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

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Authors
Marie Westwood, Review Manager, Kleijnen Systematic Reviews Ltd, UK
Manuela Joore, Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Centre, the Netherlands
Janneke Grutters, Research Fellow, Department of Health Services Research, Maastricht University, the Netherlands
Ken Redekop, Associate Professor, Institute for Medical Technology Assessment, Erasmus University, Rotterdam, the Netherlands
Nigel Armstrong, Health Economist, Kleijnen Systematic Reviews Ltd, UK
Kelly Lee, Health Economist, Kleijnen Systematic Reviews Ltd, UK
Viktoria Gloy, Researcher, Basel Institute of Clinical Epidemiology and Biostatistics, University Hospital Basel, Switzerland
Heike Raatz, Research Associate, Basel Institute of Clinical Epidemiology and Biostatistics, University Hospital Basel, Switzerland
Kate Misso, Information Specialist, Kleijnen Systematic Reviews Ltd, UK
Johan Severens, Professor of Evaluation in Healthcare, Institute of Health Policy and Management, Erasmus university Rotterdam, the Netherlands
Jos Kleijnen, Director, Kleijnen Systematic Reviews Ltd, UK

Correspondence to
Marie Westwood
Kleijnen Systematic Reviews Ltd
Unit 6, Escrick Business Park
Riccall Road
Escrick
York YO19 6FD
Tel: 01904 727983
Email: marie@systematic-reviews.com

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Contributions 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 results. Nigel Armstrong and Kelly Lee contributed to planning and interpretation of 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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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 x-ray 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 e.g. 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 healthcare 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 (ICER)	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 which 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 analytic 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 costs	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 their ability to perform the ordinary tasks of living.
Quality-adjusted life year (QALY)	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 where tumour tissue is ablated using the heat generated from the high frequency alternating current.
Receiver Operating Characteristic (ROC) curve	A graph which illustrates the trade-offs between sensitivity and specificity which 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 (TACE)	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-diseases persons with a negative test result.
True positive	Correct positive test result – number of diseased persons with a positive test result.

LIST OF ABBREVIATIONS

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader.

AASLD	American Association for the Study of Liver Diseases
AFP	alpha-fetoprotein
ALT	alanine aminotransferase
ASP	aspartate aminotransferase
CCC	cholangiocarcinoma
CEA	carcinoembryonic antigen
CEAC	cost-effectiveness acceptability curve
CECT	contrast enhanced computed tomography
CEMRI	contrast enhanced magnetic resonance imaging
CEUS	contrast enhanced ultrasound
CI	confidence interval
CRC	colorectal carcinoma
CT	computed tomography
DPTA	diethyl triamine pentaacetic acid
DTA	diagnostic test accuracy
EASL	European Association for the Study of the Liver
FLL	focal liver lesion
FN	false negative
FNB	fine-needle biopsy
FNH	focal nodular hyperplasia
FP	false positive
Gd-CEMRI	gadolinium contrast-enhanced magnetic resonance imaging
Gd-EOB-DTPA	gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid
γ-GT	gamma glutamyltransferase
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HRQoL	Health-Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
MDCT	multi-detector computed tomography
MRI	magnetic resonance imaging
NA	not applicable
NR	not reported
OR	odds ratio
PEI	percutaneous ethanol injection
PMAT	percutaneous microwave ablation therapy
PMCT	percutaneous microwave coagulation therapy
QALY	Quality-Adjusted Life Year
QUADAS	Quality Assessment of Diagnostic Accuracy Studies tool
RFA	radiofrequency ablation
RN	regenerative nodule
ROC	Receiver Operating Characteristic

RON	Romanian New Leu
SCT	spiral computed tomography
SPIO-CEMRI	superparamagnetic iron oxide contrast-enhanced magnetic resonance imaging
SROC	Summary Receiver Operating Characteristic
TACE	transarterial chemoembolisation
TFE	turbo field echo
TNM	Tumour lymph Node Metastasis
TSE	turbo spin echo
TN	true negative
TP	true positive
US	ultrasound

1 EXECUTIVE SUMMARY

1.1 Background

Ultrasound scanning, along with other imaging technologies such as computed tomography (CT) and magnetic resonance imaging (MRI) are important in diagnosing and planning treatment for many patients with liver disease. Liver imaging will sometimes identify focal abnormalities in the liver which cannot be characterised initially and another test may therefore be needed to fully explain the abnormality. The main aim of this subsequent liver imaging is to distinguish between liver cancers and benign abnormalities which are 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 un-enhanced ultrasound (US) scan. If the liver abnormality is not characterised by this test, the patient is usually referred for additional imaging using MRI and/or 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.

1.2 Objectives

To compare the clinical and cost-effectiveness of contrast enhanced ultrasound (CEUS) using the contrast agent SonoVue® with contrast-enhanced CT and contrast-enhanced MRI for the assessment of adults with focal liver lesions (FLL), in whom previous liver imaging is inconclusive.

1.3 Methods

A systematic review was conducted to summarise the evidence on the clinical-effectiveness of CEUS using the contrast agent SonoVue®, compared with contrast-enhanced CT or MRI, for the assessment of adults with focal liver lesions (FLL) in whom previous liver imaging has been inconclusive. Search strategies were be based on target condition (primary or secondary liver cancer) and intervention (SonoVue® CEUS), 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.[1-3] The following databases were searched from 2000 to September/October 2011: MEDLINE; MEDLINE In-Process; EMBASE; the Cochrane Databases; Database of Abstracts of Reviews of Effects (DARE); NHS Economic Evaluation Database (NHS EED); Health Technology Assessment Database (HTA); Science Citation Index (SCI). Research registers and conference proceedings were also searched. Systematic review methods followed the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care and the NICE Diagnostic Assessment Programme interim methods statement.[1, 4] The risk of bias in included diagnostic test accuracy (DTA) studies was assessed using a modified version of the QUADAS-2 tool,[5] and the single included controlled clinical trial was assessed using an adaptation Cochrane Collaboration's tool for assessing risk of bias.[6] Results were summarised in tables and text, stratified by clinical indication for imaging (characterisation of FLLs detected on routine surveillance of cirrhosis patients using un-enhanced US, detection of liver metastases in patients with known primary malignancy (colorectal carcinoma (CRC)), characterisation of incidentally detected FLLs visualised on un-enhanced US, assessment of response to treatment in known 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), and this group included one study which used a sub-optimal reference standard. 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 which used a sub-optimal reference standard; these analyses were conducted using MetaDiSc 1.4.[7]. Between study clinical heterogeneity was assessed qualitatively, statistical heterogeneity was assessed using the chi-squared test and inconsistency was quantified using the I^2 statistic.[8]

In the health economic analysis, the cost-effectiveness of contrast enhanced ultrasound using the contrast agent SonoVue® (CEUS) for the assessment of adults with focal liver lesions, in whom un-enhanced ultrasound or other liver imaging is inconclusive. The analyses focused on those populations where clinical opinion indicated there was most likely to be a benefit from the use of CEUS. These were also the populations from which most of the data on test performance was derived (see above); specifically some studies on the detection of metastases included patients with primaries other than CRC, but these patients were in the minority, no separate data were available for accuracy in detecting liver metastases from primaries other than CRC, and clinical opinion advised that liver metastases from CRC were the main focus of testing as these were considered most likely to be susceptible to successful treatment. Therefore, the health economic analysis assessed the value of CEUS in the following three populations:

- Detection of hepatocellular carcinoma through surveillance of patients with cirrhosis;
- Detection of liver metastases in patients with colorectal cancer;
- Characterisation of incidentally detected focal liver lesions.

Three separate models were used to assess the cost-effectiveness of CEUS in the above populations:

- A cirrhosis surveillance model;
- A liver metastases of colorectal cancer model;
- An incidentally detected focal liver lesions (FLL) model.

In each model, CEUS was compared to contrast enhanced computer tomography (CECT), contrast enhanced magnetic resonance imaging using gadolinium as contrast agent (Gd-CEMRI) and/or contrast enhanced magnetic resonance imaging using superparamagnetic iron oxide as contrast agent (SPIO-CEMRI). In the models the average costs, expected life years, and expected quality adjusted life years per patient were calculated for each of the above mentioned comparators, if evidence on test performance was 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). [9] The population of interest consisted of persons with a diagnosis of compensated cirrhosis deemed eligible to enter a surveillance programme (aged 70 years or less with no pre-existing medical conditions that would preclude treatment with liver transplant or hepatic resection (including current alcohol or intravenous drug abuse)). It was a probabilistic state transition

(Markov) cohort model constructed using Excel. The time horizon was lifetime and the cycle duration was one month. Patients in the model can develop hepatocellular carcinoma (HCC). In the base case analysis surveillance takes place every six months, and stops for people who reach the age of 70 years old. During this surveillance, through un-enhanced ultrasound combined with CEUS, CECT or CEMRI for inconclusive un-enhanced ultrasound, the probability of detecting a small (< 2 cm) or medium (2-5 cm) HCC is dependent on the accuracy of each test. In the base case, accuracy was based on a study by Leoni et al [10]. Large (> 5 cm) tumours are always detected at surveillance. If the tumour is not detected (false negatives), it grows and might be detected at the next surveillance, or if the tumour becomes symptomatic. Patients without HCC who are incorrectly diagnosed with HCC (false positives) are assumed to be rapidly discovered before treatment.

The liver metastases from colorectal cancer model is a modified version of the metastatic model developed by Brush et al [11]. The model was adapted to assess the cost-effectiveness of CEUS compared to CECT and CEMRI in detecting metastases from colorectal cancer after an inconclusive un-enhanced ultrasound scan. The population of interest consisted of patients who had previously had surgical treatment for primary CRC and who, during routine follow-up assessment, were identified as potentially having a metastatic recurrence. 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 one year. The probability of correctly detecting absence or presence of metastases depends on the accuracy of each test. In the base case, accuracy was based on a study by Mainenti et al [12]. In this model, for patients with undetected metastases (false negatives) it was assumed that the true diagnosis would be identified within a year if the patient were still alive. These patients are expected to have lower quality of life and prognosis, only in the first year. In the base case analysis, ppatients who are inaccurately diagnosed as having metastases (false positives) receive biopsy through which the incorrect diagnosis is discovered. They are therefore not unnecessarily treated.

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. The prognosis and costs seen amongst patients diagnosed with HCC were modelled using the cirrhosis model, whilst the prognosis and costs amongst patients with liver metastases were modelled using the liver metastases model. The model used in this assessment was a decision analytic model with a lifetime time horizon. The sources of diagnostic accuracy were the findings from the systematic review performed as part of the assessment. The sensitivity and specificity of CEUS and CECT in detecting any malignancy were based on the results of a

meta-analysis of four studies. CEUS and CEMRI could only be compared on the basis of one study. All in all, the diagnostic accuracy results of the three technologies were very similar. The costs and prognosis of HCC patients (as well as patients with other infrequently occurring malignancies) were estimated using the HCC model described above, whilst the costs and prognosis of metastasis patients were based on the metastasis model (also described above). 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 one 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.

1.4 Results

Twenty of the 21 studies included in the systematic review were diagnostic test accuracy (DTA) studies. 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. Reporting quality was generally poor and a number of studies were only reported as conference abstracts. '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 patients groups (e.g. exclusion of 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 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 populations or clinical applications considered.

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 across studies. Studies assessing CEMRI used three contrast agents: gadolinium (Gd), a vascular contrast agent; superparamagnetic iron oxide (SPIO), a hepatocyte-specific contrast agent; gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced (Gd-EOB-DTPA-CEMRI), a 'combined' vascular and hepatocyte-specific contrast agent. There was no consistent evidence for any significant difference in test performance between the three imaging modalities and three MRI contrast media assessed. However, estimates of sensitivity and specificity for each imaging modality were inconsistent, even where studies used similar definitions of a positive

test for HCC. One study indicated that CEUS in particular may be better at ruling out HCC in FLLs between 11 and 30 mm (sensitivities for CEUS and Gd-CEMRI were 91.9% and 94.6%, respectively) than in small FLLs ≤10mm (sensitivities 27.3% and 72.7%, respectively), although this study did not use a definition of HCC consistent with that given in the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) guideline on the use of CEUS.[13] Inconsistent estimates of sensitivity across studies, mean that it is unclear whether 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, where very small FLLs (<10 mm) are 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 positive criteria for liver metastases, where reported. In addition, 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. 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 main target condition reported by studies of patients with incidentally detected FLLs was ‘any malignancy.’ Studies were consistent in their definitions of the criteria for HCC, which were similar to those reported in the EFSUMB guideline.[13] 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 detection of ‘any liver malignancy’ using CEUS or 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 (using Gd-CEMRI in all patients, with the addition of SPIO-CEMRI in an un-specified number of cases), reported sensitivity estimates of 90.0% and 81.8%, respectively, and corresponding specificity estimates of 66.7% and 63.0%. Data from one study indicated that combined imaging using both CEUS and CECT, where 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 live 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 >95% and specificity estimates >80% for complete response, using CEUS, CECT and CECT or Gd-CEMRI. 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.

The only controlled clinical trial identified indicated that the inclusion of CEUS in pre-treatment imaging protocols for patients undergoing radiofrequency ablation (RFA) for HCC may reduce incidence of disease progression, new HCC and repeat RFA, and increase local progression- and new tumour-free survival, compared with un-enhanced US. However, this was a small, non-randomised study, which had a number of methodological weaknesses and 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.

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-enhanced CEMRI. None of the studies identified reported any information on patient preferences.

The cost-effectiveness analysis of the use of CEUS in patients with an inconclusive unenhanced ultrasound 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 characterisation of incidentally detected FLLs, while it was similar in terms of costs and effects in the detection of liver metastases from colorectal cancer.

In the surveillance of cirrhosis, CEUS was found to be as effective as, but £379 (95%CI: £324 to £1,060) less costly than CECT. This indicates that CEUS dominates CECT. Gd-CEMRI was found to be £1,063 (95%CI: £449 to £1,492) more costly than CEUS, and gained 0.022 (95%CI: -0,002 to 0,050) more QALYs. This resulted in an ICER of £48,545 per QALY gained. This ICER would be deemed unacceptable given a threshold of £20,000 per additional QALY. CEUS can therefore be considered the most cost-effective option when used after

inconclusive un-enhanced ultrasound. These base case results were based on one source for accuracy, being Leoni et al.[10] Using the two other studies that compared CEUS and CECT corroborated the dominance of CEUS over CECT, showing even lower effectiveness of CECT. CEUS was cost-effective compared to Gd-CEMRI in most sensitivity analyses, except when all positive un-enhanced ultrasound examinations were subject to confirmatory testing instead of only the inconclusive ultrasounds, and when the proportion of patients having an inconclusive ultrasound was lower. In these two cases Gd-CEMRI was cost effective when compared with. CEUS with ICERs of £12.806 and £16,121, respectively. However, using the study by Blondin et al.[14] as a source for test accuracy resulted in Gd-CEMRI being dominated by CEUS.

In the diagnosis of liver metastases from colorectal cancer, CEUS was found to have similar costs and effects compared to CECT. While at a lifetime time horizon they yielded equal QALYs per patient, CEUS was found to cost £1 (95%CI: -£1.26 to £1.28) more than CECT. Both Gd-CEMRI and SPIO-CEMRI were dominated by CECT in this population because they were more costly and equally effective. However, in this base case analysis it was assumed that patients who were incorrectly diagnosed with liver metastases would receive biopsy to discover this mistake before they were treated. 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 this would happen 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,[15] [16] CEUS was found to dominate CECT Gd-CEMRI yielded 0.014 (95%CI: -0.063 to 0.062) more QALYs, but was also £587 (95%CI: -£1,007 to £1,488) more costly than CEUS, resulting in an ICER of £43,318 per QALY gained. As this is above a threshold of £20,000 per QALY, Gd-CEMRI would be deemed not cost-effective compared to CEUS.

In the characterisation of incidentally detected focal liver lesions, CEUS was found to be very slightly (0.00016 QALYs; 95%CI: -0.00110 to 0.00140) more effective than CECT, and £52 (95%CI: -£81 to -£22) less costly. Compared to CEMRI, CEUS was also slightly more effective (0.0039 QALYs; 95%CI: -0.0058 to 0.0135) and less costly (£131; 95%CI: -£194 to -£69). An increased prior probability of malignant lesions increased the QALYs gained by CEUS compared to both CECT and CEMRI, thereby confirming its dominance. Also 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 this did not alter the dominance of CEUS over CECT.

1.5 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 surveillance of cirrhosis patients using un-enhanced US; detection of liver metastases in patients with known primary cancers (CRC); characterisation of incidentally detected FLLs identified by un-enhanced US. However, some caution is required in the interpretation of these findings as studies were generally small and heterogeneous with respect to 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 un-enhanced ultrasound 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 characterisation of incidentally detected FLLs, while it was similar in terms of costs and effects in the detection of liver metastases from colorectal cancer. 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 rapid rule-out of malignancy, equivalent diagnostic performance may be sufficient for SonoVue® CEUS to be preferred over other imaging modalities when un-enhanced 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 un-enhanced US examination. Although this would be unlikely to reduce waiting times (compared to 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.

1.6 Suggested research priorities

Standardisation of the definition positive imaging test for each target condition (HCC, liver metastases), followed by further, high quality DTA studies is needed to confirm our findings, particularly in relation to surveillance of patients with cirrhosis. 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 imaging-related adverse events; studies comparing all three imaging modalities could provide a useful vehicle for the collection of information of patients' preferences. Further investigation of the potential role of CEMRI, using both vascular and hepatocyte-specific or 'combined' contrast agents, may also be warranted. The ideal study to address questions of clinical effectiveness would be a large multi-centre 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, in order to minimise performance bias. Long-term, observational studies assessing the clinical consequences of incorrect initial diagnoses may also be informative.

2 OBJECTIVE

To compare the clinical and cost-effectiveness of contrast enhanced ultrasound (CEUS) using the contrast agent SonoVue® with contrast-enhanced CT and contrast-enhanced MRI for the assessment of adults with focal liver lesions (FLL), in whom previous liver imaging has been inconclusive.

3 BACKGROUND AND DEFINITION OF THE DECISION PROBLEM(S)

3.1 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 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,[17, 18] and NICE has issued guidance on a number of individual interventions for primary hepatocellular carcinoma 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 males and 2.9 per 100,000 females)[19] it is the second most rapidly increasing cancer in males and the third in females, (increases of 38% and 28%, respectively, in the last decade).[20] However, 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 (US) for contrast-enhanced magnetic resonance imaging (CEMRI) and/or contrast enhanced computed tomography (CECT), may result in a wait of several months.

Because SonoVue® contrast-enhanced ultrasound (CEUS) should be used only where un-enhanced 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 un-enhanced US and who have proceeded to CEUS are likely to

have FLLs (seen at un-enhanced ultrasound), the nature of which remains uncertain. Detection of FLLs at un-enhanced 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 un-related 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 un-enhanced ultrasound. Other, relevant applications include the detection of specific types of malignant FLL (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% to 100% and 95% to 100% respectively,[21] but this review did not provide any comparison with the accuracy of other imaging techniques.

3.2 Description of technologies under assessment (SonoVue®)

SonoVue® (Bracco UK Ltd) is a second generation contrast agent which uses 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.[13] Low solubility gas contrast agents, such as SonoVue®, allow imaging at low mechanical index which, in turn, leads to effective tissue signal suppression.[13] First generation agents have now been superseded by second generation agents and are no longer available in Europe.

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 was CEUS of the liver.

SonoVue® 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 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.[22]

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: hepatic arterial phase (starting approximately 10 to 20 seconds after injection of the contrast agent into a peripheral vein and lasting for approximately 10 to 15 seconds); portal venous phase (following the hepatic arterial phase and lasting till approximately 2 minutes after initial injection); late phase (following portal venous phase and lasting until clearance of the contrast agent from the hepatic parenchyma, up to 4 to 6 minutes after 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 contrast agent from the lesion compared with normal liver tissue.[13]

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 up-dated.[13] 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

The EFSUMB guidelines provide information on the typical enhancement patterns associated with various types of benign and malignant liver lesions;[13] Table 1 shows the typical enhancement patterns described for the malignant lesions considered in this assessment.

Table 1: Typical enhancement patterns of malignant focal liver lesions

	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

When considering the post-treatment assessment of patients who have undergone percutaneous ablation therapies, CEUS can potentially provide useful information where un-enhanced ultrasound cannot. This is because assessment of vascularisation and tissue perfusion is essential to enable differentiation of tissue necrosis from residual tumour.[13]

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

3.3 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. 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), which are taken up by Kupffer cells in the normal liver and benign lesions and may therefore aid identification of malignant lesions, which are generally deficient in Kupffer cells, particularly where such lesions are hypervascular,[23, 24] or 'combined' vascular and hepatocyte-specific contrast agents such as gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA).[25] A recent systematic review compared the accuracy of SonoVue® CEUS, CECT and CEMRI for the differentiation of malignant and benign liver lesions. The reported that sensitivities were 88% (95% CI 79% to 84%), 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% t 85%).[26] 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.

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 indicated that biopsy would not be performed on the basis of un-enhanced ultrasound examination alone, therefore, biopsy was not considered a relevant comparator for CEUS.

Figure 1: Diagnostic algorithm for liver imaging - CEUS as a replacement test for CECT/CEMRI

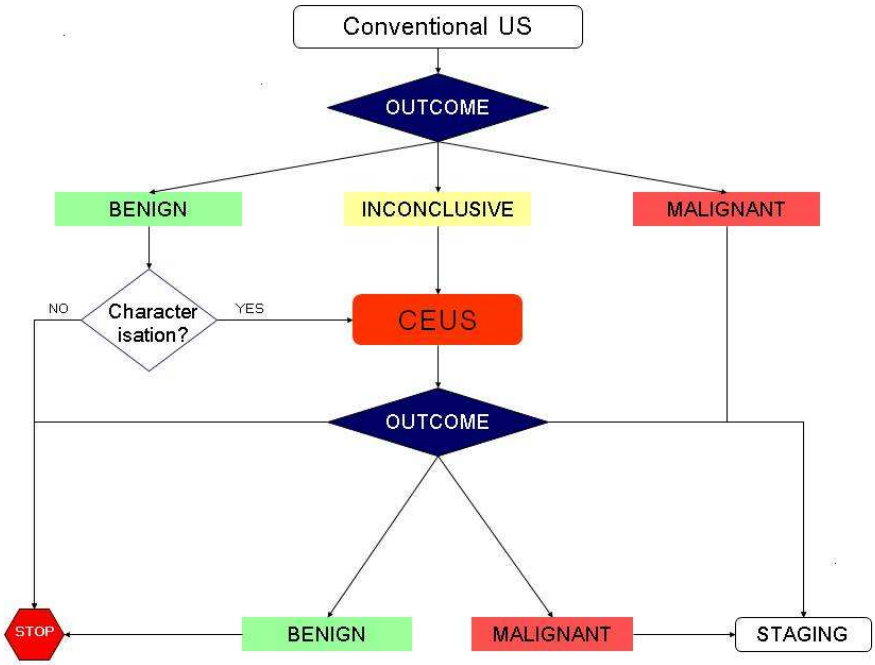
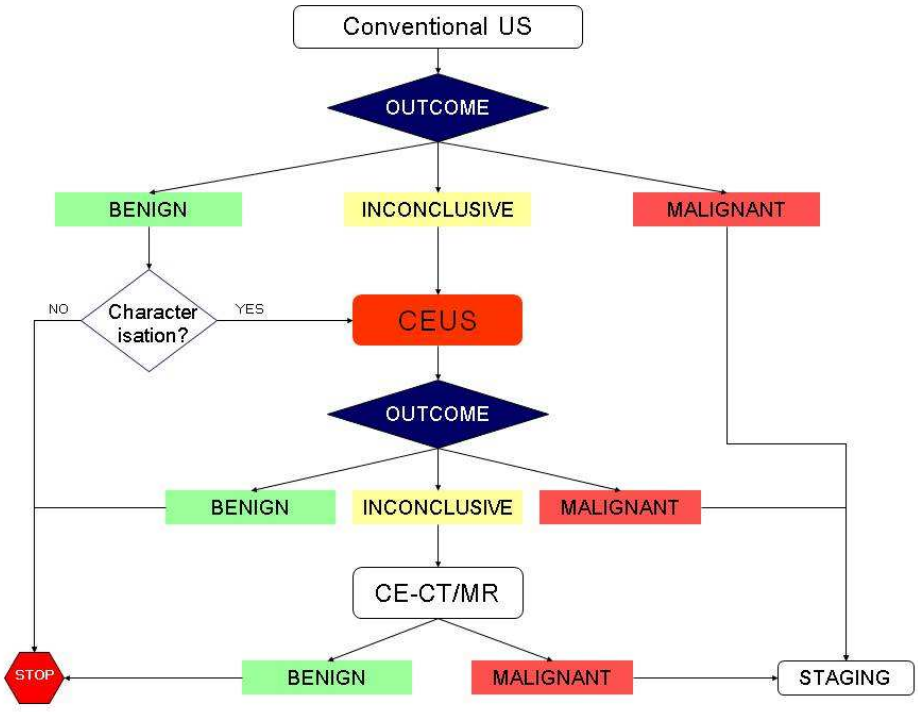


Figure 2: Diagnostic algorithm for liver imaging - CEUS as a triage test to reduce the use of CECT/CEMRI



3.4 Care pathways/current practice

FLLs found on un-enhanced ultrasound may be 'incidental' (FLLs detected in patients undergoing abdominal US for symptoms and/or biochemistry suggestive of possible liver disease, or for other reasons un-related 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 of malignant. Other relevant applications include the detection of specific types of malignant FLL such as liver metastases from colorectal cancer. 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 on 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.

