra\* or xray\* or x-ray\*)):ti,ab,kw (56)
- #35 (Chemical NEXT shift NEXT imag\*):ti,ab,kw (12)
- #36 ((ultrasonic\* or ultra-sonic\*) near/4 (scan or imag\* or tomogra\* or echogram\* or sonogra\* or detect\* or diagnos\* or scintillat\* or exam\*)):ti,ab,kw (147)
- #37 (MR NEXT imag\*):ti,ab,kw (614)
- #38 (ultraso\* or ultra-so\* or sonogra\* or Echotomogra\* or Echo-tomogra\* or doptone or echoscope\* or echosound\* or tomogra\* or Echogra\* or zeugmatogra\* or echogra\* or tomoechogra\* or tomodensitomet\*):ti,ab,kw (21,304)
- #39 "ultrasound without contrast":ti,ab,kw (0)
- #40 ("ultrasonography without contrast" or "ultrasonograph without contrast"):ti,ab,kw (0)
- #41 ((Un-enhanced or Unenhanced) near/4 (sonogra\* or ultra-so\* or ultraso\* or Echotomogra\* or Echo-tomogra\* or doptone or echoscope\* or echosound\* or tomogra\* or Echogra\* or zeugmatogra\* or echogra\* or tomoechogra\* or tomodensitomet\*)):ti,ab,kw (11)
- #42 (Positron NEXT emission NEXT tomogra\*):ti,ab,kw (1362)
- #43 (#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42) (31,232)
- #44 (#20 AND #43), from 2000 to 2011 (27) (limited to NHS EED only)

### **NHS Economic Evaluation Database (Internet)**

Top-up search to supplement search of NHS EED via The Cochrane Library (Wiley).

Records added to CRD databases between 1 January 2011 and 12 October 2011.

[www.york.ac.uk/inst/crd/](http://www.york.ac.uk/inst/crd/)

Searched 12 October 2011.

1. ((liver or hepato\* or hepatic\* or FLL or FLLs)) OR ((hepatoma\* or hemangiosarcoma\* or hemangio-sarcoma\* or haemangiosarcoma\* or haemangio-sarcoma\*)) OR ((BFLl or BFLLS or HCC or HCCs)) OR ((Cholangiocarcinoma\* or Cholangio-carcinoma\*)) IN NHSEED WHERE PD FROM 01/01/2011 TO 12/10/2011 (40)
2. ((Bile NEXT duct\*)) IN NHSEED WHERE PD FROM 01/01/2011 TO 12/10/2011 (4)
3. #1 OR #2 (43)

### **Health Economic Evaluations Database (Internet): up to 12 October 2011**

<http://onlinelibrary.wiley.com/book/10.1002/9780470510933>

Searched 12 October 2011.

Compound search (all data), unable to limit by date

ultraso\* OR ultra-so\* OR sonogra\* OR Echotomogra\*

AND

liver OR hepato\* OR hepatic\* OR FLL OR FLLs OR hepatoma\* OR hemangiosarcoma\* OR hemangio-sarcoma\* OR haemangiosarcoma\* OR haemangio-sarcoma\* OR BFLl OR BFLLS OR HCC OR HCCs OR Cholangiocarcinoma\* OR Cholangio-carcinoma

N=78

MSCT OR MDST OR MRI OR FDGPET OR FDG-PET

AND

liver OR hepato\* OR hepatic\* OR FLL OR FLLs OR hepatoma\* OR hemangiosarcoma\* OR hemangio-sarcoma\* OR haemangiosarcoma\* OR haemangio-sarcoma\* OR BFLl OR BFLLS OR HCC OR HCCs OR Cholangiocarcinoma\* OR Cholangio-carcinoma

N= 19

MDCT OR IOUS OR MRI OR FMRI OR NMRI OR FNMRI

AND

liver OR hepato\* OR hepatic\* OR FLL OR FLLs OR hepatoma\* OR hemangiosarcoma\* OR hemangio-sarcoma\* OR haemangiosarcoma\* OR haemangio-sarcoma\* OR BFLL OR BFLLs OR HCC OR HCCs OR Cholangiocarcinoma\* OR Cholangio-carcinoma

N= 17

pet OR petscan\* OR positron OR CAT OR CTA

AND

liver OR hepato\* OR hepatic\* OR FLL OR FLLs OR hepatoma\* OR hemangiosarcoma\* OR hemangio-sarcoma\* OR haemangiosarcoma\* OR haemangio-sarcoma\* OR BFLL OR BFLLs OR HCC OR HCCs OR Cholangiocarcinoma\* OR Cholangio-carcinoma

N= 11

CT OR cine-ct OR 3dcta OR 3d-cta

AND

liver OR hepato\* OR hepatic\* OR FLL OR FLLs OR hepatoma\* OR hemangiosarcoma\* OR hemangio-sarcoma\* OR haemangiosarcoma\* OR haemangio-sarcoma\* OR BFLL OR BFLLs OR HCC OR HCCs OR Cholangiocarcinoma\* OR Cholangio-carcinoma

N=58

64slice\* OR 64-slice\* OR 64row\* OR 64-row\* OR 64-detect\*

AND

liver OR hepato\* OR hepatic\* OR FLL OR FLLs OR hepatoma\* OR hemangiosarcoma\* OR hemangio-sarcoma\* OR haemangiosarcoma\* OR haemangio-sarcoma\* OR BFLL OR BFLLs OR HCC OR HCCs OR Cholangiocarcinoma\* OR Cholangio-carcinoma

N= 0

scan\* OR imag\* OR tomogra\* OR angiogra\* OR angio-gra\* OR xray\* OR x-ray\*

AND

liver OR hepato\* OR hepatic\* OR FLL OR FLLs OR hepatoma\* OR hemangiosarcoma\* OR hemangio-sarcoma\* OR haemangiosarcoma\* OR haemangio-sarcoma\* OR BFLL OR BFLLs OR HCC OR HCCs OR Cholangiocarcinoma\* OR Cholangio-carcinoma

N= 128

MR AND imag\*

AND

liver OR hepato\* OR hepatic\* OR FLL OR FLLs OR hepatoma\* OR hemangiosarcoma\* OR hemangio-sarcoma\* OR haemangiosarcoma\* OR haemangio-sarcoma\* OR BFLL OR BFLLs OR HCC OR HCCs OR Cholangiocarcinoma\* OR Cholangio-carcinoma

N= 5

Echo-tomogra\* OR doptone OR Echogra\*

AND

liver OR hepato\* OR hepatic\* OR FLL OR FLLs OR hepatoma\* OR hemangiosarcoma\* OR hemangio-sarcoma\* OR haemangiosarcoma\* OR haemangio-sarcoma\* OR BFLL OR BFLLs OR HCC OR HCCs OR Cholangiocarcinoma\* OR Cholangio-carcinoma

N= 0

zeugmatogra\* OR echogra\* OR tomoechogra\* OR tomodensitomet\* OR echoscope\* OR echosound\*

AND

liver OR hepato\* OR hepatic\* OR FLL OR FLLS OR hepatoma\* OR hemangiosarcoma\* OR hemangio-sarcoma\* OR haemangiosarcoma\* OR haemangio-sarcoma\* OR BFLL OR BFLLS OR HCC OR HCCs OR Cholangiocarcinoma\* OR Cholangio-carcinoma  
N=0

HEED search retrieved 128 records.

### Science Citation Index (Web of Science): 2000–7 October 2011

Searched 12 October 2011.

#34	432	#8 AND #22 AND #33
#33	407,965	#27 NOT #32
#32	1,077,839	#31 OR #30 OR #29 OR #28
#31	1,035,567	TS=(cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamster or feline or ovine or canine or bovine or sheep)
#30	14,241	TS=((energy or oxygen) SAME expenditure)
#29	4365	TS=(metabolic SAME cost)
#28	31,943	TS=((energy or oxygen) SAME cost)
#27	461,648	#23 OR #24 OR #25 OR #26
#26	27,939	TS=(budget*)
#25	561	TS=(value NEAR/1 money)
#24	9239	TS=(expenditure* not energy)
#23	435,234	TS=(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic*)
#22	616,323	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#21	37,784	TS=(Positron SAME emission SAME tomogra*)
#20	301	TS=((Un-enhanced or Unenhanced) near/4 (sonogra* or ultra-so* or ultraso* or Echotomogra* or Echo-tomogra* or doptone or echoscope* or echosound* or tomogra* or Echogra* or zeugmatogra* or echogra* or tomoechogra* or tomodensitomet*))
#19	318,584	TS=(ultraso* or ultra-so* or sonogra* or Echotomogra* or Echo-tomogra* or doptone or echoscope* or echosound* or tomogra* or Echogra* or zeugmatogra* or echogra* or tomoechogra* or tomodensitomet*)
#18	39,221	TS=(MR SAME imag*)
#17	3837	TS=((ultrasonic* or ultra-sonic*) near/4 (scan or imag* or tomogra* or echogram* or sonogra* or detect* or diagnos* or scintillat* or exam*))
#16	1747	TS=(Chemical SAME shift SAME imag*)
#15	19,251	TS=((electron SAME beam) SAME (scan* or imag* or tomogra* or angiogra* or angio-gra* or xray* or x-ray*))
#14	153,267	TS=((nmr or comput* or mr) near/4 (scan* or imag* or tomogra* or angiogra* or angio-gra* or xray* or x-ray*))
#13	1863	TS=(64slice* or 64-slice* or 64row* or 64-row* or 64-detect*)
#12	143	TS=(3dcta or 3d-cta)
#11	161,518	TS=(CAT or CTA or CT or cine-ct)
#10	82,730	TS=(pet or petscan* or positron)
#9	133,925	TS=(MSCT or MDST or MRI or FDGPET or FDG-PET or MDCT or IOUS or MRI or FMRI or NMRI or FNMRI)
#8	239,569	#7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
#7	9838	TS=((Bile SAME duct*) SAME (cancer* or met* or malignan* or lesion* or carcinoma* or tumor* or tumour* or neoplas* or adeno* or angiom* or sarcoma*))
#6	4832	TS=(Cholangiocarcinoma* or Cholangio-carcinoma*)
#5	1970	TI=(BFLL or BFLLS or HCC or HCCs OR FLL or FLLS)



#4	1584	TS=((Focal SAME liver SAME lesion*) SAME (cancer* or met or mets or metasta* or malignan* or carcinoma* or tumor* or tumour* or neoplas* or adeno* or angiom* or sarcoma* or angiosarcoma*))
#3	10,317	TS=(hepatoma* or hemangiosarcoma* or hemangio-sarcoma* or haemangiosarcoma* or haemangio-sarcoma*)
#2	230,112	TS=((liver* or hepat*) SAME (cancer* or met* or malignan* or carcinoma* or tumor* or tumour* or neoplas* or adeno* or angiom* or sarcoma* or angiosarcoma*))
#1	24,461	TS=((Metasta* or meta-sta*) AND (liver or hepato* or hepatic*))

### **Additional NHS Economic Evaluation Database search (Wiley)**

Search limited to 2000–11.

Searched 21 October 2011.

- #1 MeSH descriptor Neoplasm Metastasis, this term only (1725)
- #2 MeSH descriptor Neoplasm Seeding, this term only (25)
- #3 MeSH descriptor Neoplasms, Unknown Primary, this term only (32)
- #4 (Metasta\* or meta-sta\*):ti,ab,kw (10,876)
- #5 (#1 OR #2 OR #3 OR #4) (10,908)
- #6 (liver or hepato\* or hepatic\*):ti,ab,kw (30,235)
- #7 (#5 AND #6) (1342)
- #8 MeSH descriptor Liver Neoplasms explode all trees (1521)
- #9 MeSH descriptor Bile Duct Neoplasms explode all trees (128)
- #10 MeSH descriptor Carcinoma, Hepatocellular, this term only (769)
- #11 MeSH descriptor Cholangiocarcinoma, this term only (41)
- #12 (FLL or FLLs):ti,ab (0)
- #13 ((liver\* or hepat\*) near/3 (cancer\* or met\* or malignan\* or carcinoma\* or tumor\* or tumour\* or neoplas\* or adeno\* or angiom\* or sarcoma\* or angiosarcoma\*)):ti,ab,kw (5985)
- #14 (hepatoma\* or hemangiosarcoma\* or hemangio-sarcoma\* or haemangiosarcoma\* or haemangio-sarcoma\*):ti,ab,kw (71)
- #15 ((Focal NEXT liver NEXT lesion\*) and (cancer\* or met or mets or metasta\* or malignan\* or carcinoma\* or tumor\* or tumour\* or neoplas\* or adeno\* or angiom\* or sarcoma\* or angiosarcoma\*)):ti,ab,kw (20)
- #16 (BFLL or BFLLS or HCC or HCCs):ti,ab (563)
- #17 (Cholangiocarcinoma\* or Cholangio-carcinoma\*):ti,ab,kw (70)
- #18 ((Bile NEXT duct\*) near/3 (cancer\* or met\* or malignan\* or lesion\* or carcinoma\* or tumor\* or tumour\* or neoplas\* or adeno\* or angiom\* or sarcoma\*)):ti,ab,kw (236)
- #19 (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18) (6625)
- #20 (#19), from 2000 to 2011 (85) (limited to NHS EED only)

**Additional health economics search: guidelines****Guidelines International Network (Internet)**

[www.g-i-n.net](http://www.g-i-n.net)

Search limited to 2000–9 November 2011.

Searched 9 November 2011.

Terms searched	Hits	Filename
Free-text: FLL OR FLLS OR BFLL OR BFLLS OR HCC OR HCCs	0	–
Free-text: Liver OR hepato* OR hepatic*	111	GU_Gin_res1.end
Free-text: hemangio*	0	–
Free-text: Cholangiocarcinoma*	0	GU_Gin_res2.end
Free-text: Angiosarcoma*	0	–
Free-text: Bile AND duct*	1	GU_Gin_res3.end
MESH: Liver Neoplasms (C04.588.274.623)	20	GU_Gin_res3.end
Free-text: Hepatocellular	5	GU_Gin_res4.end
Total (before deduplication)	137	–
Total (after deduplication)	114	–

**National Guidelines Clearinghouse (Internet)**

[www.guideline.gov/](http://www.guideline.gov/)

Search limited to 2000–9 November 2011.

Searched 10 November 2011.

Advanced search

Terms searched	Hits
FLL OR FLLS OR BFLL OR BFLLS OR HCC OR HCCs OR Liver OR hepato* OR hepatic*	343
hemangio*OR Cholangiocarcinoma*OR Angiosarcoma* OR (Bile AND duct*)	11
Total	354

**National Institute for Health and Care Excellence guidance (Internet)**

<http://guidance.nice.org.uk/>

Searched 10 November 2011.

Browsed: liver neoplasms = **11**

**TRIP database (Internet)**

[www.tripdatabase.com/](http://www.tripdatabase.com/)

Searched 10 November 2011.

Search limited to guidelines only, 2000–11.

Terms searched	Hits
(FLL or BFLL or HCC) from:2000 to:2011	45
(title:Liver or hepato* or hepatic) (not FLL or BFLL or HCC) from:2000 to:2011	51
(title:hemangio* or Cholangiocarcinoma*) (not FLL or BFLL or HCC) from:2000 to:2011	3
(title:bile duct) (not Liver or hepato* or hepatic) from:2000 to:2011	2
Total	101

**Health Technology Assessment database (Internet)**

[www.york.ac.uk/inst/crd/](http://www.york.ac.uk/inst/crd/)

Search limited to 2000–11.

Searched 10 November 2011.

1. ((Bile NEXT duct\*)) IN HTA (10)
2. ((liver or hepato\* or hepatic\* or FLL or FLLs)) OR ((hepatoma\* or hemangiosarcoma\* or hemangio-sarcoma\* or haemangiosarcoma\* or haemangio-sarcoma\*)) OR ((BFLL or BFLLS or HCC or HCCs)) OR ((Cholangiocarcinoma\* or Cholangio-carcinoma\*)) IN HTA FROM 2000 TO 2011 (204)
3. #1 OR #2 (209)
4. (#3) IN HTA FROM 2000 TO 2011 (209)

## Appendix 2 Study-specific guide to completion of QUADAS-2

The version of QUADAS-2 used in this assessment splits domain 2 into 'index test' and 'comparator' and includes additional signalling questions to accommodate primary studies that assess multiple tests. Only the 'patient selection' domain includes an applicability domain as it was considered that the inclusion criteria matched the review question for the 'index test', 'comparator' and 'reference standard' domains.

Before starting the risk of bias assessment we considered the relevance of each signalling question to our review, as well as the potential need for additional questions. Further criteria were then defined, as needed, to ensure consistent application of signalling questions and to help in the judgement of the risk of bias. Many signalling questions were not further specified and the answer was judged to be 'yes' if it was clearly reported in the study. If the answer to a signalling question was not clearly reported the question was judged as 'unclear' unless specified differently. 'No' was answered if it was clear from the reporting that an aspect was not fulfilled. Details of the assessment criteria used are reported below.

### Domain 1: patient selection

#### *Risk of bias*

Question 1: Was a consecutive or random sample of patients enrolled?

- 'yes' = low risk of bias
- 'unclear' = unclear risk of bias
- 'no' = high risk of bias.

Question 2: Was a case-control design avoided?

- 'yes' = low risk of bias
- 'unclear' = unclear risk of bias
- 'no' = high risk of bias.

Question 3: Did the study avoid inappropriate exclusions?

- 'no' for <10% of patients or 'yes' = low risk of bias
- 'unclear' = unclear risk of bias
- 'no' for  $\geq 10\%$  of patients = high risk of bias.

#### *Concerns regarding applicability*

- Included patients were adults with FLLs with uncertain diagnosis on standard US or other imaging modalities = 'low concern'.
- Included patients were adults with known liver malignancy who were being assessed for recurrence or response to treatment = 'low concern'.
- Included patients were adults with FLLs detected on standard US or other imaging, in which it was not clear if these examinations were diagnostic = 'unclear concern'.

## Domain 2a: index test

### *Risk of bias*

Question 1: Were the index test results interpreted without knowledge of the results of the reference standard?

Question 2: Were the index test results interpreted without knowledge of the comparator?

Question 3: Did the study prespecify the threshold for a positive result?

The same criteria applied to each of the three signalling questions:

- 'yes' = low risk of bias
- 'unclear' = unclear risk of bias
- 'no' = high risk of bias.

## Domain 2b: comparator test

### *Risk of bias*

Question 1: Were the comparator test results interpreted without knowledge of the results of the reference standard?

Question 2: Were the comparator test results interpreted without knowledge of the index test?

Question 3: Did the study prespecify the threshold for a positive result?

The same criteria applied to each of the three signalling questions:

- 'yes' = low risk of bias
- 'unclear' = unclear risk of bias
- 'no' = high risk of bias.

## Domain 3: reference standard

### *Risk of bias*

Question 1: Is the reference standard likely to correctly classify the target condition?

- 'yes' if  $\geq 90\%$  of test results were confirmed using the reference standard specified by the inclusion criteria (pathology for test positive and pathology or minimum 6 months' follow-up for test negative) = low risk of bias
- 'unclear' = unclear risk of bias
- 'no' if  $< 90\%$  of test results were confirmed using the reference standard specified by the inclusion criteria (pathology for test positive and pathology or minimum 6 months' follow-up for test negative) = high risk of bias.

Question 2: Were the reference standard results interpreted without knowledge of the results of the index test?

Question 3: Were the reference standard results interpreted without knowledge of the results of the comparator test?

The same criteria applied to signalling questions 2 and 3:

- 'yes' = low risk of bias
- 'unclear' = unclear risk of bias
- 'no' = high risk of bias.

## Domain 4: flow and timing

Question 1: Was there an appropriate interval between index test and reference standard?

The time interval between index and reference standard (pathology) had to be  $\leq 1$  month to be judged as 'adequate' and follow-up had to be  $\geq 6$  months to be judged as 'adequate'.

- 'no' for  $< 10\%$  of patients or 'yes' = low risk of bias
- the answer was judged to be 'unclear' if the time interval was not reported or if it was unclear what proportion of patients had an inadequate time interval between index test and reference standard = unclear risk of bias
- 'no' for  $\geq 10\%$  of patients = high risk of bias.

Question 2: Was there an appropriate interval between comparator test and reference standard?

The time interval between index and reference standard (pathology) had to be  $\leq 1$  month to be judged as 'adequate' and follow-up had to be  $\geq 6$  months to be judged as 'adequate'.

- 'no' for  $< 10\%$  of patients or 'yes' = low risk of bias
- the answer was judged to be 'unclear' if the time interval was not reported or if it was unclear what proportion of patients had an inadequate time interval between index test and reference standard = unclear risk of bias
- 'no' for  $\geq 10\%$  of patients = high risk of bias.

Question 3: Was there an appropriate interval between index test and comparator test?

The time interval between index and comparator had to be  $\leq 1$  month to be judged as 'adequate'.

- 'no' for  $< 10\%$  of patients or 'yes' = low risk of bias
- the answer was judged to be 'unclear' if the time interval was not reported or if it was unclear what proportion of patients had an inadequate time interval between index test and reference standard = unclear risk of bias
- 'no' for  $\geq 10\%$  of patients = high risk of bias.

Question 4: Did all patients receive a reference standard?

- 'no' for  $< 10\%$  of patients or 'yes' = low risk of bias
- 'unclear' = unclear risk of bias
- 'no' for  $\geq 10\%$  of patients = high risk of bias.

Question 5: Did all patients receive the same reference standard?

Acceptable reference standards were defined separately for test-positive and test-negative patients. The following criteria are therefore applied separately to test-positive and test-negative patients:

- 'no' for  $< 10\%$  of test-positive patients and  $< 10\%$  of test-negative patients, or 'yes' = low risk of bias
- 'unclear' = unclear risk of bias
- 'no' for  $\geq 10\%$  of test-positive or test-negative patients = high risk of bias.

Question 6: Were all patients included in the analysis?

- 'no' for  $< 10\%$  of patients or 'yes' = low risk of bias
- 'unclear' = unclear risk of bias

- 'no' for  $\geq 10\%$  of patients = high risk of bias.

The following criteria were used to reach a per-domain judgement of risk of bias:

- if at least one of the signalling questions of a domain had an answer associated with a high risk of bias the domain was judged to have a high risk of bias
- if the answer to any of the signalling questions was 'unclear' and the answers to the remaining questions were 'yes', the risk of bias was judged to be unclear
- the answer to all the signalling questions had to be 'yes' for the domain to be judged as having a low risk of bias.

## Appendix 3 Quality assessment: QUADAS-2 results

This appendix presents completed QUADAS-2 assessments for all included studies.

### Blondin 2011<sup>48</sup>

#### Domain 1: patient selection

##### A. Risk of bias

Describe methods of patient selection:

Retrospective selection of patients with liver cirrhosis from a database (radiological information system) of patients who underwent CEMRI and CEUS

Was a consecutive or random sample of patients enrolled?	No
Was a case-control design avoided?	No
Did the study avoid inappropriate exclusions?	Unclear
<b>Could the selection of patients have introduced bias?</b>	<b>Risk: high</b>

##### B. Concerns regarding applicability

Describe included patients (previous testing, presentation, intended use of index test and setting):

Patients with liver cirrhosis and FLLs diagnosed with CEUS and CEMRI

<b>Is there concern that the included patients do not match the review question?</b>	<b>Concern: high</b>
--	----------------------

#### Domain 2a: index test

##### A. Risk of bias

Describe how the index test and any comparator tests were conducted and interpreted:

CEUS and CEMRI results were interpreted by two experts who were blinded (no more details given on blinding); index and comparator tests were conducted with maximum 4 weeks in between

Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Were the index test results interpreted without knowledge of the comparator?	Unclear
If a threshold was used, was it prespecified?	Yes
<b>Could the conduct or interpretation of the index test have introduced bias?</b>	<b>Risk: unclear</b>



**Domain 2b: comparator test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

CEUS and CEMRI results were interpreted by two experts who were blinded (no more details given on blinding); index and comparator test were conducted with maximum 4 weeks in between

Were the comparator test results interpreted without knowledge of the results of the reference standard? Unclear

Were the comparator test results interpreted without knowledge of the index test? Unclear

If a threshold was used, was it prespecified? Yes

**Could the conduct or interpretation of the comparator test have introduced bias? Risk: unclear**

**Domain 3: reference standard****A. Risk of bias**

Describe the reference standard and how it was conducted and interpreted:

Histology was carried out for all FLLs, before imaging results were analysed

Is the reference standard likely to correctly classify the target condition? Yes

Were the reference standard results interpreted without knowledge of the results of the index test? Yes

Were the reference standard results interpreted without knowledge of the results of the comparator test? Yes

**Could methods used to conduct or interpret the reference standard have introduced bias? Risk: low**

**Domain 4: flow and timing****A. Risk of bias**

Describe any patients who did not receive the index test, comparator(s) and/or reference standard or who were excluded from the 2x2 table(s):

All patients received each test.

Describe the time interval and any interventions carried out between index, comparator(s) and reference standard:

Time between index and comparator tests and reference standard was not reported. Time between index and comparator tests was maximum 4 weeks.