3.4.1 Incidentally detected FLL

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, focal nodular hyperplasia, focal fatty sparing and adenoma. Malignant FLLs include primary cancer of the liver, known as hepatocellular carcinoma, and secondary cancers of the liver (metastases) resulting from primary cancers occurring elsewhere in the body (for example colorectal cancer, 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, due to 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), and radiofrequency ablation.) 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.[27]

3.4.2 Cirrhosis surveillance

Guidelines form the UK hepatocellular group advise that for all patients with cirrhosis who might be suitable candidates for treatment for hepatocellular carcinoma (HCC), surveillance using abdominal ultrasound and alpha-fetoprotein estimation should be considered [18]. If surveillance is offered, it should involve abdominal ultrasound assessments in combination with serum alpha-fetoprotein estimation at six month intervals. If the ultrasound is inconclusive, confirmatory testing will take place using contrast-enhanced CT (CECT) or contrast-enhanced MRI (CEMRI). The decision about whether to use CEMRI or CECT as the next imaging modality, following the initial ultrasound scan, is highly dependent on clinician preferences and local availability. While 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. This implies that it can sometimes take up to six 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.[18] Biopsy is rarely required for diagnosis as this can usually be established radiologically, and seeding of tumour in the needle tract occurs in 1 to 3%. Therefore, it is advised to avoid biopsy of potentially operable lesions where possible. An HCC can be curatively treated with surgery, either hepatic resection or liver transplantation.[18] Palliative treatments include percutaneous ethanol injection, radiofrequency ablation and transarterial chemoembolisation.

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 post-operative liver failures 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) and 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, where 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 intra-hepatic dissemination of the tumour has not occurred. Liver transplantation is an option for early stage HCC (< 5cm or with up to 3 nodules < 3 cm), but is not recommended for more advanced stages. If resection or transplantation are 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 are not considered appropriate. During tumour growth, the tumour becomes highly arterialised, meaning most blood that supplies the tumour is from the hepatic artery. During transarterial embolisation (TAE) acute arterial obstruction is provoked, which causes ischemic 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 transarterial chemoeembolisation (TACE). TACE is indicated if the tumour has multiple nodules, without affecting blood vessels or dissemination outside the liver. Completeness of 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, though is not recommended by the American Association for the Study of Liver Diseases (AASLD).[17]

Patients at an advanced stage of the disease, characterized 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. [17]

3.4.3 Liver metastases for colorectal cancer

For cancers of both the colon and the rectum, surgical resection is the mainstay of definitive treatment.[28] After surgical resection, patients may present with metastases. Metastases often first occur in the liver and may be the only site of spread in 30 to 40% of patients with advanced disease.[29] For a patient discovered to have isolated liver metastases, CT of the chest, abdomen, and pelvis should be performed to determine whether metastases at multiple sites are present. Isolated liver metastases of colorectal origin are commonly resected, with or without pre-operative chemotherapy. In cases of small liver metastases, colon and liver resection might also 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 performed, however, response to treatment is generally poor. Ablative therapy may also be considered, however, this is only recommended in the context of randomised controlled trials. As with HCC, recurrence of metastases after liver resection occurs in up to 60% of the patients.[29]

Patients without metastases are advised to undergo regular surveillance with a minimum of two CTs of the chest, abdomen and pelvis in the first three years and regular serum carcinoembryonic antigen tests (at least every 6 months in the first 3 years).[28] Follow-up after liver resection is very dependent on local protocols, but may include CT chest and liver and carcinoembryonic antigen testing for five years.

4 ASSESSMENT OF CLINICAL EFFECTIVENESS

A systematic review was conducted to summarise the evidence on the clinical-effectiveness of SonoVue® contrast-enhanced ultrasound, for the assessment of focal liver lesions 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, the NICE Diagnostic Assessment Programme interim methods statement and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.[1, 2, 4]

4.1 Inclusion and exclusion criteria

Participants

Study populations eligible for inclusion were:

Adults (≥18 years) in whom previous liver imaging has been inconclusive, including patients being assessed for:

- Suspected primary hepatocellular carcinoma (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

Comparators tests eligible for inclusion were:

- Contrast-enhanced computed tomography (CECT)
- Contrast-enhanced magnetic resonance imaging (CEMRI)

Reference standard

Studies reporting the diagnostic accuracy of SonoVue® CEUS for the detection of liver malignancies were required to use histology, following biopsy or surgical excision, to confirm 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 six 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 which use European Association for the Study of the Liver (EASL)/American Association for the Study of Liver Diseases (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

Studies reporting the following outcomes were considered relevant:

- 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 pre-treatment 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® CES

For included studies reporting any of the above outcome measures, the following outcomes were 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 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.[30]

Study design

The following study designs were eligible for inclusion:

- 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 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, where the index test was compared with one or more of the comparators and the reference standard. Test accuracy studies of the index test alone were included where 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:

- 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

4.2 Search strategy

Search strategies were 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.[1-3]

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

- MEDLINE (2000-2011/09/wk 4) (OvidSP)
- MEDLINE In-Process Citations and Daily Update (2000-2011/10/05) (OvidSP)
- EMBASE (2000-2011/wk 39) (OvidSP)
- Cochrane Database of Systematic Reviews (CDSR) (Cochrane Library Issue 10:2011) (Wiley)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library Issue 4:2011) (Wiley)
- Database of Abstracts of Reviews of Effects (DARE) (2000-2011/10/06) (via Cochrane Library)
- Health Technology Assessment Database (HTA) (2000-2011/10/06) (via Cochrane Library)
- Database of Abstracts of Reviews of Effects (DARE) (2011/01/01-2011/10/06) (CRD website)
- Health Technology Assessment Database (HTA) (2011/01/01-2011/10/06) (CRD website)
- Science Citation Index (SCI) (2000-2011/10/06) (Web of Science)
- NIHR Health Technology Assessment (HTA) (2000-2011) (Internet)

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

- NIH Clinicaltrials.gov (2000-2011/10/07) (Internet)
  http://www.clinicaltrials.gov/
- Current Controlled Trials (2000-2011/10/07) (Internet)
  http://www.controlled-trials.com/
- WHO International Clinical Trials Registry Platform (ICTRP) (2000-2011/10/07) (Internet)
- http://www.who.int/ictrp/en/
- EU Clinical Trials Register (EU CTR) (2000-2011/10/08) (Internet)
  https://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 checklist [31]. 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 for the following conference abstracts:

- European Federation of Ultrasound in Medicine & Biology (EUROSON) (2007-8,2011) (Internet)
  2011 = http://www.wfumb2011.org/index.php?pid=70
  2008 = https://www.thieme-connect.com/ejournals/toc/ultraschall/33697/grouping/54161
  2007 = http://www.interplan.de/pages/euroson2007/front_content.php?idcat=82
- Radiological Society of North America (RSNA) (2006-2010) (Internet)
  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) (2006-2011) (Internet)
  2011 = http://www.myesr.org/cms/website.php?id=/en/past_congresses/ecr_2011/ecr_2011_book_of_abstracts.htm
  2010 = http://www.myesr.org/cms/website.php?id=/en/ecr_2010/book_of_abstracts.htm
  2009 = http://www.myesr.org/cms/website.php?id=/en/ecr_2009/ecr_2009_book_of_abstracts.htm
  2008 = http://www.abstractsonline.com/viewer/?mkey={9AF35541-5128-444B-9D15-447022358A3F}
  2007 = http://www.abstractsonline.com/viewer/?mkey={9A26688A-5BBE-4366-AE14-5AC99DF8F8E4}
  2006 = http://www.abstractsonline.com/viewer/?mkey={6748FA35-D7A5-44B0-B8D4-4E2E51850B06}

We planned to search British Medical Ultrasound Society (BMUS) conference abstracts (2006-2011), but these were not available on-line.

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

References in retrieved articles were checked for additional studies.

4.3 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, after discussion, 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 manufacturers and excluded at the full paper screening stage are noted in Appendix 5. Appendix 5 also includes a list of studies, referenced by manufacturers, which were excluded at title and abstract screening.

Where 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 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); study results. All but one of the studies included in the review were DTA studies and the results extracted for these studies were: unit of analysis (patient or lesion); numbers of true positive (TP), false negative (FN), false positive (FP) and true negative (TN) 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 which compared assessment with conventional imaging (CECT or CEMRI) plus un-enhanced US to assessment with conventional imaging (CECT or CEMRI) plus SonoVue® CEUS prior to radiofrequency ablation (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.

4.4 Quality assessment

The evidence-based QUADAS tool,[32-34] is recommended for assessing the methodological quality of test accuracy studies.[1, 2] A revised version of QUADAS (QUADAS-2) has recently been published.[5] 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 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 which only assess 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 of the systematic review (section 4.6) 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.[6]

4.5 Methods of analysis/synthesis

The results of DTA studies included in this review were summarised by clinical indication for imaging (characterisation of FLLs detected on routine surveillance of cirrhosis patients using un-enhanced US, detection of liver metastases in patients with known primary malignancy, characterisation of incidentally detected FLLs visualised on un-enhanced 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. Where 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 numbers 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.

Where 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;[35-37] 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 which used a sub-optimal reference standard (as described in the protocol modification noted in section 4.1). 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 which used a sub-optimal reference standard; these analyses were conducted using MetaDiSc 1.4.[7].

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,[8] though these measures are of limited value given the small number of studies involved. There were no data sets of sufficient size (minimum ten) to allow statistical exploration of sources of heterogeneity by including additional co-variables in the SROC model.

Where meta-analysis was considered unsuitable for the data identified (e.g. due to the heterogeneity and/or small numbers 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 ROC plane.

4.6 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 bibliographic database searches. No additional studies were identified from searches of clinical trials registries. Of the total of 175 publications considered potentially relevant, three[38-40] could not be obtained within the time scale of this assessment; these were held in British Library stacks which 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;[41-44] 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, with reasons for exclusions, of all publications excluded at the full paper screening stage.

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.[45-47] 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,[10, 14, 48-52] four assessed the performance of SonoVue® CEUS for the detection of liver metastases in patients with known primary cancers (CRC),[12, 15, 16, 45] six concerned the use of SonoVue® CEUS for the characterisation of incidentally detected FLLs,[47, 53-57] and three considered the use of SonoVue® CEUS to assess response to treatment in patients with liver cancer.[46, 58, 59] The remaining study was a controlled trial which compared assessment with conventional imaging (CECT or CEMRI) plus un-enhanced US to assessment with conventional imaging (CECT or CEMRI) plus SonoVue® CEUS prior to RFA.[60] 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.

All included studies were published 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®.[56, 57] and 13 studies did not report any information on funding sources.

Table 2 shows the details of 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.

Figure 3: Flow of studies through the review process

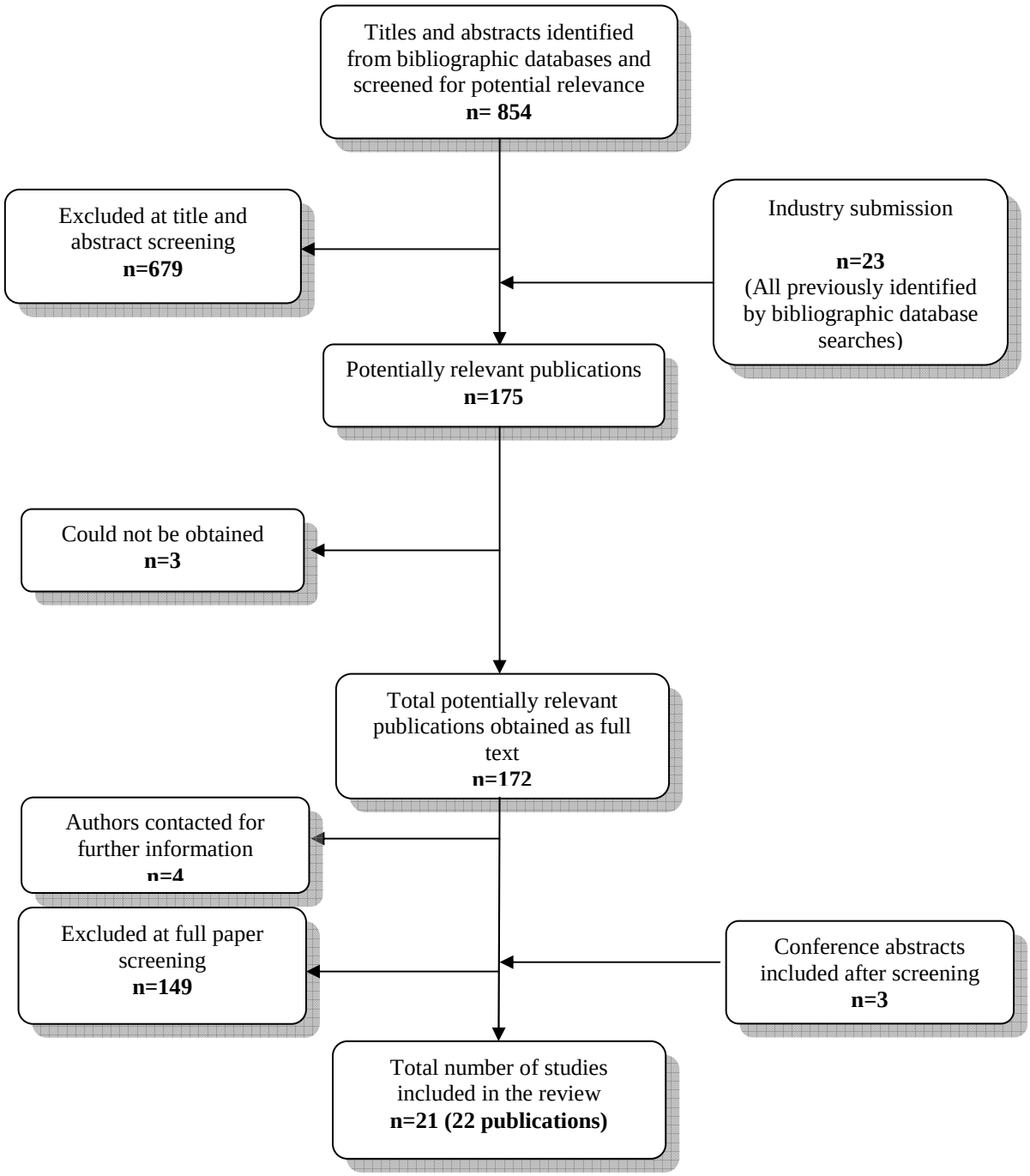


Table 2: Included studies

Study ID	Study design	Objective	US (CCTs and RCTs only)	Combined imaging	Comparator CECT	Comparator CEMRI	Any liver malignancy	Primary HCC	Metastases	Treatment success	Study design and outcome extracted
Blondin 2011 [14]	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 heptaobiliary contrast-enhanced MRI of the liver in evaluating focal liver lesions in patients with liver cirrhosis.'				✓		✓			DTA Accuracy data (characterisation of FLLs detected at cirrhosis surveillance): HCC versus benign.
Catala 2007[53]	Prospective cohort of adult (≥18 years) patients with FLLs detected on US. December 2002 to August 2003 Single centre Spain	'To compare the diagnostic accuracy of real-time evaluation by CEUS using SonoVue versus SCT in the characterisation of FLL and to determine the degree of correlation between the two techniques.'		✓	✓		✓	✓	✓		DTA Accuracy data (characterisation of incidentally detected FLLs): Separate data for HCC, liver metastases, and any liver malignancy.

Study ID	Study design	Objective	US (CCTs and RCTs only)	Combined imaging	Comparator CECT	Comparator CEMRI	Any liver malignancy	Primary HCC	Metastases	Treatment success	Study design and outcome extracted
	One author supported, in part, by a grant from the Carolina Foundation										
Chen 2007[60] related publication[61] excluded as duplicate	Prospective controlled clinical trial of patients with HCC who were being assessed before RFA treatment. July 2002 to 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.'	✓					✓		✓	CCT

Study ID	Study design	Objective	US (CCTs and RCTs only)	Combined imaging	Comparator CECT	Comparator CEMRI	Any liver malignancy	Primary HCC	Metastases	Treatment success	Study design and outcome extracted
Clevert 2009[16]	Prospective cohort of consecutive patients with suspected liver malignancy.[a] Recruitment dates NR Two centre Germany Funding NR	To assess the diagnostic performance of CHI with SonoVue® compared with biphasic multi-slice CECT, for the detection of malignant liver lesions.			✓		✓[a]				DTA Accuracy data (detection of liver metastases).[a]
Dai 2008[48]	Prospective cohort of consecutive patients with confirmed cirrhosis, without extrahepatic malignancy, who had indeterminate liver nodules on surveillance US. March 2004 to March 2005	'To investigate the diagnostic value for indeterminate small (1-2 cm) hepatic nodules detected by surveillance ultrasound in patients with cirrhosis using CEUS compared with helical CECT.'			✓			✓			DTA Accuracy data (characterisation of FLLs detected at cirrhosis surveillance): HCC versus benign.

Study ID	Study design	Objective	US (CCTs and RCTs only)	Combined imaging	Comparator CECT	Comparator CEMRI	Any liver malignancy	Primary HCC	Metastases	Treatment success	Study design and outcome extracted
	Single centre China Funding NR										
Feng 2007[58] Chinese language	Prospective cohort of patients with known liver malignancy (21 HCC, 3 metastases), undergoing cryosurgery. November 2004 to 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.'		✓						✓	DTA Accuracy data (detection of treatment success).

Study ID	Study design	Objective	US (CCTs and RCTs only)	Combined imaging	Comparator CECT	Comparator CEMRI	Any liver malignancy	Primary HCC	Metastases	Treatment success	Study design and outcome extracted
Flor 2010[45] (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 focal liver lesions in patients with known primary cancer.'							✓		DTA Accuracy data (detection of liver metastases).
Forner 2008[49]	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.	'To evaluate the accuracy of CEUS and dynamic MRI for the diagnosis of nodules 20 mm or smaller detected during US surveillance.'				✓		✓			DTA Accuracy data (characterisation of FLLs detected at cirrhosis surveillance): HCC versus

Study ID	Study design	Objective	US (CCTs and RCTs only)	Combined imaging	Comparator CECT	Comparator CEMRI	Any liver malignancy	Primary HCC	Metastases	Treatment success	Study design and outcome extracted
	November 2003 to August 2006 Two centre Spain and USA Supported by grants from: Instituto de Salud Carlos III, Spain; BBVA foundation; Fundación Cientifica de la Asociación Española de Ayuda contra el Cáncer, Spain, grant no.s. PI 05/150, 06/132 and 05/645. NIH-NIDDK grant no. 1R01DK076986-0										benign

Study ID	Study design	Objective	US (CCTs and RCTs only)	Combined imaging	Comparator CECT	Comparator CEMRI	Any liver malignancy	Primary HCC	Metastases	Treatment success	Study design and outcome extracted
Gierbliński 2008[54]	Prospective cohort of patients with incidentally detected solid liver lesions, referred for biopsy. June 2005 to March 2006 Single centre Poland Funding NR	'To determine if CEUS is an accurate method to differentiate FLLs and reduce the need for fine needle biopsy.'					✓				DTA Accuracy data (characterisation of incidentally detected FLLs): any malignancy versus benign
Giorgio 2007[50]	Prospective study of consecutive patients with cirrhosis and a single liver nodule ≤30 mm identified on surveillance US. September 2003 to June 2004.	'To evaluate the role of low mechanical index CEUS for the characterisation of small HCC in cirrhotic patients, by comparing results to ultrafast gadolinium-enhanced MRI.'				✓		✓			DTA Accuracy data (characterisation of FLLs detected at cirrhosis surveillance): HCC versus benign

Study ID	Study design	Objective	US (CCTs and RCTs only)	Combined imaging	Comparator CECT	Comparator CEMRI	Any liver malignancy	Primary HCC	Metastases	Treatment success	Study design and outcome extracted
	Single centre Italy Funding NR										
Jonas 2011[15] (abstract only)	Prospective study of consecutive patients with CRC metastases, who were considered candidates for curative surgery and who underwent complete pre-operative work-up. 2005 to 2007 Single centre Sweden Funding NR	'To assess the sensitivity and specificity of 4 imaging modalities (CEUS, CECT, CEMRI, and FDG-PET) in detecting liver metastases in patients with colorectal cancer.'			✓	✓			✓		DTA Accuracy data (detection of liver metastases)

Study ID	Study design	Objective	US (CCTs and RCTs only)	Combined imaging	Comparator CECT	Comparator CEMRI	Any liver malignancy	Primary HCC	Metastases	Treatment success	Study design and outcome extracted
Leoni 2010[10]	Retrospective analysis of a study of consecutive patients with cirrhosis 1 to 3 liver nodules (1-3 cm) detected at surveillance US. September 2003 to 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.'			✓	✓		✓			DTA Accuracy data (characterisation of FLLs detected at cirrhosis surveillance): HCC versus benign
Li 2007[55]	Prospective study of patients with FLLs detected at US and un-enhanced CT. Recruitment dates NR	'To compare the efficacy of contrast-enhanced pulse-inversion harmonic sonography for the characterisation of focal liver lesions with that of			✓		✓				DTA Accuracy data (characterisation of incidentally detected FLLs): any malignancy

Study ID	Study design	Objective	US (CCTs and RCTs only)	Combined imaging	Comparator CECT	Comparator CEMRI	Any liver malignancy	Primary HCC	Metastases	Treatment success	Study design and outcome extracted
	Single centre China Supported by the Clinical New Technology Foundation of Southwest Hospital (SWH2005A004)	contrast-enhanced helical CT.'									versus benign.
Lüttich 2006[46] (abstract only)	Cohort of patients with HCC undergoing RFA treatment. Recruitment dates NR Single centre Spain Funding NR					✓				✓	DTA Accuracy data (detection of treatment success).

Study ID	Study design	Objective	US (CCTs and RCTs only)	Combined imaging	Comparator CECT	Comparator CEMRI	Any liver malignancy	Primary HCC	Metastases	Treatment success	Study design and outcome extracted
Mainenti 2010[12]	Prospective study of consecutive patients with histologically proven CRC, who were scheduled for surgery. July 2005 to March 2007 Single centre Italy Funding NR	'To compare CEUS, MDCT, MRI with extra-cellular contrast agent (Gd-CEMRI), MRI with intra-cellular contrast agent (SPIO-CEMRI), and PET/CT in the detection of hepatic metastases from CRC.			✓	✓			✓		DTA Accuracy data (detection of liver metastases).
Quaia 2009[51]	Prospective study of patients with cirrhosis who had at least one hepatocellular nodule detected on surveillance US. Recruitment dates 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.'		✓	✓			✓			DTA Accuracy data (characterisation of FLLs detected at cirrhosis surveillance): HCC versus

Study ID	Study design	Objective	US (CCTs and RCTs only)	Combined imaging	Comparator CECT	Comparator CEMRI	Any liver malignancy	Primary HCC	Metastases	Treatment success	Study design and outcome extracted
	Two centre Italy Funding NR										benign
Sangiovani 2010[52, 62]	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	‘ To assess the sensitivity, specificity and economic impact of all possible sequential combinations of contrast imaging techniques in patients with cirrhosis with 1-2 cm liver nodules undergoing US surveillance.’		✓	✓	✓		✓			DTA Accuracy data (characterisation of FLLs detected at cirrhosis surveillance): HCC versus benign

Study ID	Study design	Objective	US (CCTs and RCTs only)	Combined imaging	Comparator CECT	Comparator CEMRI	Any liver malignancy	Primary HCC	Metastases	Treatment success	Study design and outcome extracted
	Aldo Antognozzi).										
Seitz 2009[56] Linked to Seitz 2010 2010[57]	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 (2x2 data could not be extracted for the remaining patients). May 2004 to December 2006 Multi-centre	'To evaluate the diagnostic value of CEUS for the characterisation of focal liver lesions in a prospective multi-centre study in clinical practice. For this purpose CEUS was compared with SCT the standard radiological method.'			✓			✓	✓		DTA Accuracy data (characterisation of incidentally detected FLLs): Separate data for HCC, liver metastases, and any liver malignancy.

Study ID	Study design	Objective	US (CCTs and RCTs only)	Combined imaging	Comparator CECT	Comparator CEMRI	Any liver malignancy	Primary HCC	Metastases	Treatment success	Study design and outcome extracted
	Germany, Austria and Switzerland Funded by Bracco Research (Konstanz, Germany) for the online data forms, quality control, calculations and statistical analyses										
Seitz 2010[57] Linked to Seitz 2009[56]	Cohort of 269 who underwent MRI from a prospective study of 1349 consecutive patients with newly detected FLL identified on US. Data extracted for the subgroup of patients (84) in whom diagnosis was histologically confirmed (2x2 data could not be extracted for the	To assess the diagnostic performance of CEUS (compared with MRI) in a large patient cohort with FLL recently discovered by US, but not yet characterised.				✓		✓	✓		DTA Accuracy data (characterisation of incidentally detected FLLs): Separate data for HCC, liver metastases, and any liver malignancy.

Study ID	Study design	Objective	US (CCTs and RCTs only)	Combined imaging	Comparator CECT	Comparator CEMRI	Any liver malignancy	Primary HCC	Metastases	Treatment success	Study design and outcome extracted
	remaining patients). May 2004 to December 2006 Multicenter Germany Funding by Bracco Research (Konstanz, Germany) for the online data forms, quality control, calculations and statistical analyses										
Solbiati 2006[47] (abstract only)	Retrospective analysis of data from patients with incidentally detected FLLs.	To assess the diagnostic performance and cost-effectiveness of CEUS in the characterisation of			✓		✓				DTA Accuracy data (characterisation of incidentally

Study ID	Study design	Objective	US (CCTs and RCTs only)	Combined imaging	Comparator CECT	Comparator CEMRI	Any liver malignancy	Primary HCC	Metastases	Treatment success	Study design and outcome extracted
	5-year experience, dates not specified. Single Centre Italy Funding NR	FLLs.									detected FLLs: Any malignancy versus benign.
Zhou 2007[59] Chinese language	Retrospective analysis of data from patients undergoing non-surgical treatment for HCC. June 2005 to June 2006 Single centre China Funding NR	'To investigate the value of CEUS for non-surgical treatment response in HCC.'			✓					✓	DTA Accuracy data (detection of treatment success).

Study ID	Study design	Objective	US (CCTs and RCTs only)	Combined imaging	Comparator CECT	Comparator CEMRI	Any liver malignancy	Primary HCC	Metastases	Treatment success	Study design and outcome extracted
CCT: controlled clinical trial; CECT: contrast-enhanced computed tomography; CEMRI: contrast-enhanced magnetic resonance imaging; CEUS: contrast-enhanced ultrasound; CHI: contrast-enhanced harmonic imaging; CRC: colorectal carcinoma; DTA: Diagnostic test accuracy study; FLL: focal liver lesion; HCC: hepatocellular carcinoma; MDCT: multi-detector computed tomography; SCT: spiral computed tomography; SPIO: superparamagnetic iron oxide; US: un-enhanced ultrasound. a: 52 of the 59 positive diagnoses were liver metastases, therefore this study was classifies as 'detection of metastases'.											

4.6.1 Accuracy of SonoVue® CEUS for the characterisation of FLLs detected on surveillance of patients with cirrhosis

Seven studies reported comparisons of SonoVue® CEUS with other imaging techniques for the characterisation of focal liver lesions detected on un-enhanced US surveillance of patients with known cirrhosis.[10, 14, 48-52] One study, by Sangiovani et al. was reported as both a full paper[52] and a conference abstract.[62] All the studies in this section reported accuracy data for the differentiation of HCC from other liver lesions only and one study[50] 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 cholangiocarcinoma (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.[49, 50, 52] Studies generally focused on the characterisation of small to medium FLLs. Four studies pre-specified the size of FLLs considered, ≤30mm[10, 50, 51] or ≤20mm.[52] In two studies, the mean size was 15±3 mm and 14 mm (range 7 to 20 mm). [48, 49] The remaining study did not specify lesion size as an inclusion criterion or report mean lesion size.[14] Two studies explicitly excluded lesions <10 mm[10, 52] and one study reported stratified data for different lesion sizes (≤10 mm and 11-30 mm).[50] Two studies compared SonoVue® CEUS with CECT,[48, 51] three studies compared SonoVue® CEUS with CEMRI,[14, 50, 63] and the remaining two studies compared SonoVue® CEUS with both CECT and CEMRI.[10, 52] One study included in this section explicitly reported that patients had an uncertain diagnosis following un-enhanced US.[48] Five studies had prior un-enhanced US examination as an inclusion criterion, and the 'concern regarding applicability' criterion for quality assessment was rated 'unclear' for these studies (Table 3).[10, 49-52] 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' for this study.[14] Comparators and imaging criteria used to define positive for HCC varied across studies and no meta-analyses were therefore undertaken. All but one[10] 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'.[48, 50] Four studies were rated as 'high' risk of bias for the 'patient selection'

domain, due to retrospective study design,[14] or inappropriate exclusions.[10, 51, 52] Two studies excluded very small lesions (<10 mm);[10, 52] as these lesions may be more difficult to characterise, their exclusion may result in over estimations of test performance. One study excluded lesions with peripheral enhancement on CECT, which was considered to be indicative of a high probability of haemangioma.[51] 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 imaging test results[10] and in the other because a high proportion of lesions (approximately 40%) were excluded because a histopathological reference standard was not performed.[51] One study was also rated as 'high' risk of bias for the 'reference standard' domain because a sub-optimal reference standard (concordance between at least two imaging test results) was used in the majority of cases.[10]

The two studies which compared CEUS and CECT had slightly differing definitions of a positive imaging test (hyper-enhancement in the arterial phase followed by portal-venous wash-out[48] and hyper-enhancement in the arterial phase with or without portal-venous wash-out).[51] 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,[48] and in the other study all lesions were in the size range 10-30 mm.[51] The study by Dai et al[48] reported slightly higher estimates of test performance, particularly for CECT specificity (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%).[48] The definition of HCC used by this study corresponded most closely with that reported in the EFSUMB guidelines on the use of CEUS,[13] Table 1, section 2.2. Quaia et al reported sufficient data to allow calculation of sensitivity and specificity for the combination of CEUS and CECT, where a positive finding on either imaging technique was 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.[51]

Three studies compared CEUS and CEMRI; two used gadolinium-enhanced CEMRI (Gd-CEMRI),[49, 50] and one used gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced CEMRI (Gd-EOB-DTPA-CEMRI), a 'combined' vascular and hepatocyte-specific contrast agent.[14] The two studies which compared CEUS and Gd-CEMRI used different definitions of a positive imaging test result and only Forner et al[63] reported data for a definition of HCC which corresponded with that given in the EFSUMB guidelines,[13] which

they described as “conclusive” HCC. Forner et al also reported data for a definition of “suspicious” HCC (hyper-enhancement in the arterial phase without portal-venous wash-out).[49] Sensitivity and specificity were similar for CEUS and Gd-CEMRI, using either criteria. Specificity tended to increase and sensitivity to decrease, for both imaging modalities, where the stricter “conclusive” definition of HCC was used. This study did not stratify data by lesion size, however, very small lesions (≤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 American Association for the Study of Liver Disease (AASLD) criteria (concordant, ‘conclusive’ findings on CEUS and CEMRI) resulted in 100% specificity, but low sensitivity (33%); data not reported. Giorgio et al. used (arterial phase) hypervascularity as the definition of a positive test and stratified data by lesion size.[50] There was no significant difference in the performance of CEUS and Gd-CEMRI for the differentiation of HCC from benign lesions, in FLLs between 11 and 30 mm and both techniques had sensitivity and specificity values >85% (Table 4). For very small FLLs (≤10 mm), the sensitivity of CEUS was lower than that of CEMRI (27% versus 73%); for both imaging techniques, sensitivity was poor when the analysis was restricted to very small FLLs.[50] Imaging test performance estimates were similar for the ‘all lesion’ data set from Georgio et al. and the “suspicious” diagnostic criteria data set from Forner et al.; these data sets were similar in terms of diagnostic criteria and distribution of lesion size. The study which used Gd-EOB-DTPA-CEMRI did not report any information on lesion size.[14] The criteria used to define a positive imaging test result matched the definition of HCC given in the EFSUMB guidelines.[13] Sensitivity estimates were similar and high (>90%) for both CEUS and Gd-EOB-DTPA-CEMRI (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[10, 52] both reported data using a definition of HCC corresponding to that given in the EFSUMB guidelines;[13] one also reported data using arterial hyper-enhancement and portal venous wash-out separately as the definitions of HCC.[52] Both studies assessed Gd-CEMRI and one study also assessed CEMRI using superparamagnetic iron oxide (SPIO), a contrast agent which is selectively taken up by Kupffer cells in the normal liver and benign lesions and can therefore be used to identify HCC, which are generally deficient in Kupffer cells.[52] Where 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 tended to report higher estimates of sensitivity. Sensitivity estimates from these studies were generally lower

than those from studies, with an EFSUMB-consistent definition HCC, which compared only CECT with CEUS [48] or CEMRI with CEUS.[14, 49] Leoni et al reported that Gd-CEMRI had the highest sensitivity, 81.8% (95% CI 69.1 to 90.9%) of the imaging modalities assessed.[10] Both studies reported sufficient data to allow calculation of sensitivity and specificity estimates, where a positive result on any of the three imaging modalities was treated as index test positive. Data from Leoni et al 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.[10] By contrast, combined imaging modality data from Sangiovani et al did not appear to indicate significant improvements in sensitivity.[52]

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 of 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[14]	☹	?	?	☺	☺	☹
Dai 2008[48]	☺	☺	☺	?	☺	☺
Forner 2008[49]	?	?	☺	?	?	?
Giorgio 2007[50]	☺	☺	☺	☺	☺	?
Leoni 2010[10]	☹	☺	☺	☹	☹	?
Quaia 2009[51]	☹	☺	☺	?	☹	?
Sangiovanni[52, 62]	☹	?	?	☺	☺	?

☺Low Risk ☹High Risk ? Unclear Risk

Table 4: Accuracy of SonoVue® CEUS, compared with other imaging techniques, for the characterisation focal liver lesions detected during routine surveillance of patients with known cirrhosis

Study ID	Patient or lesion data (n)	Index test or comparator	Reference standard	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	ND	Adverse events	Acceptability to patients
HCC												
SonoVue® CEUS compared with CECT												
Dai 2008[48]	n=103 FLL in 72 patients (per lesion data)	CEUS SonoVue® HCC=+ve[b]	Histopathology following biopsy, with negative biopsy confirmed by a minimum of 6 months follow-up	51	5	6	41	91.1 (95% CI 80.4 to 97.0)[a]	87.2 (95% CI 74.3 to 95.2)[a]	None	NR	NR
		CECT with Somatom Plus 4 (Siemens Medical Systems) HCC=+ve[b]		45	11	1	46	80.4 (95% CI 67.6 to 89.8)[a]	97.9 (95% CI 88.7 to 99.9)[a]			
Quaia 2009[51]	n=121 FLL (≤30 mm), in 106 patients (per lesion data)	CEUS sulphur hexafluoride filled microbubbles HCC=+ve[c] (readers 1&2)	FNB in all lesions	64	8	15	34	88.9 (95% CI 79.3 to 95.1) [a]	69.4 (95% CI 54.6 to 81.7) [a]	n=4 inadequate CEUS examinations excluded from study	NR	NR
				63	9	18	31	87.5 (95% CI 77.6 to 94.1) [a]	63.3 (95% CI 48.3 to 76.6) [a]			
		CECT Aquilion, Toshiba or Brilliance, Philips HCC=+ve[c] (readers 1&2)		53	19	14	35	73.6 (95% CI 61.9 to 83.3) [a]	71.4 (95% CI 56.7 to 83.4) [a]	n=10 inadequate CECT examinations excluded from study		
				51	21	14	35	70.8(95% CI 58.9 to 81.0) [a]	71.4 (95% CI 56.7 to 83.4) [a]			
		CEUS + CECT HCC=either test +ve (readers 1&2)		70	2	14	35	97.2 (95% CI 90.3 to 99.7) [a]	71.4 (95% CI 56.7 to 83.4) [a]	See above		
				70	2	15	34	97.2 (95% CI 90.3 to 99.7) [a]	69.4 (95% CI 54.6 to 81.7) [a]			
SonoVue® CEUS compared with CEMRI												
Blondin 2011[14]	n=47 FLL, in 33 patients	CEUS SonoVue® HCC=+ve[b]	Histology (surgery or biopsy) in all lesions	38	3	3	3	93 (95% CI 80 to 98)[a]	50 (95% CI 42 to 88)[a]	None	NR	NR
		Gd- EOB-DTPA		37	4	1	5	90 (95% CI	83 (95% CI			

		CEMRI Magnetom Avanto Siemens HCC=+ve[b]						77 to 97)[a]	36 to 100)[a]			
Forner 2008[49]	n=89 patients (one lesion per patient)	CEUS SonoVue® HCC suspicious[d] or conclusive[b] = +ve	FNB for test +, imaging follow-up for test –ve.	47	13	4	25	78.3 (95% CI 65.8 to 87.9)[a]	86.2 (95% CI 68.3 to 96.1)[a]			
		CEUS SonoVue® HCC conclusive[b] = +ve		31	29	2	27	51.7 (95% CI 38.4 to 64.8)[a]	93.1 (95% CI 77.2 to 99.2)[a]			
		Gd-CEMRI Siemens Symphony HCC suspicious[d] or conclusive[b]= +ve		51	9	3	26	85.0 (95% CI 73.4 to 92.9)[a]	89.7 (95% CI 72.6 to 97.8)[a]			
		Gd-CEMRI Siemens Symphony HCC conclusive[b] = +ve		37	23	1	28	61.7 (95% CI 48.2 to 73.9)[a]	96.6 (95% CI 82.2 to 99.9)[a]			
Giorgio 2007[50]	n=73 FLL (one lesion per patient)	CEUS SonoVue® HCC=+ve[e]	Ultrasound-guided FNB in all patients	37	11	1	24	77.1 (95% CI 62.7 to 88.0) [a]	96.0 (95% CI 79.6 to 99.9) [a]	None	No side effects observed in any patients	NR
	n=21 FLL (≤10 mm)			3	8	0	10	27.3 (95% CI 6.0 to 61.0) [a]	100 (95% CI 69.2 to 100) [a]			
	n=52 FLL (11-30 mm)			34	3	1	14	91.9 (95% CI 78.1 to 98.3) [a]	93.3 (95% CI 68.1 to 99.8) [a]			
	n=73 FLL (one lesion per patient)	Gd-CEMRI HCC=+ve[f]		43	5	3	22	89.6 (95% CI 77.3 to 96.5) [a]	88.0 (95% CI 68.8 to 97.5) [a]		NR	
	n=21 FLL (≤10 mm)			8	3	1	9	72.7 (95% CI 39.0 to 94.0) [a]	90.0 (95% CI 55.5 to 99.7) [a]			
	n=52 FLL (11-30 mm)			35	2	2	13	94.6 (95% CI 81.8 to 99.3) [a]	86.7 (95% CI 59.5 to 98.3) [a]			

SonoVue® CEUS compared with CECT and CEMRI												
Leoni 2007[10]	n=75 FLL in 60 patients(10-30 mm)	CEUS SonoVue® HCC=+ve[g]	≥2 concordant imaging results (n=44), FNB (n=14) or follow-up at 3 month intervals (n=1) for +ve test FNB (n=7), or follow-up at 3 month intervals (n=9) for test -ve	37	18	2	18	67.3 (95% CI 53.3 to 79.3) [a]	90.0 (95% CI 68.3 to 98.8) [a]	None	NR	NR
		CECT Emotion 6, Siemens HCC=+ve[g]		37	18	2	18	67.3 (95% CI 53.3 to 79.3) [a]	90.0 (95% CI 68.3 to 98.8) [a]			
		Gd-CEMRI, Signa, GE HCC=+ve[g]		45	10	1	19	81.8 (95% CI 69.1 to 90.9) [a]	95.0 (95% CI 75.1 to 99.9) [a]			
	n=68 FLL (10-30 mm)	SPIO-CEMRI, Signa, GE HCC=+ve[g]		35	15	1	17	70.0 (95% CI 55.4 to 82.1) [a]	94.4 (95% CI 72.7 to 99.9) [a]	7 FLL not assessed with SPIO-MRI		
	n=75 FLL (10-30 mm)	CEUS + CECT + CEMRI HCC= any test +ve		54	1	5	15	98.2 (95% CI 90.3 to 100) [a]	75.0 (95% CI 50.9 to 91.3) [a]	None		
Sangiovani 2010[52, 62]	n=55 FLL selected from 67 FLL in 64 patients (10-20 mm)	CEUS SonoVue® HCC=+ve[b]	FNB in all lesions	9	25	0	21	26.5 (95% CI 12.9 to 44.4) [a]	100 (95% CI 83.9 to 100) [a]	None	NR	NR
		CEUS SonoVue® HCC=+ve[h]		23	11	5	16	67.6 (95% CI 49.5 to 82.6) [a]	76.2 (95% CI 52.8 to 91.8) [a]			
		CEUS SonoVue® HCC=+ve[i]		13	21	1	20	38.2 (95% CI 22.2 to 56.4) [a]	95.2 (95% CI 76.2 to 99.9) [a]			
		CECT Definition, Siemens HCC=+ve[b]		16	18	0	21	47.1 (95% CI 29.8 to 64.9) [a]	100 (95% CI 83.9 to 100) [a]			
		CECT Definition, Siemens HCC=+ve[h]		22	12	4	17	64.7 (95% CI 46.5 to 80.3) [a]	81.0 (95% CI 58.1 to 94.6) [a]			
		CECT Definition, Siemens HCC=+ve[i]		18	16	0	21	52.9 (95% CI 35.1 to 70.2) [a]	100 (95% CI 83.9 to 100) [a]			

	n=53[j] FLL (10-20 mm)	Gd-CEMRI Avanto, Siemens HCC=+ve[b]		14	18	0	21	43.8 (95% CI 26.4 to 62.3 [a]	100 (95% CI 83.9 to 100) [a]			
		Gd-CEMRI Avanto, Siemens HCC=+ve[h]		21	11	8	13	65.6 (95% CI 46.8 to 81.4) [a]	61.9 (95% CI 38.4 to 81.9) [a]			
		Gd-CEMRI Avanto, Siemens HCC=+ve[i]		19	13	1	20	59.4 (95% CI 40.6 to 76.3) [a]	95.2 (95% CI 76.2 to 99.9) [a]			
		CEUS+CECT+CEMRI HCC=at least one test +ve[b]		22	12	0	21	64.7 (95% CI 46.5 to 80.3) [a]	100 (95% CI 83.9 to 100) [a]			
Liver metastases												
No studies identified												
Any malignancy												
No studies identified												

CECT: contrast enhanced computed; CEMRI: contrast enhanced magnetic resonance imaging; CEUS: contrast enhanced ultrasound; tomography; CI: confidence interval; HCC: hepatocellular carcinoma; FLL: focal liver lesion; FN: false negative; FNB: fine-needle biopsy; FP: false positive; Gd-CEMRI: gadolinium contrast-enhanced magnetic resonance imaging (vascular contrast agent); Gd-EOB-DTPA: gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (combined vascular and hepatocyte-specific contrast agent); ND: non-diagnostic; SPIO-CEMRI: superparamagnetic iron oxide contrast-enhanced magnetic resonance imaging (hepatocyte-specific contrast agent); TN: true negative; TP: true positive; US: un-enhanced ultrasound

a: calculated values

b: hyper-enhancement in the arterial phase and hypo-enhancement in the portal venous and late phases (portal venous wash-out)

c: hyper-enhancement in the arterial phase and iso- or hyper-enhancement in the portal venous and late phases with evidence of peripheral rim-like enhancement, or hyper-enhancement in the arterial phase and hypo-enhancement in the portal venous and late phases with or without peripheral vascular rim

d: hyper-enhancement in the arterial phase, without wash-out in the venous phase

e: hyper-echogenicity related to hyper-vascularity on US

f: typical pattern of round area of hyper-vascularity and lack of portal supply

g: hyper-enhancement in the arterial phase, “typical enhancement pattern for HCC”

h: arterial hyper-vascularity

i: portal venous wash-out

j: two patients were excluded from analyses because they could not undergo CEMRI

4.6.2 Accuracy of SonoVue® CEUS 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 colorectal carcinoma.[12, 15] Both studies reported per lesion accuracy data and one study[12] 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.[15] 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'.[16] One further study, which did not include a comparator test, was included in this section.[45] This study was included in the review because it reported inclusion criteria of 'indeterminate MDCT-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 only reported as conference abstracts,[15, 45], resulting a frequent judgement of 'unclear' risk of bias on quality assessment domains. Of the two full papers in this section[12, 16], Clevert et al[16] 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[15] 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 whilst including only patients with known liver metastases.

Where definitions of a positive imaging test were reported, studies which 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.[12, 15] Jonas et al reported 100% specificity and similar, high (83% to 97%) estimates of sensitivity for all three imaging modalities (CEUS, CECT and SPIO-CEMRI) (Table 6).[15] Mainenti et al reported

similar, high (83% to 100%) specificity values for all imaging modalities and for both per lesion and per patient data.[12] Per patient sensitivity estimates were also consistent across all imaging modalities (83% in all cases).[12] However, for both CEUS and CECT, the sensitivity estimates appeared lower for per lesion data (50% and 69%, respectively) than for per patient data.[12] For both CEMRI methods, the per lesion estimate of sensitivity (81%) was similar to the per patient estimate.[12] By contrast, Clevert et al reported per patient data and found similar, high (>95%) estimates of sensitivity for both CEUS and CECT (Table 6).[16] 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[16]	☺	☺	☺	?	☹	?
Flor 2010[45] (abstract only)	?	?	NA	?	?	☺
Jonas 2011[15] (abstract only)	☹	?	?	?	?	☹
Mainenti 2010[12]	☺	☺	☺	?	☺	?