Was there an appropriate interval between index test and reference standard? Unclear

Was there an appropriate interval between comparator test and reference standard? Unclear

Was there an appropriate interval between index test and comparator test? Yes

Did all patients receive a reference standard? Yes

Did patients receive the same reference standard? Yes

Were all patients included in the analysis? Yes

**Could the patient flow have introduced bias? Risk: low**

**Catala 2007<sup>52</sup>****Domain 1: patient selection****A. Risk of bias**

Describe methods of patient selection:

Patients ≥ 18 years with FLLs detected on standard US. A total of 213 patients assessed for inclusion, with 77 enrolled  
Excluded if pregnant or nursing, if more than 1 month between CEUS and spiral computed tomography (unclear if these patients may be systematically different) and if positive lesions not confirmed by pathology

Was a consecutive or random sample of patients enrolled?	No
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
<b>Could the selection of patients have introduced bias?</b>	<b>Risk: high</b>

**B. Concerns regarding applicability**

Describe included patients (previous testing, presentation, intended use of index test and setting):

Adult patients with FLLs detected at standard US. Not clear if standard US was diagnostic

<b>Is there concern that the included patients do not match the review question?</b>	<b>Concern: unclear</b>
--	-------------------------

**Domain 2a: index test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

Independently, by experienced radiologists, who were unaware of the diagnosis and the results of other imaging tests

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Were the index test results interpreted without knowledge of the comparator?	Yes
If a threshold was used, was it prespecified?	Yes
<b>Could the conduct or interpretation of the index test have introduced bias?</b>	<b>Risk: low</b>

**Domain 2b: comparator test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

Independently, by experienced radiologists, who were unaware of the diagnosis and the results of other imaging tests

Were the comparator test results interpreted without knowledge of the results of the reference standard?	Yes
Were the comparator test results interpreted without knowledge of the index test?	Yes
If a threshold was used, was it prespecified?	Yes
<b>Could the conduct or interpretation of the comparator test have introduced bias?</b>	<b>Risk: low</b>

**Domain 3: reference standard****A. Risk of bias**


---

Describe the reference standard and how it was conducted and interpreted:

All index test-positive FLLs were confirmed pathologically following biopsy or surgery. Index test-negative lesions were confirmed by MRI and a minimum of 12 months' follow-up

Is the reference standard likely to correctly classify the target condition? Yes

Were the reference standard results interpreted without knowledge of the results of the index test? Unclear

Were the reference standard results interpreted without knowledge of the results of the comparator test? Unclear

**Could methods used to conduct or interpret the reference standard have introduced bias? Risk: unclear**

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**Domain 4: flow and timing****A. Risk of bias**


---

Describe any patients who did not receive the index test, comparator(s) and/or reference standard or who were excluded from the 2×2 table(s):

A total of 213 patients were originally recruited; 77 were included in the analysis. Patients were excluded if there was >1 month between CEUS and SCT, or if positive lesions were not confirmed by pathology

Describe the time interval and any interventions between index, comparator(s) and reference standard:

Time between index test and comparator was ≤1 month; time between tests and pathology reference standard not specified; follow-up period appropriate

Was there an appropriate interval between index test and reference standard? Unclear

Was there an appropriate interval between comparator test and reference standard? Unclear

Was there an appropriate interval between index test and comparator test? Yes

Did all patients receive a reference standard? No

Did patients receive the same reference standard? No

Were all patients included in the analysis? No

**Could the patient flow have introduced bias? Risk: high**

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**Clevert 2009<sup>51</sup>****Domain 1: patient selection****A. Risk of bias**

Describe methods of patient selection:

Prospective cohort of 100 consecutive patients with suspected hepatic tumours

Exclusion criteria were lesion >5 cm, more than five lesions, strong allergic reactions, liver or kidney disease with confirmed elevation of laboratory parameters, acute heart failure, acute myocardial infarction, subcutaneous emphysema, meteorism, tachypnea and aerobilia

The majority of test-positive patients were diagnosed with liver metastases, but previous investigations and diagnostic status with respect to primary tumours were unclear

Was a consecutive or random sample of patients enrolled? Yes

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Yes

**Could the selection of patients have introduced bias? Risk: low**

**B. Concerns regarding applicability**

Describe included patients (previous testing, presentation, intended use of index test and setting):

Previous investigations and diagnostic status with respect to primary tumours were unclear

**Is there concern that the included patients do not match the review question? Concern: unclear**

**Domain 2a: index test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

CEUS interpreters blinded. Reference standard performed after both tests

Were the index test results interpreted without knowledge of the results of the reference standard? Yes

Were the index test results interpreted without knowledge of the comparator? Yes

If a threshold was used, was it prespecified? Yes

**Could the conduct or interpretation of the index test have introduced bias? Risk: low**

**Domain 2b: comparator test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

Interpreted blind to index test; reference standard performed after both tests

Were the comparator test results interpreted without knowledge of the results of the reference standard? Yes

Were the comparator test results interpreted without knowledge of the index test? Yes

If a threshold was used, was it prespecified? Yes

**Could the conduct or interpretation of the comparator test have introduced bias? Risk: low**

**Domain 3: reference standard****A. Risk of bias**


---

Describe the reference standard and how it was conducted and interpreted:

No details of blinding or interpretation reported

Is the reference standard likely to correctly classify the target condition? Yes

Were the reference standard results interpreted without knowledge of the results of the index test? Unclear

Were the reference standard results interpreted without knowledge of the results of the comparator test? Unclear

**Could methods used to conduct or interpret the reference standard have introduced bias? Risk: unclear**

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**Domain 4: flow and timing****A. Risk of bias**


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Describe any patients who did not receive the index test, comparator(s) and/or reference standard or who were excluded from the 2x2 table(s):

100 patients, with one lesion per patient. Positive tests were confirmed histologically and negative tests by imaging follow-up over 2 years. A total of 21 patients were excluded from the CT analysis (eight did not undergo CT and 13 had non-diagnostic CT results)

Describe the time interval and any interventions between index, comparator(s) and reference standard:

Imaging tests were performed on the same day. Follow-up was >6 months but time between imaging and histological confirmation was not reported

Was there an appropriate interval between index test and reference standard? Unclear

Was there an appropriate interval between comparator test and reference standard? Unclear

Was there an appropriate interval between index test and comparator test? Yes

Did all patients receive a reference standard? Yes

Did patients receive the same reference standard? Yes

Were all patients included in the analysis? No

**Could the patient flow have introduced bias? Risk: high**

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**Dai 2008<sup>43</sup>****Domain 1: patient selection****A. Risk of bias**

Describe methods of patient selection:

498 consecutive patients with cirrhosis; study included 72 patients with 103 indeterminate liver nodules detected on surveillance US

Nine patients had been previously treated for HCC

Was a consecutive or random sample of patients enrolled? Yes

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Yes

**Could the selection of patients have introduced bias? Risk: low**

**B. Concerns regarding applicability**

Describe included patients (previous testing, presentation, intended use of index test and setting):

Adult patients with cirrhosis and indeterminate FLLs detected at surveillance US

**Is there concern that the included patients do not match the review question? Concern: low**

**Domain 2a: index test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

In consensus, by two experienced sonologists, who were unaware of the diagnosis and the results of other imaging tests

Were the index test results interpreted without knowledge of the results of the reference standard? Yes

Were the index test results interpreted without knowledge of the comparator? Yes

If a threshold was used, was it prespecified? Yes

**Could the conduct or interpretation of the index test have introduced bias? Risk: low**

**Domain 2b: comparator test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

In consensus, by two experienced radiologists, who were unaware of the diagnosis and the results of other imaging tests

Were the comparator test results interpreted without knowledge of the results of the reference standard? Yes

Were the comparator test results interpreted without knowledge of the index test? Yes

If a threshold was used, was it prespecified? Yes

**Could the conduct or interpretation of the comparator test have introduced bias? Risk: low**

**Domain 3: reference standard****A. Risk of bias**


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Describe the reference standard and how it was conducted and interpreted:

All patients underwent biopsy (malignant and benign FLLs) within 15 days after CEUS; a negative biopsy was followed up for at least 6 months, including US, CT and testing for AFP

Is the reference standard likely to correctly classify the target condition? Yes

Were the reference standard results interpreted without knowledge of the results of the index test? Unclear

Were the reference standard results interpreted without knowledge of the results of the comparator test? Unclear

**Could methods used to conduct or interpret the reference standard have introduced bias? Risk: unclear**

---

**Domain 4: flow and timing****A. Risk of bias**


---

Describe any patients who did not receive the index test, comparator(s) and/or reference standard or who were excluded from the 2×2 table(s):

498 patients with cirrhosis; 72 with indeterminate liver nodules on US were included in the study

Describe the time interval and any interventions between index, comparator(s) and reference standard:

All patients underwent biopsy within 15 days after CEUS; all patients underwent CECT within 15 days before or after CEUS

Was there an appropriate interval between index test and reference standard? Yes

Was there an appropriate interval between comparator test and reference standard? Yes

Was there an appropriate interval between index test and comparator test? Yes

Did all patients receive a reference standard? Yes

Did patients receive the same reference standard? Yes

Were all patients included in the analysis? Yes

**Could the patient flow have introduced bias? Risk: low**

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**Feng 2007<sup>57</sup>**

Chinese-language paper.

**Domain 1: patient selection****A. Risk of bias**

Describe methods of patient selection:

Prospective cohort of 23 patients with 26 malignant lesions (23 HCC and three metastases) undergoing cryosurgery

Was a consecutive or random sample of patients enrolled? Unclear

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Unclear

**Could the selection of patients have introduced bias? Risk: unclear****B. Concerns regarding applicability**

Describe included patients (previous testing, presentation, intended use of index test and setting):

Patients being assessed for treatment response

**Is there concern that the included patients do not match the review question? Concern: low****Domain 2a: index test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

No details of interpretation reported. Reference standard followed imaging

Were the index test results interpreted without knowledge of the results of the reference standard? Yes

Were the index test results interpreted without knowledge of the comparator? Unclear

If a threshold was used, was it prespecified? Yes

**Could the conduct or interpretation of the index test have introduced bias? Risk: unclear****Domain 2b: comparator test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

No details of interpretation reported. Reference standard followed imaging

Were the comparator test results interpreted without knowledge of the results of the reference standard? Yes

Were the comparator test results interpreted without knowledge of the index test? Unclear

If a threshold was used, was it prespecified? Yes

**Could the conduct or interpretation of the comparator test have introduced bias? Risk: unclear**



**Domain 3: reference standard****A. Risk of bias**


---

Describe the reference standard and how it was conducted and interpreted: Unclear if those making the diagnosis were aware of imaging results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Were the reference standard results interpreted without knowledge of the results of the comparator test?	Unclear
<b>Could methods used to conduct or interpret the reference standard have introduced bias?</b>	<b>Risk: unclear</b>

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**Domain 4: flow and timing****A. Risk of bias**


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Describe any patients who did not receive the index test, comparator(s) and/or reference standard or who were excluded from the 2×2 table(s): All patients underwent imaging tests within 2 weeks of each other and within 1 week to 3 months after treatment. All diagnoses were confirmed by histopathology	
Describe the time interval and any interventions between index, comparator(s) and reference standard: Time between imaging tests and reference standard was not reported	
Was there an appropriate interval between index test and reference standard?	Unclear
Was there an appropriate interval between comparator test and reference standard?	Unclear
Was there an appropriate interval between index test and comparator test?	Yes
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
<b>Could the patient flow have introduced bias?</b>	<b>Risk: unclear</b>

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**Flor 2010<sup>39</sup>**

Abstract only.

**Domain 1: patient selection****A. Risk of bias**

Describe methods of patient selection:

Prospective cohort of 18 patients with known primary cancer and indeterminate liver lesions (&lt;1.5 cm) detected at MDCT

Was a consecutive or random sample of patients enrolled? Unclear

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Unclear

**Could the selection of patients have introduced bias? Risk: unclear****B. Concerns regarding applicability**

Describe included patients (previous testing, presentation, intended use of index test and setting):

Patients with known primary cancer and indeterminate liver lesions (&lt;1.5 cm) detected at MDCT

**Is there concern that the included patients do not match the review question? Concern: low****Domain 2a: index test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

No details reported

Were the index test results interpreted without knowledge of the results of the reference standard? Unclear

If a threshold was used, was it prespecified? Unclear

**Could the conduct or interpretation of the index test have introduced bias? Risk: unclear****Domain 2b: comparator test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

Not applicable

Were the comparator test results interpreted without knowledge of the results of the reference standard?

Were the comparator test results interpreted without knowledge of the index test?

If a threshold was used, was it prespecified?

**Could the conduct or interpretation of the comparator test have introduced bias? Risk: not applicable**

**Domain 3: reference standard****A. Risk of bias**


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Describe the reference standard and how it was conducted and interpreted:

Biopsy or 3- to 6-month follow-up was used as the reference standard. No further details were reported

Is the reference standard likely to correctly classify the target condition? Yes

Were the reference standard results interpreted without knowledge of the results of the index test? Unclear

Were the reference standard results interpreted without knowledge of the results of the comparator test? Not applicable

**Could methods used to conduct or interpret the reference standard have introduced bias? Risk: unclear**

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**Domain 4: flow and timing****A. Risk of bias**


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Describe any patients who did not receive the index test, comparator(s) and/or reference standard or who were excluded from the 2×2 table(s):

All 18 patients appear to have received a reference standard. Numbers confirmed by biopsy/follow-up were not reported

Describe the time interval and any interventions between index, comparator(s) and reference standard:

Time between index test and biopsy was not reported

Was there an appropriate interval between index test and reference standard? Unclear

Was there an appropriate interval between comparator test and reference standard? Not applicable

Was there an appropriate interval between index test and comparator test? Not applicable

Did all patients receive a reference standard? Yes

Did patients receive the same reference standard? Unclear

Were all patients included in the analysis? Yes

**Could the patient flow have introduced bias? Risk: unclear**

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**Forner 2008<sup>44</sup>****Domain 1: patient selection****A. Risk of bias**

Describe methods of patient selection:

Prospective cohort of 89 patients with Child–Pugh A/B cirrhosis and a new solid (5–20 mm) nodule detected on surveillance US

No patients had history of HCC

Was a consecutive or random sample of patients enrolled? Unclear

Was a case–control design avoided? Yes

Did the study avoid inappropriate exclusions? Yes

**Could the selection of patients have introduced bias? Risk: unclear**

**B. Concerns regarding applicability**

Describe included patients (previous testing, presentation, intended use of index test and setting):

Adult patients with cirrhosis and new FLLs detected at surveillance US. Diagnostic status following conventional US was not specified

**Is there concern that the included patients do not match the review question? Concern: unclear**

**Domain 2a: index test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

Interpreted by two experienced radiologists. Article states 'blindly', but nature of blinding is unspecified

Were the index test results interpreted without knowledge of the results of the reference standard? Unclear

Were the index test results interpreted without knowledge of the comparator? Unclear

If a threshold was used, was it prespecified? Yes

**Could the conduct or interpretation of the index test have introduced bias? Risk: unclear**

**Domain 2b: comparator test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

Interpreted by two experienced radiologists who were unaware of biopsy results

Were the comparator test results interpreted without knowledge of the results of the reference standard? Yes

Were the comparator test results interpreted without knowledge of the index test? Unclear

If a threshold was used, was it prespecified? Yes

**Could the conduct or interpretation of the comparator test have introduced bias? Risk: low**

**Domain 3: reference standard****A. Risk of bias**


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Describe the reference standard and how it was conducted and interpreted:

All index test-positive FLLs were confirmed pathologically following biopsy or surgery. Index test-negative lesions were confirmed by MRI and a minimum of 12 months' follow-up

Is the reference standard likely to correctly classify the target condition? Yes

Were the reference standard results interpreted without knowledge of the results of the index test? Unclear

Were the reference standard results interpreted without knowledge of the results of the comparator test? Unclear

**Could methods used to conduct or interpret the reference standard have introduced bias? Risk: unclear**

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**Domain 4: flow and timing****A. Risk of bias**


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Describe any patients who did not receive the index test, comparator(s) and/or reference standard or who were excluded from the 2×2 table(s):

89 patients all received index test, comparator and a reference standard

Describe the time interval and any interventions between index, comparator(s) and reference standard:

Times between index test, comparator and reference standard were not reported

Was there an appropriate interval between index test and reference standard? Unclear

Was there an appropriate interval between comparator test and reference standard? Unclear

Was there an appropriate interval between index test and comparator test? Unclear

Did all patients receive a reference standard? Yes

Did patients receive the same reference standard? Yes

Were all patients included in the analysis? Yes

**Could the patient flow have introduced bias? Risk: unclear**

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**Georgio 2007<sup>45</sup>****Domain 1: patient selection****A. Risk of bias**

Describe methods of patient selection:

Prospective cohort of 73 consecutive patients with cirrhosis and a single nodule ( $\leq 30$  mm) detected on US  
Patients with a history of heart disease excluded (because of a rare side effect of SonoVue)

Was a consecutive or random sample of patients enrolled? Yes

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Yes

**Could the selection of patients have introduced bias? Risk: low**

**B. Concerns regarding applicability**

Describe included patients (previous testing, presentation, intended use of index test and setting):

Adult patients with cirrhosis and single FLL detected at US. Diagnostic status following conventional US was not specified

**Is there concern that the included patients do not match the review question? Concern: unclear**

**Domain 2a: index test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

Interpreted by one operator with 20 years' experience. Index test performed before comparator and reference standard

Were the index test results interpreted without knowledge of the results of the reference standard? Yes

Were the index test results interpreted without knowledge of the comparator? Yes

If a threshold was used, was it prespecified? Yes

**Could the conduct or interpretation of the index test have introduced bias? Risk: low**

**Domain 2b: comparator test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

Interpreted by one radiologist who was unaware of index test results. Comparator test performed before reference standard

Were the comparator test results interpreted without knowledge of the results of the reference standard? Yes

Were the comparator test results interpreted without knowledge of the index test? Yes

If a threshold was used, was it prespecified? Yes

**Could the conduct or interpretation of the comparator test have introduced bias? Risk: low**

**Domain 3: reference standard****A. Risk of bias**


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Describe the reference standard and how it was conducted and interpreted:

Biopsy performed in all patients the day after both imaging studies were complete. No details of blinding were reported

Is the reference standard likely to correctly classify the target condition? Yes

Were the reference standard results interpreted without knowledge of the results of the index test? Unclear

Were the reference standard results interpreted without knowledge of the results of the comparator test? Unclear

**Could methods used to conduct or interpret the reference standard have introduced bias? Risk: unclear**

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**Domain 4: flow and timing****A. Risk of bias**


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Describe any patients who did not receive the index test, comparator(s) and/or reference standard or who were excluded from the 2x2 table(s):

73 patients all received the index test, comparator and a reference standard; same reference standard was used in all patients

Describe the time interval and any interventions between index, comparator(s) and reference standard:

Comparator was performed the day after the index test and the reference standard the day after that

Was there an appropriate interval between index test and reference standard? Yes

Was there an appropriate interval between comparator test and reference standard? Yes

Was there an appropriate interval between index test and comparator test? Yes

Did all patients receive a reference standard? Yes

Did patients receive the same reference standard? Yes

Were all patients included in the analysis? Yes

**Could the patient flow have introduced bias? Risk: low**

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**Gierbliński 2008<sup>53</sup>****Domain 1: patient selection****A. Risk of bias**

Describe methods of patient selection:

Prospective cohort of 100 patients with incidentally detected liver lesions and inconclusive unenhanced US and/or CT. Patients with current or previous malignancy, with lesions with features of haemangioma or who were unable to undergo biopsy were excluded

Was a consecutive or random sample of patients enrolled? Unclear

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? No

**Could the selection of patients have introduced bias? Risk: high**

**B. Concerns regarding applicability**

Describe included patients (previous testing, presentation, intended use of index test and setting):

Adult patients with incidentally detected FLLs in whom US and/or CT could not rule out malignancy. Not clear how many patients had CT

**Is there concern that the included patients do not match the review question? Concern: unclear**

**Domain 2a: index test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

Interpreted by two experienced gastroenterologists; blinding unspecified

Were the index test results interpreted without knowledge of the results of the reference standard? Unclear

Were the index test results interpreted without knowledge of the comparator? Yes

If a threshold was used, was it prespecified? Yes

**Could the conduct or interpretation of the index test have introduced bias? Risk: unclear**

**Domain 2b: comparator test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

Not applicable

Were the comparator test results interpreted without knowledge of the results of the reference standard?

Were the comparator test results interpreted without knowledge of the index test?

If a threshold was used, was it prespecified?

**Could the conduct or interpretation of the comparator test have introduced bias? Risk: not applicable**



**Domain 3: reference standard****A. Risk of bias**


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Describe the reference standard and how it was conducted and interpreted:

All FLLs were confirmed pathologically following biopsy. Biopsy-negative lesions were confirmed by clinical and imaging follow-up

Is the reference standard likely to correctly classify the target condition? Yes

Were the reference standard results interpreted without knowledge of the results of the index test? Yes

Were the reference standard results interpreted without knowledge of the results of the comparator test? Not applicable

**Could methods used to conduct or interpret the reference standard have introduced bias? Risk: low**

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**Domain 4: flow and timing****A. Risk of bias**


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Describe any patients who did not receive the index test, comparator(s) and/or reference standard or who were excluded from the 2×2 table(s):

89 patients all received index test, comparator and a reference standard

Describe the time interval and any interventions between index, comparator(s) and reference standard:

Time between index test and reference standard was not reported

Was there an appropriate interval between index test and reference standard? Unclear

Was there an appropriate interval between comparator test and reference standard? Not applicable

Was there an appropriate interval between index test and comparator test? Not applicable

Did all patients receive a reference standard? Yes

Did patients receive the same reference standard? Yes

Were all patients included in the analysis? Yes

**Could the patient flow have introduced bias? Risk: unclear**

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**Jonas 2011**<sup>50</sup>

Abstract only.

**Domain 1: patient selection****A. Risk of bias**

Describe methods of patient selection:

Prospective cohort of 20 consecutive patients with CRC liver metastases who could be rendered tumour free by a single-stage surgical intervention and who underwent complete preoperative workup

Note: study states aim as determining the sensitivity and specificity for detection of metastases, but all included patients appear to have metastases

Patients with concomitant resectable extrahepatic disease and previous hepatobiliary surgery, other than cholecystectomy, were excluded

Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
<b>Could the selection of patients have introduced bias?</b>	<b>Risk: high</b>

**B. Concerns regarding applicability**

Describe included patients (previous testing, presentation, intended use of index test and setting):

Adult patients with CRC liver metastases. Initial diagnostic status unclear (see previous note)

<b>Is there concern that the included patients do not match the review question?</b>	<b>Concern: high</b>
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**Domain 2a: index test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

No details of blinding or interpretation reported

Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Were the index test results interpreted without knowledge of the comparator?	Unclear
If a threshold was used, was it prespecified?	Unclear
<b>Could the conduct or interpretation of the index test have introduced bias?</b>	<b>Risk: unclear</b>

**Domain 2b: comparator test****A. Risk of bias**


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Describe how the index test and any comparator tests were conducted and interpreted:

No details of blinding or interpretation reported

Were the comparator test results interpreted without knowledge of the results of the reference standard? Unclear

Were the comparator test results interpreted without knowledge of the index test? Unclear

If a threshold was used, was it prespecified? Unclear

**Could the conduct or interpretation of the comparator test have introduced bias? Risk: unclear**

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**Domain 3: reference standard****A. Risk of bias**


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Describe the reference standard and how it was conducted and interpreted:

No details of blinding or interpretation reported

Is the reference standard likely to correctly classify the target condition? Yes

Were the reference standard results interpreted without knowledge of the results of the index test? Unclear

Were the reference standard results interpreted without knowledge of the results of the comparator test? Unclear

**Could methods used to conduct or interpret the reference standard have introduced bias? Risk: unclear**

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**Domain 4: flow and timing****A. Risk of bias**


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Describe any patients who did not receive the index test, comparator(s) and/or reference standard or who were excluded from the 2×2 table(s):

20 patients, 48 lesions, by lesion analysis. All patients appear to have received index test and both comparators. All resected, imaging-positive lesions were confirmed histologically and all patients had at least 36 months' imaging follow-up. Per 2×2 patient data were not reported/derivable and the number of lesions per patient was unclear

Describe the time interval and any interventions between index, comparator(s) and reference standard:

No details of the timing of the tests were reported

Was there an appropriate interval between index test and reference standard? Unclear

Was there an appropriate interval between comparator test and reference standard? Unclear

Was there an appropriate interval between index test and comparator test? Unclear

Did all patients receive a reference standard? Yes

Did patients receive the same reference standard? Yes

Were all patients included in the analysis? Unclear

**Could the patient flow have introduced bias? Risk: unclear**

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**Leoni 2010<sup>42</sup>****Domain 1: patient selection****A. Risk of bias**

Describe methods of patient selection:

Prospective consecutive cohort of cirrhotic patients with one to three hepatic nodules between 1 and 3 cm on US surveillance. Included both newly detected and recurrence of nodules

Patients in whom the nodules to be included in the study had been pretreated, those with contraindications to imaging and those with neoplastic portal thrombosis or extrahepatic metastases were excluded

Was a consecutive or random sample of patients enrolled? Yes

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? No

**Could the selection of patients have introduced bias? Risk: high**

**B. Concerns regarding applicability**

Describe included patients (previous testing, presentation, intended use of index test and setting):

Diagnostic status following unenhanced imaging unclear

**Is there concern that the included patients do not match the review question? Concern: unclear**

**Domain 2a: index test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

Unclear if those interpreting CEUS had knowledge of other imaging test results

Were the index test results interpreted without knowledge of the results of the reference standard? Yes

Were the index test results interpreted without knowledge of the comparator? Yes

If a threshold was used, was it prespecified? Yes

**Could the conduct or interpretation of the index test have introduced bias? Risk: low**

**Domain 2b: comparator test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

Interpreted blind to other imaging test results, and biopsy/follow-up occurred after imaging

Were the comparator test results interpreted without knowledge of the results of the reference standard? Yes

Were the index test results interpreted without knowledge of the comparator? Yes

If a threshold was used, was it prespecified? Yes

**Could the conduct or interpretation of the comparator test have introduced bias? Risk: low**

**Domain 3: reference standard****A. Risk of bias**


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Describe the reference standard and how it was conducted and interpreted:

Non-invasive positive diagnoses were interpreted without knowledge of other imaging studies. No details of interpretation of biopsy and follow-up were reported

Is the reference standard likely to correctly classify the target condition? No

Were the reference standard results interpreted without knowledge of the results of the index test? Unclear

Were the reference standard results interpreted without knowledge of the results of the comparator test? Unclear

**Could methods used to conduct or interpret the reference standard have introduced bias? Risk: high**

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**Domain 4: flow and timing****A. Risk of bias**


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Describe any patients who did not receive the index test, comparator(s) and/or reference standard or who were excluded from the 2×2 table(s):

Prospective cohort of 60 cirrhotic patients with at least one to three hepatic nodules (1–3 cm) on US (75 nodules). Positive nodules confirmed by two concordant imaging test results, FNB or follow-up at 3-month intervals. Negative nodules confirmed by FNB or follow-up at 3-month intervals. Seven nodules (<10%) were not examined by SPIO-MRI and were excluded from the analysis of test performance

Describe the time interval and any interventions between index, comparator(s) and reference standard:

No details of the timing of examinations were reported

Was there an appropriate interval between index test and reference standard? Unclear

Was there an appropriate interval between comparator test and reference standard? Unclear

Was there an appropriate interval between index test and comparator test? Unclear

Did all patients receive a reference standard? Yes

Did patients receive the same reference standard? No

Were all patients included in the analysis? No

**Could the patient flow have introduced bias? Risk: high**

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**Li 2007<sup>54</sup>****Domain 1: patient selection****A. Risk of bias**

Describe methods of patient selection:

Prospective cohort of 109 patients examined with unenhanced US and unenhanced CT. Exclusions not specified

Was a consecutive or random sample of patients enrolled? Unclear

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Unclear

**Could the selection of patients have introduced bias? Risk: unclear****B. Concerns regarding applicability**

Describe included patients (previous testing, presentation, intended use of index test and setting):

Diagnostic status following baseline imaging unclear

**Is there concern that the included patients do not match the review question? Concern: unclear****Domain 2a: index test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

Interpreted blind to comparator; reference standard performed after both tests

Were the index test results interpreted without knowledge of the results of the reference standard? Yes

Were the index test results interpreted without knowledge of the comparator? Yes

If a threshold was used, was it prespecified? Yes

**Could the conduct or interpretation of the index test have introduced bias? Risk: low****Domain 2b: comparator test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

Interpreted blind to index test; reference standard performed after both tests

Were the comparator test results interpreted without knowledge of the results of the reference standard? Yes

Were the comparator test results interpreted without knowledge of the index test? Yes

If a threshold was used, was it prespecified? Yes

**Could the conduct or interpretation of the comparator test have introduced bias? Risk: low**

**Domain 3: reference standard****A. Risk of bias**


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Describe the reference standard and how it was conducted and interpreted:

No details of blinding or interpretation reported

Is the reference standard likely to correctly classify the target condition? Yes

Were the reference standard results interpreted without knowledge of the results of the index test? Unclear

Were the reference standard results interpreted without knowledge of the results of the comparator test? Unclear

**Could methods used to conduct or interpret the reference standard have introduced bias? Risk: unclear**

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**Domain 4: flow and timing****A. Risk of bias**


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Describe any patients who did not receive the index test, comparator(s) and/or reference standard or who were excluded from the 2×2 table(s):

109 patients, one lesion per patient. All patients appear to have received the index test, comparator and reference standard. Reference standard was histology in all patients. Seven lesions could not be visualised by CECT and three could not be visualised by CEUS. For our analysis, non-visualised lesions were classified as negative (false-negative or true-negative according to final diagnosis)

Describe the time interval and any interventions between index, comparator(s) and reference standard:

Reference standard was performed within 2 weeks of the index test and comparator

Was there an appropriate interval between index test and reference standard? Yes

Was there an appropriate interval between comparator test and reference standard? Yes

Was there an appropriate interval between index test and comparator test? Yes

Did all patients receive a reference standard? Yes

Did patients receive the same reference standard? Yes

Were all patients included in the analysis? Yes

**Could the patient flow have introduced bias? Risk: low**

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**Lüttich 2006<sup>40</sup>**

Abstract only.