☺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 (n)	Index test or comparator	Reference standard	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	ND (n patients/lesions)	Adverse events	Acceptability to patients
CRC												
SonoVue® CEUS compared with CECT and CEMRI												
Jonas 2011[15] (abstract only)	n= 48 FLL in 20 patients (by lesion data)	CEUS SonoVue® M=+ve	Histology in all resected test +ve lesions. All patients followed-up for at least 36 months	26	4	0	18	86.7 (95% CI 69.3 to 96.2)[a]	100 (95% CI 81.5 to 100)[a]	NR	NR	NR
		SPIO-CEMRI M=+ve		29	1	0	18	96.7 (95% CI 82.8 to 99.9)[a]	100 (95% CI 81.5 to 100)[a]			
		CECT M=+ve		25	5	0	18	83.3 (95% CI 65.3 to 94.4)[a]	100 (95% CI 81.5 to 100)[a]			
Mainenti 2010[12]	n=34 patients	CEUS SonoVue® M = +ve[b]	FNB for imaging test +ve 12 months follow-up for imaging test negative	5	1	4	24	83.3 (95% CI 35.9 to 99.6)[a]	85.7 (95% CI 67.3 to 96.0)[a]	None	NR	NR
	n=57 FLL			8	8	5	36	50.0 (95% CI 24.7 to 75.3)[a]	87.8 (95% CI 73.8 to 95.9)[a]			
	n=34 patients	CECT with Aquilion 4 (Toshiba Medical Systems) M = +ve[c]		5	1	1	27	83.3 (95% CI 35.9 to 99.6)[a]	96.4 (95% CI 81.7 to 99.9)[a]			
	n=57 FLL			11	5	7	34	68.8 (95% CI 41.3 to 89.0)[a]	82.9 (95% CI 67.9 to 92.8)[a]			
	n=34 patients	Gd-CEMRI M = +ve[d]		5	1	0	28	83.3 (95% CI 35.9 to 99.6)[a]	100 (95% CI 87.7 to 100)[a]			
	n=57 FLL			13	3	0	41	81.3 (95%	100 (95%			

								CI 54.4 to 96.0)[a]	CI 91.4 to 100)[a]			
	n=34 patients	SPIO-CEMRI M = +ve[e]		5	1	1	27	83.3 (95% CI 35.9 to 99.6)[a]	96.4 (95% CI 81.7 to 99.9)[a]			
	n=57 FLL			13	3	1	40	81.3 (95% CI 54.4 to 96.0)[a]	97.6 (95% CI 87.1 to 99.9)[a]			
Other primary tumours												
SonoVue® CEUS compared with CECT												
Clevert 2009[16]	n=100 patients (maximum 5 lesions per patient)	CHI SonoVue® Any liver malignancy=+ve[f]	Histology for all FLLs	58	1	1	40	98.3 (95% CI 90.9 to 100)[a]	97.6 (95% CI 87.1 to 99.9)[a]	None	NR	NR
	n=92[g] patients (maximum 5 lesions per patient)	CECT, Somatom Sensation 16 or 64 Any liver malignancy=+ve[f]		56	2	6	15	96.6 (95% CI 88.1 to 99.6)[a]	71.4% (95% CI 47.8 to 88.7)[a]	13 (excluded from analysis)	NR	NR
SonoVue® CEUS following inconclusive CECT/CEMRI												
Flor 2010[45] (abstract only)	n=26 FLL	CEUS SonoVue® M=+ve	FNB or 3-6 month follow-up	4	1	0	21	80.0 (95% CI 28.4 to 99.5)[a]	100 (95% CI 83.9 to 100)[a]	None	NR	NR

CECT: contrast enhanced computed tomography; CEMRI: contrast enhanced magnetic resonance imaging; CEUS: contrast enhanced ultrasound; CHI: contrast-enhanced harmonic imaging; CI: confidence interval; CRC: colorectal cancer; FLL: focal liver lesion; FN: false negative; FNB: fine-needle biopsy; FP: false positive; Gd-CEMRI: gadolinium contrast-enhanced magnetic resonance imaging (vascular contrast agent); ND: non-diagnostic; ; SPIO-CEMRI: superparamagnetic iron oxide contrast-enhanced magnetic resonance imaging (hepatocyte-specific contrast agent); TN: true negative; TP: true positive

a: calculated values

b: lesion with a wide echogenic spectrum, poorly defined margins and hypo-perfused or with peripheral enhancement

c: hypo-dense lesion with poorly defined margins, appearing hypo-perfused or with irregular peripheral enhancement

d: lesion with moderate hypo-intensity on T1-weighted image and hyper-intensity on T2-weighted image, or iso-intense in both, which appeared hypo-perfused or irregular peripheral enhancement

e: lesion with moderate hypo-intensity on T1-weighted image and hyper-intensity on T2-weighted image, or iso-intense in both, which did not concentrate intra-cellular contrast agent
f: the majority of malignant liver lesions (52/59) were metastases
g: eight patients did not receive CT

4.6.3 Accuracy of SonoVue® CEUS for the characterisation of incidentally detected FLLs

Five studies reported comparisons of SonoVue® CEUS with other imaging techniques for the characterisation of incidentally detected liver lesions, identified by un-enhanced US.[47, 53, 55-57] 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 identification of liver metastases.[53, 56, 57] All but one of the studies in this section reported data on one lesion per patient and the remaining study[47] 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[47, 53, 55, 56] and one of these[53] also reported data on the combined performance of SonoVue® CEUS and CECT combined, when a positive result on either test was treated as positive. One study compared SonoVue® CEUS with CEMRI.[56] 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 un-enhanced US, though all patients had prior un-enhanced US examination, therefore the applicability criterion for quality assessment was rated 'unclear' in all cases (Table 7). One further study, which did not include a comparator test, was included in this section.[54] This study was included in the review because it reported inclusion criteria 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 Seitz 2009[56] and Seitz 2010[57] is highly likely, as these two publications by the same group reported a very similar study design and identical recruitment periods; Seitz 2009[56] reported a comparison of SonoVue® CEUS with CECT and Seitz 2010[57] reported a comparison of SonoVue® CEUS with CEMRI in a smaller group of patients. All but one[47] 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[54] excluded patients who were unable to undergo biopsy and both Seitz studies[56, 57] divided participants into two subgroups based on probable diagnoses after un-enhanced ultrasound ("suspected benign" and "suspected malignant"). For the Seitz studies, accuracy data could only be extracted for the "suspected malignant" subgroup; this may have resulted in a higher than usual prevalence of malignancy and possible over estimate of test performance. Two studies were also rated as 'high' risk of bias for the 'flow and timing' domain, in one case[53] because more than half of the participants initially recruited were excluded from the analyses (either because more than one month had elapsed between SonoVue® CEUS and CECT, or because positive lesions could not be confirmed by pathology) and in the second case[47] because the reference standard used was not independent of index test results. This study was also rated 'high' risk of bias for the 'reference standard' domain because a sub-optimal reference standard (concordance between at least to 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.[47, 53, 55-57] The primary analysis, in all studies, was for the differentiation of malignant from benign lesions. Studies used similar criteria to define HCC (hyper-enhancement in the arterial phase followed by portal venous wash-out) 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,[13] (Table 1, section 2.2). Pooled estimates of test performance for distinguishing malignant from benign FLLs, derived from the four studies that compared CEUS with CECT,[47, 53, 55-57] 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 which used a sub-optimal reference standard,[47] 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[47] resulted in a large reduction in sample size (694 FLLs from a total sample size of 1,038 FLLs) and hence greater imprecision

(wider confidence intervals) in the estimates of sensitivity and specificity. The single study which 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 un-specified number of patients. One study reported sufficient data to allow calculation of sensitivity and specificity for the combination of CEUS and CECT, where a positive finding on either imaging technique was treated as 'test positive.'[53] These data indicated that the addition of CECT to the imaging work-up would not would not increase the accuracy of diagnosis over that obtained by CEUS alone; the sensitivity and specificity of CEUS for differentiating malignant form 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, (Table 8). Three studies reported sufficient data to derive estimates of test performance by lesion type (HCC and liver metastases), two comparing CEUS and CECT[53, 56] and one comparing CEUS and CEMRI.[57] The sensitivity and specificity of CEUS and CECT were similar for the characterisation of HCC, (Table 8). 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%).[56] The sensitivity and specificity of CEUS and CEMRI were similar for both HCC and liver metastases, (Table 8).[57]

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[53]	☹	☺	☺	?	☹	?
Gierblinski 2008[54]	☹	?	NA	☺	?	?
Li 2007[55]	?	☺	☺	?	☺	?
Seitz 2009[56]	☹	?	?	?	?	?
Seitz 2010[57]	☹	?	?	?	?	?
Solbiati 2006[47] (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 focal liver lesions

Study ID	Patient or lesion data (n)	Index test or comparator	Reference standard	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	ND	Adverse events	Acceptability to patients
HCC												
SonoVue® CEUS compared with CECT												
Catala 2007[53]	n=77 patients (one lesion per patient)	CEUS SonoVue® HCC=+ve[b]	Histology following biopsy or surgery for test +ve, MRI and follow-up ≥12 months for test –ve	41	4	2	30	91.1 (95% CI 78.8 to 97.5)[a]	93.8 (95% CI 79.2 to 99.2)[a]	None	NR	NR
		CECT with Somatom Plus 4 (Siemens Medical Systems) HCC =+ve[b]		39	6	2	30	86.7 (95% CI 73.2 to 94.9)[a]	93.8 (95% CI 79.2 to 99.2)[a]			
		CEUS + CECT HCC=either test +ve		42	3	2	30	93.3 (95% CI 81.7 to 98.6)[a]	93.8 (95% CI 79.2 to 99.2)[a]			
Seitz 2009[56] related publication[57]	Subgroup B (suspected malignant lesion)[c] n=158 FLL, (one lesion per patient)	CEUS SonoVue® HCC=+ve	FNB n=154 (remaining 4 lesions excluded)	34	6	4	110	85.0 (95% CI 70.2 to 94.3)[a]	96.5 (95% CI 91.3 to 99.0)[a]	None	NR	NR
		CECT HCC=+ve		28	12	6	108	70.0 (95% CI 53.5 to 83.4)[a]	94.7 (95% CI 88.9 to 98.0)[a]			
SonoVue® CEUS compared with CEMRI												
Seitz 2010[57] related publication[56]	Subgroup B (suspected malignant lesion)[c] n=84 FLL (one lesion per patient)	CEUS SonoVue® HCC=+ve	FNB n=82 (n= 2 excluded)	23	6	11	42	79.3 (95% CI 60.3 to 92.0)[a]	79.2 (95% CI 65.9 to 89.2)[a]	NR	NR	NR
		Gd-CEMRI and SPIO-CEMRI in some cases (number un-specified) HCC=+ve		24	5	13	40	82.8 (95% CI 64.2 to 94.2)[a]	75.5 (95% CI 61.7 to 86.2)[a]			
SonoVue® CEUS following inconclusive CECT/CEMRI												
Gierbliński	n=100 patients	CEUS SonoVue®	FNB with	7	2	1	90	77.8 (95%	98.9 (95%	None	NR	NR

2008[54]	(one lesion per patients)	HCC = +ve[b]	clinical and imaging follow-up for biopsy –ve patients					CI 40.0 to 97.2)[a]	CI 94.0 to 100)[a]			
Liver metastases												
SonoVue® CEUS compared with CECT												
Catala 2007[53]	n=77 patients (one lesion per patient)	CEUS SonoVue® M=+ve[d]	Histology following biopsy or surgery for test +ve, MRI and follow-up ≥12 months for test –ve	11	1	0	65	91.7 (95% CI 61.5 to 99.8)[a]	100 (95% CI 94.5 to 100)[a]	None	NR	NR
		CECT with Somatom Plus 4 (Siemens Medical Systems) M=+ve[d] pattern		11	1	0	65	91.7 (95% CI 61.5 to 99.8)[a]	100 (95% CI 94.5 to 100)[a]			
		CEUS + CECT M=either test +ve		11	1	0	65	91.7 (95% CI 61.5 to 99.8)[a]	100 (95% CI 94.5 to 100)[a]			
Seitz 2009[56] related publication[57]	subgroup B (suspected malignant lesion)[c] n=158 FLL (one lesion per patient)	CEUS SonoVue® M=+ve	FNB n=154 (n=4 excluded)	52	4	17	81	92.9 (95% CI 82.7 to 98.0)[a]	82.7 (95% CI 73.7 to 89.6)[a]	None	NR	NR
		CECT M=+ve		38	18	23	75	67.9 (95% CI 54.0 to 79.7)[a]	76.5 (95% CI 66.9 to 84.5)[a]			
SonoVue® CEUS compared with CEMRI												
Seitz 2010[57] related publication[56]	Subgroup B (suspected malignant lesion)[c] n=84 FLL (one lesion per patient)	CEUS SonoVue® M=+ve	FNB n=82 (n=2 excluded)	17	5	15	45	77.3 (95% CI 54.6 to 92.2)[a]	75.0 (95% CI 62.1 to 85.3)[a]	NR	NR	NR
		Gd-CEMRI and SPIO-CEMRI in some cases (number un-specified) HCC=+ve		14	8	14	46	63.6 (95% CI 40.7 to 82.8)[a]	76.7 (95% CI 64.0 to 86.6)[a]			

SonoVue® CEUS following inconclusive CECT/CEMRI												
Gierbliński 2008[54]	n=100 patients (one lesion per patient)	CEUS SonoVue® M=+ve[e]	FNB with clinical and imaging follow-up for biopsy –ve patients	13	1	2	84	92.9 (95% CI 66.1 to 99.8)[a]	97.7 (95% CI 91.9 to 99.7)[a]	None	NR	NR
Any malignancy												
SonoVue® CEUS compared with CECT												
Catala 2007[53]	n=77 patients (one lesion per patient)	CEUS SonoVue® any malignancy (HCC[b] or M[d]) = +ve	Histology following biopsy or surgery for index test +ve, MRI and follow-up ≥12 months for index test –ve	52	5	2	18	91.2 (95% CI 80.7 to 97.1)[a]	90.0 (95% CI 68.3 to 98.8)[a]	None	NR	NR
		CESCT with Somatom Plus 4 (Siemens Medical Systems) any malignancy (HCC[b] or M[d]) = +ve		50	7	2	18	87.7 (95% CI 76.3 to 94.9)[a]	90.0 (95% CI 68.3 to 98.8)[a]			
		CEUS + SCT +ve=either test +ve		53	4	2	18	93.0 (95% CI 83.0 to 98.1)[a]	90.0 (95% CI 68.3 to 98.8)[a]			
Li 2007[55]	n=109 patients (one lesion per patient)	CEUS SonoVue® any malignancy (HCC[f], CCC[g], M[h]) = +ve	Histopathology following surgical resection or FNB	72	9	2	26	88.9 (95% CI 80.0 to 94.8)[a]	92.9 (95% CI 76.5 to 99.1)[a]	3 lesions not visualised. All were malignant and are classified as FN in this table.	NR	NR
		CECT with Somatom Sensation Test +ve=any malignancy (HCC, CCC, M)		67	14	6	22	82.7 (95% CI 72.7 to 90.2)[a]	78.6 (95% CI 59.0 to 91.7)[a]	7 lesions were not visualized. 5 were malignant and are classified as FN in this table. 2 were benign and are classified as TN in		

										this table.		
Seitz 2009[56] related publication[57]	subgroup B (suspected malignant lesion)[c] n=158 FLL (one lesion per patient)	CEUS SonoVue® any malignancy=+ve[i]	FNB n=154 (n=4 excluded)	104	5	7	38	95.4 (95% CI 89.6 to 98.5)[a]	84.4 (95% CI 70.5 to 93.5)[a]	None	NR	NR
		CECT any malignancy=+ve		99	10	8	37	90.8(95% CI 83.8 to 95.5)[a]	82.2 (95% CI 67.9 to 92.0)[a]			
Solbiati 2006[47] (abstract only)	n=694 FLL in 686 patients, one lesion missing from analysis (per lesion data)	CEUS SonoVue® any malignancy (HCC, M, CCC)=+ve	Concordant CEUS and CT result (n=656) or fine needle biopsy where results were discordant (n=38)	478	17	7	191	96.6 (95% CI 94.6 to 98.0)[a]	96.5 (95% CI 92.9 to 98.6)[a]	1 (results missing for one lesion)	NR	NR
		CECT any malignancy (HCC, M, CCC)=+ve		486	9	4	194	98.2 (95% CI 96.6 to 99.2)[a]	98.0 (95% CI 94.9 to 99.4)[a]			
SonoVue® CEUS compared with CEMRI												
Seitz 2010[57] related publication[56]	subgroup B (suspected malignant lesion)[c] n=84 FLL (one lesion per patient)	CEUS SonoVue® any malignancy=+ve[e]	FNB n=82 (n=2 excluded)	50	5	9	18	90.9 (95% CI 80.0 to 97.0)[a]	66.7 (95% CI 46.3 to 83.5)[a]	9 lesions (6 benign and 3 malignant) ; these were classified as FP and FN, respectively, in this table	NR	NR
		Gd-CEMRI and SPIO-CEMRI in some cases (number un-specified) HCC=+ve		45	10	10	17	81.8 (95% CI 69.1 to 90.9)[a]	63.0 (95% CI 42.4% to 80.6)[a]	9 lesions (3 benign and 6 malignant) ; these were classified as FP and FN, respectively, in this table		
SonoVue® CEUS following inconclusive CECT/CEMRI												
Gierbliński 2008[54]	n=100 patients (one lesion per patient)	CEUS SonoVue® any malignancy (HCC[b] or M[e]) = +ve	FNB with clinical and imaging follow-up for biopsy –ve patients	21	2	3	74	91.3 (95% CI 72.0 to 98.9)[a]	96.1 (95% CI 89.0 to 99.2)[a]	None	NR	NR

CCC: cholangiocarcinoma; CECT: contrast enhanced computed; CEMRI: contrast enhanced magnetic resonance imaging; CEUS: contrast enhanced ultrasound; tomography; CI: confidence interval; HCC: hepatocellular carcinoma; FLL: focal liver lesion; FN: false negative; FNB: fine-needle biopsy; FP: false positive; Gd-CEMRI: gadolinium contrast-enhanced magnetic resonance imaging (vascular contrast agent); M: metastases; ND: non-diagnostic; SPIO-CEMRI: superparamagnetic iron oxide contrast-enhanced magnetic resonance imaging (hepatocyte-specific contrast agent); TN: true negative; TP: true positive

a: calculated values

b: hyper-enhancement in the arterial phase and hypo- or iso-enhancement in the portal venous and late phases

c: sub-group A (suspected benign lesions) excluded

d: hypo to high enhancement in the arterial phase; hypo-enhancement, quick wash-out, or rim-like enhancement in the portal venous phase; hypo-enhancement in the late phase

e: rim-like enhancement in the arterial phase and hypo-enhancement in the portal venous and late phases

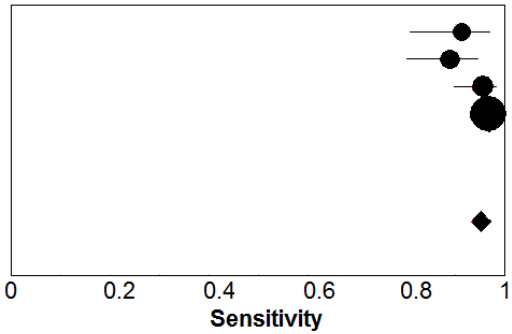
f: tortuous intra-tumoural vessels and diffuse enhancement in the arterial phase, decreasing in the portal venous and late phases

g: variable intra-tumoural vessels and heterogeneous peripheral enhancement in the arterial phase, decreasing in the portal and late phases. Dilation of the bile ducts near the tumour many be accentuated after enhancement

h: enhancing peripheral rim, variable intra-tumoural enhancement in the arterial phase, decreasing in the portal and late phases

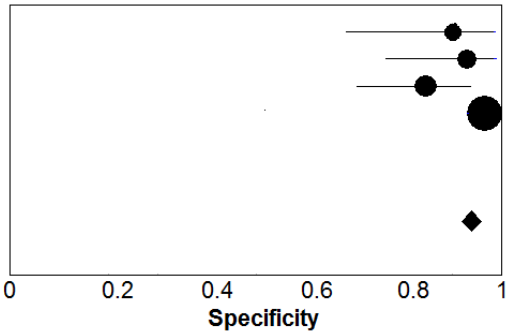
i: hypoenhancement in the late phase

Figure 4: Forest plot of sensitivity and specificity of CEUS for the detection of any liver malignancy in patients with incidentally detected FLLs



91.2% (95% CI 80.7 to 97.1%)
88.9% (95% CI 80.0 to 94.8%)
95.4% (95% CI 89.6 to 98.5%)
96.6% (95% CI 94.6 to 98.0%)

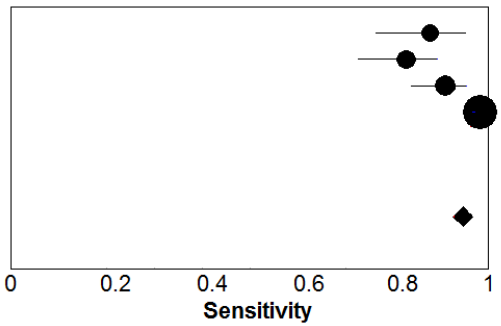
95.1% (95% CI93.3 to 96.6%)
χ^2=9.07 (p=0.028)
I^2=66.9%



90.0% (95% CI 68.3 to 98.8%)
92.9% (95% CI 76.5 to 99.1%)
84.4% (95% CI 70.5 to 93.5%)
96.5% (95% CI 92.9 to 98.6%)

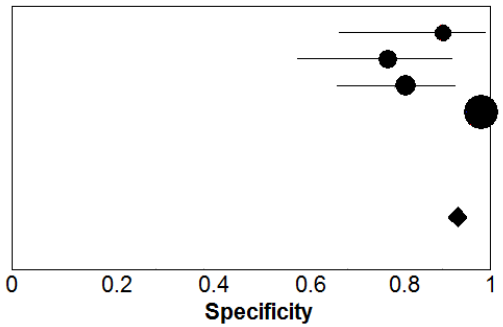
93.8% (95% CI 90.4 to 96.3%)
χ^2=8.19 (p=0.042)
I^2=63.4%

Figure 5: Forest plot of sensitivity and specificity of CECT for the detection of any liver malignancy in patients with incidentally detected FLLs



87.7% (95% CI 76.3 to 94.9%)
82.7% (95% CI 72.7 to 90.2%)
90.8% (95% CI 83.8 to 95.5%)
98.2% (95% CI 96.6 to 99.2%)

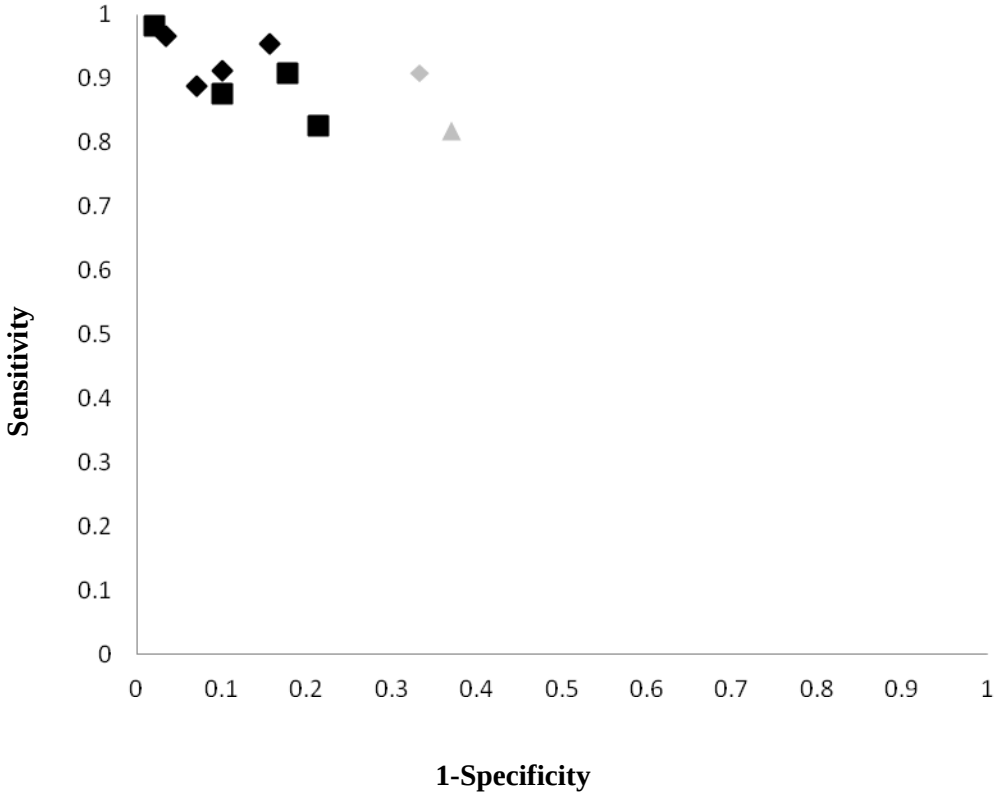
94.6% (95% CI 92.7 to 96.1%)
χ^2=37.61 (p=0.000)
I^2=92.0%



90.0% (95% CI 68.3 to 98.8%)
78.6% (95% CI 59.0 to 91.7%)
82.2% (95% CI 67.9 to 92.0%)
98.0% (95% CI 94.9 to 99.4%)

93.1% (95% CI 89.6 to 95.8%)
χ^2=22.34 (p=0.000)
I^2=86.6%

Figure 6: ROC plane plot comparing performance of imaging tests for the differentiation of malignant from benign lesions in patients with incidentally detected FLLs



black symbols: studies comparing CEUS and CECT; **grey** symbols: studies comparing CEUS and MRI; ◊: CEUS data; □: CECT data; Δ: CEMRI data

4.6.4 Accuracy of SonoVue® CEUS 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).[46, 58, 59] Two were Chinese language publications[58, 59] and the other was only published as a conference abstract.[46] The two Chinese studies reported per lesion data, with one[58] reporting only one lesion per patient and the remaining study reported only per patient data.[46] The studies assessed patients following cryosurgery,[58] RFA,[46] and 'non-surgical treatment'.[59] Sample sizes were small; in total, studies reported data for 105 lesions (102 HCC and 3 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'.

The two Chinese studies compared CEUS with CECT or CEMRI (numbers of patients receiving CECT and CEMRI, respectively, were not specified),[58] and with CECT.[59] Both studies reported similar, high, sensitivity (95.5% to 100%) and specificity (83.3% to 100%) for all imaging modalities, though small sample sizes resulted in wide confidence intervals (Table 10). One study reported sufficient data to allow the calculation of sensitivity and specificity for the combination of CEUS and CECT, where a negative finding on either imaging technique was treated as 'test negative' for complete response.[59] 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%). The remaining study compared CEUS with Gd-CEMRI and included only 15 patients undergoing RFA, with five final diagnoses of 'complete ablation.'[46] 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 4.5%).

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[58]	?	?	?	?	?	☺
Lüttich 2006[46] (abstract only)	?	?	?	?	?	☺
Zhou 2007[59]	?	?	?	?	?	☺

☺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 (n)	Index test or comparator	Reference standard	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	ND	Adverse events	Acceptability to patients
Feng 2007[58] Chinese language	n=26 malignant (23 HCC, 3 M) lesions in 23 patients treated with cryosurgery	CEUS SonoVue® Test +ve=complete response to treatment	Histopathological diagnosis	20	1	0	5	100 (95% CI 83.2 to 100)[a]	83.3 (95% CI 35.9 to 99.6)[a]	None	NR	NR
		CECT or CEMRI Test +ve=complete response to treatment		21	0	1	4	95.5 (95% CI 77.2 to 99.9)[a]	100 (95% CI 39.8 to 100)[a]			
Lüttich 2006[46] (abstract only)	n=15 patients treated with RFA	Sulphur hexafluoride CEUS Test +ve=complete ablation	Biopsy	4	1	9	1	80.0 (95% CI 28.4 to 99.5)[a]	10.0 (95% CI 3.0 to 44.5)[a]	None	NR	NR
		Gd-CEMRI Test +ve=complete ablation		4	1	9	1	80.0 (95% CI 28.4 to 99.5)[a]	10.0 (95% CI 3.0 to 44.5)[a]			
Zhou 2007[59] Chinese language	n=64 HCC lesions in 56 patients who had undergone non-surgical treatment	CEUS SonoVue® Test +ve=complete 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 fine needle biopsy	45	1	1	17	97.8 (95% CI 88.5 to 99.9)[a]	94.4 (95% CI 72.7 to 99.9)[a]	None	NR	NR
		CECT Somatom balance, Siemens Test +ve=response to treatment (no enhancement)		45	1	3	15	97.8 (95% CI 88.5 to 99.9)[a]	83.3 (95% CI 58.6 to 96.4)[a]			
		CEUS + CECT Either test -ve (partial enhancement)=negative		45	1	0	18	97.8 (95% CI 88.5 to 99.9)[a]	100 (95% CI 81.5 to 100)[a]			

CECT: contrast enhanced computed tomography; CEUS: contrast enhanced ultrasound; CI: confidence interval; FN: false negative; FP: false positive; Gd-CEMRI: gadolinium-enhanced contrast MRI; HCC: hepatocellular carcinoma; ND: non-diagnostic; M: metastases; RFA: radiofrequency ablation; TN: true negative; TP: true positive
a: calculated values

4.6.5 Effectiveness of SonoVue® CEUS for treatment planning in patients with known liver malignancy

One controlled clinical compared SonoVue® CEUS with un-enhanced US (control), when added to routine imaging (CECT or CEMRI) for pre-treatment assessment of patients undergoing RFA for HCC.[60] 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 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 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 (Table 11). Finally 14 patients who were considered unsuitable for RFA after imaging assessment (9 in the CEUS group and 5 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 CEUS and control groups. Use of CEUS in the pre-treatment imaging protocol was found to significantly reduce incidence of tumour progression, new HCC and repeat RFA over a two year follow-up period; odds ratios 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 (Table 12). The use of CEUS also increased local progression free survival, mean difference 7.2 months (95% CI 6.6 to 7.8), and new tumour-free survival, mean difference 11.7 months (95% CI 11.1 to 12.3).

Table 11 provides a summary of the risk of bias assessment for this study and Table 12 summarises 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 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 only of 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 un-enhanced US, for treatment planning in patients with known liver malignancy

Study ID	Population	Intervention (n)	Comparator (n)	Outcome[b]	n with outcome (I)	n with outcome (C)	OR (95% CI)	Mean±sd (I)	Mean±sd (C)	Mean difference (95% CI)
Chen 2007[60] related publication[61]	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) [a]	NA	NA	NA
				Tumour progression	6	15	0.35 (95% CI 0.13 to 0.95)[a]	NA	NA	NA
				New HCC	13	29	0.34 (95% CI 0.16 to 0.72)[a]	NA	NA	NA
				Repeat RFA	17	36	0.33(95% CI 0.17 to 0.66)[a]	NA	NA	NA
				Local progression-free survival	NA	NA	NA	40.5±1.9 months	33.3±2.2 months	7.2 (95% CI 6.6 to7.8)[a]
				New tumour-free survival	NA	NA	NA	38.1±2.0 months	26.4±2.0 months	11.7 (95% CI 11.1 to 12.3)[a]
				Post-therapy complications	1	3	0.32(95% CI 0.03 to 3.15)[a]	NA	NA	NA

C: comparator (US); CECT: contrast-enhanced CT; CEMRI: contrast-enhanced magnetic resonance imaging; CEUS: contrast-enhanced ultrasound; CI: confidence interval; HCC: hepatocellular carcinoma; I: intervention (CEUS); NA: not applicable; OR: odds ratio; RFA: radiofrequency ablation; US: un-enhanced ultrasound

a: calculated values

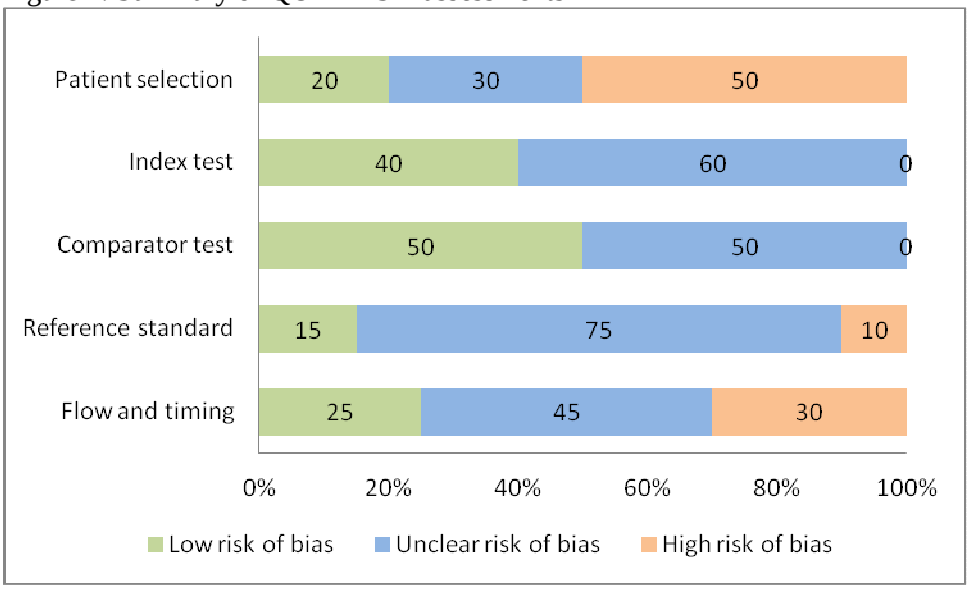
b: outcomes were determined by imaging follow-up 1 month after RFA and every following 2-3 months in the first year and 4-6 months in the second year. RFA was considered successful if there was no contrast enhancement in or around the tumour, the margins of the ablation zone were clear and smooth, the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

4.7 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 un-enhanced US; four compared the performance of imaging modalities for the detection of liver metastases in patients with known primary cancers (CRC); six compared the performance of imaging modalities for the characterisation of incidentally detected FLLs identified by un-enhanced US; three compared the performance of imaging modalities for the determination of treatment response in patients with liver cancers.

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 only reported 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 patients 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 latter two studies were also rated as 'high' risk of bias for the 'reference standard' domain.

Figure 7: Summary of QUADAS-2 assessments



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 (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 wash-out, arterial enhancement alone, and portal venous wash-out 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 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 sensitivity estimate arising from a study which included very small (≤10 mm) FLLs. Two studies comparing all three imaging modalities reported similar, high (>90% in most cases) specificity estimates 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; 82% and 44% for Gd-CEMRI. Sensitivity estimates from these two studies were generally lower than those for studies which 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 ≤10mm (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 where 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 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, where very small FLLs (<10 mm) are not considered.

Studies of the diagnosis of liver metastases using imaging with vascular contrast media (CEUS, CECT, and Gd-CEMRI), where definitions of a positive imaging test were reported,

gave various descriptions of peripheral rim enhancement as the criteria 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 colorectal carcinoma (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 wash-out 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,[13] Table 1, section 2.2. 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 un-specified 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, where 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 live 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 >95% and specificity estimates >80% for complete response, using CEUS, CECT and CECT or Gd-CEMRI. 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 pre-treatment 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 un-enhanced 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.

5 ASSESSMENT OF COST-EFFECTIVENESS

5.1 Search strategy

Searches were undertaken to identify cost-effectiveness studies of ultrasound, 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 [31]. 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 present:

- MEDLINE (2000-2011/09/wk4) (OvidSP)
- MEDLINE In-Process Citations and Daily Update (2000-2011/10/10) (OvidSP)
- EMBASE (2000-2011/wk 40) (OvidSP)
- NHS Economic Evaluation Database (NHS EED) (2000-2011) (via Cochrane Library)
- NHS Economic Evaluation Database (NHS EED) (2011/01/01-2011/10/12) (CRD website)
- Health Economic Evaluation Database (HEED) (2000-2011/10/12) (Wiley) http://onlinelibrary.wiley.com/book/10.1002/9780470510933
- Science Citation Index (SCI) (2000-2011/10/07) (Web of Science)

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

- National Guidelines Clearinghouse (NGC) (2005-2011/11/10) (Internet) http://www.guideline.gov/
- GIN: International Guidelines Library (GIN) (2005-2011/11/10) http://www.g-i-n.net
- National Institute for Health and Clinical Excellence (NICE) Guidance (up to 2011/11/10) (Internet) http://guidance.nice.org.uk/
- TRIP database (limited to Guidelines) (2005-2011/11/10) (Internet) http://www.tripdatabase.com/
- Health Technology Assessment Database (HTA) (2005-2011/11/10) (CRD website)

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

References in retrieved articles were checked for additional studies.

5.2 Review of Economic analyses of SonoVue®

We screened 1194 titles and abstracts, from which we selected 40 papers. After full paper screening we excluded 36 studies and kept 4, which matched our inclusion criteria of an economic analysis which related to SonoVue®. A summary of each of these studies is provided in Table 13 with a quality check-list based on Drummond et al. (Table 14).[64]

Faccioli et al[65] developed a decision model in order to assess the costs of testing for benign focal liver lesions (BFLLs) after the introduction of contrast-enhanced ultrasound. 398 BFLL (angiomas, focal nodular hyperplasias, and pseudolesions) patients with suspicious lesions at baseline US from department of radiology in 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.

Equipment costs (purchase and service contract costs), agents and related costs (contrast agents, saline solution, medical supplies, and films), and human resource costs (radiologist, technician, nurse, 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 staffs and administrators (per. Minute) were derived from Societa Italiana di Radiologia Medica (SIRM) publication. The formula for the total saving calculation was CT*n-[(CEUS-US)*n], with n representing the number of examinations. The cost year was 2006.

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

Romanini [66] et al conducted a multicentre prospective study to evaluate the economic and clinical outcomes after the introduction of CEUS in diagnostic procedures for incidentally

detected FLLs. Four hundred and eighty five patients presenting with uncharacterised FLLs, without liver cirrhosis, were recruited in the study from January 2002 to October 2005. All patients underwent two diagnostic strategies, i.e. 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, CEUS was 76.13 euros, CT with or without contrast agent was 164.75 euros and 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, i.e. 162.70 euros per patient. From the hospitals' perspective, the total expenditure incurred by the conventional approach was 147,045 euros, compared to 61,979 euros by the CEUS strategy. The reimbursement to the hospital per person for conventional strategy was 277 euros, 26 euros less than the original spending by the hospital; for CEUS strategy, reimbursement agency only paid 114.79 euros for the hospital, 13 euros less than the hospital's spending.

Sirli[67] et al 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 detection. All the CEUS liver evaluations performed during September 2009 to March 2010 were included in the study. The cost of a CEUS positive diagnosis was compared with a CECT and/or CEMRI positive diagnosis. The-cost of CECT/CEUS examination was added when the CEUS result was inconclusive:

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

CEUS provided conclusive diagnoses 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 205400 RON for CEMRI. To sum up, by adopting CEUS as first line FLL detection, the cost saving per person was 45.5 RON compared with CT as first line and 334.2 RON with MRI as first line.

Sangiovanni et al[52] conducted a study to assess the diagnostic accuracy and also the economic impact of all possible diagnostic strategy combinations in characterising FLLs (including only 1-2 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 the cost using two approaches. The first was in accordance with American Association for the Study of Liver Disease (AASLD) guideline, where the final diagnosis of HCC needed concordant results from at least two imaging techniques; a third examination only recommended when the previous two were discordant. FNB was only performed 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 only performed if all 3 scans were inconclusive.

- The AASLD approach implied 3 possible permutations i.e.
  - 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 6 possible permutations i.e.
  - 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 per person. This strategy was 79 euros cheaper per person compared with CEUS+MRI→CT→FNB and 144 euros cheaper per person than CT+MRI→CEUS→FNB. The most inexpensive strategy by study criteria approach was CEUS→CT→MRI→FNB: 535 euros per person, within the range of 9 to 45 euros cheaper compared to the rest of strategies.

The study conducted by Zaim et al[68] assessed cost-effectiveness when CEUS was applied as the second line imaging technique in FLL characterisation. Patients with an 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 six months of follow-up. Those with malignant lesions were treated with curative or palliative treatments. Costs included diagnostic techniques (US, CEUS, CT, MRI, laboratory tests, and liver biopsy), surgical resection, intensive care stays, duration of hospitalisation, outpatient visits, various treatment strategies (radiofrequency ablation (RFA), transarterial chemoembolisation (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. 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 8,309 euros; this was less than that for patients following the conventional strategy, which was 8,761 euros per person. The aggregate cost saving was 452 euros per person, of which 160 euros constituted the diagnostic phase and 292 euros treatment phase. Total discounted life years (LYs) gained per patient were 1.538 for CEUS strategy and 1.536 for conventional strategy. The results of probabilistic sensitivity analyses indicated that, when the cost-effectiveness threshold was 20,000euros/LY, the CEUS strategy was cost-effective in 90% of the simulation and MRI/CT strategy was cost-effective in only 10% of simulation.

Although all 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 was the only paper which modelled disease management and reported relevant health outcomes; however, the follow-up lasted only 24 months.

Table 13: Summary of economic studies

Study details	Şirli et al. [67]	Zaim et al. [68]	Romanini et al [66]
Time horizon	Not available	24 months	NA
Objective	To evaluate if CEUS is a cost-efficient method for the first-line	To evaluate cost-effectiveness of application of CEUS as a diagnostic imaging technique in the front-line characterization of FLL in the Netherlands	To evaluate the clinical and economic consequences of the introduction of CEUS into the diagnostic clinical algorithm for the characterization of incidental FLLs
Source of effectiveness information/testing accuracy data	316 FLLs were included in CEUS evaluation performed during 6 months period	A total of 170 prospectively enrolled patients older than 18 years were included in a single centre study at EMC, NL	The inclusion of participants are consecutive patients with FLL presenting from Jan. 2002 to Oct. 2005(In total 575FLLs)
Comparators	1. CEUS→CECT(if the result is inconclusive) 2. CEUS→CEMRI(if the result is inconclusive 3. CECT 4. CEMRI	1. CEUS 2. CEMRI 3. CECT 4. Reference standard	1. US→CEUS→(if inconclusive)CECT/CEMRI 2. US→CECT/CEMRI→(if inconclusive) CEMRI
Reference standard	Not available	Imaging (MRI/CT), biopsy/surgical specimens, and clinical judgment	CECT/CEMRI
Unit costs	Source: mean costs practiced in Timisoara	Source: Farmacotherapeutisch Kompas (CVZ), Dutch tariffs and Erusmus Medical Centre (EMC) (all costs reported in 2009 were inflated to 2010 values using Centraal Bureau voor de Statistiek(CBS) Netherlands website)	NHS Italy and hospitals
Measure of benefit	Is measured by the amount of money saved	Life year gained	Is measured by the amount of money saved
Study type	Costs comparison study (prospective study)	Cost-effectiveness study	Cost analysis
Model assumptions	NA	1. The costs and effectiveness calculation for metastatic patients does not include secondary sites 2. Life expectancy of benign group was assume to be the same 3. It was assumed that time horizon does not capture patients undergoing liver transplantation-only screening for liver transplantation was included in the analysis	NA

Study details	Şirli et al. [67]	Zaim et al. [68]	Romanini et al [66]
		4. All treatment, follow-up and non-follow-up costs and probabilities were assumed based on the reference standard	
Perspective	NA	Hospital in Netherland	NHS and hospitals in Italy
Discount rate	NA	Costs: 4% Effects: 1.5%	NA
Uncertainty around cost-effectiveness ratio expressed	NA	*CEUS strategy was cost-effective at a threshold of 20,000euro/LY in 90% of the simulation *MRI/CT strategy was be cost-effective at a threshold 20,000euro/LY in 10% of the simulation	NA
Sensitivity analysis	NA	Resource use and unit costs data were tested by varying the costs by +30% and -30% from the mean	NA
Outcome (cost and Lys/QALYs) per comparator	*CEUS first-line+ CT second line=75,690 *CEUS first-line+ MRI second line=99,780 *CT first-line=90,060 MRI first-line=105,620 (currency=RON)	*Total discounted per patient costs with CEUS= 8,379euro *Total discounted per patient costs with MRI/CT= 8,761euro *Total discounted per patient life years(LYs) were 1.538 for CEUS *Total discounted per patient life years(LYs) were 1.536 for MRI/CT	NHS: *US→CT/MRI:134,576.60euro *US→CEUS:55,674.30euro Hospitals: *US→CT/MRI:147,045euro *US→CEUS:61,979euro
Summary of incremental analysis		*Incremental per patient cost for CEUS was estimated -452euro(-160euro for diagnostic phase and -292euro for treatment phase)	*Total saving for NHS:78,902euro (162.70euro per patient) *Total saving for hospitals:85,065.96euro (175.39euro per patient)

Study details	Faccioli et al. [65]	Sangiovanni et al.2010[52]
Time horizon	NA	NA
Objective	To perform a cost analysis of CEUS in the study of benign FLL with intermediate appearance on US.	To assess the sensitivity, specificity, diagnostic accuracy and economic impact of all possible sequential combinations of contrast imaging techniques in patients with cirrhosis with 1-2 cm liver nodules undergoing US surveillance.
Source of effectiveness	398 BFLL patients between	64 patients with 67 de novo liver

Study details	Faccioli et al. [65]	Sangiovanni et al.2010[52]
information/testing accuracy data	2002 and 2005	nodules
Comparators	US→CEUS→(when inconclusive)MRI/CT	➢ AASLD approach • 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 ➢ Study criteria • 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
Reference standard	NA	Histology FNB
Unit costs	*Hospital Administrative Office *Societa Italiana di Radiologia Medica (SIRM) publication *Resource Management Service of this hospital	Italian National Health System
Measure of benefit	Is measured by the amount of money saved	Is measured by the amount of money saved
Study type	Cost analysis	Cost analysis
Model assumptions	NA	NA
Perspective	Radiology Department of this hospital	Italian NHS
Discount rate	NA	NA
Uncertainty around cost-effectiveness ratio expressed	NA	NA
Sensitivity analysis	NA	NA
Outcome (cost and	Total cost saving from 2002	➢ AASLD approach

Study details	Faccioli et al. [65]	Sangiovanni et al.2010[52]
Lys/QALYs) per comparator	to 2005:47055.33 euros	• CEUS and CT→(when inconclusive)MRI→ (if required)FNB: 26440 euros (479 euros per patient) • CEUS and MRI→(when inconclusive)CT→ (if required)FNB: 30922 euros (558 euros per patient) • CT and MRI→(when inconclusive)CEUS→(if required)FNB: 33898 euros (623 euros per patient) ➢ Study criteria • CEUS→ (when inconclusive)CT→ (when inconclusive)MRI→ (if required)FNB: 28667 euros (535 euros per patient) • CEUS→ (when inconclusive)MRI→ (when inconclusive)CT→ (if required)FNB:30215 euros (545 euros per patient) • CT→(when inconclusive)CEUS→(when inconclusive)MRI→ (if required)FNB: 28909euros (544 euros per patient) • CT→(when inconclusive)MRI→(when inconclusive)CEUS→ (if required)FNB: 29346 euros (553 euros per patient) • MRI→(when inconclusive)CEUS→(when inconclusive)CT→ (if required)FNB: 30970euros (580 euros per patient) • MRI→(when inconclusive)CT→(when inconclusive)CEUS→ (if required)FNB: 30607 euros (577 euros per patient)
Summary of incremental analysis	Equivalent to 118.23 euros saving per person	

Table 14: Economic study quality checklist

	Sangiovanni et al [52]. 2011	Sirli et al [67]. 2010	Romanini et al [66]. 2007	Faccioli et al [65]. 2007	Zaim et al [68]. 2011
Study design					
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	√	√	√	√	√
Data collection					
The source(s) of effectiveness estimates used are stated	√	√	√	√	×
Details of the design and results of 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 were 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	√	√	×	√	×

	Sangiovanni et al [52]. 2011	Sirli et al [67]. 2010	Romanini et al [66]. 2007	Faccioli et al [65]. 2007	Zaim et al [68]. 2011
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	√	√	√	√	√
Analysis and interpretation of results					
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
Details of statistical tests and confidence intervals 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	√	√	√	√	√

5.3 Model structure and methodology

In the health economic analysis, the cost-effectiveness of contrast enhanced ultrasound using the contrast agent SonoVue® (CEUS) for the assessment of adults with focal liver lesions, in whom un-enhanced ultrasound or other liver imaging is inconclusive. In the analyses we focused on the clinical applications where the most data on test performance was available for (see previous chapters), and where 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:

- Detection of hepatocellular carcinoma through surveillance of patients with cirrhosis;
- Detection of liver metastases in patients with colorectal cancer;
- Characterisation of incidentally detected focal liver lesions.

The comparators included the following liver imaging techniques:

- Contrast enhanced computer tomography (CECT);
- Contrast enhanced magnetic resonance imaging using gadolinium as contrast agent (Gd-CEMRI);
- Contrast enhanced magnetic resonance imaging using superparamagnetic iron oxide as contrast agent (SPIO-CEMRI).

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

- A cirrhosis surveillance model;
- A liver metastases of colorectal cancer model;
- An incidentally detected focal liver lesions (FLL) model.

In all models the mean costs, life years gained 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, below.

5.3.1 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). [9] This model was developed to assess the cost-effectiveness of several surveillance strategies in cirrhotic patients using periodic serum α-fetoprotein (AFP) testing and/or liver ultrasound examination with CT as a confirmatory imaging technique, to detect HCC, followed by

treatment with liver transplantation or resection, where appropriate. One of the research recommendations made by the authors was to assess the value of contrast-enhanced ultrasound 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.

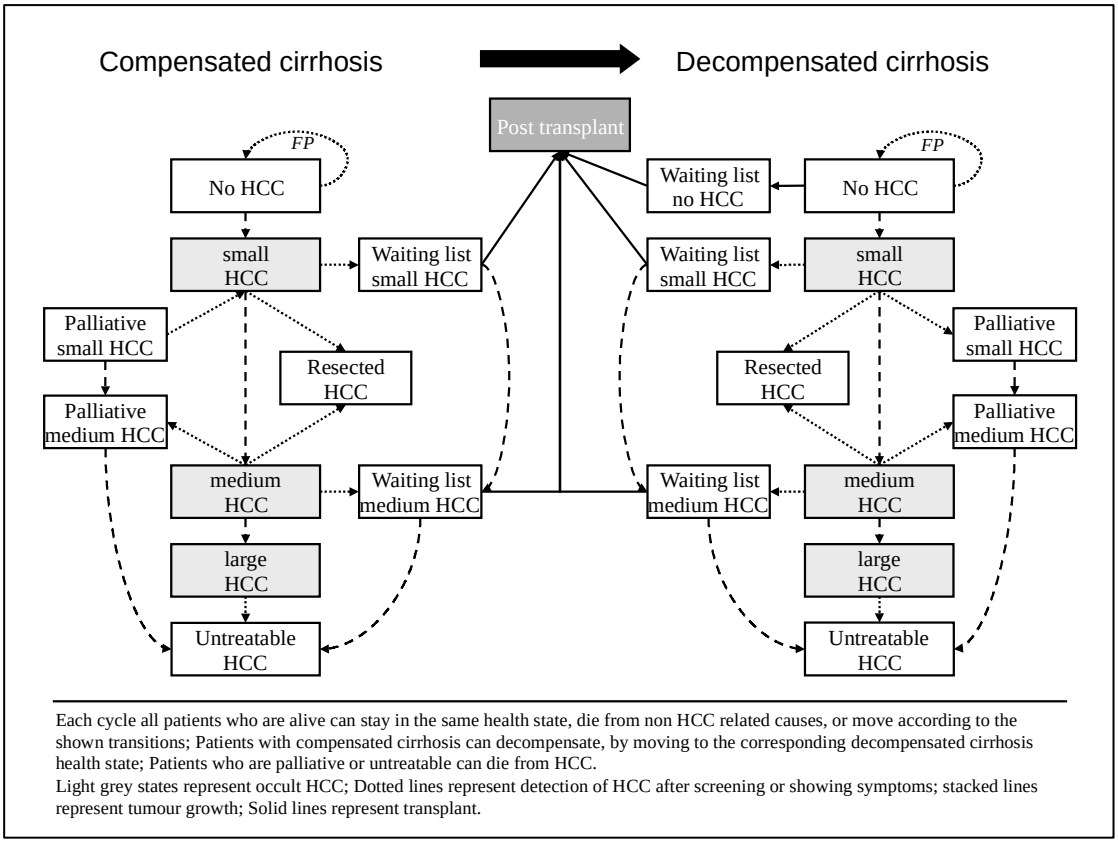
The population of interest in the cirrhosis surveillance model in this assessment consisted of persons with a diagnosis of compensated cirrhosis deemed eligible to enter a surveillance programme (aged 70 years or less with no pre-existing medical conditions that would preclude treatment with liver transplant 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. [9] A probabilistic state transition (Markov) cohort model, constructed using Excel, was used. The time horizon was lifetime and the cycle duration was one 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 people with compensated and decompensated cirrhosis. People 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 people 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 surrogate measure of all characteristics of tumour progression. Hence, tumour progression was modelled by a tumour growth rate. Detectability and treatability of the tumour are dependent on the tumour size. For example, for larger tumours there is a greater likelihood of detection. Incidental/symptomatic presentation of HCC is possible for people with both compensated and decompensated cirrhosis, for all tumour sizes, although with significantly lower probabilities for small and medium sized tumours.