**Domain 1: patient selection****A. Risk of bias**

Describe methods of patient selection:

Cohort of 15 patients with HCC lesions undergoing RFA treatment

Was a consecutive or random sample of patients enrolled? Unclear

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Unclear

**Could the selection of patients have introduced bias? Risk: unclear****B. Concerns regarding applicability**

Describe included patients (previous testing, presentation, intended use of index test and setting):

Patients being assessed for response to treatment

**Is there concern that the included patients do not match the review question? Concern: low****Domain 2a: index test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

No details of interpretation reported. Reference standard followed CEUS

Were the index test results interpreted without knowledge of the results of the reference standard? Yes

Were the index test results interpreted without knowledge of the comparator? Unclear

If a threshold was used, was it prespecified? Unclear

**Could the conduct or interpretation of the index test have introduced bias? Risk: unclear****Domain 2b: comparator test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

No details of interpretation reported. Reference standard followed CEUS

Were the comparator test results interpreted without knowledge of the results of the reference standard? Unclear

Were the comparator test results interpreted without knowledge of the index test? Unclear

If a threshold was used, was it prespecified? Unclear

**Could the conduct or interpretation of the comparator test have introduced bias? Risk: unclear**



**Domain 3: reference standard****A. Risk of bias**


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Describe the reference standard and how it was conducted and interpreted: Unclear if those making the diagnosis were aware of imaging results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Were the reference standard results interpreted without knowledge of the results of the comparator test?	Unclear
<b>Could methods used to conduct or interpret the reference standard have introduced bias?</b>	<b>Risk: unclear</b>

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**Domain 4: flow and timing****A. Risk of bias**


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Describe any patients who did not receive the index test, comparator(s) and/or reference standard or who were excluded from the 2×2 table(s): All patients underwent both imaging tests within 4 weeks of treatment. All patients had results confirmed by biopsy	
Describe the time interval and any interventions between index, comparator(s) and reference standard: Time between tests and reference standard was not reported	
Was there an appropriate interval between index test and reference standard?	Unclear
Was there an appropriate interval between comparator test and reference standard?	Unclear
Was there an appropriate interval between index test and comparator test?	Yes
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
<b>Could the patient flow have introduced bias?</b>	<b>Risk: unclear</b>

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**Mainenti 2010<sup>49</sup>****Domain 1: patient selection****A. Risk of bias**

Describe methods of patient selection:

Prospective cohort of 34 consecutive patients with histologically proven CRC who were scheduled for surgery  
Patients who refused to participate and those who had contraindications to one of the examinations were excluded

Was a consecutive or random sample of patients enrolled? Yes

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Yes

**Could the selection of patients have introduced bias? Risk: low**

**B. Concerns regarding applicability**

Describe included patients (previous testing, presentation, intended use of index test and setting):

Diagnostic status following unenhanced imaging unclear

**Is there concern that the included patients do not match the review question? Concern: unclear**

**Domain 2a: index test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

Interpreted blind to comparator; reference standard performed after both tests

Were the index test results interpreted without knowledge of the results of the reference standard? Yes

Were the index test results interpreted without knowledge of the comparator? Yes

If a threshold was used, was it prespecified? Yes

**Could the conduct or interpretation of the index test have introduced bias? Risk: low**

**Domain 2b: comparator test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

Interpreted blind to index test; reference standard performed after both tests

Were the comparator test results interpreted without knowledge of the results of the reference standard? Yes

Were the comparator test results interpreted without knowledge of the index test? Yes

If a threshold was used, was it prespecified? Yes

**Could the conduct or interpretation of the comparator test have introduced bias? Risk: low**

**Domain 3: reference standard****A. Risk of bias**


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Describe the reference standard and how it was conducted and interpreted:

No details of blinding or interpretation reported

Is the reference standard likely to correctly classify the target condition? Yes

Were the reference standard results interpreted without knowledge of the results of the index test? Unclear

Were the reference standard results interpreted without knowledge of the results of the comparator test? Unclear

**Could methods used to conduct or interpret the reference standard have introduced bias? Risk: unclear**

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**Domain 4: flow and timing****A. Risk of Bias**


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Describe any patients who did not receive the index test, comparator(s) and/or reference standard or who were excluded from the 2x2 table(s):

34 patients, 57 lesions; both per-lesion and per-patient data reported. Positive tests were confirmed by biopsy or resection. All patients were followed up for 6 and 12 months, either to confirm negative tests or to detect newly developed metastases

Describe the time interval and any interventions between index, comparator(s) and reference standard:

Surgery was performed within 10 days of imaging and imaging tests were performed over a 4- to 8-day period

Was there an appropriate interval between index test and reference standard? Yes

Was there an appropriate interval between comparator test and reference standard? Yes

Was there an appropriate interval between index test and comparator test? Yes

Did all patients receive a reference standard? Yes

Did patients receive the same reference standard? Yes

Were all patients included in the analysis? Yes

**Could the patient flow have introduced bias? Risk: low**

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**Quaia 2009<sup>46</sup>****Domain 1: patient selection****A. Risk of bias**

Describe methods of patient selection:

Prospective cohort of cirrhotic patients with at least one hepatic nodule on US surveillance

Only those nodules  $\leq 3$  cm that underwent biopsy after CT were included

Nodules with peripheral enhancement at CECT were excluded because of a high probability of haemangioma diagnosis

Was a consecutive or random sample of patients enrolled? Unclear

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? No

**Could the selection of patients have introduced bias? Risk: high**

**B. Concerns regarding applicability**

Describe included patients (previous testing, presentation, intended use of index test and setting):

Diagnostic status following unenhanced imaging unclear

**Is there concern that the included patients do not match the review question? Concern: unclear**

**Domain 2a: index test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

Interpreted blind to comparator, reference standard and clinical details

Were the index test results interpreted without knowledge of the results of the reference standard? Yes

Were the index test results interpreted without knowledge of the comparator? Yes

If a threshold was used, was it prespecified? Yes

**Could the conduct or interpretation of the index test have introduced bias? Risk: low**

**Domain 2b: comparator test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

Interpreted blind to index test, reference standard and clinical details

Were the comparator test results interpreted without knowledge of the results of the reference standard? Yes

Were the comparator test results interpreted without knowledge of the index test? Yes

If a threshold was used, was it prespecified? Yes

**Could the conduct or interpretation of the comparator test have introduced bias? Risk: low**

**Domain 3: reference standard****A. Risk of bias**


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Describe the reference standard and how it was conducted and interpreted:

No details of blinding or interpretation reported

Is the reference standard likely to correctly classify the target condition? Yes

Were the reference standard results interpreted without knowledge of the results of the index test? Unclear

Were the reference standard results interpreted without knowledge of the results of the comparator test? Unclear

**Could methods used to conduct or interpret the reference standard have introduced bias? Risk: unclear**

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**Domain 4: flow and timing****A. Risk of bias**


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Describe any patients who did not receive the index test, comparator(s) and/or reference standard or who were excluded from the 2×2 table(s):

Prospective cohort of 180 cirrhotic patients with at least one hepatic nodule on US surveillance (195 nodules)

74 nodules were excluded because of a lack of histological diagnosis ( $n = 60$ ), technical inadequacy of CT ( $n = 10$ ) or inadequacy of CEUS examination ( $n = 4$ ); 106 patients with 121 nodules finally included

Reference standard biopsy in all nodules

Describe the time interval and any interventions between index, comparator(s) and reference standard:

CT was performed 2–30 days after CEUS. Biopsy was within 15 days of CT

Was there an appropriate interval between index test and reference standard? Yes

Was there an appropriate interval between comparator test and reference standard? Yes

Was there an appropriate interval between index test and comparator test? Yes

Did all patients receive a reference standard? No

Did patients receive the same reference standard? Yes

Were all patients included in the analysis? No

**Could the patient flow have introduced bias? Risk: high**

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**Sangiovanni 2010<sup>47,61</sup>****Domain 1: patient selection****A. Risk of bias**

Describe methods of patient selection:

Prospective cohort of cirrhotic patients with at least one hepatic nodule on US surveillance

Only 1- to 2-cm nodules were included in the analysis

Patients with a pre-existing liver nodule, poor liver function indicating transplantation regardless of HCC, or no defined nodule were excluded

Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
<b>Could the selection of patients have introduced bias?</b>	<b>Risk: high</b>

**B. Concerns regarding applicability**

Describe included patients (previous testing, presentation, intended use of index test and setting):

Diagnostic status following unenhanced imaging unclear

<b>Is there concern that the included patients do not match the review question?</b>	<b>Concern: unclear</b>
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**Domain 2a: index test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

Interpreted blind to reference standard

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Were the index test results interpreted without knowledge of the comparator?	Unclear
If a threshold was used, was it prespecified?	Yes
<b>Could the conduct or interpretation of the index test have introduced bias?</b>	<b>Risk: unclear</b>

**Domain 2b: comparator test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

Interpreted blind to reference standard

Were the comparator test results interpreted without knowledge of the results of the reference standard?	Yes
Were the comparator test results interpreted without knowledge of the index test?	Unclear
If a threshold was used, was it prespecified?	Yes
<b>Could the conduct or interpretation of the comparator test have introduced bias?</b>	<b>Risk: unclear</b>

**Domain 3: reference standard****A. Risk of bias**


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Describe the reference standard and how it was conducted and interpreted:

Reference standard interpreted without knowledge of clinical or imaging results

Is the reference standard likely to correctly classify the target condition? Yes

Were the reference standard results interpreted without knowledge of the results of the index test? Yes

Were the reference standard results interpreted without knowledge of the results of the comparator test? Yes

**Could methods used to conduct or interpret the reference standard have introduced bias? Risk: low**

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**Domain 4: flow and timing****A. Risk of bias**


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Describe any patients who did not receive the index test, comparator(s) and/or reference standard or who were excluded from the 2×2 table(s):

Prospective cohort of 64 cirrhotic patients with at least one hepatic nodule (67 nodules). All nodules confirmed by biopsy

Describe the time interval and any interventions between index, comparator(s) and reference standard:

Biopsy was performed within 2 months of nodule detection

Was there an appropriate interval between index test and reference standard? Yes

Was there an appropriate interval between comparator test and reference standard? Unclear

Was there an appropriate interval between index test and comparator test? Unclear

Did all patients receive a reference standard? Yes

Did patients receive the same reference standard? Yes

Were all patients included in the analysis? No

**Could the patient flow have introduced bias? Risk: high**

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**Seitz 2009<sup>55</sup>****Domain 1: patient selection****A. Risk of bias**

Describe methods of patient selection:

The study used a cohort of 267 out of 1349 patients of a prospective study of consecutive patients with newly detected FLLs identified on US. The 267 patients were divided into subgroups A and B. Subgroup A had mainly benign diagnoses and subgroup B had mainly malignant diagnosis; 2×2 data with an appropriate reference standard were extractable only for subgroup B

Patients with specific liver lesions diagnosed by typical US echomorphology, such as cysts or haemangiomas, in a non-steatotic liver without clinical signs and symptoms, as well as malignant tumours with infiltration into hepatic vessels, were excluded; patients who were critically ill or who suffered from pulmonary hypertension or unstable angina, as well as pregnant and nursing women, were also excluded.

Was a consecutive or random sample of patients enrolled?	No
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
<b>Could the selection of patients have introduced bias?</b>	<b>Risk: high</b>

**B. Concerns regarding applicability**

Describe included patients (previous testing, presentation, intended use of index test and setting):

Patients with newly detected FLLs on US; primary diseases not specified

<b>Is there concern that the included patients do not match the review question?</b>	<b>Concern: unclear</b>
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**Domain 2a: index test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

The definitive CEUS diagnosis was made at the time of the US examination by the physician performing CEUS; US carried out by the local investigators; US investigator not blinded to the results of the preceding CT in eight cases

Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Were the index test results interpreted without knowledge of the comparator?	Yes
If a threshold was used, was it prespecified?	Yes
<b>Could the conduct or interpretation of the index test have introduced bias?</b>	<b>Risk: unclear</b>



**Domain 2b: comparator test****A. Risk of bias**


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Describe how the index test and any comparator tests were conducted and interpreted:

No details of blinding reported. Reporting radiologists had access to the patients' clinical information

Were the comparator test results interpreted without knowledge of the results of the reference standard? Unclear

Were the comparator test results interpreted without knowledge of the index test? Unclear

If a threshold was used, was it prespecified? Yes

**Could the conduct or interpretation of the comparator test have introduced bias? Risk: unclear**

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**Domain 3: reference standard****A. Risk of bias**


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Describe the reference standard and how it was conducted and interpreted:

Subgroup B: diagnosis was based on US-guided FNB; no definitive diagnosis could be obtained in four patients

Is the reference standard likely to correctly classify the target condition? Yes

Were the reference standard results interpreted without knowledge of the results of the index test? Unclear

Were the reference standard results interpreted without knowledge of the results of the comparator test? Unclear

**Could methods used to conduct or interpret the reference standard have introduced bias? Risk: unclear**

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**Domain 4: flow and timing****A. Risk of bias**


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Describe any patients who did not receive the index test, comparator(s) and/or reference standard or who were excluded from the 2x2 table(s):

Four patients with inconclusive histology were excluded from the analyses (<10% of patients)

Describe the time interval and any interventions between index, comparator(s) and reference standard:

Times between index and comparator tests and reference standard were not reported

Was there an appropriate interval between index test and reference standard? Unclear

Was there an appropriate interval between comparator test and reference standard? Unclear

Was there an appropriate interval between index test and comparator test? Unclear

Did all patients receive a reference standard? Yes

Did patients receive the same reference standard? Yes

Were all patients included in the analysis? No

**Could the patient flow have introduced bias? Risk: unclear**

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**Seitz 2010<sup>56</sup>****Domain 1: patient selection****A. Risk of bias**

Describe methods of patient selection:

The study used a cohort of 269 out of 1349 patients of a prospective study of consecutive patients with newly detected FLLs identified on US. The 269 patients were divided into subgroups A and B. Subgroup A had mainly benign diagnoses and subgroup B had mainly malignant diagnosis; 2×2 data with an appropriate reference standard were extractable only for subgroup B

Patients with specific liver lesions diagnosed by typical US echomorphology, such as cysts or haemangiomas, in a non-steatotic liver without clinical signs and symptoms, as well as malignant tumours with infiltration into hepatic vessels, were excluded

Was a consecutive or random sample of patients enrolled?	No
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
<b>Could the selection of patients have introduced bias?</b>	<b>Risk: high</b>

**B. Concerns regarding applicability**

Describe included patients (previous testing, presentation, intended use of index test and setting):

Patients with newly detected FLLs on US; primary diseases not specified

<b>Is there concern that the included patients do not match the review question?</b>	<b>Concern: unclear</b>
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**Domain 2a: index test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

The definitive CEUS diagnosis was made at the time of the US examination by the physician performing CEUS; US carried out by the local investigators

Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Were the index test results interpreted without knowledge of the comparator?	Unclear
If a threshold was used, was it prespecified?	Yes
<b>Could the conduct or interpretation of the index test have introduced bias?</b>	<b>Risk: unclear</b>

**Domain 2b: comparator test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

No details of blinding reported. Reporting radiologists had access to the patients' clinical information

Were the comparator test results interpreted without knowledge of the results of the reference standard?	Unclear
Were the comparator test results interpreted without knowledge of the index test?	Unclear
If a threshold was used, was it prespecified?	Yes
<b>Could the conduct or interpretation of the comparator test have introduced bias?</b>	<b>Risk: unclear</b>

**Domain 3: reference standard****A. Risk of bias**


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Describe the reference standard and how it was conducted and interpreted:

All index test-positive and -negative FLLs were confirmed pathologically following biopsy in subgroup B

Is the reference standard likely to correctly classify the target condition? Yes

Were the reference standard results interpreted without knowledge of the results of the index test? Unclear

Were the reference standard results interpreted without knowledge of the results of the comparator test? Unclear

**Could methods used to conduct or interpret the reference standard have introduced bias? Risk: unclear**

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**Domain 4: flow and timing****A. Risk of bias**


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Describe any patients who did not receive the index test, comparator(s) and/or reference standard or who were excluded from the 2×2 table(s):

Two patients with inconclusive histology were excluded from the analyses (<10% of patients)

Describe the time interval and any interventions between index, comparator(s) and reference standard:

Times between index and comparator tests and reference standard were not reported

Was there an appropriate interval between index test and reference standard? Unclear

Was there an appropriate interval between comparator test and reference standard? Unclear

Was there an appropriate interval between index test and comparator test? Unclear

Did all patients receive a reference standard? Yes

Did patients receive the same reference standard? Yes

Were all patients included in the analysis? No

**Could the patient flow have introduced bias? Risk: unclear**

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**Solbiati 2006<sup>41</sup>**

Abstract only.

**Domain 1: patient selection****A. Risk of bias**

Describe methods of patient selection:

Retrospective cohort of patients with incidentally detected FLLs on unenhanced US

Was a consecutive or random sample of patients enrolled?

No

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Unclear

**Could the selection of patients have introduced bias?****Risk: high****B. Concerns regarding applicability**

Describe included patients (previous testing, presentation, intended use of index test and setting):

Diagnostic status following unenhanced imaging unclear

**Is there concern that the included patients do not match the review question?****Concern: unclear****Domain 2a: index test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

Unclear if those interpreting CEUS had knowledge of other imaging test results. Biopsy performed after imaging

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

Were the index test results interpreted without knowledge of the comparator?

Unclear

If a threshold was used, was it prespecified?

Unclear

**Could the conduct or interpretation of the index test have introduced bias?****Risk: unclear****Domain 2b: comparator test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

Unclear if those interpreting CECT had knowledge of other imaging test results. Biopsy performed after imaging

Were the comparator test results interpreted without knowledge of the results of the reference standard?

Unclear

Were the comparator test results interpreted without knowledge of the index test?

Unclear

If a threshold was used, was it prespecified?

Unclear

**Could the conduct or interpretation of the comparator test have introduced bias?****Risk: unclear**

**Domain 3: reference standard****A. Risk of bias**

Describe the reference standard and how it was conducted and interpreted:

Reference standard was a combination of CEUS and CT in most cases. No details of interpretation of biopsy and follow-up were reported

Is the reference standard likely to correctly classify the target condition? No

Were the reference standard results interpreted without knowledge of the results of the index test? No

Were the reference standard results interpreted without knowledge of the results of the comparator test? No

**Could methods used to conduct or interpret the reference standard have introduced bias? Risk: high**

**Domain 4: flow and timing****A. Risk of bias**

Describe any patients who did not receive the index test, comparator(s) and/or reference standard or who were excluded from the 2x2 table(s):

Retrospective cohort of 694 lesions in 686 patients. Reference standard was concordant imaging test results in most ( $n = 656$ ) lesions and FNB in case of discordance ( $n = 38$ ). One lesion was missing from the analysis

Describe the time interval and any interventions between index, comparator(s) and reference standard:

No details of the timing of examinations were reported

Was there an appropriate interval between index test and reference standard? Unclear

Was there an appropriate interval between comparator test and reference standard? Unclear

Was there an appropriate interval between index test and comparator test? Unclear

Did all patients receive a reference standard? Yes

Did patients receive the same reference standard? No

Were all patients included in the analysis? No

**Could the patient flow have introduced bias? Risk: high**

**Zhou 2007<sup>58</sup>**

Chinese-language paper.

**Domain 1: patient selection****A. Risk of bias**

Describe methods of patient selection:

Retrospective analysis of data from 56 patients with 64 HCC lesions undergoing non-surgical treatment

Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
<b>Could the selection of patients have introduced bias?</b>	<b>Risk: unclear</b>

**B. Concerns regarding applicability**

Describe included patients (previous testing, presentation, intended use of index test and setting):

Patients being assessed for response to treatment

<b>Is there concern that the included patients do not match the review question?</b>	<b>Concern: low</b>
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**Domain 2a: index test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

No details of interpretation reported. Reference standard followed imaging

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Were the index test results interpreted without knowledge of the comparator?	Unclear
If a threshold was used, was it prespecified?	Yes
<b>Could the conduct or interpretation of the index test have introduced bias?</b>	<b>Risk: unclear</b>

**Domain 2b: comparator test****A. Risk of bias**

Describe how the index test and any comparator tests were conducted and interpreted:

No details of interpretation reported. Reference standard followed imaging

Were the comparator test results interpreted without knowledge of the results of the reference standard?	Yes
Were the comparator test results interpreted without knowledge of the index test?	Unclear
If a threshold was used, was it prespecified?	Yes
<b>Could the conduct or interpretation of the comparator test have introduced bias?</b>	<b>Risk: unclear</b>

**Domain 3: reference standard****A. Risk of bias**


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Describe the reference standard and how it was conducted and interpreted:

Unclear if those making the diagnosis were aware of imaging results; 3-month follow-up may not be adequate to confirm tumour response

Is the reference standard likely to correctly classify the target condition? Unclear

Were the reference standard results interpreted without knowledge of the results of the index test? Unclear

Were the reference standard results interpreted without knowledge of the results of the comparator test? Unclear

**Could methods used to conduct or interpret the reference standard have introduced bias? Risk: unclear**

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**Domain 4: flow and timing****A. Risk of bias**


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Describe any patients who did not receive the index test, comparator(s) and/or reference standard or who were excluded from the 2×2 table(s):

All patients underwent both imaging tests within 1 week of treatment. Patients with a positive response on imaging were followed up for 3 months. Patients with a negative response on imaging (residual tumour detected) had diagnosis confirmed by FNB

Describe the time interval and any interventions between index, comparator(s) and reference standard:

See above. Note: 3-month follow-up may not be adequate to confirm tumour response

Was there an appropriate interval between index test and reference standard? Unclear

Was there an appropriate interval between comparator test and reference standard? Unclear

Was there an appropriate interval between index test and comparator test? Yes

Did all patients receive a reference standard? Yes

Did patients receive the same reference standard? Yes

Were all patients included in the analysis? Yes

**Could the patient flow have introduced bias? Risk: unclear**

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## Appendix 4 Data extraction tables



## Details of the methods and interpretation of the index test (assessed technology), comparator test(s) and reference standard (for test accuracy studies only) used in included studies

Study	SonoVue CEUS details	Comparator test(s) details	Reference standard details
Blondin 2011 <sup>48</sup>	<p>Aplio 80 scanner (Toshiba Medical Systems, Neuss, Germany)</p> <p>Real time B-mode sonography; low mechanical index (0.2–0.4)</p> <p>CEUS was carried out after administration of a 2.4-ml bolus of SonoVue (Nycomed, Germany) into the antecubital vein</p> <p>Images were interpreted by a internist and a radiologist; both were blinded</p>	<p>1.5T MRI (MAGNETOM Avanto, Siemens Medical Solutions, Erlangen, Germany)</p> <p>The contrast agent used was Gd-EOB-DTBA (Primovist®, Bayer Schering Pharma, Berlin, Germany), injected at 2 ml/second via the antecubital vein</p> <p>Axial T1- and T2-weighted imaging with contrast enhancement in the arterial (after 20 seconds), venous (after 60 seconds) and equilibrium (after 180 seconds) phases as well as the late phase (after 15 minutes, consisting of a coronal and axial T1) were used for analysis</p> <p>Images were interpreted by two independent blinded radiologists</p>	<p>Histology after biopsy or surgery in all lesions</p>
Catala 2007 <sup>52</sup>	<p>Sequoia 512 scanner (Acuson, Mountain View, CA). CEUS used specific software Coherent Contrast Imaging with the same convex array probe as baseline US</p> <p>Baseline US of the liver (to identify FLLs) in the fundamental mode, using a greyscale and a multifrequency 4 × C1 convex array probe</p> <p>CEUS was carried out after administration of a 2.4-ml bolus of SonoVue (Bracco, Milan, Italy) followed by a 5-ml saline flush. Enhancement patterns were studied for up to 3.5 minutes, including the arterial (0–49 seconds), portal (50–120 seconds) and late (&gt; 120 seconds) phases.</p> <p>The following settings were used: insonating frequency: 3 MHz; acoustic power: – 75dB to – 90dB; frame rate: 17–20; double focus; low mechanical index (&lt;0.2)</p> <p>Images were interpreted by two independent radiologists with more than 5 years' experience of liver CEUS; disagreements were resolved by a third radiologist. Images were interpreted without knowledge of the final diagnosis or absence of signs of chronic liver disease on US/SCT</p>	<p>SCT scanner (Somatom Plus 4, Siemens)</p> <p>Scans in a cranial–caudal direction with a 5-mm collimation in the arterial phase and an 8-mm collimation in the other phases (pitch 1.5) for a single held breath at a spiral acquisition of up to 15 seconds. Acquisition of the arterial phase started 6 seconds after the automatic detection of peak aortic enhancement; portal and late venous phases were scanned 70 and 180 seconds after the start of the injection of the contrast agent</p> <p>The contrast agent used was 100 ml iopromide, 300 mg iodine/ml (Ultravist®, Schering AG, Berlin, Germany) via the antecubital vein at 4 ml/second</p> <p>Images were interpreted by two independent radiologists with more than 5 years' experience of liver CT; disagreements were resolved by a third radiologist. Images were interpreted without knowledge of the final diagnosis or other imaging results, but with knowledge of the presence or absence of signs of chronic liver disease on US/SCT</p>	<p>All malignant lesions were histologically confirmed: biopsy (n = 52); partial hepatic resection (n = 3); explanation (n = 2). For benign FLLs the final diagnosis was obtained by biopsy (n = 2); MRI and follow-up ≥ 12 months (n = 18)</p>

Study	SonoVue CEUS details	Comparator test(s) details	Reference standard details
Chen 2007 <sup>59</sup> (related publication Chen 2007 <sup>60</sup> )	Esaote Technos DU8 (Esaote SpA, Genoa, Italy) or Philips iU22 (Philips Medical Systems, Bothell, WA), using 2.5- to 5-MHz probes CEUS was carried out after administration of a 2.4-ml intravenous bolus of SonoVue (Bracco) injected over 2–3 seconds; low mechanical index (0.04–0.1) Images were assessed by three experienced radiologists	US without contrast CT or MRI was performed within 1 week before RFA in both groups. CT examinations were performed with a GE LightSpeed 64-slice spiral CT scanner. MRI was performed with a GE EchoSpeed 1.5T scanner Images were assessed by three experienced radiologists	Reference standard not applicable (not a test accuracy study) Outcomes of treatment were determined by imaging follow-up 1 month after RFA and every following 2–3 months in the first year and every 4–6 months in the second year. RFA was considered successful if there was no contrast enhancement in or around the tumour, the margins of the ablation zone were clear and smooth and the ablation zone extended beyond the tumour borders
Clewert 2009 <sup>51</sup>	Multifrequency curved array transducer, 2.5–4 MHz (Logic 9, GE Healthcare, Milwaukee, WI). Transmitted energy reduced to <30%, with a low mechanical index (0.15) After B-scan analysis of vascularisation with power Doppler US, CEUS used intravenous administration of a 2.4-ml bolus of SonoVue (Bracco) followed by a 10-ml bolus of saline Scanning was carried out during the arterial phase (<30 seconds), the portal venous phase (40–120 seconds) and the late phase (> 120 seconds) CEUS was performed by two blinded radiologists with >7 years of clinical US experience. Interpretation was by consensus	Biphasic contrast-enhanced CT using a 16- or 64-slice scanner (Somatom Sensation 16 or 64, Siemens). Image volume included the whole liver. Unenhanced axial sections were not performed Contrast agent was 120 ml of Solutrast® (Bracco, Milan, Italy), iodine concentration 300 mg/ml, administered as an intravenous bolus (flow rate 5 ml/second), followed by 50 ml of saline The appropriate delay for the arterial and venous phases was determined by semiautomatic bolus tracking on the thoracic aorta Acquisition direction was craniocaudal. Images were reconstructed as thin-slice (3 mm) maximum-intensity projections in the axial and coronal planes CT examinations were performed by two blinded, experienced radiologists	Malignant liver lesions were confirmed by biopsy For haemangioma, US follow-up for 2 years and MRI or multiphase CT follow-up for 1 year was used to confirm the diagnosis No details of who interpreted the reference standard examinations were reported

Study	SonoVue CEUS details	Comparator test(s) details	Reference standard details
Dai 2008 <sup>43</sup>	<p>Technos MPX scanner (Esaote Biomedica, Genoa, Italy)</p> <p>Baseline US of the liver (to identify FLLs) using 3.5-MHz convex probe</p> <p>CEUS was carried out after intravenous administration of SonoVue (Bracco) as a 2.4-ml bolus within 2–3 seconds with continuous observation for 6 minutes from injection time using the same convex probe as baseline US; low mechanical index (0.05–0.06)</p> <p>Images were interpreted in consensus by two blinded sinologists with at least 10 years' experience who were unaware of the results of other imaging techniques and pathology</p>	<p>SCT scanner (Somatom Plus 4, Siemens)</p> <p>5 mm collimation and 7.5 mm/second table speed. CT images were obtained before and 25 seconds (arterial phase), 60 seconds (portal venous phase) and 2–4 minutes (late phase) after the start of contrast injection</p> <p>The contrast agent used was 100 ml Omnipaque® (Amersham Health, Princeton, NJ), 300 mg/ml iodine, at a rate of 3.5 ml/second</p> <p>Images were interpreted in consensus by two radiologists with at least 10 years' experience of CT who were unaware of the results of other imaging techniques and pathology</p>	<p>Histopathology in all patients.</p> <p>US-guided biopsy with two- to threefold aspiration of each nodule using an 18-gauge needle</p> <p>Histopathological diagnoses were made in consensus by two pathologists with more than 20 years' experience</p> <p>Negative biopsies were confirmed by further follow-up for a minimum of 6 months</p>
Feng 2007 <sup>57</sup> (Chinese language)	<p>US and CEUS using Sequoia 512 scanner. CEUS was carried out following injection of 2 ml of SonoVue (Bracco); low mechanical index (0.19)</p> <p>Imaging was conducted between 1 week and 3 months after cryosurgery, and all imaging tests were conducted within 2 weeks of each other</p> <p>No details of who interpreted CEUS were reported</p>	<p>CECT or CEMRI, no details reported</p> <p>Imaging was conducted between 1 week and 3 months after cryosurgery, and all imaging tests were conducted within 2 weeks of each other</p> <p>No details of who interpreted CECT and CEMRI were reported</p>	<p>Histopathological diagnosis; no further details reported</p>
Flor 2009 <sup>39</sup> (abstract only)	<p>US and CEUS using Logic 9</p> <p>CEUS performed after bolus injection of 4.8 ml of SonoVue (Bracco); low mechanical index (&lt;0.2)</p> <p>No details of interpretation were reported</p>	<p>None</p>	<p>Biopsy or follow-up at 3–6 months</p> <p>No further details were reported</p>
Forner 2008 <sup>44</sup>	<p>US used Sequoia 512 scanner</p> <p>Baseline US of the liver (to identify FLLs) using a multifrequency 4C1 convex and 4V1 storial array probe</p> <p>CEUS was carried out after administration of a 2.4-ml bolus of SonoVue (Bracco); observation for up to 3.5 minutes from injection time</p> <p>CEUS used contrast coherent imaging (CCI, Siemens-Acuson, Mountain View, CA, USA) and the 4C1 convex array probe; low mechanical index (&lt;0.2). Enhancement patterns were studied during the vascular phase up to 3.5 minutes, including the arterial (0–49 seconds), portal (50–179 seconds) and late (&gt; 180 seconds) phases</p> <p>Images were recorded blindly and reviewed by at least two radiologists. Doubtful images were interpreted by consensus</p>	<p>Symphony 1.5T system (Siemens), using a phased-array torso coil</p> <p>Transverse T1-weighted and T2-weighted MRI and multiphase contrast-enhanced dynamic breath-hold three-dimensional MRI of the whole liver with fat suppression</p> <p>The contrast agent used was gadolinium (gadodiamide 0.5 mmol/l, Omniscan-Amersham), injected at 0.2 ml/kg and 2 ml/second. Bolus tracking was used to obtain arterial phase (20 seconds after injection), portal venous phase (60–65 seconds after injection) and late phase (100–110 seconds after injection) images</p> <p>Images were interpreted by two radiologists experienced in liver MRI who were unaware of the biopsy results</p>	<p>All imaging-positive nodules were confirmed with FNB using a 20-gauge or 18-gauge needle and multiple passages. Specimens were routinely processed and stained with haematoxylin–eosin</p> <p>Imaging-negative patients were followed up with CEUS every 3 months and MRI every 6 months. Median follow-up 23 months (range 4 to 41 months)</p>

Study	SonoVue CEUS details	Comparator test(s) details	Reference standard details
Gierbliński 2008 <sup>53</sup>	<p>Baseline US/CT not specified</p> <p>CEUS was carried out after administration of a 2.4-ml bolus (86 patients) or a 4.8-ml bolus (14 patients) of SonoVue (Bracco) followed by 10 ml of 0.9% saline; low mechanical index (&lt;0.09). Philips HDI 5000 SonoCT (Philips Medical Systems, Bothell, WA) using a 2- to 5-MHz curved linear-array transducer</p> <p>Imaging duration was 4 minutes: arterial phase 15–30 seconds after injection, portal phase 35–90 seconds after injection and late venous phase 90–240 seconds after injection</p> <p>Images were interpreted by gastroenterologists with 2 years' experience of CEUS, who were blind to the initial US and CT results</p>	None	<p>FNB in all patients with a 20-gauge Chiba aspirating needle or 19-gauge trucut biopsy; this diagnosis was considered final if the lesion was positive</p> <p>Negative biopsies were confirmed by clinical and imaging follow-up (median 10 months)</p> <p>Biopsies were assessed by a pathologist blinded to the CEUS results and follow-up imaging was evaluated by blinded examiners</p>
Giorgio 2007 <sup>45</sup>	<p>All abdominal US scans were performed with Prosound SSD-5500 PHD Extended (Aloka, Tokyo, Japan) using a 3- to 6-MHz convex array broadband probe</p> <p>CEUS was carried out after administration of a 2.4-ml bolus of SonoVue (Bracco) followed by a 5-ml saline flush; low mechanical index (0.11)</p> <p>The scan lasted up to 5 minutes and the whole vascular phase was observed: arterial (15–30 seconds after injection), portal (30–60 seconds after injection), sinusoidal (60–240 seconds after injection)</p> <p>One operator with over 20 years' experience of CEUS performed all studies the day before the MRI studies</p>	<p>1.5T Symphony system</p> <p>Three contiguous sets of T1-weighted, in-phase, breath-hold, spoiled gradient-echo images</p> <p>The contrast agent used was a 20-ml bolus of gadobenate dimeglumine (MultiHance<sup>®</sup>, Bracco, Milan, Italy), injection rate 3.0 ml/second, followed by 40 ml of saline. Evaluation of arterial, portal and delayed phases was obtained through the whole liver at 22, 48 and 90 seconds after injection start</p> <p>Images were interpreted by one experienced radiologist who was unaware of the CEUS results</p>	<p>US-guided FNB in all patients using a 19-gauge modified Menghini cutting needle</p> <p>Biopsy was performed the day after both imaging investigations were complete</p>
Jonas 2011 <sup>50</sup> (abstract only)	<p>SonoVue CEUS; no further details reported</p>	<p>MRI with hepatocyte-specific contrast (Primovist); no further details reported</p> <p>Triple-phase contrast-enhanced abdominal CECT; no further details reported</p>	<p>All patients underwent intraoperative US and imaging (CEUS, CECT or CEMRI) follow-up at 3, 6, 12, 24 and 36 months</p> <p>Histology was used to confirm all resected metastases detected on preoperative imaging</p> <p>No further details reported</p>

Study	SonoVue CEUS details	Comparator test(s) details	Reference standard details
Leoni 2010 <sup>42</sup>	<p>Technos MPX scanner for unenhanced US CEUS (Esatune, CnTI or Technos MPX, Esaote Biomedica, Genoa, Italy) was conducted after administration of SonoVue (Bracco), dose not reported; low mechanical index (0.04–0.07)</p> <p>The examination was assessed in both the arterial and late phases (up to 3 minutes recorded)</p> <p>Images were interpreted by an operator with at least 3 years' experience of CEUS, immediately after the examination by the same operator</p>	<p>Helical MDCT with Emotion 6 system (Siemens)</p> <p>Unenhanced and contrast-enhanced images for arterial, portal venous and delayed phases</p> <p>The contrast agent used was an intravenous bolus injection of 2 ml/kg of non-ionic contrast (Iomeron® 350, Bracco, Milan, Italy) at 4 ml/second. Scans started 5 seconds (arterial phase) after reaching the threshold, 70 seconds (portal venous phase) and 170 seconds (delayed phase)</p> <p>MRI performed with 1.5T system (Signa, GE Medical Systems, WI, USA) using a body-phased array multicoil. Unenhanced sequences were breath-hold T1 weighted</p> <p>Contrast-enhanced images acquired after injection of ferucarbotran (Resovist®, Schering, Berlin, Germany) 10 µmol/kg bolus, followed by a 10-ml saline flush. Two sets of SPIO-enhanced images (10 and 20 minutes after contrast injection) using breath-hold T2-weighted sequences with fat saturation. Dynamic three-dimensional MRI performed after administration of gadolinium (gadopentetate dimeglumine, Magnevist®, Schering, Berlin, Germany) 0.2 ml/kg, injection at 2 ml/second, followed by a 20-ml saline flush. The time delay for the arterial, portal venous and delayed phases was 18, 80 and 180 seconds respectively</p> <p>CT and MRI examinations were interpreted in consensus by two operators experienced in liver imaging who were blind to the results of other contrast imaging</p>	<p>Two or more contrast imaging techniques positive was treated as a correct positive diagnosis that did not require further confirmation (EASL and AASLD guidelines for non-invasive diagnosis)</p> <p>Patients with no or one positive contrast-enhanced imaging test were confirmed using US-guided FNB (19-gauge modified Menghini needle, haematoxylin and eosin stain) or follow-up (US or CT) at 3-month intervals</p> <p>Diagnosis of HCC was made according to the International Working Party criteria<sup>110</sup></p>
Li 2007 <sup>54</sup>	<p>HDI 5000 scanner used for baseline US and CEUS. In patients with more than one FLL detected at baseline US, only the largest lesion was subjected to CEUS</p> <p>CEUS was carried out after administration of a 2.4-ml bolus injection of SonoVue (Bracco) to the cubital vein, followed by a 5-ml saline flush; low mechanical index (0.09–0.15) pulse-inversion harmonic imaging, with a convex-array broadband transducer</p> <p>Scans covered the entire vascular phase (up to 5 minutes): arterial phase (0–40 seconds), portal venous phase (41–100 seconds), late phase (101–300 seconds)</p> <p>Images were interpreted in consensus by two sonologists who were unaware of the CECT results</p>	<p>A three-phase contrast-enhanced protocol was used: unenhanced CT scan followed by intravenous infusion of 100–120 ml (4 ml/second) of non-ionic, iodine-containing contrast media (Ultravist 370). Scans were obtained in the arterial, portal venous and late phases, with bolus test trigger</p> <p>Data obtained through the whole liver in a craniocaudal direction during a single breath-hold helical acquisition (6–8 seconds)</p> <p>Images were interpreted by two radiologists who were blinded to the results of CEUS</p>	<p>Histopathology following surgical resection or FNB with an 18-gauge needle within 2 weeks after CEUS and CECT</p>

Study	SonoVue CEUS details	Comparator test(s) details	Reference standard details
Lüttich 2006 <sup>40</sup> (abstract only)	<p>CEUS using sulphur hexafluoride, 4 weeks after treatment (RFA)</p> <p>No further details reported</p>	<p>Gadolinium-enhanced CEMRI, 4 weeks after treatment (RFA)</p> <p>No further details reported</p>	<p>All patients were biopsied after CEUS</p> <p>No further details reported</p>
Mainenti 2010 <sup>49</sup>	<p>HDI 5000 scanner with a large band frequency convex transducer (3.5–7.5 MHz) used for baseline US and CEUS</p> <p>CEUS was carried out after administration of a 5-ml injection of SonoVue (Bracco) to the cubital vein, followed by a 10-ml saline flush; pulse inversion harmonic imaging and low mechanical index (&lt;0.09)</p> <p>Scans covered the arterial phase (25 seconds), portal venous phase (70 seconds) and delayed phase (300 seconds)</p> <p>Images were interpreted by two observers with &gt; 10 years' experience each who were blinded to the results of other tests. When there was disagreement, the final decision was made by a consensus panel of the original two plus one additional observer</p>	<p>Four-slice MDCT (Aquilion 4, Toshiba Medical Systems, Tochigi-ken, Japan)</p> <p>Scans acquired from the diaphragm to the pubic symphysis. Parameters: 4 x 3 mm beam collimation, pitch 5.5, 120 kV, 300 mA, rotation time 0.5 seconds, effective slice thickness 3 mm</p> <p>Contrast-enhanced imaging was performed 75 seconds after an intravenous bolus (3 ml/second) of 150 ml iodinated, non-ionic iopromide (Ultravist, 370 mg iodine/ml)</p> <p>1.5T MRI system (Gyrosan Intera 1.5T, Philips Medical Systems, Best, the Netherlands), with a phased-array body coil. Transverse breath-hold T1-weighted and T2-weighted images with and without fat saturation</p> <p>Extracellular enhanced CEMRI performed after bolus injection of 0.1 mmol/kg gadopentetate dimeglumine (Magnevist) at a rate of 3 ml/second, followed by a 20-ml saline flush. Images were acquired during the arterial (25 seconds), portal (60 seconds) and equilibrium (180 seconds) phases</p> <p>Intracellular enhanced CEMRI performed after intravenous injection of 0.12–0.7 mmol/kg of ferucarbotran. Images were obtained 15 minutes from the end of the injection, repeating the transverse breath-hold T2-weighted image with and without fat saturation</p> <p>All images (both CT and MRI) were interpreted by two observers with &gt; 10 years' experience each, who were blinded to the results of other tests. When there was disagreement, the final decision was made by a consensus panel of the original two plus one additional observer. Imaging tests (including CEUS) were performed randomly over a 4- to 8-day period</p>	<p>All patients underwent surgery within 10 days of the last imaging examination. In all patients who were imaging test positive for metastases, biopsy or resection of at least one lesion was performed</p> <p>All patients were followed up by MDCT (same technique as described) at 6 and 12 months, either to assess the size of a benign classified FLL or to assess the development of new metastases</p> <p>Comparisons of imaging with the reference standard were made by a different radiologist (with at least 10 years' experience) from those undertaking the initial blinded assessments</p>

Study	SonoVue CEUS details	Comparator test(s) details	Reference standard details
Quaia 2009 <sup>46</sup>	<p>Sequoia system using a convex array 2- to 4-MHz 4C1 transducer used for baseline greyscale and colour or power Doppler unenhanced US, followed by CEUS, in both participating centres</p> <p>CEUS was carried out after administration of a 2.4-ml bolus injection of SonoVue (Bracco), followed by a 10-ml saline flush; low mechanical index (0.09–0.14), dynamic range 65 dB, temporal resolution between frames 75–100 ms (10–13 frames per second). Each nodule was examined</p> <p>Scans covered the arterial phase (10–40 seconds), portal venous phase (45–90 seconds) and delayed sinusoidal phase (100 seconds to microbubble disappearance)</p> <p>Images were reviewed independently by two radiologists with 2–8 years' experience in liver imaging, who were blinded to clinical history, biopsy results and other imaging results</p>	<p>64-row MDCT system (Aquilion, Toshiba, or Brilliance, Philips, Cleveland, OH, USA). CT performed 2–30 days after CEUS</p> <p>Breath-hold scan; technical parameters: rotation time 400 ms; beam collimation 64 x 0.5 mm (Aquilion), 64 x 0.625 mm (Brilliance); normalise pitch 1; z-axis coverage 32 mm; reconstruction interval 0.3 mm; 120kV; 180–250 mA; field of view 40 cm</p> <p>Unenhanced CT, followed by CECT. Contrast-enhanced imaging performed 8 seconds after 2 ml/kg intravenous bolus of iodinated contrast (Iomeron 400, 400 mg iodine/ml, Bracco), 5 ml/s, followed by a 50-ml saline flush. The arterial phase started 18 seconds after the threshold was reached, the portal venous phase 70–80 seconds after the start of contrast injection and the delayed equilibrium phase 180–210 seconds after the start of contrast injection</p> <p>Images were reviewed in the same way as for CEUS</p>	<p>US-guided biopsy using an 18- to 20-gauge modified Menghini needle. Samples stained with haematoxylin–eosin and Masson's trichrome method. Biopsy performed within 15 days of CT</p> <p>A senior pathologist from each centre made the diagnosis</p>
Sangiovanni 2010 <sup>47,61</sup>	<p>iU22 system using a multifrequency 2- to 5-MHz convex transducer, for both baseline greyscale US of the upper abdomen and CEUS</p> <p>CEUS was carried out after administration of a 2.4-ml bolus injection of SonoVue (Bracco), followed by a 10-ml saline flush; low mechanical index (&lt;0.1)</p> <p>Scans covered the entire vascular phase (3 minutes): arterial phase (0–35 seconds), portal phase (35–120 seconds) and late phase (120–180 seconds)</p> <p>Examinations were interpreted by two expert echographers who were unaware of the biopsy results</p>	<p>64-MDCT Definition system (Siemens)</p> <p>Technical parameters: 2.5-mm slice thickness; rotation time 0.5 s</p> <p>The contrast agent used was 1.5 mg/kg of iodinated contrast, Iomeron 400, injected at a rate of 4 ml/s</p> <p>Acquisition time, from the start of contrast injection, was 40 seconds for the arterial phase, 80 seconds for the portal venous phase and 180 seconds for the delayed phase</p> <p>Images were interpreted by one experienced radiologist who was unaware of the biopsy results</p> <p>MRI performed with a 1.5T system (Avanto, Siemens). All patients underwent transverse T1-weighted and T2-weighted MRI and multi-phasic 3D CEMRI of the whole liver, with fat suppression</p> <p>Dynamic MRI was performed with a three-dimensional volumetric interpolated breath-hold examination sequence in the axial plane by using the following parameters: 4.7/2.3, 10-degree flip angle, 320 x 157 matrix, slice thickness of 3 mm</p> <p>The contrast agent used was gadolinium (gadobenate dimeglumine 0.5 mmol/l, MultiHance), injected at 0.2 ml/kg and 2 ml/second. Arterial, portal venous and delayed venous phases acquired at 30 seconds, 80 seconds and 180 seconds from the start of contrast injection</p> <p>Images were interpreted by one experienced radiologist who was unaware of the biopsy results</p>	<p>Histology following FNB using a 21-gauge trenchant needle, carried out within 2 months of detection of nodule</p> <p>Formalin-fixed paraffin-embedded liver sections were examined by an experienced liver pathologist who was unaware of the results of clinical and imaging examinations</p> <p>Benign FLLs were followed up by imaging: by US every 3 months and by CT/MRI every 6 months</p>

Study	SonoVue CEUS details	Comparator test(s) details	Reference standard details
Seitz 2009 <sup>55</sup>	<p>The US device used was not specified (different 'high-end' US devices and different contrast software)</p> <p>CEUS was conducted after administration of a 1.2- to 4.8-ml intravenous bolus of SonoVue (Bracco), followed by a 10-ml saline flush. The dose could be doubled or a second dose could be given. Low mechanical index (&lt;0.4)</p> <p>Imaging lasted up to 5 minutes: arterial phase (5–25 seconds), portal venous phase (25–60 seconds) and late phase (&gt; 120 seconds)</p> <p>For patients with multiple lesions, the dominant lesion was analysed; when lesions had different sonomorphology in the late phase each lesion was analysed separately with additional contrast media injection</p> <p>US was performed by physicians with &gt; 5 years' experience; at least 2 years' experience with CEUS in liver tumours. CEUS was performed up to 4 weeks before the CT examination. The definitive CEUS diagnosis was made at the time of the US examination by the physician performing it. The US investigator was not blinded to the results of the preceding CT in eight cases</p>	<p>The SCT device used was not specified</p> <p>Single- or multislice CT collimation and reconstructed slice thickness at least 5 mm; the liver SCT examination performed as three-phasic-SCT: native scan application of 140 ml of iodinated contrast media (non-ionic, various vendors, iodine concentration &gt;300 mg/ml; flow &gt; 3 ml/second). Two additional scans: early phase (25–30 seconds) and late phase (60–90 seconds)</p> <p>All reporting radiologists had access to the patients' clinical information</p>	<p>Subgroup A: final diagnosis was achieved by SCT or proven clinical data including follow-up</p> <p>Subgroup B: diagnosis was based on US-guided FNB</p>
Seitz 2010 <sup>56</sup>	<p>The US device used was not specified (different 'high end' US devices and different contrast software)</p> <p>CEUS was conducted after administration of a 1.2 to 4.8 ml intravenous bolus of SonoVue (Bracco), followed by a 10-ml saline flush. The dose could be doubled or a second dose could be given. Low mechanical index (&lt;0.4)</p> <p>Imaging lasted up to 5 minutes: Arterial phase (5–25 seconds), portal venous phase (25–60 seconds) and late phase (&gt; 120 seconds)</p> <p>If multiple lesions, those suspicious for malignancy or if benign the largest lesion were analysed. Where lesions had different sonomorphology in the late phase each lesion was analysed separately with additional contrast media injection</p> <p>US was performed by physicians with more than 5 years' experience, at least 2 years' experience with CEUS in liver tumours: CEUS was performed up to 4 weeks prior to MRI examination. The definitive CEUS diagnosis was made at the time of the US examination by the physician performing it</p>	<p>The MRI device used was not specified; MRI device with minimum of 1.5 Tesla</p> <p>T1-weighted localiser; T2 TSE axial. Three-dimensional TFE dynamics breath-hold native, arterial, portal venous using gadolinium DTPA [15 ml ProHance® (gadoteridol), 78.61 mg/ml], 5–8 mm slice thickness. Resovist contrast used in 88/269 MRI studies</p>	<p>Subgroup A: final diagnosis was made by MRI, proven clinical data and follow-up for &gt; 6 months</p> <p>Subgroup B: diagnosis was based on US-guided FNB</p>



Study	SonoVue CEUS details	Comparator test(s) details	Reference standard details
Solbiati 2006 <sup>41</sup> (abstract only)	CEUS was performed with contrast-specific software (CPS, Acuson-Siemens, and CnTI, Esaote) after bolus injection of 2.4 ml of SonoVue (Bracco); low mechanical index No details of interpretation were reported	Triphasic, helical CECT No further details were reported	When CEUS and CECT results were concordant, this was treated as a correct diagnosis that did not require further confirmation (EASL and AASLD guidelines for non-invasive diagnosis) When there was a discordant result FNB was used as the reference standard No details of who made the diagnosis
Zhou 2007 <sup>38</sup> (Chinese language)	Sequoia 512 system with a 2.5- to 6.0-MHz probe CEUS was carried out after administration of a 2.4-ml bolus injection of SonoVue (Bracco) followed by a 5-ml saline flush; low mechanical index (0.15–0.21) Arterial phase 30 seconds, portal venous phase 60 seconds, late phase 180 seconds Imaging carried out within 1 week of treatment. No details of who interpreted images	Somatom Balance system (Siemens) Iodinated contrast medium, iohexol (350 mg/ml iodine, Omnipaque) was used Arterial phase 30 seconds, portal venous phase 60 seconds, late phase 180 seconds Imaging carried out within 1 week of treatment. No details of who interpreted images	Imaging-positive results were confirmed by US-guided FNB Imaging-negative results were confirmed by follow-up imaging at 3 months No details of who made the diagnosis

DTPA, diethylenetriamine penta-acetic acid; SCT, spiral computed tomography; TFE, turbo field echo; TSE, turbo spin echo.

## Inclusion/exclusion criteria and participant characteristics of included studies

Study	Participant number	Inclusion criteria	Exclusion criteria	Participant characteristics																				
Blondin 2011 <sup>48</sup>	33 patients, 47 lesions (per-lesion data)	Patients with liver cirrhosis, identified from a radiology database, who had received MRI of the liver with Primovist and CEUS with SonoVue with no more than 4 weeks in between each examination. Histology of the FLL had to be performed	Known malignancy	Mean age: 63 ± 11 years 25 men/8 women Chronic liver disease: 33 (due to viral hepatitis 15; alcohol abuse 13; haemochromatosis 1; unknown reason 4, therefore classified as cryptogen) Mean nodule size: not specified Final diagnosis: HCC 41; RN 6																				
Catala 2007 <sup>52</sup>	213 patients assessed for inclusion, 77 patients with 77 FLLs enrolled. For patients with multiple FLLs, the histologically confirmed or largest lesion was selected	Adult patients (≥ 18 years) with FLLs detected on US Only FLLs evaluated with an interval of no more than 1 month between CEUS and SCT were included Malignant FLLs were included only if confirmed by pathology	Patients who were pregnant or nursing	Mean age: 62 ± 11 years 45 men/32 women Chronic liver disease: 53 Mean nodule size: 3.5 ± 2.2 cm Final diagnosis: HCC 45; metastases 12; haemangioma 10; FNH 8																				
Chen 2007 <sup>59</sup> (related publication Chen 2007 <sup>60</sup> )	179 patients originally recruited (intervention CEUS 92, comparator US 87); 165 patients who were suitable for RFA (intervention CEUS 83, comparator US 82) were included in the analyses	Patients with HCC who were being assessed for RFA. Patients were allocated alternately to intervention and comparator groups	14 patients who were not suitable for RFA were excluded from the analyses	<table border="1"> <thead> <tr> <th>Intervention (CEUS)</th> <th>Comparator (US)</th> </tr> </thead> <tbody> <tr> <td><i>n</i> = 92</td> <td><i>n</i> = 87</td> </tr> <tr> <td>Mean age (years)</td> <td>67.5</td> </tr> <tr> <td>Male/female (<i>n</i>)</td> <td>59/33</td> </tr> <tr> <td>TNM stage II/III (<i>n</i>)</td> <td>55</td> </tr> <tr> <td>Child–Pugh A (<i>n</i>)</td> <td>67</td> </tr> <tr> <td>Mean tumour size (cm)</td> <td>3.6 ± 1.1</td> </tr> <tr> <td>Mean no. of tumours</td> <td>1.6 ± 0.7</td> </tr> <tr> <td>CECT (<i>n</i>)</td> <td>81</td> </tr> <tr> <td>CEMRI (<i>n</i>)</td> <td>11</td> </tr> </tbody> </table>	Intervention (CEUS)	Comparator (US)	<i>n</i> = 92	<i>n</i> = 87	Mean age (years)	67.5	Male/female ( <i>n</i> )	59/33	TNM stage II/III ( <i>n</i> )	55	Child–Pugh A ( <i>n</i> )	67	Mean tumour size (cm)	3.6 ± 1.1	Mean no. of tumours	1.6 ± 0.7	CECT ( <i>n</i> )	81	CEMRI ( <i>n</i> )	11
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Study	Participant number	Inclusion criteria	Exclusion criteria	Participant characteristics
Clevert 2009 <sup>51</sup>	100 consecutive patients with suspected malignant liver lesions (maximum five lesions per patient); 21 patients were excluded from the CT analysis, eight because they did not undergo CT and 13 because CT imaging was inconclusive	Patients with suspected liver malignancy whose liver could be visualised completely by US examination	Exclusion criteria: tumour lesion > 5 cm, more than five lesions, strong allergic reactions, liver or kidney disease with confirmed elevation of laboratory parameters, acute heart failure, acute myocardial infarction, subcutaneous emphysema, meteorism, tachypnea, aerobilia	Mean age: 57 years (range 25–83 years) 57 men/43 women Final diagnosis (by patient): liver metastases 52 (primary tumour site: colon 43, breast 5, neuroendocrine 2, renal 2); HCC 7; haemangioma 15; FNH 7; complicated cyst 5; abscess 2; focal fatty degeneration 12
Dai 2008 <sup>43</sup>	498 patients with cirrhosis assessed for inclusion; 72 patients with indeterminate hepatic nodules included; 103 FLLs enrolled	Patients with confirmed cirrhosis and indeterminate hepatic nodules on US	NR	Mean age: 59 years (range 35–80 years) 59 men/13 women Cirrhosis, without extrahepatic malignancies: 72 Previous treatment for HCC: 9 Elevated AFP: 9 Mean nodule size: $1.5 \pm 0.3$ cm Final diagnosis (by nodule): HCC 56; RN 47
Feng 2007 <sup>57</sup> (Chinese language)	23 patients with 26 malignant lesions undergoing cryosurgery	NR	NR	Mean age: 57 years (range 45–68 years) 20 men/3 women Initial diagnosis: HCC 21 (23 lesions); metastases 2 (3 lesions) Mean tumour size: 31.5 mm (range 16.7–42.6 mm) Final diagnosis (by lesion): complete treatment response 21; recurrence 5
Flor 2009 <sup>39</sup> (abstract only)	18 patients with known primary cancer and indeterminate liver lesions ( $n = 26$ ) detected at MDCT. All lesions were < 1.5 cm	NR	NR	Mean age: 65 years 6 men/12 women Primary cancer: colon 8; breast 3; lung 2; pancreas 2; kidney 1; pleura 1; tongue 1 Final diagnosis: metastases 5; cysts 11; focal steatosis 2; haemangioma 2; intrahepatic biliary tract 1; CT artifacts 5