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 un-enhanced ultrasound followed by CEUS, CECT, Gd-CEMRI or SPIO-CEMRI as a confirmatory imaging test. In the base case analysis surveillance was every six months, and stopped for people who reached the age of 70 years. It was also assumed that compliance was 100%. The decisions trees are shown in Figure 9.

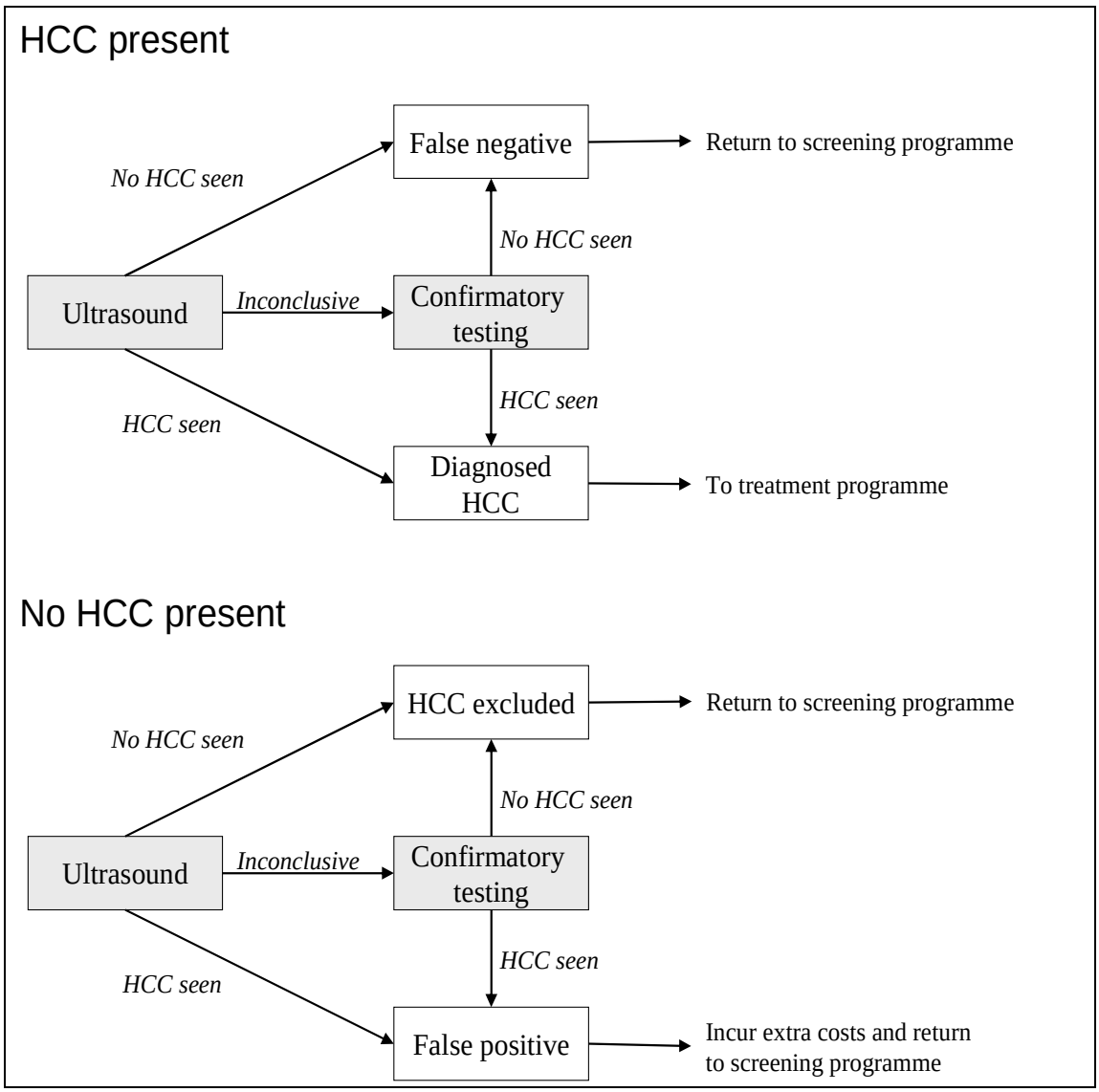
Figure 8: Model diagram Cirrhosis Surveillance, based on Thomson Coon et al.[9]



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 prioritization of people waiting for a transplant. During the time on the waiting list people are subject to the same natural history process as those 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 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 percutaneous ethanol injection (PEI), radiofrequency ablation (RFA) and transarterial chemoembolisation (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 transarterial chemoembolosation for a proportion of these people. An overview of the key structural assumptions is provided in below. A more detailed description of the model structure can be found in Thompson Coon et al. [9]

Figure 9: Decision trees for the cirrhosis model



The confirmatory tests are the comparators in this analysis: CEUS, CECT, Gd-CEMRI, SPIO-CEMRI.

Summary of structural assumptions (adapted from Thompson Coon et al.) [9]

- All tumours are uni-nodular, 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 an 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 old.
- 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 work-up.
- 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.

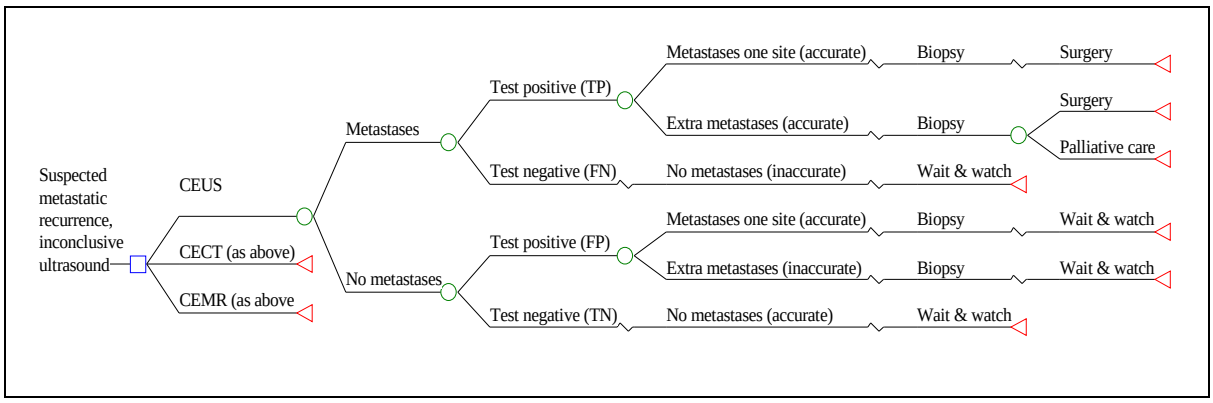
5.3.2 Liver metastases of colorectal cancer model

The colorectal cancer metastases model is a modified version of the metastatic model developed by Brush et al. [11] This model was developed to assess the cost-effectiveness of FDG PET/CT as an add-on device in detecting metastatic cancer compared to conventional imaging (CT). The model was adapted to assess the cost-effectiveness of CEUS compared to CECT , Gd-CEMRI and SPIO-CEMRI in detecting metastases from colorectal cancer after an inconclusive un-enhanced ultrasound scan. In addition to changing the comparators in the model, we added the costs of a whole body CT scan for all patients with positive test to detect whether metastases at extra sites are present. We also changed the way false-positives were handled, and changed the watch and wait strategy to correspond with latest guidance. The watch and wait strategy was not only given 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 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 one 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 un-enhanced abdominal ultrasound scan. When this ultrasound was deemed inconclusive, the patient entered the decision tree. He could then receive CEUS, CECT, Gd-CEMRI or SPIO-CEMRI. Similarly to the Brush model, the decision tree splits the patient population according to their true disease status (metastatic recurrence or no metastatic recurrence) prior to applying the diagnostic test accuracy estimates, so that accurate and inaccurate diagnoses can be identified.

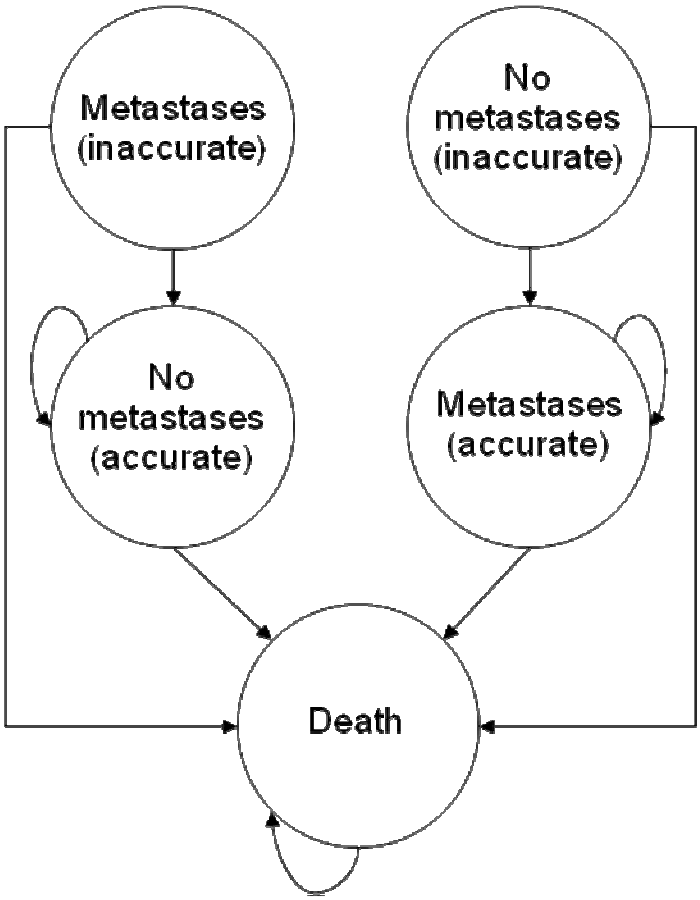
Figure 10: Graphical representation of the liver metastases from colorectal cancer model



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 biopsy to confirm the metastases before treatment and it was assumed that biopsy is 100% accurate. Thus, in contrast to the Brush model, 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., [11] it was assumed that all patients with metastases at a single site will receive pre-operative chemotherapy and surgery for metastases, and that patients with metastases at multiple sites are assumed to be non-curable and will receive either pre-operative chemotherapy followed by surgery and palliative care, or chemotherapy and palliative care. In line with the Brush model, patients with a negative test result are followed up in a watch and wait strategy for three years. Also in line with the Brush 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 (either CEUS, CECT, Gd-CEMRI or SPIO-CEMRI, depending on the comparator), a whole body CT and a biopsy.

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 three years, patients without metastases and those who were treated, were assumed to be followed up using the wait and watch strategy.

Figure 11: Simplified schematic diagram of the Markov model for follow-up of patients in the CRC metastases model



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 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 biopsy and are therefore not treated for their metastases.

- All patients with metastases at a single site will receive pre-operative chemotherapy and metastatic surgery.
- Patients with both hepatic and extra-hepatic metastases are assumed to be non-curable and will receive one of two treatment options: pre-operative 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 three 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.

5.3.3 Incidentally detected FLL model

Patients with incidentally detected focal liver lesions (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.

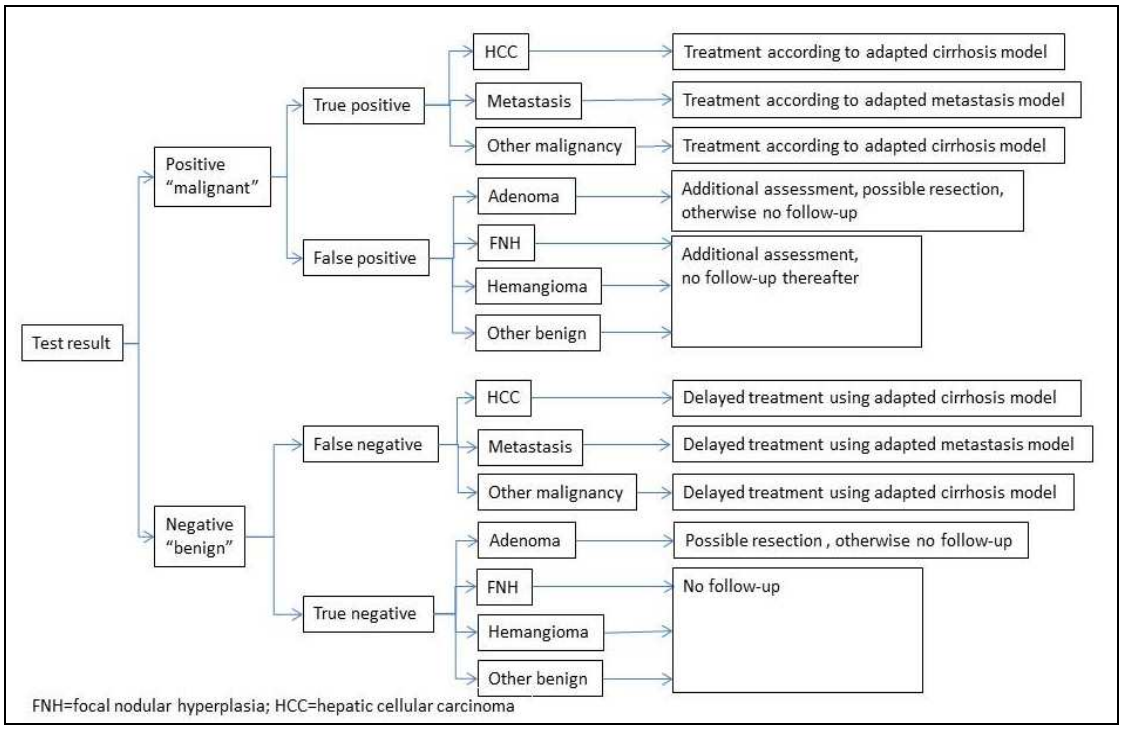
The prognosis, costs and QALYs seen amongst patients diagnosed with HCC were modelled using the cirrhosis model, while the prognosis, costs and QALYs amongst patients with liver metastases were modelled using the liver metastases model. The incidentally detected FLL model therefore incorporated elements of the cirrhosis model described above in section 5.3.1, elements of the liver metastases model described in section 5.3.2, 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, while none of the patients in the cirrhosis surveillance model have HCC at the start of the simulation, all HCC patients in the incidentally detected FLL model will have it at the start of the simulation.

The economic and health consequences of false positive and false negative results were modelled in the following ways. Firstly, it was assumed that patients with HCC who were not correctly identified at baseline would be correctly diagnosed within several months, since 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 which would bias the assessment against CEUS and in favour of the comparators (CECT, CEMRI), since a false positive result might lead to even greater costs than simply one extra visit and since CEUS was found to have a lower rate of false positives in the diagnostic test accuracy studies.

The costs, life-years and QALYs seen with patients having a malignancy other than HCC or metastases were assumed to be equal to those seen with HCC patients (see Figure 12). These other types of malignant lesions (e.g. lymphoma) were infrequently seen amongst 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 amongst 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 limited effect on the cost-effectiveness of CEUS versus the comparators for two reasons: the values for sensitivity of CEUS and the comparators were very similar and the prior 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.

Figure 12: Description of patient categories and their treatments used in the incidentally detected FLL model



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 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 due to 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 focal liver lesions that are metastatic can be estimated using the model for liver metastasis from colorectal cancer, because the highest proportion of liver metastases will originate from CRC. For example, Catala et al. 2007[53] reported that 7 of the 12 patients with metastases in their study had colorectal cancer, and this corresponds with findings elsewhere in the literature as well as frequencies reported by one of the clinicians queried during this study.

5.4 Model parameters

5.4.1 Cirrhosis surveillance model

5.4.1.1 Test performance

It was assumed that the surveillance strategy started with unenhanced ultrasound. The test performance of ultrasound used in the model was based on the study by Bennett et al, 2002,[69] as used in the HTA report by Thompson Coon et al. [9] 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).

Table 15: Test performance of ultrasound used in the decision trees for cirrhosis model (based on Bennett et al.) [69]

Parameter		**Value**	**Distribution**				
				TP	**FN**	**FP**	**TN**
Sensitivity	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 above			

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

Additional imaging takes place following an inconclusive un-enhanced ultrasound. The percentage of un-enhanced ultrasound examinations which are inconclusive was estimated to be 43%, based on information provided by the manufacturer of SonoVue® during the scoping phase of this assessment. In the systematic review seven studies[10, 14, 48-51, 62] 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 detecting a HCC, as well as the proportion of people with a false positive test result, were taken from the study by Leoni et al.[10] The main reason for using this study was that this study used diagnostic criteria matching the EFSUMB guidance on the use of CEUS, [13] and reported data on the performance of CEUS, CECT and Gd-CEMRI in the same population, while most other studies compared CEUS to either CECT or CEMRI. A potential disadvantage of using Leoni et al was the use, in this study, of a sub-optimal 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 (2-5 cm) tumours. The sensitivity for the

detection of large HCCs was assumed to be 100% for all confirmatory imaging tests and this assumption was agreed by the clinical experts.

Table 16: Test performance of confirmatory imaging used in the decision trees for cirrhosis model (based on Leoni et al.)[10]

Parameter		**Value**	**Distribution**				
				TP	**FN**	**FP**	**TN**
Sensitivity for detecting	CEUS	0.67	Dirichlet	37	18	2	18
small and medium tumours*	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 above			
	CECT	0.03	Dirichlet	See above			
	Gd CEMRI	0.01	Dirichlet	See above			

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

5.4.1.2 Transition probabilities

The transition probabilities were all taken from the cirrhosis surveillance model reported in Thompson Coon et al. [9] 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.

Table 17: Parameters used in cirrhosis Markov model affecting transition probabilities

Parameter		**Value**	**Source**	**Distribution**		**Range of values used in sensitivity analysis**	
						lower	**upper**
Mean age at start	ALD	53.3	Roberts et al. [70]	Normal	Se = 0.1789	43.3	63.3
	HBV	44.0	Fattovich et al. [71]	Normal	Se = 0.1789	34.0	54.0
	HCV	54.0	Fattovich et al. [72]	Normal	Se = 0.1789	44.0	64.0
% male	ALD	67.1	ONS [73]	Beta	$\alpha = 211, \beta = 90$	50.0	90.2
	HBV	86.5	Fattovich et al. [71]	Beta	$\alpha = 302, \beta = 47$	82.6	89.7
	HCV	58.1	Fattovich et al. [72]	Beta	$\alpha = 223, \beta = 161$	53.1	62.9
Upper age limit for surveillance		70	AA*	Lognormal	Mean of logs = 4.249, σ = 0.006	60	80
Composition of mixed aetiology cohort	ALD	57.6	EO#	fixed		-	-
	HBV	7.3	EO#	fixed		-	-
	HCV	35.1	EO#	fixed		-	-
Annual incidence of cirrhosis decomposition	ALD	3.3%	Assumed same as HBV	Beta	$\alpha = 5, \beta = 156$	-	-
	HBV	3.3%	Fattovich et al. [74]	Beta	$\alpha = 5, \beta = 156$	-	-
	HCV	5.3%	Fattovich et al. [74]	Beta	$\alpha = 7, \beta = 129$	-	-
Annual incidence of HCC	ALD	1.7%	Fattovich et al. [75]	Beta	$\alpha = 10, \beta = 574$	-	-
	HBV	2.2%	Fattovich et al. [75]	Beta	$\alpha = 9, \beta = 392$	-	-
	HCV	3.7%	Fattovich et al. [75]	Beta	$\alpha = 47, \beta = 1237$	-	-
Tumour growth rate	Small to medium	0.056	Taouli et al. [76]	Beta PERT^	$\lambda = 4$	0.036	0.089
	Medium to large	0.036	Taouli et al. [76]	Beta PERT^	$\lambda = 4$	0.023	0.056
Annual symptomatic /incidental presentation rate for HCC	Small	1.6%	Rates calibrated to be in line with Trevisani et al. [77]	Beta	$\alpha = 160, \beta = 9840$	0%	16.2%
	Medium	12.1%		Beta	$\alpha = 121, \beta = 879$	0%	30.3%
	Large	50%		Beta	$\alpha = 500, \beta = 500$	0%	100%
Proportion with decompensated cirrhosis who are listed for OLT		90%	AA*	Beta PERT^	$\lambda = 4$	80%	100%
Proportion with HCC who receive resection	Small	20%	AA*	Beta PERT^	$\lambda = 4$	10%	30%
	Medium	5%	AA*	Beta PERT^	$\lambda = 4$	2%	10%
Proportion with HCC who are listed for OLT	Small	75%	AA*	Beta PERT^	$\lambda = 4$	65%	85%

Parameter		Value	Source	Distribution		Range of values used in sensitivity analysis	
						lower	upper
	Medium	85%	AA*	Beta PERT^	λ = 4	80%	88%
Proportion with HCC who are deemed surgically untreatable	Small	5%	AA*	fixed			
	Medium	10%	AA*	fixed			
Monthly probability of receiving OLT once on waiting list		0.2541	UK Transplant[78]	Beta	α = 577, β = 1694	-	-
Annual mortality rate due to compensated cirrhosis		0%	AA*	fixed		-	-
Annual mortality rate due to decompensated cirrhosis	ALD	17.7%	Average HBV & HCV	Beta	α = 17, β = 81	12.7%	32.5%
	HBV	22.5%	Fattovich et al. [74]	Beta	α = 7, β = 26	18.9%	32.5%
	HCV	12.9%	Fattovich et al. [72]	Beta	α = 8, β = 57	12.7%	14.0%
90 day mortality rate for patients undergoing OLT	ALD	6.0%	UK Transplant [78]	Beta PERT^	λ = 4	0.0%	12.6%
	HBV	15.0%	UK Transplant [78]	Beta PERT^	λ = 4	4.7%	25.3%
	HCV	7.4%	UK Transplant [78]	Beta PERT^	λ = 4	3.0%	11.8%
Proportion of patients surviving 1 year following OLT	ALD	92.0%	UK Transplant [78]	Beta PERT^	λ = 4	84.5%	99.5%
	HBV	78.0%	UK Transplant [78]	Beta PERT^	λ = 4	65.9%	90.1%
	HCV	87.6%	UK Transplant [78]	Beta PERT^	λ = 4	81.9%	93.3%
Proportion of patients surviving 5 year following OLT	ALD	54.7%	UK Transplant [78]	Beta PERT^	λ = 4	38.2%	71.3%
	HBV	68.5%	UK Transplant [78]	Beta PERT^	λ = 4	54.3%	82.8%
	HCV	55.8%	UK Transplant [78]	Beta PERT^	λ = 4	41.0%	70.6%
90 day mortality rate for patients undergoing resection		3.9%	Llovet et al. [79]	Beta PERT^	λ = 4	1.3%	10.8%
Proportion of patients surviving 1 year following resection		85.0%	Llovet et al. [79]	Beta PERT^	λ = 4	79.0%	88.0%
Proportion of patients surviving 3 year following resection		62.0%	Llovet et al. [79]	Beta PERT^	λ = 4	54.0%	76.0%
Proportion of patients surviving 5 year following resection		51.0%	Llovet et al. [79]	Beta PERT^	λ = 4	36.0%	58.0%
Annual mortality rate associated with occult large HCC		72.9%	Greten et al. [80]	Beta PERT^	λ = 4	34.6%	97.3%
Annual mortality rate associated with known large HCC		64.4%	Greten et al. [80]	Beta PERT^	λ = 4	33.6%	84.8%

* Author assumption in Thompson Coon et al. [9]

Expert opinion in Thompson Coon et al. [9]

^ In the beta PERT distribution λ is the scale parameter that scales the height of the distribution. If the scale parameter equals 4, the distribution approximates the normal distribution.

5.4.1.3 Costs

The costs of CEUS (in addition to un-enhanced ultrasound) were based on expert opinion, both from clinicians and the manufacturer. The costs of the contrast were assumed to be £48.70 (estimate supplied by the manufacturer and agreed by clinicians). These costs include the costs of cannulation. In addition, we expected CEUS to take more time than the un-enhanced ultrasound. Therefore, we used the difference between the reference costs of an ultrasound of less than 20 minutes (£55) and an ultrasound of more than 20 minutes (£71) as the additional time costs of CEUS.[81] 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 appointment, orthotopic liver transplantation (OLT) and resection were based on NHS Reference Costs (NSRC) 2011.[81]

All other cost inputs were based on Thompson Coon et al.,[9] and recalculated to the 2011 price level.[82] A detailed description of these costs can be found in the above referenced HTA report. The parameters used in the model affecting costs are listed in Table 18.