Study	Participant number	Inclusion criteria	Exclusion criteria	Participant characteristics
Forner 2008 <sup>44</sup>	89 patients with cirrhosis and a single new FLL detected at screening	Patients with cirrhosis (Child–Pugh class A or B) and no history of HCC in whom a new solid nodule (5–20 mm) was detected on US	Patients with poor liver function who would undergo transplantation regardless of HCC diagnosis; patients with significant comorbidities; patients with severe clotting alterations or contraindications for CEUS, CEMRI or FNB	Median age: 65 years (range 37–83 years) 53 men/36 women Cirrhosis: 89 Median AST: 81 U/l (range 25–322 U/l) Median ALT: 70 U/l (range 16–537 U/l) Median prothrombin ratio: 78.5% (range 35–100%) Median bilirubin: 1 mg/dl (range 0.3–4.1 mg/dl) Median baseline AFP: 8 ng/ml (range 1–1154 ng/ml) Median nodule size: 14 mm (7–20 mm) Final diagnosis: HCC 60; CCC 1; RN 24; haemangioma 3; FNH 1
Gierbliński 2008 <sup>53</sup>	100 patients with 100 incidentally detected FLLs who were referred for liver biopsy	Patients with incidentally detected FLLs referred for biopsy following inconclusive US and/or CT, which had suggested the possibility of malignancy	Patients with current or previous neoplastic disease; patients with lesions with features characteristic of haemangioma; patients in whom biopsy was not possible	No details of age and sex of patients reported Final diagnosis: HCC 9; metastases 14; haemangioma 34; FNH 19; skip area in fatty liver 1; focal steatosis 10; adenoma 1; dysplastic nodule 1; hyperregenerative nodule 1
Giorgio 2007 <sup>45</sup>	73 patients with cirrhosis and a single FLL detected at surveillance US	Patients with cirrhosis and a single liver nodule ≤30 mm detected on US	Patients with heart disease (because of rare adverse event reported for SonoVue)	Mean age: 63 years (range 40–84 years) 49 men/24 women Cirrhosis: 73 (HCV associated 65, alcoholic 2, alcoholic and HCV associated 2, HBV associated 3, cryptogenic 1) Child–Pugh class A: 46, Child–Pugh class B: 27 AFP <20 ng/ml: 73 Final diagnosis: HCC 48; RN 8; dysplastic nodule 4; focal steatosis 6; haemangioma 4; metastases 1; non-Hodgkin's lymphoma 1; FNH 1
Jonas 2011 <sup>50</sup> (abstract only)	20 patients with CRC and 48 liver lesions	Patients with CRC liver metastases who underwent complete preoperative workup and could be rendered tumour free by a single-stage surgical intervention	Patients with concomitant resectable extrahepatic disease and previous hepatobiliary surgery, other than cholecystectomy	No details on primary disease, age and sex of patients reported Mean size of metastases: 24 mm (range 8–80 mm) All patients had CRC and metastasis was the only diagnosis reported

Study	Participant number	Inclusion criteria	Exclusion criteria	Participant characteristics
Leoni 2010 <sup>42</sup>	60 patients with cirrhosis and 75 FLLs (28 newly detected and 32 recurrent)	Adult patients (> 18 years) with cirrhosis and one to three liver nodules between 1 and 3 cm, which were visible on US	Previously treated nodules; contraindications to imaging, allergy to contrast agent, claustrophobia or magnetic or metallic devices in the body; neoplastic portal thrombosis or extrahepatic metastases	Mean age: 65 years (range 40–83 years) 52 men/8 women HCV 33; HBV 18; HCV and HBV 1; history of heavy alcohol intake 6; cryptogenetic 2 Child–Pugh class A/B/C: 40/18/2 Bilirubin: 1.9 ± 2.2 mg/dl Median AFP: 11 ng/ml (range 2–2849 ng/ml) AST: 96 ± 78 U/l ALT: 82 ± 57 U/l gamma-GT: 97 ± 72 U/l Alkaline phosphatase: 305 ± 119 U/l Final diagnosis (by lesion): HCC 55; not HCC 20
Li 2007 <sup>54</sup>	109 patients with incidentally detected FLLs; one FLL assessed per patient. For patients with multiple FLLs, the largest and most conspicuous lesion on US was selected	Patients with FLLs, examined by US and unenhanced CT	Not specified	Mean age: 49 ± 12 years (range 18–79 years) 72 men/37 women Mean nodule size: 2.9 ± 1.3 cm (range 0.9–12.8 cm) Final diagnosis: HCC 61; metastases 15; CCC 5; haemangioma 12; RN 5; FNH 3; adenoma 3; focal necrosis 4; angiomyolipoma 1
Lüttich 2006 <sup>40</sup> (abstract only)	15 patients with HCC who were being treated by RFA	NR	NR	No details reported
Mainenti 2010 <sup>49</sup>	34 patients with CRC and 57 liver lesions	Patients with histologically proven CRC who were scheduled for surgery	Patients who refused to participate in the study; patients with known contraindications to one of the examinations	No patient had cirrhosis or had received previous radio- or chemotherapy Mean age: 63 years (range 29–81 years) 20 men/14 women Metastatic lesion size: 3–80 mm Final diagnosis (by lesion): metastases 16; haemangioma 11; cysts 29; focal fatty liver 1

Study	Participant number	Inclusion criteria	Exclusion criteria	Participant characteristics
Quaia 2009 <sup>46</sup>	180 patients with cirrhosis and 195 nodules detected on surveillance US were initially recruited (up to two nodules per patient); 106 patients with 121 nodules finally included	Patients with a definite diagnosis of cirrhosis (Child–Pugh class A or B) and at least one hepatocellular nodule identified on surveillance US. Selection of nodules was based on the largest diameter and best visualisation Only those nodules ≤ 3 cm that underwent biopsy after CT corresponding to nodules not characterised by the Barcelona criteria (nodule ≤ 2 cm or nodule > 2 cm with hypervascularity during the arterial phase without hypovascularity during the portal venous phase, or with isovascularity during the arterial phase and hypovascularity during the portal phase, or hypovascularity in all phases) were included in the study	Nodules with peripheral enhancement at CECT were excluded because of a high probability of haemangioma diagnosis Nodules were excluded because of a lack of histological diagnosis (n = 60), technical inadequacy of CT (n = 10) or inadequacy of CEUS examination (n = 4)	Cirrhosis: 180 (HBV 85, HCV 52, HBV and HCV 3, alcohol abuse 40) 106 included patients: Mean age: 70 ± 7 years 68 men/38 women Mean nodule size: 1.9 ± 1.1 cm (range 1–3 cm) Final diagnosis (by nodule): HCC 72; dysplastic nodule 10; RN 15; haemangioma 12; other benign 3; pseudotumour 9
Sangiiovanni 2010 <sup>47,61</sup>	64 patients with cirrhosis and abnormal US findings on surveillance were originally included (67 liver nodules); 55 small nodules (1–2 cm) were included in the analysis, 10 were > 2 cm and 2 were < 1 cm. All nodules > 2 cm could be correctly diagnosed by at least one imaging modality	Patients with compensated cirrhosis (Child–Pugh A or B) who were under surveillance with US and had a new liver nodule detected	Patients with a pre-existing liver nodule; patients with poor liver function (Child–Pugh C) indicating liver transplantation regardless of HCC status; patients with an echo-coarse US pattern without a well-defined nodule	64 patients: Mean age 65 years (range 44–80 years) 47 men/17 women Child–Pugh A 63; Child–Pugh B 1 HBV 10; HCV 40; alcohol abuse 4 Median AFP: 11 ng/ml (range 1–2156 ng/ml) AFP > 200 ng/ml: 3 Final diagnosis (by nodule for 1- to 2-cm nodules): HCC 34; CCC 1, low-grade dysplastic nodule 3; RN 17
Seitz 2009 <sup>55</sup>	267 patients with incidentally detected FLLs: subgroup A (suspected benign lesions): 109 patients, 111 FLLs; subgroup B (suspected malignant lesions): 158 patients, 158 FLLs. For the dominant lesion (most suspicious for malignancy or largest) was analysed	Patients with newly detected FLLs on US	Patients with specific liver lesions diagnosed by typical US echomorphology such as cysts or haemangiomas in a nonsteatotic liver without clinical signs and symptoms, as well as malignant tumours with infiltration into hepatic vessels; patients who were critically ill or who suffered from pulmonary hypertension or unstable angina, as well as pregnant and nursing women	Subgroup A + B (not specified by subgroup): Mean age: 60.3 years (range 21–89 years) 121 men/146 women Final diagnosis (subgroup A): HCC 7; metastases 7; haemangioma 48; FNH 31; fatty-sparing lesion 5; abscess 4; cyst 3; undefined 6 Final diagnosis (subgroup B): HCC 40; metastases 56; haemangioma 9; FNH 14; adenoma 2; lymphoma 3; fatty-sparing lesion 6; other benign lesion 14; other malignant lesion 10; undefined 4

Study	Participant number	Inclusion criteria	Exclusion criteria	Participant characteristics
Seitz 2010 <sup>56</sup>	269 patients with incidentally detected FLLs (one lesion per patient). For patients with multiple FLLs, the dominant lesion (most suspicious for malignancy or largest) was analysed Subgroup A (suspected benign lesions): 185 Subgroup B (suspected malignant lesions): 84	Patients with newly detected FLLs on US	Patients with typical findings of simple cysts, hypercholeic haemangioma in a non-steatotic liver or fatty-sparing lesions without clinical signs and symptoms; patients with malignant tumours infiltrating hepatic vessels	Subgroup A: Mean age: 49.9 years (range 16–82 years) 58 men/127 women Final diagnosis: metastases 3; haemangioma 122; FNH 43; fatty-sparing lesion 2; abscess 1; cyst 4; cyst + haemorrhage 1; echinococcus 2; other benign lesion 2; undefined 5 Subgroup B: Mean age: 59.6 years (range 28–82 years) 53 men/31 women Final diagnosis: HCC 29; CCC 2; metastases 22; haemangioma 8; FNH 5; liver adenoma 1; fatty-sparing lesion 3; abscess 2; necrosis/scar 3; cyst 2; haemangioendothelioma 1; angiosarcoma 1; angiolipoma 1; RN 1; peliosis 1; undefined 2
Solbiati 2006 <sup>41</sup> (abstract only)	686 patients with 694 incidentally detected FLLs	NR	NR	No details of age and sex of patients were reported Final diagnosis: HCC 275; metastases 214; CCC 6; haemangioma 167; FNH 11; adenoma 4; cyst 3; pseudolesion 13
Zhou 2007 <sup>58</sup> (Chinese language)	56 patients with 64 HCC lesions who were undergoing non-surgical treatment	Patients with HCC who were undergoing non-surgical treatment	NR	Mean age 42 ± 13.8 years (range 21–68 years) 40 men/16 women Mean lesion diameter: 3.4 ± 1.6 cm (range 1.0–8.0 cm) Treatment: TACE 4; PEI 8; PMCT 11; RFA 5; TACE + PEI 4; TACE + PMCT 3; PEI + PMCT 11; PEI + PMAT + PMCT 10

ALT, alanine aminotransferase; AST, aspartate aminotransferase; FNH, focal nodular hyperplasia; gamma-GT, gamma-glutamyltransferase; NR, not reported; PMAT, percutaneous microwave ablation therapy; PMCT, percutaneous microwave coagulation therapy; RN, regenerative nodule; SCT, spiral computed tomography.

## Appendix 5 Table of excluded studies with rationale

The following is a list of studies excluded at the full-paper screening stage of the review, along with the primary reasons for their exclusion. For simplicity, studies were assigned a single reason for exclusion; however, many studies failed more than one inclusion criterion. Studies listed in submissions from the manufacturer of SonoVue are labelled 'M'. Studies provided in submissions from manufacturers that related solely to clinical applications outside the scope of the current assessment (i.e. anatomy other than the liver) are not listed.

The reasons for study exclusion are coded as follows:

**Population:** The study did not consider characterisation of FLLs (incidentally detected by unenhanced US or detected by surveillance US in patients with cirrhosis), detection of liver metastases in patients with known primary tumours or assessment of response to treatment/recurrence in patients with liver cancer.

**Index test:** The study did not assess the effectiveness of CEUS using SonoVue.

**Comparator:** The study did not compare the effectiveness of CEUS using SonoVue with that of CEMRI and/or CECT.

**Reference standard:** For test accuracy studies, the study did not use histology following biopsy or surgical excision or clinical/radiological follow-up for a minimum of 6 months for patients who had a negative index test result. For studies on the characterisation of FLLs only (suspected HCC), the EASL/AASLD non-invasive diagnostic criteria (two concordant imaging test results) were also considered an acceptable reference standard.

**Outcomes:** The study did not report any of the outcomes specified in *Chapter 3, Inclusion and exclusion criteria* or, for DTA studies, insufficient data were reported to allow the construction of 2×2 contingency tables (numbers of true-positive, false-negative, false-positive and true-negative test results).

**Study design:** The study design was not one of those specified in *Chapter 3, Inclusion and exclusion criteria* or the study included <10 participants in the relevant patient groups.

**Duplicate:** The study was a duplicate publication.

**Authors contacted:** The study did not report sufficient information for inclusion assessment and authors were contacted for additional information but no response was received.

1. Albrecht T, Hohmann J, Oldenburg A, Skrok J, Wolf KJ. Detection and characterisation of liver metastases. *Eur Radiol* 2004;**14**:P25–33. (**Reference standard**)
2. Andreano A, Meneghel E, Bovo G, Ippolito D, Salvioni A, Filice C, *et al.* Contrast-enhanced ultrasound in planning thermal ablation of liver metastases: should the hypervascular halo be included in the ablation volume? *J Ultrasound* 2010;**13**:158–63. (**Outcomes**)
3. Aube C, Lebigot J. [Contrast ultrasonography: value in diagnosis and characterisation of hepatic tumors.] *Gastroenterol Clin Biol* 2003;**27**:B63–70. (**Study design**)
4. Banghui P, Chiche L, Alkofer B, Salame E, Bouvard N, Lepennec V. Imaging modalities before liver resection for colorectal metastases: which, when and how many? Paper presented at the 9th World



- Congress of the International Hepato-Pancreato-Biliary Association, Buenos Aires, Argentina, 18–22 April 2010. *HPB* 2010;**12**(Suppl. 1):100. (**Authors contacted**)
5. Bartolotta TV, Taibbi A, Galia M, Runza G, Matranga D, Midiri M, *et al.* Characterization of hypoechoic focal hepatic lesions in patients with fatty liver: diagnostic performance and confidence of contrast-enhanced ultrasound. *Eur Radiol* 2007;**17**:650–61. (**Comparator**)
  6. Bartolotta TV, Sandonato L, Taibbi A, Latteri S, Soresi M, Lombardo G, *et al.* [Focal liver lesions: clinical usefulness of contrast-enhanced ultrasound in the selection of surgical patients.] *Chir Ital* 2009;**61**:295–307. (**Comparator**)
  7. Bartolotta TV, Taibbi A, Midiri M, La Grutta L, De Maria M, Lagalla R. Characterisation of focal liver lesions undetermined at grey-scale US: contrast-enhanced US versus 64-row MDCT and MRI with liver-specific contrast agent. *Radiol Med* 2010;**115**:714–31. (**Reference standard**)
  8. Bartolotta TV, Taibbi A, Midiri M, Matranga D, Solbiati L, Lagalla R. Indeterminate focal liver lesions incidentally discovered at gray-scale US: role of contrast-enhanced sonography. *Invest Radiol* 2011;**46**:106–15. (**Reference standard**)
  9. Bauditz J, Schade T, Wermke W. [Sonographic diagnosis of hilar cholangiocarcinomas by the use of contrast agents.] *Ultraschall Med* 2007;**28**:161–7. (**Index test**)
  10. Bauditz J, Quinkler M, Beyersdorff D, Wermke W. Improved detection of hepatic metastases of adrenocortical cancer by contrast-enhanced ultrasound. *Oncol Rep* 2008;**19**:1135–9. (**Index test**)
  11. Bauditz J, Zeitz M, Wermke W. Malignant liver tumors: monitoring of local ablation by contrast enhanced ultrasound and computed tomography. Paper presented at the 61st Annual Meeting of the American Association for the Study of Liver Diseases: the Liver Meeting, Boston, MA, 29 October–2 November 2010. *Hepatology* 2010;**52**:963A. (**Outcomes**)
  12. Beaton C, Cochlin D, Kumar N. Contrast enhanced ultrasound should be the initial radiological investigation to characterise focal liver lesions. *Eur J Surg Oncol* 2010;**36**:43–6. (**Reference standard, M**)
  13. Bernardini I, Mucciarini C, Razzini G, Guerzoni R, Blanzieri S, Bellentani S, *et al.* The role of contrast-enhanced ultrasound in detection of liver metastases from colorectal cancer: 2 years update results. Paper presented at the 35th ESMO Congress, Milan, Italy, 8–12 October 2010. *Ann Oncol* 2010;**21**:viii215. (**Population**)
  14. Bleuzen A, Huang C, Olar M, Tchienbou J, Tranquart F. Diagnostic accuracy of contrast-enhanced ultrasound in focal lesions of the liver using cadence contrast pulse sequencing. *Ultraschall Med* 2006;**27**:40–8. (**Reference standard**)
  15. Cantisani V, Ricci P, Erturk M, Pagliara E, Drudi F, Calliada F, *et al.* Detection of hepatic metastases from colorectal cancer: prospective evaluation of gray scale US versus SonoVue low mechanical index real time-enhanced US as compared with multidetector-CT or Gd-BOPTA-MRI. *Ultraschall Med* 2010;**31**:500–5. (**Reference standard, M**)
  16. Caturelli E, Ghittoni G, Roselli P, Anti M. Sensitivity rates in characterizing hepatocellular carcinomas. *AJR Am J Roentgenol* 2005;**185**:1079–80. (**Study design**)
  17. Chami L, Lassau N, Malka D, Ducreux M, Bidault S, Roche A, *et al.* Benefits of contrast-enhanced sonography for the detection of liver lesions: comparison with histologic findings. *AJR Am J Roentgenol* 2008;**190**:683–90. (**Comparator**)
  18. Chen LD, Xu HX, Xie XY, Lu MD, Xu ZF, Liu GJ, *et al.* Enhancement patterns of intrahepatic cholangiocarcinoma: comparison between contrast-enhanced ultrasound and contrast-enhanced CT. *Br J Radiol* 2008;**81**:881–9. (**Population**)

19. Chen MH, Dai Y, Yan K, Fan ZH, Yin SS, Yang W, *et al.* The role of contrast-enhanced ultrasound on the diagnosis of small hepatocellular carcinoma ( $\leq 3$  cm) in patients with cirrhosis. *Hepatol Res* 2006;**35**:281–8. **(Population)**
20. Chen MH, Yang W, Yan K, Dai Y, Wu W, Fan ZH, *et al.* The role of contrast-enhanced ultrasound in planning treatment protocols for hepatocellular carcinoma before radiofrequency ablation. *Clin Radiol* 2007;**62**:752–60. **(Duplicate)**
21. Chiesara F, Baccini F, Merola E, Rinzivillo M, Panzuto F, Capurso G, *et al.* Contrast enhanced ultrasonography (CEUS) and quantitative perfusion analysis in the assessment of neuroendocrine liver metastases. *Gastroenterology* 2011;**140**:S875. **(Population)**
22. Cijevschi Prelipcean C, Pintilei I, Nedelciuc O, Chirita D, Dranga M, Mihai C. Liver tumors: the vascularisation pattern assessed by contrast-enhanced ultrasound. Paper presented at the 21st Conference of the Asian Pacific Association for the Study of the Liver (APASL), Bangkok, Thailand, 17–20 February 2011. *Hepatol Int* 2011;**5**:480–1. **(Reference standard)**
23. Cokkinos DD, Blomley MJ, Harvey CJ, Lim A, Cunningham C, Cosgrove DO. Can contrast-enhanced ultrasonography characterize focal liver lesions and differentiate between benign and malignant, thus providing a one-stop imaging service for patients? *J Ultrasound* 2007;**10**:186–93. **(Outcomes)**
24. Dai Y, Chen MH, Yin SS, Yan K, Fan ZH, Wu W, *et al.* Focal liver lesions: can SonoVue-enhanced ultrasound be used to differentiate malignant from benign lesions? *Invest Radiol* 2007;**42**:596–603. **(Comparator)**
25. De Sanctis R, Quadrini S, Tedeschi M, Stumbo L, Gori B, Del Signore E, *et al.* Early response evaluation of antiangiogenic therapy: use of contrast-enhanced ultrasonography (CE-US) in hepatocellular carcinoma. *Ann Oncol* 2009;**20**:92. **(Study design)**
26. Dietrich CF, Kratzer W, Strobel D, Danse E, Fessl R, Bunk A, *et al.* Assessment of metastatic liver disease in patients with primary extrahepatic tumors by contrast-enhanced sonography versus CT & MRI. *World J Gastroenterol* 2006;**12**:1699–705. **(Reference standard)**
27. Ding H, Wang WP, Huang BJ, Wei RX, He NA, Qi Q, *et al.* Imaging of focal liver lesions: low-mechanical-index real-time ultrasonography with SonoVue. *J Ultrasound Med* 2005;**24**:285–97. **(Comparator)**
28. D’Onofrio M, Rozzanigo U, Caffarri S, Zogno A, Procacci C. Contrast-enhanced US of hepatocellular carcinoma. *Radiol Med* 2004;**107**:293–303. **(Population)**
29. D’Onofrio M, Martone E, Faccioli N, Zamboni G, Malago R, Mucelli RP. Focal liver lesions: sinusoidal phase of CEUS. *Abdom Imaging* 2006;**31**:529–36. **(Reference standard)**
30. D’Onofrio M, Faccioli N, Zamboni G, Malago R, Caffarri S, Fattovich G, *et al.* Focal liver lesions in cirrhosis: value of contrast-enhanced ultrasonography compared with Doppler ultrasound and alpha-fetoprotein levels. *Radiol Med* 2008;**113**:978–91. **(Reference standard)**
31. Dumitru E, Dumitru IM, Alexandrescu L, Rugina S. Contrast enhanced ultrasonography (CEUS) helps characterization of focal liver lesions in HIV positive patients. Paper presented at the 21st Conference of the Asian Pacific Association for the Study of the Liver (APASL), Bangkok, Thailand, 17–20 February 2011. *Hepatol Int* 2011;**5**:482. **(Comparator)**
32. Ercolani G, Zanello M, Rojas L, Ravaioli M, Cescon M, Gaudio MD, *et al.* A prospective comparative evaluation of pre-and intraoperative imaging techniques in chemo-pretreated or not pretreated patients with colorectal liver metastases. Paper presented at the 9th Congress of the European-African HPBA (E-AHPBA), Cape Town, South Africa, 12–16 April 2011. *HPB* 2011;**13**:25–6. **(Authors contacted)**

33. Fan ZH, Chen MH, Dai Y, Wang YB, Yan K, Wu W, *et al.* Evaluation of primary malignancies of the liver using contrast-enhanced sonography: correlation with pathology. *AJR Am J Roentgenol* 2006;**186**:1512–19. **(Outcomes)**
34. Fracanzani AL, Maraschi A, Burdick L, Bertelli C, Fatta E, Bonelli N, *et al.* Contrast-enhanced ultrasonography (CEUS) and spiral computed tomography (CT) in the assessment of efficacy of percutaneous ablation treatments of hepatocellular carcinoma in cirrhosis. *J Hepatol* 2008;**48**:S145. **(Reference standard)**
35. Frieser M, Kiesel J, Lindner A, Bernatik T, Haensler JM, Janka R, *et al.* Efficacy of contrast-enhanced US versus CT or MRI for the therapeutic control of percutaneous radio-frequency ablation in the case of hepatic malignancies. *Ultraschall Med* 2011;**32**:148–53. **(Reference standard)**
36. Gaiani S, Celli N, Piscaglia F, Cecilioni L, Losinno F, Giangregorio F, *et al.* Usefulness of contrast-enhanced perfusional sonography in the assessment of hepatocellular carcinoma hypervascular at spiral computed tomography. *J Hepatol* 2004;**41**:421–6. **(Outcomes)**
37. Galassi M, Granito A, Piscaglia F, Borghi A, Lucidi V, Golfieri R, *et al.* Impact of gadoxetic acid (Gd-EOB-DTPA)-enhanced MR on the non-invasive diagnosis of small hepatocellular carcinoma. Paper presented at the Italian Association for the Study of the Liver (AISF) Annual Meeting, Rome, Italy, 24–25 February 2011. *Dig Liver Dis* 2011;**43**:S82. **(Outcomes)**
38. Gallotti A, D’Onofrio M, Ruzzenente A, Martone E, De Robertis R, Guglielmi A, *et al.* Contrast-enhanced ultrasonography (CEUS) immediately after percutaneous ablation of hepatocellular carcinoma. *Radiol Med* 2009;**114**:1094–105. **(Reference standard)**
39. Gheorghe L, Carabelea A, Vadan R, Becheanu G. QUIZ HQ 54. Contrast-enhanced ultrasound (CEUS) for the detection and assessment of treatment efficacy in focal liver lesions. *J Gastrointestin Liver Dis* 2009;**18**:473–4. **(Study design)**
40. Giangregorio F, Comparato G, Marinone MG, Di Stasi M, Sbolli G, Aragona G, *et al.* Imaging detection of new HCCs in cirrhotic patients treated with different techniques: comparison of conventional US, spiral CT, and 3-dimensional contrast-enhanced US with the navigator technique (Nav 3D CEUS). *J Ultrasound* 2009;**12**:12–21. **(Reference standard)**
41. Giangregorio F, Aragona G, Marinone G, Comparato G, Fanigliulo L, Di Stasi M, *et al.* Contrast-enhanced US (CEUS) in early evaluation of non-surgical treatment of HCC can change the patient’s follow-up and survival. Paper presented at the 45th Annual Meeting of the European Association for the Study of the Liver (EASL) International Liver Congress, Vienna, Austria, 14–18 April 2010. *J Hepatol* 2010;**52**:S90–1. **(Outcomes)**
42. Giangregorio F, Marinone M, Aragona G, Comparato G, Fanigliulo L, Sbolli G, *et al.* Echographic detection of hepatocellular carcinoma (HCC) during followup in cirrhotic patients with previous HCC: comparison among US, CT and a new panoramic 3-dimensional contrast-enhanced US with navigator system (3-D NAV CEUS). Paper presented at the 16th National Congress of Digestive Diseases – Italian Federation of Societies of Digestive Diseases (FISMAD), Verona, Italy, 6–9 March 2010. *Dig Liver Dis* 2010;**42**:S77. **(Reference standard)**
43. Giangregorio F. Contrast-enhanced ultrasound (CEUS) for echographic detection of hepatocellular carcinoma in cirrhotic patients previously treated with multiple techniques: comparison of conventional US, spiral CT and 3-dimensional CEUS with navigator technique (3DNav CEUS). *Cancers* 2011;**3**:1763–76. **(Reference standard)**
44. Giesel FL, Delorme S, Sibbel R, Kauczor HU, Krix M. [Contrast-enhanced ultrasound for the characterization of incidental liver lesions – an economical evaluation in comparison with multi-phase computed tomography.] *Ultraschall Med* 2009;**30**:259–68. **(Study design, M)**
45. Giorgio A, Di Sarno A, Nunzia F, De Stefano G, Scognamiglio U, Coppola C, *et al.* Value of contrast enhanced ultrasound in the characterization of small nodular lesions in cirrhotic livers. Paper

- presented at the 45th Annual Meeting of the European Association for the Study of the Liver (EASL) International Liver Congress, Vienna, Austria, 14–18 April 2010. *J Hepatol* 2010;**52**:S219. **(Comparator)**
46. Giorgio A, Di Sarno A, Farella N, De Stefano G, Scognamiglio U, Coppola C, *et al.* Small nodular lesions in cirrhotic livers: characterization with contrast enhanced ultrasound. Paper presented at the 43rd Annual Meeting of the Italian Association for the Study of the Liver (AISF), Rome; Italy, 25–26 February 2010. *Dig Liver Dis* 2010;**42**:S23–4. **(Comparator)**
  47. Giorgio A. Diagnostic algorithm of hepatocellular carcinoma on cirrhosis: CEUS or no CEUS, that is the problem. *Dig Liver Dis* 2011;**43**:499. **(Study design)**
  48. Gomez Rodriguez RA, Artaza Varasa T, Gonzalez de Frutos C, Sanchez Ruano JJ, Repiso Ortega A, Perez-Grueso Macias MJ, *et al.* [Value of contrast-enhanced ultrasound in the diagnosis of hepatocarcinoma in focal lesions detected in patients with liver disease.] *Gastroenterol Hepatol* 2007;**30**:381–6. **(Reference standard)**
  49. Guo J, Liang Y, Yan JY, Liu Y. [Clinical value of real time contrast-enhanced ultrasound in differentiating benign and malignant liver lesions.] *Chin J Med Imaging Technol* 2008;**24**:1434–7. **(Comparator)**
  50. Hanle MM, Thiel R, Saur G, Mason RA, Pauls S, Kratzer W. Screening for liver metastases in women with mammary carcinoma: comparison of contrast-enhanced ultrasound and magnetic resonance imaging. *Clin Imaging* 2011;**35**:366–70. **(Outcomes)**
  51. Hohmann J, Skrok J, Puls R, Albrecht T. [Characterization of focal liver lesions with contrast-enhanced low MI real time ultrasound and SonoVue.] *Rofa* 2003;**175**:835–43. **(Reference standard)**
  52. Iavarone M, Sangiovanni A, Forzenigo LV, Massironi S, Fraquelli M, Aghemo A, *et al.* Diagnosis of hepatocellular carcinoma in cirrhosis by dynamic contrast imaging: the importance of tumor cell differentiation. *Hepatology* 2010;**52**:1723–30. **(Outcomes)**
  53. Ignee A, Livraghi T, Tranquart F, Bolondi L, Dietrich CF, Albrecht T. Revised detection of liver lesions by ultrasound-contrast medium of the second generation, compared to conventional sonography. *Endosk Heute* 2009;**22**:105–9. **(Reference standard)**
  54. Jang HJ, Kim TK, Wilson SR. Small nodules (1–2 cm) in liver cirrhosis: characterization with contrast-enhanced ultrasound. *Eur J Radiol* 2009;**72**:418–24. **(Index test)**
  55. Janica JR, Lebkowska U, Ustymowicz A, Augustynowicz A, Kamocki Z, Werel D, *et al.* Contrast-enhanced ultrasonography in diagnosing liver metastases. *Med Sci Monit* 2007;**13**(Suppl. 1):111–15. **(Reference standard)**
  56. Jung EM, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, *et al.* Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: a prospective controlled two-center study. *World J Gastroenterol* 2007;**13**:6356–64. **(Comparator)**
  57. Jung EM, Schreyer AG, Schacherer D, Menzel C, Farkas S, Loss M, *et al.* New real-time image fusion technique for characterization of tumor vascularisation and tumor perfusion of liver tumors with contrast-enhanced ultrasound, spiral CT or MRI: first results. *Clin Hemorheol Microcirc* 2009;**43**:57–69. **(Index test)**
  58. Kisaka Y, Hirooka M, Kumagi T, Uehara T, Hiasa Y, Kumano S, *et al.* Usefulness of contrast-enhanced ultrasonography with abdominal virtual ultrasonography in assessing therapeutic response in hepatocellular carcinoma treated with radiofrequency ablation. *Liver Int* 2006;**26**:1241–7. **(Index test)**

59. Kobayashi Y, Nakamura S, Toshikuni N, Tanaka H, Matsumoto E, Ohnishi H, *et al.* Contrast-enhanced dynamic ultrasonography (CE-US) differentiates hepatocellular carcinoma from dysplastic nodules: correlation with histological grading. *Gastroenterology* 2004;**126**:A494. **(Index test)**
60. Kono Y, Alton K, Rose SC, Hassanein TI, Mattrey RF. The ability of contrast-enhanced ultrasound (CEUS) to predict final outcome within 1 week after transarterial chemoembolization (TACE) for hepatocellular carcinoma (HCC). *Hepatology* 2004;**40**:706–7A. **(Index test)**
61. Kono Y, Lucidarme O, Choi SH, Rose SC, Hassanein TI, Alpert E, *et al.* Contrast-enhanced ultrasound as a predictor of treatment efficacy within 2 weeks after transarterial chemoembolization of hepatocellular carcinoma. *J Vasc Interv Radiol* 2007;**18**:57–65. **(Index test)**
62. Konopke R, Kersting S, Saeger HD, Bunk A. [Detection of liver lesions by contrast-enhanced ultrasound: comparison to intraoperative findings.] *Ultraschall Med Suppl* 2005;**26**:107–13. **(Comparator)**
63. Konopke R, Kersting S, Bergert H, Bloomenthal A, Gastmeier J, Saeger HD, *et al.* Contrast-enhanced ultrasonography to detect liver metastases. *Int J Colorectal Dis* 2007;**22**:201–7. **(Comparator)**
64. Konopke R, Bunk A, Kersting S. Contrast-enhanced ultrasonography in patients with colorectal liver metastases after chemotherapy. *Ultraschall Med Suppl* 2008;**29**:S203–9. **(Comparator)**
65. Laghi F, Catalano O, Maresca M, Sandomenico F, Siani A. Indeterminate, subcentimetric focal liver lesions in cancer patients: additional role of contrast-enhanced ultrasound. *Ultraschall Med* 2010;**31**:283–8. **(Reference standard)**
66. Lanka B, Jang HJ, Kim TK, Burns PN, Wilson SR. Impact of contrast-enhanced ultrasonography in a tertiary clinical practice. *J Ultrasound Med* 2007;**26**:1703–14. **(Study design)**
67. Larsen LPS, Rosenkilde M, Christensen H, Bang N, Bolvig L, Christiansen T, *et al.* The value of contrast enhanced ultrasonography in detection of liver metastases from colorectal cancer: a prospective double-blinded study. *Eur J Radiol* 2007;**62**:302–7. **(Reference standard)**
68. Larsen LPS, Rosenkilde M, Christensen H, Bang N, Bolvig L, Christiansen T, *et al.* Can contrast-enhanced ultrasonography replace multidetector-computed tomography in the detection of liver metastases from colorectal cancer? *Eur J Radiol* 2009;**69**:308–13. **(Reference standard)**
69. Lassau N, Lacroix J, Taieb S, Aziza R, Vilgrain V, Cuinet M, *et al.* French, multicentric, prospective study of dynamic contrast-enhanced ultrasound (DCE-US) for the evaluation of antiangiogenic treatments in 400 patients. *Paper presented at the 2010 Annual Meeting of the American Society of Clinical Oncology (ASCO), Chicago, IL, 4–9 June 2010. J Clin Oncol* 2010;**28**. **(Outcomes)**
70. Leen E. The role of contrast-enhanced ultrasound in the characterisation of focal liver lesions. *Eur Radiol* 2001;**11**:E27–34. **(Study design)**
71. Leen E, Ceccotti P, Kalogeropoulou C, Angerson WJ, Moug SJ, Horgan PG. Prospective multicenter trial evaluating a novel method of characterizing focal liver lesions using contrast-enhanced sonography. *AJR Am J Roentgenol* 2006;**186**:1551–9. **(Reference standard, M)**
72. Lemke AJ, Chopra SS, Hengst SA, Brinkmann MJ, Steinmuller T, Felix R. [Characterization of hepatic tumors with contrast-enhanced ultrasound and digital grey-scale analysis.] *Tumor Diagn Ther* 2004;**25**:276–85. **(Reference standard)**
73. Lemke AJ, Chopra SS, Hengst SA, Brinkmann MJ, Steinmuller T, Felix R. [Characterization of hepatic tumors with contrast-enhanced ultrasound and digital grey-scale analysis.] *Rofo* 2004;**176**:1607–16. **(Duplicate)**
74. Lencioni R, Cioni D, Crocetti L, Donati F, Franchini C, Giusti S, *et al.* Ultrasound imaging of focal liver lesions with a second-generation contrast agent. *Acad Radiol* 2002;**9**:S371–4. **(Reference standard)**

75. Leoni S, Piscaglia F, Granito A, Salvatore V, Cappelli A, Lucidi V, *et al.* Diagnostic accuracy of different patterns of contrast enhanced ultrasound in characterization of new nodules in liver cirrhosis with and without history of previous hepatocellular carcinoma. Paper presented at the Italian Association for the Study of the Liver (AISF) Annual Meeting, Rome, Italy, 24–25 February 2011. *Dig Liver Dis* 2011;**43**:S73–4. **(Reference standard)**
76. Li R, Guo YL, He Y, Zhang XH, Ding J, Chen ZH. [Real-time pulse-inversion sonography using contrast agent: differentiation between benign and malignant focal liver lesions.] *Chin J Med Imaging Technol* 2006;**22**:186–8. **(Comparator)**
77. Lin L, Gui YZ, Liang Z, Chen J, Lu Q, Min M. [Contrast-enhanced ultrasound in assessment of the therapeutic efficacy of high intensity focused ultrasound in treating hepatocellular carcinoma.] *World Chin J Dig* 2009;**17**:1879–82. **(Comparator)**
78. Liu GJ, Xu HX, Xie XY, Xu ZF, Zheng YL, Liang JY, *et al.* Does the echogenicity of focal liver lesions on baseline gray-scale ultrasound interfere with the diagnostic performance of contrast-enhanced ultrasound? *Eur Radiol* 2009;**19**:1214–22. **(Reference standard)**
79. Liu GJ, Wang W, Xie XY, Xu HX, Xu ZF, Zheng YL, *et al.* Real-time contrast-enhanced ultrasound imaging of focal liver lesions in fatty liver. *Clin Imaging* 2010;**34**:211–21. **(Comparator)**
80. Liu LP, Dong BW, Yu XL, Liang P, Zhang DK, An LC. Focal hypoechoic tumors of fatty liver: characterization of conventional and contrast-enhanced ultrasonography. *J Ultrasound Med* 2009;**28**:1133–42. **(Outcomes)**
81. Loria F, Loria G, Crea G, Basile S, Frosina L, Cantoni S. Comparison of unenhanced and contrast-enhanced ultrasonography in the diagnosis of focal liver lesions. Abstract MO-114. Paper presented at the 9th World Congress of the International Hepato-Pancreato-Biliary Association, Buenos Aires, Argentina, 18–22 April 2010. *HPB* 2010;**12**:100–1. **(Outcomes)**
82. Loria F, Loria G, Frosina L, Crea G, Basile S, Cantoni S. Metastatic disease of the liver: comparison of CEUS vs. US and CT in the evaluation of diagnostic performance and confidence. Paper presented at the 9th World Congress of the International Hepato-Pancreato-Biliary Association, Buenos Aires, Argentina, 18–22 April 2010. *HPB* 2010;**12**:269. **(Authors contacted)**
83. Lu MD, Yu XI, Li AH, Jiang TA, Chen MH, Zhao BZ, *et al.* Comparison of contrast enhanced ultrasound and contrast enhanced CT or MRI in monitoring percutaneous thermal ablation procedure in patients with hepatocellular carcinoma: a multi-center study in China. *Ultrasound Med Biol* 2007;**33**:1736–49. **(Reference standard)**
84. Marcus CD, Brixi-Benmansour H, Job L, Ladam-Marcus V, Lagarde S, Cadiot G. Detection and characterization of hepatic metastases from gastrointestinal endocrine tumor with contrast-specific US modes and a sulfur hexafluoride-filled microbubble contrast agent. *Gastroenterology* 2006;**130**:A193–4. **(Outcomes)**
85. Martin-Algibez A, Fernandez-Vazquez I, Lopez-Martinez C, Gallego-Gallego MS, San Roman R, Mnoz-Codocero C, *et al.* Evaluation of local recurrence after treatment for hepatocellular carcinoma by contrast-enhanced ultrasonography: comparison with dynamic computed tomography and/or magnetic resonance imaging. Paper presented at the 46th Annual Meeting of the European Association for the Study of the Liver (EASL) International Liver Congress, Berlin, Germany, 30 March–3 April 2011. *J Hepatol* 2011;**54**:S393–4. **(Reference standard)**
86. Mork H, Ignee A, Schuessler G, Ott M, Dietrich CF. Analysis of neuroendocrine tumour metastases in the liver using contrast enhanced ultrasonography. *Scand J Gastroenterol* 2007;**42**:652–62. **(Outcomes)**
87. Mucciari C, Bellentani S, Razzini G, Bernardini I, Artioli F, Iop A, *et al.* The role of contrast-enhanced ultrasound in detection of liver metastases from colorectal cancer: a prospective monocentric study. Paper presented at the 2009 Annual Meeting of the American Society of Clinical

- Oncology (ASCO), Orlando, FL, 29 May–2 June 2009. *J Clin Oncol* 2009;**27**:e15105. **(Reference standard)**
88. Muhi A, Ichikawa T, Motosugi U, Sou H, Nakajima H, Sano K, *et al.* Diagnosis of colorectal hepatic metastases: comparison of contrast-enhanced CT, contrast-enhanced US, superparamagnetic iron oxide-enhanced MRI, and gadoxetic acid-enhanced MRI. *J Magn Reson Imaging* 2011;**34**:326–35. **(Reference standard)**
  89. Nicolau C, Vilana R, Catala V, Bianchi L, Gilibert R, Garcia A, *et al.* Importance of evaluating all vascular phases on contrast-enhanced sonography in the differentiation of benign from malignant focal liver lesions. *AJR Am J Roentgenol* 2006;**186**:158–67. **(Comparator)**
  90. Oldenburg A, Hohmann J, Foert E, Skrok J, Hoffmann CW, Frericks B, *et al.* Detection of hepatic metastases with low MI real time contrast enhanced sonography and SonoVue. *Ultraschall Med* 2005;**26**:277–84. **(Reference standard)**
  91. Ooi C-C, Low S-CA, Schneider-Kolsky M, Lombardo P, Lim S-Y, Abu Bakar R, *et al.* Diagnostic accuracy of contrast-enhanced ultrasound in differentiating benign and malignant focal liver lesions: a retrospective study. *J Med Imaging Radiat Oncol* 2010;**54**:421–30. **(Reference standard)**
  92. Peschl R, Werle A, Mathis G. Differential diagnosis of focal liver lesions in signal-enhanced ultrasound using BR 1, a second-generation ultrasound signal enhancer. *Dig Dis* 2004;**22**:73–80. **(Comparator)**
  93. Piscaglia F, Bolondi L. The safety of Sonovue in abdominal applications: retrospective analysis of 23188 investigations. *Ultrasound Med Biol* 2006;**32**:1369–75. **(Study design, M)**
  94. Piscaglia F, Corradi F, Mancini M, Giangregorio F, Tamperi S, Ugolini G, *et al.* Real time contrast enhanced ultrasonography in detection of liver metastases from gastrointestinal cancer. *BMC Cancer* 2007;**7**. **(Reference standard)**
  95. Pompili M, Riccardi L, Covino M, Barbaro B, Di Stasi C, Orefice R, *et al.* Contrast-enhanced gray-scale harmonic ultrasound in the efficacy assessment of ablation treatments for hepatocellular carcinoma. *Liver Int* 2005;**25**:954–61. **(Reference standard)**
  96. Quaia E, Stacul F, Bertolotto M, Locatelli M, Mucelli RP. Characterization of focal liver lesions with pulse inversion harmonic imaging (PIHI) using a second generation US contrast agent. *Acad Radiol* 2002;**9**(Suppl. 2):S376–9. **(Reference standard)**
  97. Quaia E, Bertolotto M, Calderan L, Mosconi E, Mucelli RP. US characterization of focal hepatic lesions with intermittent high-acoustic-power mode and contrast material. *Acad Radiol* 2003;**10**:739–50. **(Outcomes)**
  98. Quaia E, Calliada F, Bertolotto M, Rossi S, Garioni L, Rosa L, *et al.* Characterization of focal liver lesions with contrast-specific US modes and a sulfur hexafluoride-filled microbubble contrast agent: diagnostic performance and confidence. *Radiology* 2004;**232**:420–30. **(Study design)**
  99. Quaia E, D’Onofrio M, Palumbo A, Rossi S, Bruni S, Cova M. Comparison of contrast-enhanced ultrasonography versus baseline ultrasound and contrast-enhanced computed tomography in metastatic disease of the liver: diagnostic performance and confidence. *Eur Radiol* 2006;**16**:1599–609. **(Reference standard)**
  100. Quaia E, D’Onofrio M, Cabassa P, Vecchiato F, Caffarri S, Pittiani F, *et al.* Diagnostic value of hepatocellular nodule vascularity after microbubble injection for characterizing malignancy in patients with cirrhosis. *AJR Am J Roentgenol* 2007;**189**:1474–83. **(Reference standard)**
  101. Quaia E, Alaimo V, Baratella E, Pizzolato R, Cester G, Medeot A, *et al.* Effect of observer experience in the differentiation between benign and malignant liver tumors after ultrasound contrast agent injection. *J Ultrasound Med* 2010;**29**:25–36. **(Outcomes)**

102. Quek L, Pua DU, Wansaicheong G. Role of contrast-enhanced ultrasound in diagnosis of indeterminate hepatic lesions. Paper presented at the 61st Annual Scientific Meeting of the Royal Australian and New Zealand College of Radiologists (RANZCR), Perth, Australia, 14–17 October 2010. *J Med Imaging Radiat Oncol* 2010;**54**:A123. **(Outcomes)**
103. Rafaelsen SR, Jakobsen AJ. Contrast enhanced ultrasonography versus multidetector-computed tomography in detection of liver metastases from colorectal cancer. A prospective, blinded, patient by patient analysis. Paper presented at the 5th European Multidisciplinary Colorectal Cancer Congress (EMCC), Nice, France, 23–30 March 2010. *Ann Oncol* 2010;**21**:i27. **(Reference standard)**
104. Rafaelsen SR, Jakobsen A. Contrast-enhanced ultrasound vs multidetector-computed tomography for detecting liver metastases in colorectal cancer: a prospective, blinded, patient-by-patient analysis. *Colorectal Dis* 2011;**13**:420–5. **(Reference standard)**
105. Ricci P, Cantisani V, Drudi F, Pagliara E, Bezzi M, Meloni F, *et al.* Is contrast-enhanced US alternative to spiral CT in the assessment of treatment outcome of radiofrequency ablation in hepatocellular carcinoma? *Ultraschall Med* 2009;**30**:252–8. **(Reference standard, M)**
106. Rojas Llimpe F, Di Fabio F, Ercolani G, Giampalma E, Serra C, Castellucci P, *et al.* Prospective comparative study on pre-operative diagnostic accuracy of different imaging techniques in colorectal cancer patients with liver metastases candidates to surgical resection (Italian PROMETEO study). Paper presented at the Joint ECCO 15–34th ESMO Multidisciplinary Congress, Berlin, Germany, 20–24 September 2009. *Eur J Cancer Suppl* 2009;**7**:348. **(Outcomes)**
107. Romanini L, Passamonti M, Aiani L, Cabassa P, Raieli G, Montermini I, *et al.* Economic assessment of contrast-enhanced ultrasonography for evaluation of focal liver lesions: a multicentre Italian experience. *Eur Radiol* 2007;**17**(Suppl. 6):F99–106. **(Comparator)**
108. Salvaggio G, Campisi A, Lo Greco V, Cannella I, Meloni MF, Caruso G. Evaluation of posttreatment response of hepatocellular carcinoma: comparison of ultrasonography with second-generation ultrasound contrast agent and multidetector CT. *Abdom Imaging* 2010;**35**:447–53. **(Reference standard)**
109. Şirli R, Sporea I, Martie A, Popescu A, Danila M. Contrast enhanced ultrasound in focal liver lesions: a cost efficiency study. *Med Ultrason* 2010;**12**:280–5. **(Study design)**
110. Societatea Romana de Ultrasonografie in Medicina si Biologie, Centrul de Cercetare in Gastroenterologie si Hepatologie C, Clinica de Gastroenterologie si Hepatologie UT, Institutul Regional de Gastroenterologie-Hepatologie C-N, Institutul Clinic Fundeni B, Clinica de Gastroenterologie C. *Contrast enhanced ultrasound for the evaluation of focal liver lesions*. NCT01329458. Bethesda, MD: National Library of Medicine; 2011. URL: <http://ClinicalTrials.gov/show/NCT01329458> (accessed 12 December 2011) **(Reference standard)**
111. Solbiati L, Tonolini M, Cova L, Nahum Goldberg S. The role of contrast-enhanced ultrasound in the detection of focal liver lesions. *Eur Radiol* 2001;**11**:E15–26. **(Reference standard)**
112. Solbiati L, Tonolini M, Cova L. Contrast-enhanced sonography with contrast pulse sequencing for guidance of percutaneous ablation of liver malignancies and assessment of therapeutic response. *Appl Radiol* 2002;**31**:25–30. **(Study design)**
113. Solbiati L, Ierace T, Tonolini M, Cova L. Guidance and monitoring of radiofrequency liver tumor ablation with contrast-enhanced ultrasound. *Eur J Radiol* 2004;**51**:S19–23. **(Study design)**
114. Soussan M, Aube C, Bahrami S, Boursier J, Valla DC, Vilgrain V. Incidental focal solid liver lesions: diagnostic performance of contrast-enhanced ultrasound and MR imaging. *Eur Radiol* 2010;**20**:1715–25. **(Outcomes)**



115. Soye JA, Mullan CP, Porter S, Beattie H, Barltrop AH, Nelson WM. The use of contrast-enhanced ultrasound in the characterisation of focal liver lesions. *Ulster Med J* 2007;**76**:22–5. (**Reference standard, M**)
116. Sporea I, Şirli R, Martie A, Popescu A, Danila M. How useful is contrast enhanced ultrasonography for the characterization of focal liver lesions? *J Gastrointestin Liver Dis* 2010;**19**:393–8. (**Outcomes**)
117. Sporea I, Badea R, Martie A, Şirli R, Socaciu M, Popescu A, *et al.* Contrast enhanced ultrasound for the characterization of focal liver lesions. *Med Ultrason* 2011;**13**:38–44. (**Outcomes**)
118. Sporea I, Badea R, Popescu A, Martie AF, Socaciu M, Şirli R, *et al.* Characterization of focal liver lesions by contrast enhanced ultrasound (CEUS) in clinical practice: a bicentric experience. Paper presented at Digestive Disease Week (DDW) 2011, Chicago, IL, 7–10 May 2011. *Gastroenterology* 2011;**140**:s926–7. (**Outcomes**)
119. Sporea I, Badea R, Popescu A, Martie A, Socaciu M, Şirli R, *et al.* How useful is contrast enhanced ultrasound (CEUS) for the characterization of focal liver lesions? Paper presented at the 21st Conference of the Asian Pacific Association for the Study of the Liver (APASL), Bangkok, Thailand, 17–20 February 2011. *Hepatol Int* 2011;**5**:481–2. (**Outcomes**)
120. Strobel D, Seitz K, Blank W, Schuler A, Dietrich C, von Herbay A, *et al.* Contrast-enhanced ultrasound for the characterization of focal liver lesions: diagnostic accuracy in clinical practice (DEGUM multicenter trial). *Ultraschall Med* 2008;**29**:499–505. (**Duplicate, M**)
121. Strobel D, Seitz K, Blank W, Schuler A, Dietrich CF, Von Herbay A, *et al.* Tumor-specific vascularization pattern of liver metastasis, hepatocellular carcinoma, hemangioma and focal nodular hyperplasia in the differential diagnosis of 1349 liver lesions in contrast-enhanced ultrasound (CEUS). *Ultraschall Med* 2009;**30**:376–82. (**Comparator, M**)
122. Strunk H, Borner N, Stuckmann G, Frohlich E, Hadizadeh D. [Contrast-enhanced ‘low MI real-time’ sonography for the assessment of the malignancy of focal liver lesions.] *Rofo* 2005;**177**:1394–404. (**Comparator**)
123. Tarantino L, De Rosa A, Sorrentino P, Tambaro O, Celiento M, Del Prete M, *et al.* Impact of contrast-enhanced ultrasonography on diagnostic work-up of focal liver anomalies: experience in a single hepatology unit. Paper presented at the 45th Annual Meeting of the European Association for the Study of the Liver (EASL) International Liver Congress, Vienna, Austria, 14–18 April 2010. *J Hepatol* 2010;**52**:s235–6. (**Outcomes**)
124. Tarantino L, Sorrentino P, Ripa C, Restivo L, Cuccorese G, Sordelli I, *et al.* Impact of contrast-enhanced ultrasonography on diagnostic work-up of focal liver anomalies: experience in a single hepatology unit. Paper presented at the 17th National Congress of Digestive Diseases – Italian Federation of Societies of Digestive Diseases (FISMAD), Turin, Italy, 5–9 March 2011. *Dig Liver Dis* 2011;**43**:s185. (**Outcomes**)
125. Tombesi P, Catellani M, Abbasciano V, Sartori S, Tassinari D. Impact of contrast-enhanced ultrasonography in a tertiary clinical practice. *J Ultrasound Med* 2008;**27**:991–2. (**Comparator**)
126. Torres CJL, Escribano PS, Alguacil MV, De Dios Vega JF. Contrast-enhanced ultrasound in the diagnosis of hepatocarcinoma detected in patients with a focal liver lesion and liver disease. Paper presented at the 60th Annual Meeting of the American Association for the Study of Liver Diseases: the Liver Meeting, Boston, MA, 30 October–3 November 2009. *Hepatology* 2009;**50**:1131A. (**Reference standard**)
127. Tranquart F, Le Gouge A, Correas JM, Ladam Marcus V, Manzoni P, Vilgrain V, *et al.* Role of contrast-enhanced ultrasound in the blinded assessment of focal liver lesions in comparison with MDCT and CEMRI: results from a multicentre clinical trial. *Eur J Cancer Suppl* 2008;**6**:9–15. (**Reference standard, M**)

128. Tranquart F, Correas JM, Marcus VL, Manzoni P, Vilgrain V, Aube C, *et al.* Real-time contrast-enhanced ultrasound in the evaluation of focal liver lesions: diagnostic efficacy and economical issues from a French multicentric study. *J Radiol* 2009;**90**:109–22. (**Comparator, M**)
129. Trillaud H, Bruel JM, Valette PJ, Vilgrain V, Schmutz G, Oyen R, *et al.* Characterization of focal liver lesions with SonoVue-enhanced sonography: international multicenter-study in comparison to CT and MRI. *World J Gastroenterol* 2009;**15**:3748–56. (**Reference standard**)
130. University Hospital (Tours), Ministry of Health France. *Characterization of focal liver lesions by real-time contrast-enhanced ultrasound imaging (CEUS)*. NCT00243633. Bethesda, MD: National Library of Medicine; 2008. URL: <http://ClinicalTrials.gov/show/NCT00243633> (accessed 12 December 2011). (**Study design**)
131. University Hospital (Tours). *Evaluation of contrast-enhanced ultrasound imaging for the early estimate of bevacizumab effect on colorectal cancer liver metastases*. NCT00489697. Bethesda, MD: National Library of Medicine; 2009. URL: <http://ClinicalTrials.gov/show/NCT00489697> (accessed 12 December 2011). (**Outcomes**)
132. Varela M, Vilana R, Bianchi L, Garcia MA, Nicolau C, Sanchez M, *et al.* Usefulness of SonoVue microbubble-enhanced ultrasonography in the assessment of the efficacy of percutaneous ablation in patients with hepatocellular carcinoma. *J Hepatol* 2004;**40**:85. (**Reference standard**)
133. Vilana R, Bianchi L, Nicolau C, Garcia M, Squarcia M, Sanchez M, *et al.* [Second-generation ultrasound contrast agents (SonoVue) in the evaluation of percutaneous treatment of hepatocellular carcinoma: comparison with multiphase CT.] *Radiologia* 2005;**47**:79–85. (**Reference standard**)
134. Vilana R, Bianchi L, Varela M, Nicolau C, Sanchez M, Ayuso C, *et al.* Is microbubble-enhanced ultrasonography sufficient for assessment of response to percutaneous treatment in patients with early hepatocellular carcinoma? *Eur Radiol* 2006;**16**:2454–62. (**Reference standard**)
135. von Herbay A, Vogt C, Willers R, Haussinger D. Real-time imaging with the sonographic contrast agent SonoVue: differentiation between benign and malignant hepatic lesions. *J Ultrasound Med* 2004;**23**:1557–68. (**Comparator**)
136. von Herbay A, Westendorff J, Gregor M. Contrast-enhanced ultrasound with SonoVue: differentiation between benign and malignant focal liver lesions in 317 patients. *J Clin Ultrasound* 2010;**38**:1–9. (**Comparator**)
137. Wang HB, Hou XJ, Wang XL, Wang H, Liu AW. [Diagnostic value of real-time grey-scale contrast-enhanced ultrasonography for hepatic tumors.] *World Chin J Dig* 2007;**15**:2726–9. (**Comparator**)
138. Wang J-H, Lu S-N, Hung C-H, Chen T-Y, Chen C-H, Changchien C-S, *et al.* Small hepatic nodules (<or = 2 cm) in cirrhosis patients: characterization with contrast-enhanced ultrasonography. *Liver Int* 2006;**26**:928–34. (**Index test**)
139. Wang W-P, Wu Y, Luo Y, Li R, Zhou X-D, Zhang J, *et al.* Clinical value of contrast-enhanced ultrasonography in the characterization of focal liver lesions: a prospective multicenter trial. *Hepatobiliary Pancreat Dis Int* 2009;**8**:370–6. (**Comparator, M**)
140. Wang ZL, Tang J, Weskott HP, Li JL, Wang W, Luo YK, *et al.* Undetermined focal liver lesions on gray-scale ultrasound in patients with fatty liver: characterization with contrast-enhanced ultrasound. *J Gastroenterol Hepatol* 2008;**23**:1511–19. (**Comparator**)
141. Wilson SR, Jang H-J, Kim TK, Burns PN. Diagnosis of focal liver masses on ultrasonography: comparison of unenhanced and contrast-enhanced scans. *J Ultrasound Med* 2007;**26**:775–87; quiz 788–90. (**Outcomes**)
142. Wu W, Chen MH, Yin SS, Yan K, Fan ZH, Yang W, *et al.* The role of contrast-enhanced sonography of focal liver lesions before percutaneous biopsy. *AJR Am J Roentgenol* 2006;**187**:752–61. (**Population**)