Table 18: Parameters used in cirrhosis Markov model: values affecting costs

Parameter	Value		Source	Distribution	Range of values used in sensitivity analysis	
					lower	upper
Unit costs						
Ultrasound scan	£55	Per scan	NSRC [81]	Beta PERT^	£40	£65
SonoVue contrast agent	£49	Per scan	Expert opinion	Beta PERT^	£40	£60
Additional time for contrast enhanced ultrasound	£16	Per scan	NSRC [81]	Beta PERT^	£0	£39
CECT (one area)	£116	Per scan	NSRC [81]	Beta PERT^	£88	£126
Gd CEMRI (one area)	£189	Per scan	NSRC [81]	Beta PERT^	£137	£226
SPIO CEMRI (one area)	£189	Per scan	NSRC [81]	Beta PERT^	£137	£226
Outpatient appointment	£150	Per appointment	NSRC [81]	Beta PERT^	£72	£228
OLT	£26,329	Per operation	NSRC [81]	Beta PERT^	£20,169	£38,406
Resection	£6,521	Per operation	NSRC [81]	Beta PERT^	£1,812	£7,246
State costs		Thompson Coon et al. [9], updated to 2011				
All compensated cirrhosis states	£1,394	Per year		Beta PERT^	£867	£1.961
All decompensated cirrhosis states	£11,335	Per year		Beta PERT^	£7,738	£14,931
All known HCC states	£1,486	Per year*		Beta PERT^	£743	£2,971
Post-OLT (year 1)	£11,923	Per patient per year		Beta PERT^	£5,835	£18,021
Post-OLT (year 2 onwards)	£1,889	Per patient per year		Beta PERT^	£992	£2,796
Post resection	£4,266	Per patient per year		Beta PERT^	£2,824	£5,752
Palliative care (small & medium)	£1,955	Per year*		Beta PERT^	£977	£3,909
Palliative care (large)	£214			Beta PERT^	£106	£428
Event costs		Thompson Coon et al. [9], updated to 2011				
False-positive diagnosis	£618	Per false positive diagnosis		Beta PERT^	£419	£961
Symptomatic/incidental diagnosis	£198	Per diagnosis		Beta PERT^	£94	£287

^ In the beta PERT distributions λ (the scale parameter that scales the height of the distribution) equals 4, which means the distribution approximates the normal distribution.

5.4.1.4 Utilities

Utilities were taken from the HTA report by Thompson Coon et al.[9]

Table 19: Parameters used in cirrhosis Markov model: utilities

Parameter	Value	Source	Distribution	Range of values used in sensitivity analysis	
				lower	upper
Compensated cirrhosis	0.75	Chong et al [83]	Beta PERT^	0.66	0.83
Decompensated cirrhosis	0.66	Chong et al [83]	Beta PERT^	0.46	0.86
Untreatable HCC	0.64	Chong et al [83]	Beta PERT^	0.44	0.86
Month of OLT	0.50	AA*	Beta PERT^	0.30	0.60
Post-OLT (year 1)	0.69	Ratcliffe et al. [84]	Beta PERT^	0.64	0.74
Post-OLT (year 1+)	0.73	Ratcliffe et al. [84]	Beta PERT^	0.67	0.78
Month of resection	0.50	AA*	Beta PERT^	0.30	0.60

* Author assumption as reported in Thompson Coon et al. [9]

^ In the beta PERT distributions λ (the scale parameter that scales the height of the distribution) equals 4, which means the distribution approximates the normal distribution.

5.4.2 Liver metastases of colorectal cancer model

5.4.2.1 Test performance

Chapter 4.6.2 reports the results of two studies identified that assessed the accuracy of CEUS compared to CECT and/or Gd-CEMRI and/or SPIO-CEMRI in detecting liver metastases in colorectal cancer patients after inconclusive un-enhanced ultrasound.[12, 15] The test performance found in the Mainenti study was used as a base case, since this compared all three alternative tests (CECT, Gd-CEMRI, SPIO-CEMRI) to CEUS.[12] 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.

Table 20: Test performance of imaging used in the decision tree, metastases model (based on Mainenti 2010)[12]

Parameter		**Value**	**Distribution**	**Observed counts (n=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

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

5.4.2.2 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 model.[11] The probability of having metastases after CRC is expected to be 40%.[85] Even though the population modelled in the present analysis has already had an inconclusive ultrasound 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.[86]

Table 21: Parameters used in the metastases model: transition probabilities (from Brush et al.) [11]

Parameter	Value	Source	Distribution	
Cancer prevalence				
Probability of having metastases	0.40	Saunders et al [85].	Beta	Se = 0.1
Probability of having metastases at one site	0.30	Lejeune et al [86]	Beta	Se = 0.1
Treatments				
Metastases: pre-operative chemotherapy and metastatic surgery	1.00	Assumption based on Brush et al [11]	Fixed	
Extra metastases: pre-operative chemotherapy and metastatic surgery	0.20	MSAC [87]	Beta	Se = 0.04
Wait and watch	1.00	Assumption based on Brush et al [11]	Fixed	
5-year overall survival				
No metastases	0.85	American Cancer Society [88]	Beta	Se = 0.01
Metastases: surgery for cure	0.24	AJCC [89]	Beta	Se = 0.03
Extra metastases: metastatic surgery and palliative care	0.12	AJCC [89]	Beta	Se = 0.04
Extra metastases: palliative care	0.06	AJCC [89]	Beta	Se = 0.04

In line with Brush et al, [11] we assumed that all patients with metastases at a single site receive pre-operative chemotherapy and metastatic surgery. Patients with extra metastases receive either pre-operative 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.[11] Patients who were inaccurately classified as having no metastases and 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 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 one 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 ten years, after which patients were assumed to have survived their disease and returned to the average mortality rate for their age. [90] To inform this mortality rate, the model assumed a starting age of 50 years, and a proportion of 55% male.[91]

5.4.2.3 Costs

Both the costs of the imaging techniques and the costs of subsequent treatment were taken into account. The costs of CEUS were similar to the cirrhosis surveillance model. Since all patients already received an un-enhanced ultrasound scan, the costs of CEUS consisted of the extra time used for CEUS as opposed to an un-enhanced US (£16) and the costs of the contrast (£48.70). CECT was assumed to scan three areas (chest, abdomen, pelvis), while CEMRI was assumed to scan two to three areas. Costs of biopsy, whole body CT and the watch and wait strategy were based on NSRC reference costs. [81] The watch and wait strategy consisted of two CECT scans over three years, and a serum carcinoembryonic antigen (CEA) test twice a year for three years.[28] Costs of treatment were based on the costs used by Brush et al.[11]

Table 22: Parameters used in the metastases model: costs

Parameter	**Value**	**Source**	**Distribution**		**Range of values used in sensitivity analysis**	
					lower	**upper**
SonoVue contrast agent	£49	Expert opinion	Beta PERT^	λ=4	£40	£60
Additional time for contrast enhanced ultrasound	£16	NSRC [81]	Beta PERT^	λ=4	£0	£39
CECT (three areas)	£162	NSRC [81]	Beta PERT^	λ=4	£120	£192
Gd CEMRI (two to three areas)	£366	NSRC [81]	Beta PERT^	λ=4	£175	£374
SPIO CEMRI (two to three areas)	£366	NSRC [81]	Beta PERT^	λ=4	£175	£374
Biopsy	£1,437	NSRC [81]	Beta PERT^	λ=4	£989	£1,798
Whole body CT	£162	NSRC [81]	Beta PERT^	λ=4	£120	£192
Chemotherapy	£11,532	BNF 58 [92]:, ISD 2009 [93] Cancer Research UK [94]	Fixed			
Surgery	£9,134	ISD 2009 [93]	Normal	Sd = 1,827		
Palliative care	£2,468	Guest et al [95]	Normal	Sd = 494		
Watch and wait	£110	NSRC NSRC [81] / NICE guideline CRC 2011 [28]	Beta pert		£82	£130

5.4.2.4 Utilities

All utility scores used in the model were based on Brush et al[11] 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.[96]

Table 23: Parameters used in the metastases model: utilities (from Brush et al.) [11]

Parameter	Value	Source	Distribution	
No metastases	0.91	Ramsey et al. [97]	Beta	Se = 0.11
Metastases at one site	0.84	Ramsey et al. [97]	Beta	Se = 0.12
Extra metastases: surgery for cure	0.74	Langenhoff et al. [98]	Beta	Se = 0.21
Extra metastases: palliative care	0.52	Tengs and Wallace [99]	Beta	Se = 0.08
Patients receiving unnecessary metastatic surgery	0.74	Langenhoff et al. [98]	Beta	Se = 0.14
Patients receiving unnecessary palliative care	0.61	Tengs and Wallace [99]	Beta	Se = 0.20
Disutility for patients who fail to receive surgery	0.30	Assumption based on Tengs and Wallace [99]	Gamma	Se = 0.08
Disutility for patients who fail to receive palliative care	0.20	Assumption based on Tengs and Wallace [99]	Gamma	Se = 0.08

5.4.3 Incidentally detected FLL model

5.4.3.1 Test performance

As noted in an earlier chapter, different studies have compared CEUS with CECT and CEMRI in its ability to characterise an incidentally FLLs. Three different types of diagnostic outcomes 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, while 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 section 5.3.3). This issue was resolved by utilising the test performance results in various ways.

The approach used in the base-case analyses was to take the results from the meta-analysis, described in section 4.6.3, of four studies which compared CEUS with CECT in their ability to differentiate between malignant and benign lesions. The following results (shown in section 4.6.1) illustrate how similar the performance of CEUS and CECT are. The confidence intervals shown were calculated using the exact method.

Table 24: Test performance of CEUS and CECT in the ability to characterise any malignancy, incidentally detected FLLs

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

In addition to using the sensitivity and specificity values from the meta-analysis, we also used the results from the individual studies (see section 4.6.3 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 since 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.[57] As noted in section 4.6.3, this study reported that all patients in a subgroup (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.

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 versus no malignancy.

With regard to the outcome of malignancy versus no malignancy, we assumed that any mistakes in diagnosis were made at random and 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. 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% (Gierblinski, 2008),[54] while in another it was 74% (Catala, 2007.[53]) 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 the table were based on the results of Bartolotta,[100] who reported a low probability of 4.3%. Since Bartolotta 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.

Table 25: Probabilities of the different types of lesions at time of assessment, incidental FLL model

Type of lesion	**prior probability**		alpha	beta
Metastases	**0.0211**	beta	3	139
HCC	**0.0141**	beta	0.05	141.950
Cholangiocarcinoma	**0.0070**	beta	1	141
Other malignancy	**0.0004**	beta	0.05	141.95
Haemangioma	**0.4996**	beta	70.95	71.05
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	**0.0563**	beta	8	134
Probability of malignant lesion	**0.0426**	beta	3	139
Probability of benign lesion	**0.9574**	beta	2	140

The incidentally detected 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., cirrhosis model and 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 lesion and compensated cirrhosis at 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 due to the presence of one or more risk factors for HCC such as newly diagnosed cirrhosis and hepatitis. The impact of delayed treatment is one less life-year, one 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).

5.4.3.2 Costs

The costs of diagnostic tests, outpatient appointment, biopsy, OLY and resection were taken from the NHS National Schedule of Reference Costs (NSRC) 2011[81]. Many of the values used in the incidentally detected FLL analyses were similar to those used in the cirrhosis analyses. All other cost inputs were based on Thompson Coon et al,[9] and recalculated to the 2011 price level using the Personal and Social Services Research Unit (PSSRU) Unit Costs 2011[82].

The costs of treating HCC and metastases were based on the calculations found in the cirrhosis surveillance and liver metastases models. However, adaptations of the cirrhosis model were needed before the results could be used for these analyses. In particular, it was assumed that it was 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. While it could be argued that some cost components (such as the costs of the initial diagnostic assessment) should be removed since they are not relevant for the incidentally detected FLL model, we nevertheless chose to leave the total costs unchanged to allow the reader to trace the origin of this cost estimate. Moreover, these costs are greatly overshadowed by the other treatment-related costs and the standard error.

Table 26: Parameters used in incidentally detected focal liver lesions model: values affecting costs

	Value	Lower	Upper	Distribution
Costs of imaging				
cost of ultrasound	16	0	39	beta PERT
cost of contrast	48.70	40	60	beta PERT
Cost of CEUS	65			
Cost of CECT	116	88.21	126.33	beta PERT
Cost of CEMRI*	189	137.27	225.89	beta PERT
*: type of contrast used in CEMRI not indicated here, since both types were used in test accuracy studies				

	Mean	Standard error	Distribution
HCC (correctly diagnosed)	24645	3980	normal
HCC (incorrectly diagnosed)	25877	3980	normal
Metastasis (correctly diagnosed)	7518	1808	normal
Metastasis (incorrectly diagnosed)	7894	1808	normal
Follow-up costs (total)	150	[min-max] £144-156	beta PERT (when varied)
Resection	6521	[min-max] £1812-7246	beta PERT

5.4.3.3 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 that 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 found using the cirrhosis and liver metastases models, since these are two important types of malignant lesion that may be detected. More information about the impact that these have on utilities is provided in the other sections of this chapter.

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, since CEUS can be performed right after the un-enhanced ultrasound, 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 due to other risk factors such as newly diagnosed cirrhosis and hepatitis. The impact of delayed treatment is 1 QALY.

- Patients diagnosed with an apparent benign lesion will have a life expectancy and quality of life equal to that seen amongst people in the general population of the same age and sex.

5.5 Additional analyses

First, one way sensitivity analyses were performed for all key parameters, especially for parameters in the models which 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 the previous Tables. 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 below for each model.

5.5.1 Cirrhosis surveillance model

The proportion of patients receiving confirmatory imaging (the proportion of patients with an inconclusive un-enhanced 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* un-enhanced ultrasound (as a minimum estimate of the patients requiring confirmatory imaging). Second, we reduced the proportion of inconclusive un-enhanced US scans considerably (20% instead of 43%). Next, we conducted sensitivity analyses on the age limit of surveillance (90 years instead of 70), the frequency of screening (every year instead of every six months) and for which tumour sizes the accuracy data were applied (small only instead of small and medium).

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.,[48] Quaia et al.,[51] Blondin et al.[14] and Giorgio et al (using data for 11-30 mm lesions).[50] Dai et al. and Blondin et al. were included as other examples of studies which used a standard (EFSUMB guidelines[13]) definition of

HCC, and Giorgio et al. and Quaia et al. were included in order to explore the effects of using other definitions of HCC. The study by Forner et al[49] was not used because it included a significant proportion of patients with very small (<10 mm) FLLs and the study by Sangiovani et al[52] was not used because it was considered to be an 'outlier' (accuracy results differed substantially from other, apparently similar studies.

5.5.2 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 model.[11] Second, we examined the impact of a 80% instead of 40% probability of having metastases. We did this because our population of patients who have already received an un-enhanced ultrasound, may be slightly different from the population in Brush et al.[11] 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.[15] to assess its impact on the expected costs and effects. We also used the sensitivity and specificity reported in Clevert et al.;[16] this study included some patients with primary cancers other than CRC, but the majority (>80%) of metastases diagnosed were from CRC.

5.5.3 Incidentally detected FLL model

A number of different parameters were varied to investigate their impact on the cost-effectiveness of CEUS. Firstly, 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 using individual studies rather than on the meta-analysis. We then examined whether assuming that all patients with HCC had medium 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.

5.6 Results

5.6.1 Cirrhosis surveillance model

5.6.1.1 Effectiveness of surveillance

In the base case, we compared CEUS, CECT and Gd-CEMRI Based on the accuracy data as found by Leoni et al.,[10] 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

5.6.1.2 Costs of surveillance

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

Table 28: Breakdown of discounted costs of cirrhosis surveillance (£)

	CEUS	**CECT**	**Gd-CEMRI**
Surveillance	**1,559**	**1,939**	**2,420**
Imaging	1,436	1,816	2,359
FP	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	2,119	2,119	2,092
Known HCC	380	380	379
Post transplant	7,822	7,822	7,931
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**

5.6.1.3 Cost-effectiveness of surveillance

CEUS was found to have the lowest discounted lifetime costs per patient (£35,744), followed by CECT (£36,124) and Gd-CEMRI (£36,807). Compared to CEUS, CECT was as effective and more costly, and was thus considered to be dominated by CEUS. Gd-CEMRI was £1,063 (95%CI: £449 to £1,492) 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 threshold of £30,000 per QALY, Gd-CEMRI was not deemed cost-effective compared to CEUS.

Table 29: Base-case cost-effectiveness results for cirrhosis surveillance

Strategy	Cost	QALY	Compared to CEUS			Compared to next cost-effective strategy			
			Incr. cost	Incr. QALY	Incr. cost/ QALY	Comparator	Incr. cost	Incr. QALY	Incr. cost/ 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	£1,063	0.022	£48,454	CEUS	£1,063	0.022	£48,454

5.6.1.4 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 un-enhanced ultrasound 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 threshold of £30,000, this indicated that Gd-CEMRI was cost-effective compared to CEUS in this analysis.

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

Strategy	Cost	QALY	Compared to CEUS			Compared to next cost-effective strategy			
			Incr. cost	Incr. QALY	Incr. cost/ QALY	Comparator	Incr. cost	Incr. QALY	Incr. cost/ 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

Second, we changed the proportion of inconclusive ultrasounds from 43% to 20% (Table 31), changed the age limit of surveillance to 90 years instead of 70 years (Table 32), changed the frequency of screening to every year instead of every 6 months (Table 33), and changed the

accuracy data to use only those which applied to small tumours instead of small and medium tumours (Table 34). Only for the sensitivity analysis changing the proportion of inconclusive ultrasounds was Gd-CEMRI found cost-effective compared to CEUS, at an ICER of £16,121. In all other sensitivity analyses, CEUS dominated CECT and was cost-effective compared to Gd-CEMRI.

Table 31: Results of sensitivity analysis for cirrhosis surveillance: Proportion inconclusive ultrasounds 20%

Strategy	Cost	QALY	Compared to CEUS			Compared to next cost-effective strategy			
			Incr. cost	Incr. QALY	Incr. cost/ QALY	Comparator	Incr. cost	Incr. QALY	Incr. cost/ 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	QALY	Compared to CEUS			Compared to next cost-effective strategy			
			Incr. cost	Incr. QALY	Incr. cost/ QALY	Comparator	Incr. cost	Incr. QALY	Incr. cost/ QALY
CEUS	36,163	10.164							
CECT	36,593	10.164	430	0.00	Dominated	CEUS	430	0.00	Dominated
Gd-CEMRI	37,367	10.188	1,1204	0.023	51,619	CEUS	1,1204	0.023	51,619

Table 33: Results of sensitivity analysis for cirrhosis surveillance: Annual screening

Strategy	Cost	QALY	Compared to CEUS			Compared to next cost-effective strategy			
			Incr. cost	Incr. QALY	Incr. cost/ QALY	Comparator	Incr. cost	Incr. QALY	Incr. cost/ QALY
CEUS	34,431	10.093							
CECT	34,629	10.093	198	0.000	dominated	CEUS	198	0.000	dominated
Gd-CEMRI	35,025	10.109	594	0.016	37,619	CEUS	594	0.016	37,619

Table 34: Results of sensitivity analysis for cirrhosis surveillance: Accuracy data for small tumours only

Strategy	Cost	QALY	Compared to CEUS			Compared to next cost-effective strategy			
			Incr. cost	Incr. QALY	Incr. cost/ QALY	Comparator	Incr. cost	Incr. QALY	Incr. cost/ QALY
CEUS	36,054	10.191							
CECT	36,432	10.191	378	0.000	Dominated	CEUS	378	0.000	Dominated
Gd-CEMRI	36,966	10.195	913	0.004	244,840	CEUS	913	0.004	244,840

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. [48] and Quaia et al.[51] These studies both compared CEUS and CECT. Dai et al used a definition of a positive test for HCC which was comparable to that used in the EFSUMB guidelines[13], where as Quaia et al. did not. Using data from either study, CEUS was found to be less costly and more effective than CECT (Table 35 and 36).

Table 35: Results of scenario analysis for cirrhosis surveillance: Dai et al. [48] used as source for accuracy data

Strategy	**Cost**	**QALY**	**Compared to CEUS**		
			Incr. cost	**Incr. QALY**	**Incr. cost/ QALY**
CEUS	36,023	10.188			
CECT	36,332	10.184	129	-0.004	Dominated

Table 36: Results of scenario analysis for cirrhosis surveillance: Quaia et al [51] used as source for accuracy data

Strategy	**Cost**	**QALY**	**Compared to CEUS**		
			Incr. cost	**Incr. QALY**	**Incr. cost/ QALY**
CEUS	36,479	10.185			
CECT	36,767	10.180	288	-0.005	Dominated

Next, we used Blondin et al.[14] and Giorgio et al.[50] as input for the accuracy of CEUS and Gd-CEMRI, Tables 37 and 38. Blondin et al used a definition of a positive test for HCC which was comparable to that used in the EFSUMB guidelines,[13] where as 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.

Table 37: Results of scenario analysis for cirrhosis surveillance: Blondin et al.[14] used as source for accuracy data

Strategy	**Cost**	**QALY**	**Compared to CEUS**		
			Incr. cost	**Incr. QALY**	**Incr. cost/ QALY**
CEUS	36,034	10.189			
Gd-CEMRI	37,078	10.192	1,044	0.004	297,695

Table 38: Results of scenario analysis for cirrhosis surveillance: Giorgio et al.[50] used as source for accuracy data

Strategy	Cost	QALY	Compared to CEUS		
			Incr. cost	Incr. QALY	Incr. cost/ QALY
CEUS	35,821	10.168			
Gd-CEMRI	37,031	10.186	1,210	0.018	68,940

Probabilistic sensitivity analysis

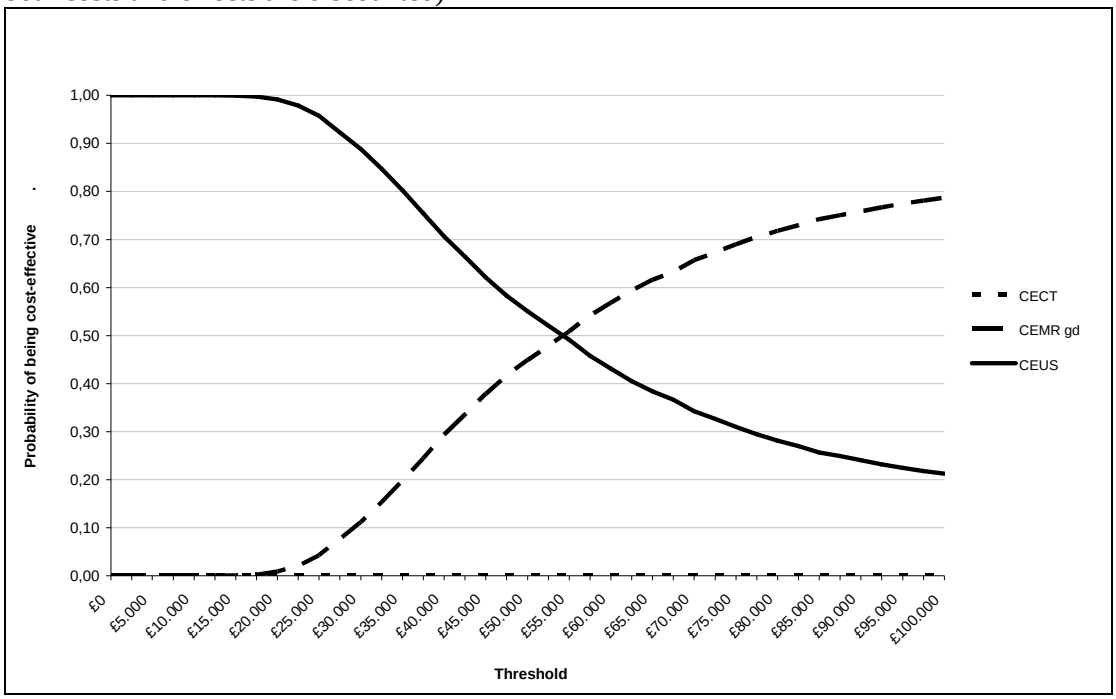
Over 5000 replications, CEUS has the highest probability of being cost-effective for thresholds lower than £55,000 (Figure 13 CEAC). Above this threshold, Gd-CEMRI has the highest probability of being cost-effective. At a threshold of £20,000 the probability that CEUS, CECT or Gd-CEMRI is cost-effective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

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

Table 39:Overview of sensitivity and scenario analyses for cirrhosis surveillance

Analysis	Comparator	Compared to CEUS		
		Incremental cost	Incremental QALY	Incremental cost/ QALY
Base case analysis				
	CECT	£379	0.000	Dominated
	Gd-CEMRI	£1,063	0.022	£48,454
Sensitivity analysis				
Imaging used as confirmatory after all positive non-enhanced ultrasound examinations	CECT	39	0.000	Dominated
	Gd-CEMRI	321	0.025	12,806
Proportion inconclusive ultrasounds 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	0.00	Dominated
	Gd-CEMRI	1,1204	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 tumours	CECT	378	0.000	Dominated
	Gd-CEMRI	913	0.004	244,840
Scenario analyses				
Dai et al. [48] used as source for accuracy data	CECT	129	-0.004	Dominated
Quaia et al [51] used as source for accuracy data	CECT	288	-0.005	Dominated
Blondin et al.[14] used as source for accuracy data	Gd-CEMRI	1,044	0.004	297,695
Giorgio et al.[50] used as source for accuracy data	Gd-CEMRI	1,210	0.018	68,940

Figure 13: Cost-effectiveness acceptability curves, cirrhosis surveillance (effects are QALYs, both costs and effects are discounted)



5.6.2 Liver metastases of colorectal cancer model

5.6.2.1 Effectiveness of diagnosing liver metastases

As indicated previously, Mainenti et al [12] found that the sensitivity of CEUS, CECT, Gd-CEMRI and SPIO-CEMRI was equal. This resulted in an equal number of cases incorrectly diagnosed without metastases (false negatives) in the base case analysis. Due to 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).