143. Xia Y, Jiang YX, Dai Q, Lv K, Gao P. [Diagnostic value of arterial enhancement pattern on contrast-enhanced ultrasound in focal liver lesions.] *Chin J Med Imaging Technol* 2008;**24**:692–5. **(Comparator)**
144. Xie L, Guang Y, Ding H, Cai A, Huang Y. Diagnostic value of contrast-enhanced ultrasound, computed tomography and magnetic resonance imaging for focal liver lesions: a meta-analysis. *Ultrasound Med Biol* 2011;**37**:854–61. **(Study design)**
145. Xu H-X, Liu G-J, Lu M-D, Xie X-Y, Xu Z-F, Zheng Y-L, *et al.* [Characterization of focal liver lesions using an innovative contrast-enhanced ultrasound technique.] *Zhonghua Wai Ke Za Zhi* 2005;**43**:1375–8. **(Comparator)**
146. Xu HX, Liu GJ, Lu MD, Xie XY, Xu ZF, Zheng YL, *et al.* Characterization of small focal liver lesions using real-time contrast-enhanced sonography: diagnostic performance analysis in 200 patients. *J Ultrasound Med* 2006;**25**:349–61. **(Reference standard)**
147. Xu HX, Liu GJ, Lu MD, Xie XY, Xu ZF, Zheng YL, *et al.* Characterization of focal liver lesions using contrast-enhanced sonography with a low mechanical index mode and a sulfur hexafluoride-filled microbubble contrast agent. *J Clin Ultrasound* 2006;**34**:261–72. **(Comparator)**
148. Xu H-X, Xie X-Y, Lu M-D, Liu G-J, Xu Z-F, Zheng Y-L, *et al.* Contrast-enhanced sonography in the diagnosis of small hepatocellular carcinoma  $\leq 2$  cm. *J Clin Ultrasound* 2008;**36**:257–66. **(Reference standard)**
149. Yan K, Chen M-H, Dai Y, Shen L, Jiang X-L. [Results of enhanced ultrasonography in assessing hepatoma treated with radiofrequency ablation.] *Zhonghua Zhong Liu Za Zhi* 2005;**27**:41–4. **(Comparator)**
150. Yarmenitis SD, Karantanas A, Bakantaki A, Papantoniou Y, Gourtsoyiannis N. Detection of colorectal cancer hepatic metastases with contrast-enhanced ultrasound: comparison with conventional B-mode ultrasound. *Dig Dis* 2007;**25**:86–93. **(Reference standard)**
151. Zhang H, He Y, Du L, Wu Y. Shorter hepatic transit time can suggest coming metastases: through-monitoring by contrast-enhanced ultrasonography? *J Ultrasound Med* 2010;**29**:719–26. **(Reference standard)**
152. Zuber-Jerger I, Schacherer D, Woenckhaus M, Jung EM, Scholmerich J, Klebl F. Contrast-enhanced ultrasound in diagnosing liver malignancy. *Clin Hemorheol Microcirc* 2009;**43**:109–18. **(Comparator)**
153. Zviniene K, Zaboriene I, Basevicius A, Pundzius J. Comparative diagnostic value of computed tomography and contrast-enhanced ultrasonography in diagnosis of focal liver lesions. *Medicina-Lithuania* 2009;**45**:751–63. **(Outcomes)**

The following is a list of those studies provided in the submission from the manufacturer of SonoVue that had already been excluded at the title and abstract screening stage. Studies provided in submissions from manufacturers that related solely to clinical applications outside the scope of the current assessment (i.e. anatomy other than the liver) are not listed:

1. Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology* 2005;**42**:1208–36.
2. Claudon M, Cosgrove D, Albrecht T, Bolondi L, Bosio M, Calliada F, *et al.* Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS): update 2008. *Ultraschall Med* 2008;**29**:28–44.
3. Faccioli N, D’Onofrio M, Comai A, Cugini C. Contrast-enhanced ultrasonography in the characterization of benign focal liver lesions: activity-based cost analysis. *Radiol Med* 2007;**112**:810–20.

4. Forner A, Vilana R, Ayuso C, Bianchi L, Sole M, Ayuso JR, *et al.* Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. *Hepatology* 2008;**47**:97–104.
5. Leen E, Ceccotti P, Moug SJ, Glen P, MacQuarrie J, Angerson WJ, *et al.* Potential value of contrast-enhanced intraoperative ultrasonography during partial hepatectomy for metastases. An essential investigation before resection? *Ann Surg* 2006;**243**:236–40.
6. Liu GJ, Xu HX, Lu MD, Xie XY, Xu ZF, Zheng YL, *et al.* Enhancement pattern of hepatocellular carcinoma: comparison of real-time contrast-enhanced ultrasound and contrast-enhanced computed tomography. *Clin Imaging* 2006;**30**:315–21.
7. Rahbin N, Siosteen AK, Elvin A, Blomqvist L, Hagen K, Hultcrantz R, *et al.* Detection and characterization of focal liver lesions with contrast-enhanced ultrasonography in patients with hepatitis C-induced liver cirrhosis. *Acta Radiol* 2008;**49**:251–7.
8. Schuler A, Reuss J, Delorme S, Hagendorff A, Giesel F. Costs of clinical ultrasound examinations: an economical cost calculation and analysis. *Ultraschall Med* 2010;**31**:379–86.
9. Seitz K, Strobel D, Bernatik T, Blank W, Friedrich-Rust M, Herbay AV, *et al.* Contrast-enhanced ultrasound (CEUS) for the characterization of focal liver lesions – prospective comparison in clinical practice: CEUS vs. CT (DEGUM multicenter trial). *Parts of this manuscript were presented at the Ultrasound Dreiländertreffen 2008, Davos. Ultraschall Med* 2009;**30**:383–9.
10. Seitz K, Bernatik T, Strobel D, Blank W, Friedrich-Rust M, Strunk H, *et al.* Contrast-enhanced ultrasound (CEUS) for the characterization of focal liver lesions in clinical practice (DEGUM Multicenter Trial): CEUS vs. MRI – a prospective comparison in 269 patients. *Ultraschall Med* 2010;**31**:492–9.



## Appendix 6 National Institute for Health and Care Excellence guidance relevant to the treatment of liver malignancies

1. National Institute for Health and Care Excellence (NICE). *Cryotherapy for the treatment of liver metastases (IPG369)*. London: NICE; 2010. URL: <http://guidance.nice.org.uk/IPG369> (accessed 26 February 2013).
2. National Institute for Health and Care Excellence (NICE). *Ex-vivo hepatic resection and reimplantation for liver cancer (IPG298)*. London: NICE; 2009. URL: <http://guidance.nice.org.uk/IPG298> (accessed 26 February 2013).
3. National Institute for Health and Care Excellence (NICE). *Laparoscopic liver resection (IPG135)*. London: NICE; 2005. URL: <http://guidance.nice.org.uk/IPG135> (accessed 26 February 2013).
4. National Institute for Health and Care Excellence (NICE). *Microwave ablation for the treatment of liver metastases (IPG406)*. London: NICE; 2011. URL: <http://guidance.nice.org.uk/IPG406> (accessed 26 February 2013).
5. National Institute for Health and Care Excellence (NICE). *Microwave ablation of hepatocellular carcinoma (IPG214)*. London: NICE; 2007. URL: <http://guidance.nice.org.uk/IPG214> (accessed 26 February 2013).
6. National Institute for Health and Care Excellence (NICE). *Radiofrequency ablation of hepatocellular carcinoma (IPG2)*. London: NICE; 2003. URL: <http://guidance.nice.org.uk/IPG2> (accessed 26 February 2013).
7. National Institute for Health and Care Excellence (NICE). *Radiofrequency-assisted liver resection (IPG211)*. London: NICE; 2007. URL: <http://guidance.nice.org.uk/IPG211> (accessed 26 February 2013).
8. National Institute for Health and Care Excellence (NICE). *Selective internal radiation therapy for non-resectable colorectal metastases in the liver (IPG401)*. London: NICE; 2011. URL: <http://guidance.nice.org.uk/IPG401> (accessed 26 February 2013).



## Appendix 7 PRISMA check list

Section/topic	No.	Checklist item	Reported on page
<b>Title</b>			
Title	1	Identify the report as a systematic review, meta-analysis or both	<i>Title page</i>
<b>Abstract</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	<i>Abstract and Executive summary</i>
<b>Introduction</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known	<i>Chapter 2, Conditions and aetiologies, and Chapter 2, Comparators,</i>
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes and study design (PICOS)	<i>Chapter 1, objective</i>
<b>Methods</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g. web address) and, if available, provide registration information including registration number	PROSPERO: CRD42011001694 ( <a href="http://www.crd.york.ac.uk/prospero/">www.crd.york.ac.uk/prospero/</a> ) NICE ( <a href="http://guidance.nice.org.uk/DT/6">http://guidance.nice.org.uk/DT/6</a> )
Eligibility criteria	6	Specify study characteristics (e.g. PICOS, length of follow-up) and report characteristics (e.g. years considered, language, publication status) used as criteria for eligibility, giving rationale	<i>Chapter 3, Inclusion and exclusion criteria,</i>
Information sources	7	Describe all information sources (e.g. databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	<i>Chapter 3, Search strategy,</i>
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	<i>Appendix 1</i>
Study selection	9	State the process for selecting studies (i.e. screening, eligibility, included in systematic review and, if applicable, included in the meta-analysis)	<i>Chapter 3, Inclusion screening and data extraction,</i>
Data collection process	10	Describe method of data extraction from reports (e.g. piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	<i>Chapter 3, Inclusion screening and data extraction,</i>
Data items	11	List and define all variables for which data were sought (e.g. PICOS, funding sources) and any assumptions and simplifications made	<i>Chapter 3, Inclusion screening and data extraction,</i>
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was carried out at the study or outcome level) and how this information is to be used in any data synthesis	<i>Chapter 3, Quality assessment,</i>



Section/topic	No.	Checklist item	Reported on page
Summary measures	13	State the principal summary measures (e.g. risk ratio, difference in means)	<i>Chapter 3, Methods of analysis/synthesis,</i>
Synthesis of results	14	Describe the methods for handling data and combining results of studies, if carried out, including measures of consistency (e.g. $I^2$ ) for each meta-analysis	<i>Chapter 3, Methods of analysis/synthesis,</i>
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g. publication bias, selective reporting within studies)	Not applicable
Additional analyses	16	Describe methods of additional analyses (e.g. sensitivity or subgroup analyses, meta-regression), if carried out, indicating which were prespecified	<i>Chapter 3, Results of the assessment of clinical effectiveness, Accuracy of SonoVue contrast-enhanced ultrasound for the characterisation of incidentally detected focal liver lesions</i>
<b>Results</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	<i>Chapter 3, Results of the assessment of clinical effectiveness, Figure 3 and Appendix 5</i>
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g. study size, PICOS, follow-up period) and provide the citations	<i>Appendix 4</i>
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12)	<i>Appendix 3 and Table 11</i>
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group; (b) effect estimates and CIs, ideally with a forest plot	<i>Chapter 3, Results of the assessment of clinical effectiveness, Tables 4, 6, 8, 10 and 12</i>
Synthesis of results	21	Present results of each meta-analysis carried out, including CIs and measures of consistency	<i>Chapter 3, Results of the assessment of clinical effectiveness, Figures 4 and 5</i>
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	Not applicable
Additional analysis	23	Give results of additional analyses, if carried out (e.g. sensitivity or subgroup analyses, meta-regression; see item 16)	<i>Chapter 3, Results of the assessment of clinical effectiveness, Accuracy of SonoVue contrast-enhanced ultrasound for the characterisation of incidentally detected focal liver lesions</i>
<b>Discussion</b>			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g. health-care providers, users and policy-makers)	<i>Chapter 5, Statement of principal findings,</i>
Limitations	25	Discuss limitations at the study and outcome level (e.g. risk of bias) and at the review level (e.g. incomplete retrieval of identified research, reporting bias)	<i>Chapter 5, Strengths and limitations of the assessment and Uncertainties,</i>
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	<i>Chapter 6,</i>
<b>Funding</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g. supply of data); role of funders for the systematic review	

# Appendix 8 Protocol

## Diagnostic Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence – Protocol

### 1. Title of project

SonoVue® (sulphur hexafluoride microbubbles) – contrast agent for contrast enhanced ultrasound in liver imaging.

### 2. Name of External Assessment Group (EAG) and project lead

Kleijnen Systematic Reviews Ltd Assessment Group.

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## Plain English Summary

Medical imaging, including ultrasound scanning, is important in diagnosing and planning treatment for a wide range of conditions including liver disease. Liver imaging will sometimes identify focal abnormalities in the liver which cannot be characterised initially and may need another test to fully explain the abnormality. The main aim of this subsequent liver imaging is to distinguish between liver cancers and benign abnormalities, which is not likely to require further treatment. Cancer in the liver is relatively rare and expert opinion suggests that 70 to 75% of liver abnormalities investigated in the NHS are found to be benign. One important factor in selecting an imaging test is 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 ultrasound scan. If the liver abnormality is not characterised by this test, the patient is usually referred for additional imaging using magnetic resonance imaging (MRI) and/or computed tomography (CT). This can lead to waits of several months with consequent distress to patients and families. In addition, there are potential drawbacks in using these other imaging techniques. CT uses ionising radiation and the intravenous contrast agent can, on rare occasions, cause kidney damage. Some patients cannot have an MRI scan due to pacemakers and others find the examination causes claustrophobia.

Imaging technology has developed very rapidly in recent years and contrast agents have been developed for use with ultrasound scanning. These contrast agents are injected, but remain in the patient's blood and are broken down by the body after a few minutes and breathed out as a gas. The use of contrast agents may improve the ability of ultrasound to distinguish between cancer in the liver and benign liver abnormalities and, because contrast enhanced ultrasound can be performed at the same appointment as conventional ultrasound, more rapid diagnoses may be possible and some CT and MRI examinations may be avoided.

The purpose of this project is to assess the benefits, risks and cost-effectiveness of contrast enhanced ultrasound using SonoVue® (Bracco UK Ltd) for the assessment of liver damage in adult patients.

### 3. Decision problem

#### 3.1 Objectives

To evaluate the clinical and cost effectiveness of contrast enhanced ultrasound (CEUS) using the contrast agent SonoVue® for the assessment of adults with focal liver lesions (FLL), in whom un-enhanced ultrasound or other liver imaging is inconclusive.

#### 4.2 Intervention technologies

SonoVue® (Bracco UK Ltd) is a contrast agent involving sulphur hexafluoride microbubbles for contrast enhanced ultrasound (CEUS) imaging in adults. It is used to enhance the echogenicity of the blood and can thus improve the signal to noise ratio in ultrasound. SonoVue® should only be used in patients where un-enhanced ultrasound is inconclusive.

SonoVue® product information lists its applications as:

- Echocardiography – provision of opacification of cardiac chambers and enhancement left ventricular echocardial border delineation in patients with suspected or known cardiovascular disease.
- Doppler ultrasound of the macrovasculature – detection or exclusion of abnormalities in the cerebral arteries, extra-cranial carotid arteries, or peripheral arteries.
- Doppler ultrasound of the microvasculature – visualising the vascularity of liver and breast lesions for lesion characterisation.

The focus of this assessment is CEUS of the liver.

SonoVue<sup>®</sup> consists of a kit containing a vial of sulphur hexafluoride gas and phospholipid powder, a pre-filled syringe of solvent (sodium chloride solution) and a transfer and ventilation system (mini spike). The saline is introduced into the vial by the mini spike delivery system and once reconstituted, microbubbles are formed. These microbubbles are the contrast agent which is injected into a peripheral vein at the ante cubital fossa. When the ultrasound probe is placed on the abdomen, ultrasound waves cause the microbubbles to resonate so that a signal is picked up by a transducer and an image is formed on a screen.

As this contrast agent is a pure blood pool agent it remains within the patient's blood vessels and, depending on the type of lesion, it shows a pattern of uptake similar to that of CT or MRI contrast agents. Generally for benign lesions the lesion will remain bright or isoechoic with the rest of the liver. For malignant lesions the area will wash out and leave a black hole.

The contrast agent is broken down by the body after a few minutes and the sulphur hexafluoride gas is exhaled through the lungs and the phospholipid component of the microbubble shell is metabolised (re-entering the endogenous phospholipid metabolic pathway). The adverse event rate associated with the use of SonoVue<sup>®</sup> for liver imaging is likely to be similar to or lower than that associated with other imaging modalities (CECT or CEMRI); a post-marketing study, published in 2006, included 23,188 abdominal investigations and reported adverse events in 29 cases, of which only two were graded as serious.<sup>1</sup>

SonoVue<sup>®</sup> is a second generation contrast agent. These agents have a flexible shell which allows continuous imaging (at a low mechanical index) without early destruction of the microbubble. First generation agents have now been superseded by second generation agents and are no longer available in Europe.

Other similar ultrasound contrast agents (e.g. Luminity<sup>®</sup>, Lantheus Medical Imaging and Optison<sup>®</sup>, GE Healthcare) are indicated for use in echocardiography only. Therefore, no equivalent alternative technologies will be considered in this assessment.

### 4.3 Population

The indication for this assessment is the detection and characterisation of FLLs in adults and the target condition is malignancies of the liver.

In this context, the term focal lesion in the liver refers to any focal area of perceived difference seen on an imaging study occurring in one specific area of the liver. FLLs can be broadly as benign (haemangioma, focal nodular hyperplasia, focal fatty infiltration or sparing and adenoma) or malignant (primary hepatocellular carcinoma, cholangiocarcinoma or liver metastases), with the detection or exclusion of malignancy being the primary aim of diagnostic imaging. The distinction between benign and malignant determines the individual's prognosis and the subsequent treatment strategy. Benign, asymptomatic liver lesions usually do not require any treatment. Depending on the specific type of lesion, the individual may be monitored and the lesion rescanned in 6 to 12 months. Once a malignant lesion is identified it is important to distinguish between primary and secondary cancers as this is likely to impact how the individual is managed. Malignant lesions may be treated by a range of interventions including chemotherapy, liver resection (surgery), and local ablative therapy. The treatment of primary hepatocellular carcinoma has been addressed in published guidelines,<sup>2,3</sup> and NICE has issued guidance on a number of individual interventions for primary hepatocellular carcinoma and liver metastases (see *Appendix 1*). However, expert opinion suggests that practice within the NHS may vary significantly across regions based on clinician preference.

Although liver cancer is rare in the UK, (age-standardised rates are 4.7 per 100,000 males and 2.9 per 100,000 females)<sup>4</sup> it is the second fastest increasing cancer in males and the third fastest in females, (increases of 38% and 28%, respectively, in the last decade).<sup>5</sup> In addition, expert opinion suggests that as many as 70 to 75% of FLLs assessed in the NHS may be benign. One possible benefit of CEUS may therefore be rapid rule-out of malignancy, with associated reduction in anxiety for patients and families;

current practice of referring patients with inconclusive un-enhanced ultrasound for contrast enhanced magnetic resonance imaging (CEMRI) and/or contrast enhanced computed tomography (CECT), may result in a wait of several months.

The European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) produced guidelines and good clinical practice recommendations for CEUS in 2004. The latest version of the guidelines was published in 2008.<sup>6</sup> The 2008 version of the EFSUMB guidelines are currently being updated. The 2008 EFSUMB guidelines recommend the use of CEUS for the characterisation of FLL in the following indications:

- patients with incidental findings on routine ultrasound
- investigation of lesions or suspected lesions in chronic hepatitis or liver cirrhosis
- investigation of lesions or suspected lesions in patients with a history of malignancy
- patients with inconclusive MRI/CT or cytology/histology results
- characterisation of portal vein thrombosis

and for the detection of FLL in the following indications:

- to rule-out liver metastases
- in selected cases, when clinically relevant for treatment planning and as a complement to CECT and/or CEMRI, to assess the number and location of liver metastases
- surveillance of patients with known malignancy
- suspected cholangiocarcinoma, where other imaging is inconclusive
- suspected liver trauma (in some situations)

Because SonoVue<sup>®</sup> should be used only where un-enhanced ultrasound is inconclusive, we consider its primary application to be for the characterisation of lesions (benign or malignant) in patients with known FLLs; most patients who have already undergone un-enhanced ultrasound and who have proceeded to CEUS are likely to have FLLs (seen at un-enhanced ultrasound), the nature of which remains uncertain. Other, relevant applications include the detection of specific types of malignant FLL (e.g. liver metastases, recurrent or residual disease following treatment of a known malignancy). CEUS may also identify additional FLLs over and above those detected on un-enhanced ultrasound. A recent systematic review reported

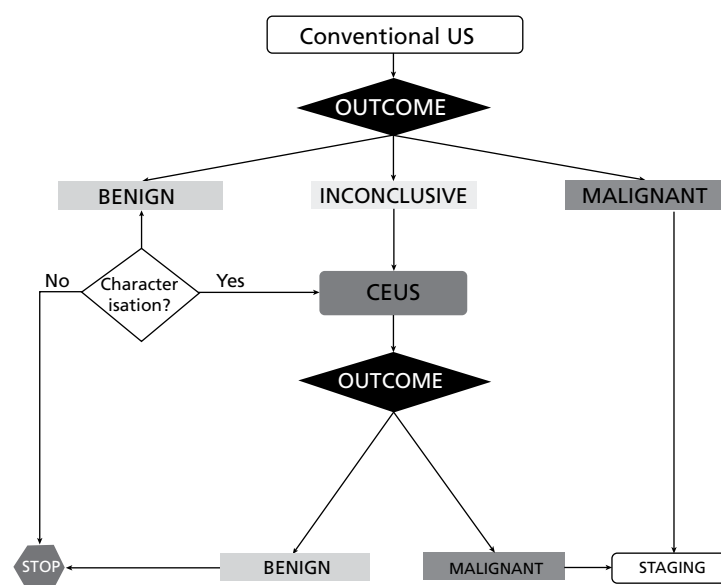
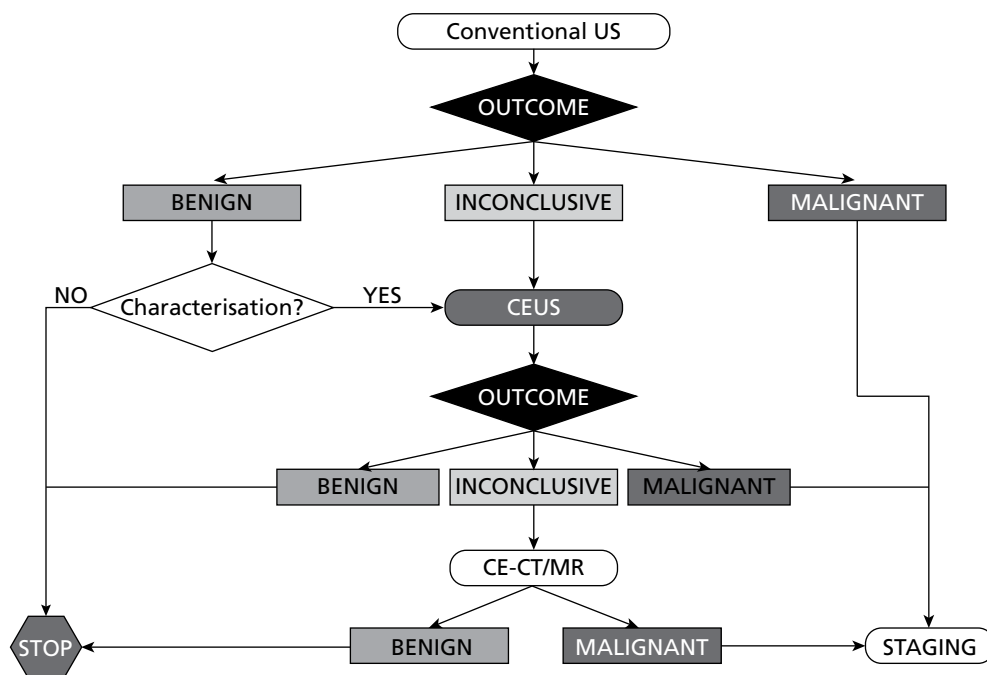


FIGURE 1



**FIGURE 2** Diagnostic algorithm for liver imaging – CEUS as a triage test to reduce the use of CECT/CEMRI.

ranges for the sensitivity and specificity of SonoVue® CEUS for the detection of liver metastases as 79% to 100% and 95% to 100% respectively,<sup>7</sup> and initial scoping searches have identified studies assessing the accuracy of SonoVue® CEUS for the detection of residual disease post-treatment.<sup>8,9</sup>

#### 4.4 Relevant comparators

Patients with inconclusive un-enhanced ultrasound are currently referred for CECT and/or CEMRI. The comparators for this assessment are therefore CECT and CEMRI. A recent systematic review compared the accuracy of SonoVue® CEUS, CECT and CEMRI for the differentiation of malignant and benign liver lesions. The reported sensitivities were 88% (95% CI 79% to 84%), 90% (95% CI 88% to 92%) and 86% (95% CI 83% to 88%), respectively, and the corresponding specificities were 81% (95% CI 79% to 84%), 77% (95% CI 71% to 82%) and 81% (95% CI 76% to 85%).<sup>10</sup> However, these data were based on indirect comparisons. CEUS could be included in the diagnostic pathway as a replacement for CECT/CEMRI (Figure 1), or as a triage step to reduce the use of CECT/CEMRI (Figure 2).

Expert opinion has indicated that biopsy would not be performed on the basis of un-enhanced ultrasound examination alone, therefore, biopsy alone is not a relevant comparator for CEUS.

## 5. Report methods for assessing clinical effectiveness

A systematic review will be conducted to summarise the evidence on the clinical effectiveness of SonoVue® CEUS for the assessment of focal liver lesions in adults in whom liver imaging with un-enhanced ultrasound has been inconclusive. Systematic review methods will follow the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care<sup>11</sup> and NICE Diagnostic Assessment Programme interim methods statement.<sup>12</sup>

### 5.1 Inclusion and exclusion criteria

#### Participants

Study populations eligible for inclusion will be:

Adults ( $\geq 18$  years) in whom liver imaging with un-enhanced ultrasound or other liver imaging has been inconclusive, including patients being assessed for:

- Suspected primary hepatocellular carcinoma
- Suspected secondary malignancy (liver metastases)
- Response to treatment/recurrence of known liver malignancy

### Setting

Relevant settings are secondary or tertiary care.

### Interventions (index test(s))

SonoVue® CEUS

### Comparators

Comparators eligible for inclusion will be:

- Contrast enhanced computed tomography (CECT)
- Contrast enhanced magnetic resonance imaging (CEMRI)

### Reference standard

The reference standard for a positive diagnosis will be histology following biopsy or surgical excision. Patients who test negative on the index test will generally not undergo biopsy or surgical treatment; clinical/radiological follow-up for a minimum of six months will therefore be considered an acceptable reference standard in these patients.

This criterion has been extended, for studies on the characterisation of FLLs only (suspected HCC), to include studies which use EASL/AASLD non-invasive diagnostic criteria (two concordant imaging test results) as the reference standard. This modification does not apply to test accuracy studies on the detection of liver metastases. This extension of the inclusion criteria was made because clinical opinion indicated that biopsy of small test positive lesions may be considered un-ethical in this population and that the original criterion (biopsy for imaging test positive patients/lesions and 6 months follow-up for imaging test negative patients/lesions) may, therefore, result in important studies being excluded.

### Outcomes

The following outcomes will be considered:

- Effect of testing on treatment plan (e.g. surgical or medical management, or palliative care), where information on the appropriateness of the final treatment plan is also reported
- Effect of testing on clinical outcome, (e.g. overall survival, progression free survival)
- Prognosis – the ability of test result to predict clinical outcome (e.g. overall survival, progression free survival, response to treatment)
- Test accuracy and number of patients/lesions classified as non-diagnostic by SonoVue® CEUS.

For included studies reporting any of the above outcome measures, the following outcomes will also be considered if reported:

- Acceptability of tests to patients or surrogate measures of acceptability (e.g. waiting time and associated anxiety).
- Adverse events associated with testing (e.g. claustrophobia, reaction to contrast media).
- Additional FLLs detected by CEUS, over and above those seen on un-enhanced ultrasound.

Radiation exposure is not considered a relevant outcome, as the population is mostly older adults in whom additional incident cancers due to imaging-related radiation are likely to be minimal. In addition a previous

technology assessment (new generation CT for cardiac imaging) showed that including radiation exposure in modelling did not influence the results of cost-effectiveness analyses.<sup>13</sup>

### Study design

The following types of studies will be included:

- Randomised or non-randomised controlled trials, where participants are assigned to the intervention or comparator tests, for treatment planning, and outcomes are compared at follow-up.
- Observational studies which report the results of multi-variable regression modelling with clinical outcome (e.g. survival, response to treatment) as the dependent variable and index test and comparator test results as independent variables. Included studies should control adequately for potential confounders (e.g. age, tumour stage, previous treatment, results of other imaging).
- Test accuracy studies, where the index test is compared with one or more of the comparators and the reference standard. Test accuracy studies of the index test alone will be included if they are conducted in patients who have previously undergone one or more of the comparator tests (e.g. a study of the accuracy of Sonovue for the diagnosis of HCC in patients with inconclusive findings on CECT), as these studies may inform cost-effectiveness modelling.

Test accuracy studies, will be required to report the absolute numbers of true-positive, false-negative, false-positive, and true-negative index test results, or sufficient information to allow their calculation. If data are incomplete, study authors will be contacted to seek clarification, where practical.

The following study/publication types will be excluded:

- Pre-clinical and animal
- Reviews, editorials, and opinion pieces
- Case reports
- Studies reporting only technical aspects of the test, or image quality
- Studies with < 10 participants

### 5.2 Search strategy

Search strategies will be based on target condition and intervention, as recommended in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.<sup>11,14,15</sup>

Additional supplementary searches will be carried out as necessary. Searches for studies for cost and quality of life will also be included, see Section 6 for further detail.

The following databases will be searched for relevant studies from 2000 to the present:

- MEDLINE (OvidSP)
- MEDLINE In-Process Citations and Daily Update (OvidSP)
- EMBASE (OvidSP)
- Cochrane Database of Systematic Reviews (CDSR) (Internet)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Internet)
- Database of Abstracts of Reviews of Effects (DARE) (Internet)
- Health Technology Assessment Database (HTA) (Internet)
- Science Citation Index (SCI) (Web of Science)
- NIHR Health Technology Assessment Programme (Internet)

Completed and ongoing trials will be identified by searches of the following resources (2000–2011):

- NIH ClinicalTrials.gov (<http://www.clinicaltrials.gov/>)



- Current Controlled Trials (<http://www.controlled-trials.com/>)
- WHO International Clinical Trials Registry Platform (ICTRP) (<http://www.who.int/ictcp/en/>)
- EU Clinical Trials Register (<https://www.clinicaltrialsregister.eu/>)

Key conference proceedings, to be identified in consultation with clinical experts, will be screened for the last five years. These may include British Medical Ultrasound Society, European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) EUROSON congress.

Identified references will be downloaded in Endnote X4 software for further assessment and handling.

References in retrieved articles and relevant systematic reviews will be checked.

Search strategies will be developed specifically for each database and the keywords associated with liver malignancies shall be adapted according to the configuration of each database.

No restrictions on language or publication status will be applied. Limits will be applied to remove animal and phantom studies. Searches will take into account generic and other product names for the intervention. Examples of the search strategies to be used are presented in *Appendix 1*; these will be adapted as necessary following consultation with clinical experts.

### 5.3 Data extraction strategy

Two reviewers will independently screen titles and abstracts of all reports identified by searches and discrepancies will be discussed. Full copies of all studies deemed potentially relevant, after discussion, will be obtained and two reviewers will independently assess these for inclusion; any disagreements will be resolved by consensus or discussion with a third reviewer.

Data relating to study details, participants, intervention and comparator tests, reference standard, and outcome measures will be extracted by one reviewer, using a piloted, standard data extraction form. A second reviewer will check data extraction and any disagreements will be resolved by consensus or discussion with a third reviewer.

### 5.4 Quality assessment strategy

The methodological quality of included studies will be assessed using standard tools.<sup>11</sup> The QUADAS tool,<sup>16,17</sup> has been recommended for assessing the methodological quality of test accuracy studies.<sup>11,14</sup> A revised version of QUADAS (QUADAS-2) has recently been released [www.QUADAS.org](http://www.QUADAS.org).<sup>18</sup> QUADAS-2 more closely resembles the approach and structure of the Cochrane risk of bias tool. The QUADAS-2 tool will be used in this assessment.

The results of the quality assessment will be used for descriptive purposes to provide an evaluation of the overall quality of the included studies and to provide a transparent method of recommendation for design of any future studies. In addition, if enough data are available from the included studies, quality components will be included as covariates in SROC models, to investigate their possible association with test performance. Based on the findings of the quality assessment, recommendations will be made for the conduct of future studies.

### 5.5 Methods of analysis/synthesis

The results of initial scoping searches suggest that trial data and prognostic data are likely to be sparse or non-existent. This section therefore focuses on the synthesis of data from test accuracy studies. If other studies are identified, we anticipate that these will be summarised in a narrative synthesis.

Where meta-analysis is considered unsuitable for some or all of the data identified (e.g. due to the heterogeneity and/or small numbers of studies), we will employ a narrative synthesis. Typically, this will involve the use of text and tables to summarise data. These will allow the reader to consider any outcomes

in the light of differences in study designs and potential sources of bias for each of the studies being reviewed. Studies will be organised by clinical application (diagnosis of primary hepatocellular carcinoma, diagnosis of liver metastases, assessment of treatment response/recurrence).

Any data included on the following outcome measures: effects of testing on treatment planning and/or clinical outcome; adverse events associated with testing; acceptability to patients will be summarized according to the size and range of the outcomes reported. For test accuracy data, absolute numbers of true-positive, false-negative, false-positive and true-negative test results, as well as sensitivity and specificity values, with 95% confidence intervals will be presented for each study and patient group reported.

Where appropriate, and where sufficient accuracy data are available, summary receiver operating characteristic (SROC) curves will be calculated to summarise test accuracy data. SROC modelling will use the bivariate approach.<sup>19–21</sup> Potential sources of heterogeneity will be investigated by extending SROC models to include study level covariates, (e.g. participant age, tumour stage, hepatitis status, cirrhosis status); the bivariate approach to modelling allows investigation of the effects of covariates on sensitivity and specificity separately.

Where data are insufficient to support meta-analyses, the following graphical representations will be presented: plots in ROC space (without summary curves) for test accuracy data; forest plots for any trial data.

A detailed commentary on the major methodological problems or biases that affected the studies will also be included, together with a description of how this may have affected the individual study results. Recommendations for further research will be made based on any gaps in the evidence or methodological flaws.

## 6. Report methods for synthesising evidence of cost-effectiveness

### 6.1 Identifying and reviewing published cost-effectiveness studies

Exploration of the literature regarding published economic evaluations, utility studies and cost studies will be performed in the literature databases listed above. In addition, specific health economic databases will be searched (e.g. NHSEED (NHS Economic Evaluation Database), and HEED (Health Economic Evaluation Database); an example search strategy is included in *Appendix 1*. Searches will focus on original papers that report on cost, cost-accuracy, cost-effectiveness or cost-utility analyses, either studying the diagnostic phase (patients with FLLs and inconclusive un-enhanced ultrasound), therapeutic phase (patients with liver malignancy), or a combination. For our assessment cost studies, utility studies and full economic evaluations, i.e. those that explicitly compare different decision options will be selected. Clinical trials as well as modelling studies and cohort studies will be relevant within the frame of our project. The intention is not to perform a systematic review, but to use the studies identified to support the development of an economic model and estimation of model input parameters that will aim to answer the research questions of this project.

The results and the methodological quality of the studies selected will be summarised. Assessment of methodological quality will follow the criteria for economic evaluations in health care as described in the NICE methodological guidance.<sup>12</sup> Data extraction will focus on technologies compared, indicated population, main results in terms of costs and consequences of the alternatives compared, and the incremental cost-effectiveness, but also on methods of modelling used (if applicable), analytical methods and robustness of the study findings.

## 6.2 Evaluation of costs, quality of life and cost-effectiveness

Decision analytic modelling will be undertaken to determine the cost-effectiveness of SonoVue® CEUS for the assessment of focal liver lesions in adults in whom liver imaging with un-enhanced ultrasound has been inconclusive. The analysis will consider the consequences of diagnostic accuracy, treatment planning, and QALYs.

### Potential diagnostic strategies

Depending on the nature of the FLL and local practice within the NHS a range of typical diagnostic strategies may emerge as current practice, which may include CECT and/or CEMRI.

The following possible diagnostic strategies arise when assessing the role of CEUS for the assessment of focal liver lesions in adults in whom liver imaging with un-enhanced ultrasound has been inconclusive:

- CEUS
- CEUS\* → CECT
- CEUS\* → CEMRI

\*Additional examination, to be conducted if previous one was not conclusive.

Comparators to be included in the model may depend on the availability of data.

### Model structure

Published studies that measure the clinical utility of SonoVue® CEUS from initial diagnosis through to final health outcomes have not been identified during the scoping phase. Consequently, it is likely that a linked evidence approach will need to be used in the modelling. That is, outcomes of the diagnostic tests to be assessed will need to be related to changes in treatment decisions, any delays in diagnosis and final health outcomes. Necessary choices and definitions regarding the structure of the model will depend on the findings from the literature review and consultation with clinical experts. In addition, the existence/availability of any other electronic models that reflect the cost-effectiveness of treatment pathways for these patients, and are representative of current care within the NHS, will be determined.

Issues relevant to analyses:

- Longer term costs and consequences will be discounted using the UK discount rates of 3.5% of both costs and effects.
- One way sensitivity analyses will be performed for all key parameters, especially for parameters in the models which are based on expert opinion.
- Probabilistic sensitivity analyses will be performed using parameter distributions instead of fixed values.
- Decision uncertainty regarding mutually exclusive alternatives will be reflected using cost-effectiveness planes and cost-effectiveness acceptability curves.

A simple draft model structure is presented (*Appendix 3*); this may be developed/expanded as indicated (*Appendix 3*) and as available data allow.

### Health outcomes

Utility values, based on literature or other sources, will be incorporated in the economic model. QALYs will be calculated from the economic modelling.

### Costs

Resource utilisation will be estimated for the diagnostic tests and treatments. Data for the cost analyses will be drawn from routine NHS sources (e.g. NHS reference costs, Personal Social Services Research Unit (PSSRU), British National Formulary (BNF)), discussions with individual hospitals and with the manufacturers of the comparators.

## 7. Handling of information from the companies

All data submitted by the manufacturers/sponsors will be considered if received by the EAG no later than 05/12/2011. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol.

Any 'commercial in confidence' data provided by manufacturers, and specified as such, will be highlighted in blue and underlined in the assessment report (followed by company name in parentheses). Any 'academic in confidence' data provided by manufacturers, and specified as such, will be highlighted in yellow and underlined in the assessment report. Any confidential data used in the cost-effectiveness models will also be highlighted.

## 8. Competing interests of authors

None

## 9. Timetable/milestones

Milestones	Completion data
Draft protocol	16/09/2011
Final protocol	14/10/2011
Progress report	w/c 05/12/2011
Draft assessment report	27/01/2012
Final assessment report	27/02/2012

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## APPENDIX 1

## Clinical effectiveness search

*Medline (OvidSP): 2000–2011/09/wk 1*

Searched 15.9.11

1. neoplasm metastasis/ or neoplasm seeding/ or neoplasms, unknown primary/ (78927)
2. (Metasta\$ or meta-sta\$).ti,ab,ot,hw. (309063)
3. or/1-2 (311269)
4. (liver or hepato\$ or hepatic\$).ti,ab,ot,hw. (864813)
5. 3 and 4 (45882)
6. exp Liver Neoplasms/ (112164)
7. exp Bile Duct Neoplasms/ (11889)
8. Carcinoma, Hepatocellular/ (50647)
9. (FLL or FLLs).ti,ab,ot. (95)
10. Cholangiocarcinoma/ (4109)
11. ((liver\$ or hepat\$) adj3 (cancer\$ or met\$ or malignan\$ or carcinoma\$ or tumo?r\$ or neoplas\$ or adeno\$ or angiom\$ or sarcoma\$ or angiosarcoma\$)).ti,ab,ot,hw. (168313)
12. (hepatoma\$ or h?emangiosarcoma\$ or h?emangio-sarcoma\$).ti,ab,ot,hw. (27634)
13. (Focal liver lesion\$ and (cancer\$ or met or mets or metasta\$ or malignan\$ or carcinoma\$ or tumo?r\$ or neoplas\$ or adeno\$ or angiom\$ or sarcoma\$ or angiosarcoma\$)).ti,ab,ot,hw. (711)
14. (BFLL or BFLLS).ti,ab,ot. (3)
15. (HCC or HCCs).ti,ab,ot. (18590)
16. (Cholangiocarcinoma\$ or Cholangio-carcinoma\$).ti,ab,ot,hw. (6158)
17. (Bile duct\$ adj3 (cancer\$ or met\$ or malignan\$ or lesion\$ or carcinoma\$ or tumo?r\$ or neoplas\$ or adeno\$ or angiom\$ or sarcoma\$)).ti,ab,ot,hw. (14419)
18. or/5-17 (198600)
19. ultrasonography/ or ultrasonography, doppler/ or exp ultrasonography, doppler, duplex/ or exp ultrasonography, doppler, pulsed/ (89506)
20. ((ultrasonic\$ or ultra-sonic\$) adj4 (scan or imag\$ or echogram\$ or sonogra\$ or detect\$ or diagnos\$ or exam\$)).ti,ot,ab,hw. (6793)
21. (ultraso\$ or ultra-so\$ or sonogra\$ or Echotomogra\$ or Echo-tomogra\$ or echoscope\$ or echosound\$ or Echogra\$ or tomoechogra\$ or tomo-echogra\$).ti,ot,ab,hw. (274775)
22. or/19-21 (279114)
23. Sulfur Hexafluoride/ (1474)
24. (hexafluoruro-sulfurico or SF6 or SF-6 or sulphur hexafluoride\$ or sulphur hexafluoride\$ or sulfur hexafluoride\$ or sulfur hexafluoride\$).af. (2133)
25. or/23-24 (2133)
26. 22 and 25 (658)
27. (Sonovue or sono-vue or Sonavoid or Sonogen or sonagen or Sonavist).af. (499)
28. (CE-US or CEUS).ti,ab,ot. (516)
29. ((hexafluoruro-sulfurico or SF6 or SF-6) adj4 (US or ultraso\$ or ultra-so\$ or sonogra\$ or Echotomogra\$ or Echo-tomogra\$ or echoscop\$ or echosound\$ or Echogra\$ or tomoechogra\$ or tomo-echogra\$ or imag\$)).af. (7)
30. ((Sulfur or Sulphur) adj2 (hexafluoride\$ or hexa-fluoride\$) adj4 (US or ultraso\$ or ultra-so\$ or sonogra\$ or Echotomogra\$ or Echo-tomogra\$ or echoscop\$ or echosound\$ or Echogra\$ or tomoechogra\$ or tomo-echogra\$ or imag\$)).af. (28)
31. (SF6US or SF6-US or SF-6US or SF-6-US).af. (0)
32. ((SF6 or SF6 or sulphur hexafluoride\$ or sulphur hexafluoride\$ or sulfur hexafluoride\$ or sulfur hexafluoride\$) adj4 (bubbl\$ or microbubbl\$ or micro-bubbl\$ or micropartic\$ or micro-partic\$)).af. (213)

33. or/27-32 (991)
34. 26 or 33 (1183)
35. 18 and 34 (365)
36. exp Liver Neoplasms/us (2702)
37. Carcinoma, Hepatocellular/us (1258)
38. exp Bile Duct Neoplasms/us (375)
39. Cholangiocarcinoma/us (137)
40. Neoplasm Metastasis/us (51)
41. Neoplasm Seeding/ra (1)
42. Neoplasms, Unknown Primary/us (21)
43. or/36-42 (3089)
44. 25 and 43 (162)
45. 35 or 44 (366)
46. limit 45 to yr="2000 -Current" (361)
47. animals/ not (animals/ and humans/) (3586762)
48. 46 not 47 (340)

## Economic evaluations search

### Medline (OvidSP): 2000–2011/09/wk 1

Searched 15.9.11

1. economics/ (26160)
2. exp "costs and cost analysis"/ (159824)
3. economics, dental/ (1851)
4. exp "economics, hospital"/ (17418)
5. economics, medical/ (8505)
6. economics, nursing/ (3853)
7. economics, pharmaceutical/ (2276)
8. (economic\$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\$).ti,ab. (345758)
9. (expenditure\$ not energy).ti,ab. (14613)
10. (value adj1 money).ti,ab. (20)
11. budget\$.ti,ab. (14766)
12. or/1-11 (459756)
13. ((energy or oxygen) adj cost).ti,ab. (2351)
14. (metabolic adj cost).ti,ab. (614)
15. ((energy or oxygen) adj expenditure).ti,ab. (13513)
16. or/13-15 (15852)
17. 12 not 16 (456159)
18. letter.pt. (726087)
19. editorial.pt. (283742)
20. historical article.pt. (279927)
21. or/18-20 (1276679)
22. 17 not 21 (431461)
23. neoplasm metastasis/ or neoplasm seeding/ or neoplasms, unknown primary/ (78927)
24. (Metasta\$ or meta-sta\$).ti,ab,ot,hw. (309063)
25. or/23-24 (311269)
26. (liver or hepato\$ or hepatic\$).ti,ab,ot,hw. (864813)
27. 25 and 26 (45882)
28. exp Liver Neoplasms/ (112164)
29. exp Bile Duct Neoplasms/ (11889)

30. Carcinoma, Hepatocellular/ (50647)
31. (FLL or FLLs).ti,ab,ot. (95)
32. Cholangiocarcinoma/ (4109)
33. ((liver\$ or hepat\$) adj3 (cancer\$ or met\$ or malignan\$ or carcinoma\$ or tumor?r\$ or neoplas\$ or adeno\$ or angioma\$ or sarcoma\$ or angiosarcoma\$)).ti,ab,ot,hw. (168313)
34. (hepatoma\$ or h?emangiosarcoma\$ or h?emangio-sarcoma\$).ti,ab,ot,hw. (27634)
35. (Focal liver lesion\$ and (cancer\$ or met or mets or metasta\$ or malignan\$ or carcinoma\$ or tumor?r\$ or neoplas\$ or adeno\$ or angioma\$ or sarcoma\$ or angiosarcoma\$)).ti,ab,ot,hw. (711)
36. (BFL or BFLLS).ti,ab,ot. (3)
37. (HCC or HCCs).ti,ab,ot. (18590)
38. (Cholangiocarcinoma\$ or Cholangio-carcinoma\$).ti,ab,ot,hw. (6158)
39. (Bile duct\$ adj3 (cancer\$ or met\$ or malignan\$ or lesion\$ or carcinoma\$ or tumor?r\$ or neoplas\$ or adeno\$ or angioma\$ or sarcoma\$)).ti,ab,ot,hw. (14419)
40. or/27-39 (198600)
41. ultrasonography/ or ultrasonography, doppler/ or exp ultrasonography, doppler, duplex/ or exp ultrasonography, doppler, pulsed/ (89506)
42. ((ultrasonic\$ or ultra-sonic\$) adj4 (scan or imag\$ or echogram\$ or sonogra\$ or detect\$ or diagnos\$ or exam\$)).ti,ot,ab,hw. (6793)
43. (ultraso\$ or ultra-so\$ or sonogra\$ or Echotomogra\$ or Echo-tomogra\$ or echoscope\$ or echosound\$ or Echogra\$ or tomoechogra\$ or tomo-echogra\$).ti,ot,ab,hw. (274775)
44. or/41-43 (279114)
45. Sulfur Hexafluoride/ (1474)
46. (hexafluoruro-sulfurico or SF6 or SF-6 or sulphur hexafluoride\$ or sulphur hexafluoride\$ or sulfur hexafluoride\$ or sulfur hexafluoride\$).af. (2133)
47. or/45-46 (2133)
48. 44 and 47 (658)
49. (Sonovue or sono-vue or Sonavoid or Sonogen or sonagen or Sonavist).af. (499)
50. (CE-US or CEUS).ti,ab,ot. (516)
51. ((hexafluoruro-sulfurico or SF6 or SF-6) adj4 (US or ultraso\$ or ultra-so\$ or sonogra\$ or Echotomogra\$ or Echo-tomogra\$ or echoscop\$ or echosound\$ or Echogra\$ or tomoechogra\$ or tomo-echogra\$ or imag\$)).af. (7)
52. ((Sulfur or Sulphur) adj2 (hexafluoride\$ or hexa-fluoride\$) adj4 (US or ultraso\$ or ultra-so\$ or sonogra\$ or Echotomogra\$ or Echo-tomogra\$ or echoscop\$ or echosound\$ or Echogra\$ or tomoechogra\$ or tomo-echogra\$ or imag\$)).af. (28)
53. (SF6US or SF6-US or SF-6US or SF-6-US).af. (0)
54. ((SF6 or SF6 or sulphur hexafluoride\$ or sulphur hexafluoride\$ or sulfur hexafluoride\$ or sulfur hexafluoride\$) adj4 (bubbl\$ or microbubbl\$ or micro-bubbl\$ or micropartic\$ or micro-partic\$)).af. (213)
55. or/49-54 (991)
56. 48 or 55 (1183)
57. 40 and 56 (365)
58. exp Liver Neoplasms/us (2702)
59. Carcinoma, Hepatocellular/us (1258)
60. exp Bile Duct Neoplasms/us (375)
61. Cholangiocarcinoma/us (137)
62. Neoplasm Metastasis/us (51)
63. Neoplasm Seeding/ra (1)
64. Neoplasms, Unknown Primary/us (21)
65. or/58-64 (3089)
66. 47 and 65 (162)
67. 57 or 66 (366)
68. limit 67 to yr="2000 -Current" (361)
69. animals/ not (animals/ and humans/) (3586762)



70. 68 not 69 (340)

71. 22 and 70 (19)

Economics filter:

Centre for Reviews and Dissemination. NHS EED Economics Filter: Medline (Ovid) monthly search [Internet]. York: Centre for Reviews and Dissemination; 2010 [cited 28.9.10]. Available from: [http://www.york.ac.uk/inst/crd/intertasc/nhs\\_eed\\_strategies.html](http://www.york.ac.uk/inst/crd/intertasc/nhs_eed_strategies.html)

## APPENDIX 2

### **NICE guidelines on interventions for the treatment of liver malignancies.**

1. Cryotherapy for the treatment of metastases. NICE interventional procedure guidance 369 (2010). Available from <http://guidance.nice.org.uk/IPG369>
2. Ex-vivo hepatic resection and reimplantation for liver cancer. NICE interventional procedure guidance 298 (2009). Available from <http://guidance.nice.org.uk/IPG298>
3. Laparoscopic liver resection. NICE interventional procedure guidance 135 (2005). Available from <http://guidance.nice.org.uk/IPG135>
4. Microwave ablation for the treatment of liver metastases. NICE interventional procedure guidance 406 (2011). Available from <http://guidance.nice.org.uk/IPG406>
5. Microwave ablation of hepatocellular carcinoma. NICE interventional procedure guidance 214 (2007). Available from <http://guidance.nice.org.uk/IPG214>
6. Radiofrequency ablation of hepatocellular carcinoma. NICE interventional procedure guidance 2 (2003). Available from <http://guidance.nice.org.uk/IPG2>
7. Radiofrequency-assisted liver resection. NICE interventional procedure guidance 211 (2007). Available from <http://guidance.nice.org.uk/IPG211>
8. Selective internal radiation therapy for non-resectable colorectal metastases in the liver. NICE interventional procedure guidance 401 (2011). Available from <http://guidance.nice.org.uk/IPG401>

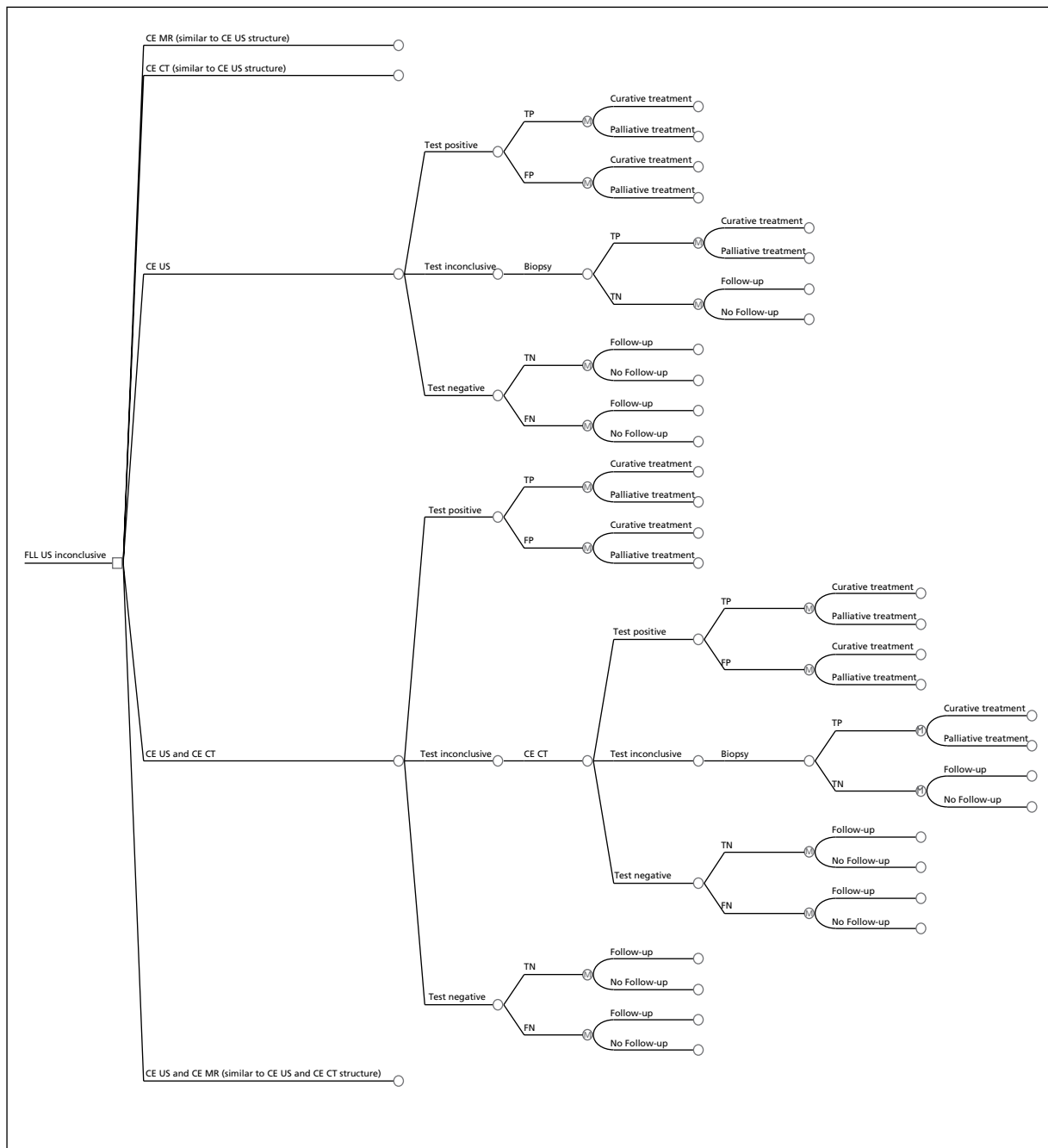
## APPENDIX 3

## Draft model structure

Different types of FLL have not yet been included in this structure. This information could be added, if evidence is available.

There seems to be reasonable possibility of detecting false test results in the course of treatment/ follow up. This is not yet incorporated in the model, but may potentially influence the outcomes of the analysis considerably.

Direct health effects of the diagnostic procedures are not yet included, this could be done if relevant.







A decorative graphic consisting of numerous thin, parallel green lines that curve from the left side of the page towards the right, creating a sense of movement and depth.

**EME  
HS&DR  
HTA  
PGfAR  
PHR**

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