Table 40: Expected number of incorrect cases, life years and QALYs for metastases 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

5.6.2.2 Costs of diagnosing liver metastases

An overview of the total discounted costs in the different cost categories per test strategy is listed in Table 41. Although CEUS is less costly than CECT, the total diagnostic costs in the CEUS strategy are higher than in the CECT strategy. This is because all patients with a

positive test result receive a whole body 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 costs, the average total discounted costs of CEUS (£7,547) per patient are slightly higher than for CECT (£7,545). The average discounted costs per patient for both Gd-CEMRI (£7,724) and SPIO-CEMRI (£7,758) are higher than for CEUS and CECT, with SPIO-CEMRI having the highest costs because of unnecessary whole body scans and biopsies.

Table 41: Breakdown of discounted costs (in £), metastases model

	CEUS	CECT	Gd-CEMRI	SPIO-CEMRI
Diagnostics	**795**	**793**	**971**	**1,006**
Initial imaging	67	169	381	381
Whole body scan	75	64	61	64
Biopsy	653	560	529	560
Treatment	**6,716**	**6,716**	**6,716**	**6,716**
Surgery/chemotherapy	3,583	3,583	3,583	3,583
Palliative care	2,901	2,901	2,901	2,901
Wait and watch	232	232	232	232
Total	**7,511**	**7,510**	**7,688**	**7,722**

5.6.2.3 Cost-effectiveness of diagnosing liver metastases

In the base case analysis, the different imaging techniques to detect liver metastases from colorectal cancer resulted in equal expected lifetime QALYs (8.364). CECT was found to be the least costly test, with expected costs of £7,510 per patient. With an expected lifetime cost of CEUS was only slightly (£1) more costly per patient (£7,511). Gd-CEMRI (£7,688) and SPIO-CEMRI (£7,722) 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 42: Costs, effects and cost-effectiveness results for metastases detection

Strategy	Cost	QALY	Compared to CEUS			Compared to next cost-effective strategy			
			Incr. cost	Incr. QALY	Incr. cost/ QALY	Comparator	Incr. cost	Incr. QALY	Incr. cost/ QALY
CEUS	7,511	8,364							
CECT	7,510	8,364	-1	0.000	Dominant	CEUS	-1	0.000	Dominant
Gd-CEMRI	7,688	8,364	177	0.000	Dominated	CECT	178	0.000	Dominated
SPIO-CEMRI	7,722	8,364	211	0.000	Dominated	CECT	212	0.000	Dominated

5.6.2.4 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 loss in QALYs (Table 43). CEUS now yields the lowest number of QALYs (8.343) and is most expensive (£8,335), while Gd-CEMRI, which is most accurate, yields the highest number of QALYs (8.364) and is least expensive (£7,158). In this sensitivity analysis, Gd-CEMRI dominates the other tests because of its better accuracy.

Table 43: Results of sensitivity analysis for metastases model: No biopsy if test is positive

Strategy	Cost	QALY	Compared to CEUS			Compared to next cost-effective strategy			
			Incr. cost	Incr. QALY	Incr. cost/ QALY	Comparator	Incr. cost	Incr. QALY	Incr. cost/ QALY
CEUS	8,335	8.343							
CECT	7,321	8.359	-1,015	0.016	Dominant	CEUS	-1,015	0.016	Dominant
Gd-CEMRI	7,158	8.364	-1,177	0.021	Dominant	CECT	-162	0.005	Dominant
SPIO-CEMRI	7,537	8.359	-798	0.016	Dominant	Gd-CEMRI	-379	0.005	Dominated

If CEUS is combined with biopsy (see results Table 42), and CECT, Gd-CEMRI and SPIO-CEMRI are not be followed by biopsy (see results Table 43), then CEUS and Gd-CEMRI are most effective, both yielding 8,364 QALYS. However, CEUS is more costly than, and 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.

Table 44: Results of sensitivity analysis for metastases model: Proportion of patients having metastases 80%

Strategy	Cost	QALY	Compared to CEUS			Compared to next cost-effective strategy			
			Incr. cost	Incr. QALY	Incr. cost/ QALY	Comparator	Incr. cost	Incr. QALY	Incr. cost/ QALY
CEUS	14,419	4.078							
CECT	14,490	4.078	71	0.000	Dominated	CEUS	71	0.000	Dominated
Gd-CEMRI	14,700	4.078	281	0.000	Dominated	CEUS	281	0.000	Dominated
SPIO-CEMRI	14,711	4.078	292	0.000	Dominated	CEUS	292	0.000	Dominated

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 2011 (Table 45).[15] This study compared CEUS, CECT and SPIO-CEMRI, and found perfect specificity for all tests, with a sensitivity of 87%, 83% and 97%, respectively. CECT was slightly (£7) more costly and slightly (0.005 QALYs) less effective than, 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.

Table 45: Results of scenario analysis for metastases model with Jonas et al [15] as source for accuracy data

Strategy	**Cost**	**QALY**	**Compared to CEUS**			**Compared to next cost-effective strategy**			
			Incr. cost	**Incr. QALY**	**Incr. cost/ QALY**	**Comparator**	**Incr. cost**	**Incr. QALY**	**Incr. cost/ QALY**
CEUS	7,468	8,369							
CECT	7,475	8,364	7	-0.005	Dominated	CEUS			Dominated
SPIO-CEMRI	8,055	8,382	587	0.014	43,318	CEUS	587	0.014	43,318

The slightly lower sensitivity and specificity of CECT compared to CEUS found by Clevert et al [16] resulted in CEUS being £300 less costly and yielding 0.002 more QALYs than CECT (Table 46).

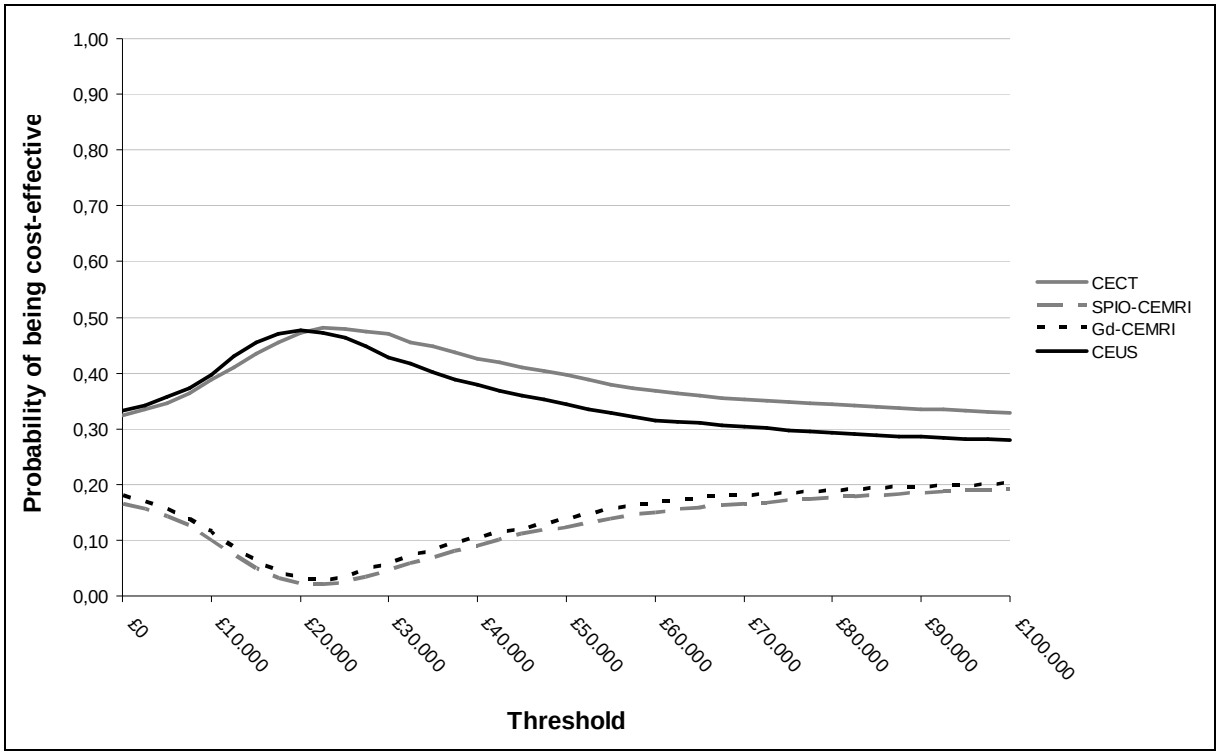
Table 46: Results of scenario analysis for metastases model with Clevert et al [16] as source for accuracy data

Strategy	**Cost**	**QALY**	**Compared to CEUS**			**Compared to next cost-effective strategy**			
			Incr. cost	**Incr. QALY**	**Incr. cost/ QALY**	**Comparator**	**Incr. cost**	**Incr. QALY**	**Incr. cost/ QALY**
CEUS	7,821	8,384							
CECT	8,121	8,382	300	-0,002	Dominated	CEUS	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 CEAC). 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 the 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-CEMR (2%).

Figure 14: Cost-effectiveness acceptability curves, liver metastases (effects are QALYs, both costs and effects are discounted)



5.6.3 Incidentally detected FLL model

5.6.3.1 Effectiveness

Table 47 shows effectiveness results from the base-case analysis. Two pairs of results are shown here: the first pair shows the results of CEUS versus CECT, while the other pair shows the results of CEUS versus CECT. The two sets kept separate since four studies compared CEUS with CECT while 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.

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

5.6.3.2 Costs

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

Table 48: Base-case cost results, 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	**470**	**522**	**511**	**642**

5.6.3.3 Cost-effectiveness

The following results were seen in the base-case analysis. 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.

Table 49: Base-case cost-effectiveness results, incidentally detected FLL model

	incremental costs (SE)	incremental QALYS (SE)	incremental costs/QALYs
CEUS vs. CECT	-£52	0.0002	dominant
CEUS vs. CEMRI	-£131	0.0026	dominant

5.6.3.4 Additional analyses

While additional analyses changed the absolute costs and effectiveness of the different strategies, they did not lead to any dramatic changes in the incremental costs and effectiveness of CEUS versus CECT or CEMRI. The most critical factor in the analyses related to the costs of the tests. The impact of any other elements (e.g., prior probabilities of a particular diagnosis, costs of treatment) was minimal since the test 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 metastases reported in the individual studies (58% of patients with HCC [53] and 36% of patients with metastasis,)[56]. While 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. However, it only increased the incremental QALYs slightly and had no effect on incremental costs and therefore essentially had no effect on the cost-effectiveness of CEUS versus CECT or CEMRI.

Table 50: Results of sensitivity analysis, incidentally detected FLL model: Prior probability of malignancy increased to maximum observed frequencies of HCC and metastasis (any type)

Comparisons	**QALYs**	**Costs**	**incremental QALYS**	**incremental costs**	
CEUS (vs. CECT)	6.654	17,121	0.0051	-£56	dominant
CECT	6.649	17,177			
CEUS (vs. MRI)	6.614	17,160	0.0855	-£202	dominant
CEMRI	6.529	17,362			

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.

We also examined the effect on the results of assuming that all patients with HCC had medium 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 diagnostic test accuracy studies (58% of patients with HCC),[53] we found that it had no effect on the cost-effectiveness of CEUS versus 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 versus CECT and CEMRI. For example, if an incorrect diagnosis of HCC and metastases led to a doubling of the costs (compared to the costs following a correct diagnosis) and the QALYs set to zero, CEUS remained the dominant strategy. Table 51 shows the results of this analysis.

Table 51: Results of sensitivity analysis, incidentally detected FLL model: More severe consequences of incorrect diagnosis of HCC and metastases

Comparisons	**QALYs**	**Costs**	**incremental QALYS**	**incremental costs**	
CEUS (vs. CECT)	13.321	486	0.0012	-£54	dominant
CECT	13.320	540			
CEUS (vs. MRI)	13.312	541	0.0196	-£162	dominant
CEMRI	13.293	702			

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, since there was still a difference in costs observed, this could be viewed as a situation of extended dominance in both comparisons.

Table 52: Results of sensitivity analysis, incidentally detected FLL model: Less severe consequences of incorrect diagnosis of HCC and metastases

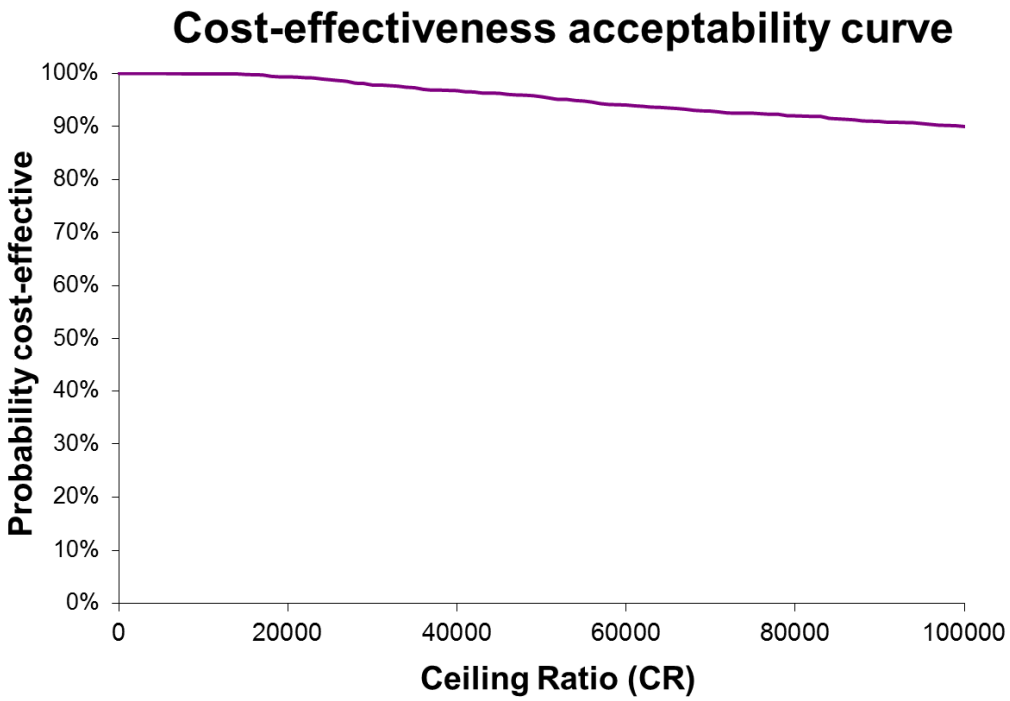
Comparisons	**QALYs**	**Costs**	**incremental QALYS**	**incremental costs**	
CEUS (vs. CECT)	13.332	469	0.0000	-£52	extended dominance
CECT	13.332	521			
CEUS (vs. MRI)	13.332	509	0.0000	-£130	extended dominance
CEMRI	13.332	639			

Probabilistic sensitivity analyses

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

Figure 15 shows the cost-effectiveness acceptability curve comparing CEUS with CECT. This curve shows that the probability of cost-effectiveness of CEUS versus CECT is greater than 95% at willingness-to-pay thresholds of up to £20,000.

Figure 15: Cost-effectiveness acceptability curve comparing CEUS with CECT, incidentally detected FLLs (effects are QALYs, both costs and effects are discounted)

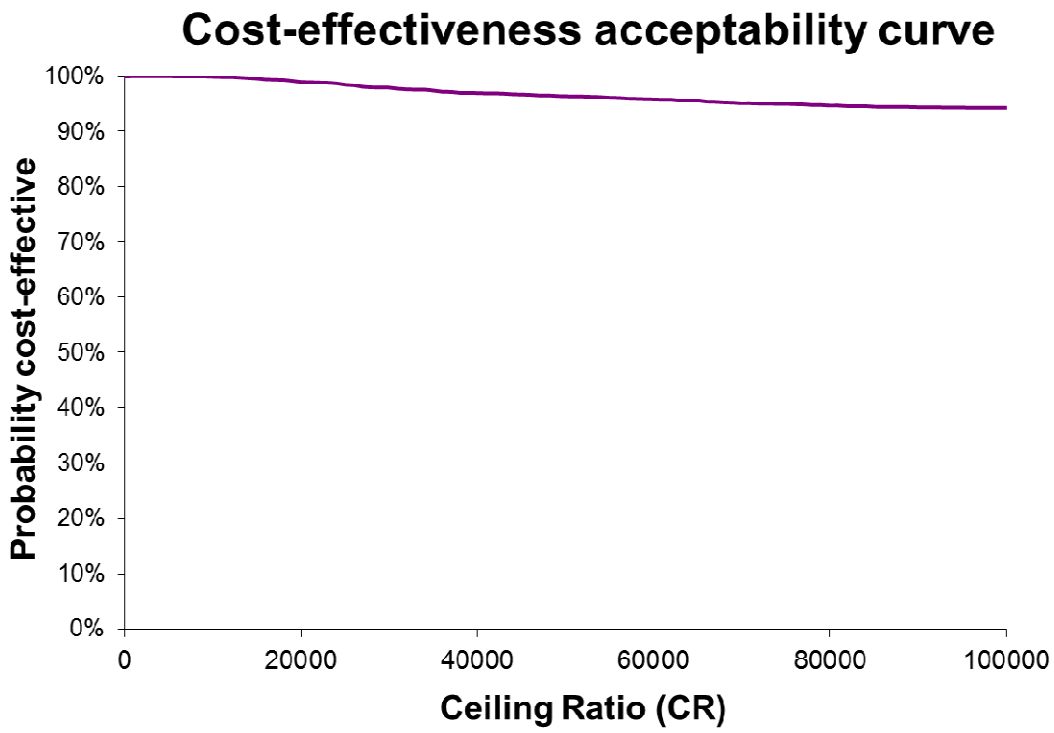


When the differences in costs and effects of CEUS versus CEMRI are visualised on the cost-effectiveness plane, it is clear that there is little doubt about the cost-savings of CEUS versus CEMRI but some uncertainty about their differences in effectiveness.

The results of probabilistic sensitivity analyses comparing CEUS with CEMRI were similar to those shown above for CEUS versus CECT. There was less certainty about the expected amount of cost-savings of CEUS versus CEMRI (mean difference: -£131, 95%CI: -194, -69) and some uncertainty about their differences in effectiveness (mean difference: 0.0039, 95%CI: -0.0058, 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 (with 95%CI: -183, -67) was found.

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

Figure 16: Cost-effectiveness acceptability curve comparing CEUS with CEMRI, incidentally detected FLLs (effects are QALYs, both costs and effects are discounted)



6 DISCUSSION

6.1 Statement of principal findings

6.1.1 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 un-enhanced 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 un-enhanced US; 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 pre-treatment 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 un-enhanced US. However, this was a small, non-randomised study, which had a number of methodological weaknesses and 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.

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 characterization of FLLs.[26, 101] 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 of patients with known primary cancers), or of the target conditions (e.g. HCC, liver metastases, or 'any liver malignancy') and one review[101] 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 only reported as conference abstracts, resulting in a high proportion of 'unclear' risk of bias ratings across QUADAS-2 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 patients groups (e.g. exclusion of patients with a low probability of malignancy); exclusion of patients with low probability of disease might result in under estimations of test accuracy, though 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 latter 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 un-enhanced 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 (<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 where such lesions are hypervascular;[23, 24] Gd-EOB-DTPA-CEMRI, a 'combined' vascular and hepatocyte-specific contrast agent.[25] There was no consistent evidence for any significant difference in test performance between the three imaging modalities and three MRI contrast media assessed. Where a definition of HCC consistent with that given in the EFSUMB guidelines (arterial phase enhancement followed by portal-venous washout) was used,[13] estimates of the sensitivity and specificity of each of the imaging modalities assessed varied across studies. There was some evidence, from one study which compared CEUS and Gd-CEMRI, that these imaging techniques may be better at ruling out HCC in FLLs between 11 and 30 mm (sensitivities for CEUS and Gd-CEMRI were 92% and 95%, respectively) than in small FLLs ≤10mm (sensitivities 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 <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, where 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 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, where very small FLLs (<10 mm) are not considered.

Studies of the diagnosis of liver metastases using imaging with vascular contrast media (CEUS, CECT, and Gd-CEMRI), where 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 which were similar to those reported in the EFSUMB guidelines on the use of CEUS.[13] 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 un-specified 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, where 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 >95% and specificity estimates >80% for complete response, using CEUS, CECT and CECT or Gd-CEMRI. 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.

6.1.2 Cost-effectiveness

The cost-effectiveness analysis of the use of CEUS in patients with an inconclusive un-enhanced ultrasound 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 characterisation of incidentally detected FLLs, while it was similar in terms of costs and effects in the detection of liver metastases from colorectal cancer.

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 £1,063 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 thresholds of £20,000 and £30,000 per additional QALY. CEUS can therefore be considered the most cost-effective option after inconclusive unenhanced ultrasound. These base case results were based on one source for accuracy, being Leoni et al.[10] Using the two other studies that compared CEUS and CECT corroborated the dominance of CEUS over CECT, showing even lower effectiveness of CECT. Compared to Gd-CEMRI, CEUS was cost-effective in most sensitivity analyses, except when all positive un-enhanced ultrasound examinations were subject to confirmatory testing instead of the inconclusive ultrasounds, and when the proportion of patients having an inconclusive ultrasound was considerably lower (20% instead of 43%). These two analyses resulted in acceptable ICERs for Gd-CEMRI compared to CEUS of £12.806 and £16,121, respectively.

In the diagnosis of liver metastases from colorectal cancer, CEUS was found to have similar costs and effects compared to CECT. While at a lifetime time horizon they yielded equal

QALYs per patient, CEUS was found to cost £1 more than CECT. Both Gd-CEMRI and SPIO-CEMRI were dominated by CECT in this population because they were more costly and equally effective. However, in this base case analysis it was assumed that patients who were incorrectly diagnosed with liver metastases would receive biopsy to discover this mistake before they were treated. 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 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 [15 16], 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 threshold of £30,000 per QALY, Gd-CEMRI is deemed not cost-effective compared to CEUS.

The third and final evaluation involved the comparison of CEUS with CECT and CEMRI in the characterisation of incidentally focal liver lesions. 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 to 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 versus 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.

6.2 Strengths and limitations of assessment

6.2.1 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 un-published studies. Because of the known difficulties in identifying test accuracy studies using study design-related search terms,[3] 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, e.g. a significant difference between the treatment and control groups which 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 randomised controlled trials 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.[102] Formal assessment of publication bias in systematic reviews of test accuracy studies remains problematic and reliability is limited.[102] We did not undertake a statistical assessment of publication bias in this review. However, our search strategy included a variety of routes to identify un-published 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 the methods section (4.1) of this report. 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 (Appendix 5). The review process followed recommended methods to minimise the potential for error and/or bias;[1] studies were independently screened for inclusion by two reviewers and data extraction and quality assessment were done 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 and checked by a second (VG and HR)

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.[5] The QUADAS tool has been recommended for assessing the methodological quality of

test accuracy studies,[1, 2] and has been widely adopted by researchers and key organisations such as the Cochrane Collaboration, the National Institute for Health and Clinical Excellence (NICE) in the UK, and Institut für Qualität and Wirtschaftlichkeit im Gesundheitswesen (IQWiG) in Germany. It has been mentioned in more than 200 abstracts on the DARE database and has been cited more than 500 times. The revised version of QUADAS (QUADAS-2) has recently been published.[5] 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 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 domain 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, which 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 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, only relevant 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 (Appendix 3) and in summary in the results section (4.6). 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 only reported as conference abstracts.

The systematic review conducted for this assessment represents an improvement upon previously published systematic reviews,[26, 101, 103] in that it focuses upon studies which 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 target condition of imaging.

Hierarchical or bivariate models are considered the optimal methods for estimating SROC curves and pooled estimates of sensitivity and specificity.[1, 35] 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 (HSROC) model in the absence of other study-level covariates.[36] 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 sub-optimal 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-analyses 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 respect 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 included studies reported per lesion data (multiple lesions per patient). This 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 analyses.[104] Un-corrected estimates of sensitivity and specificity derived from such data are likely to be accurate, but imprecision will be underestimated.[104] Of greater concern are those studies which 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.[53, 55-57] 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 of 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 un-ethical 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) which used European Association for the Study of the Liver (EASL)/American Association for the Study of Liver Diseases (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.[10, 47] 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[33] and the up-date of this review, conducted during the development of QUADAS-2, found two contradictory studies one reporting no effect of incorporation bias upon accuracy and one reporting increased sensitivity and reduced specificity in the presence of incorporation bias (un-published 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 where un-enhanced US examination was considered inconclusive. Although all study participants had imaging-detected FLLs prior to SonoVue® CEUS, only one study[48] explicitly stated that un-enhanced 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.

The majority of included studies reported no information on funding; two studies reported funding from the manufacturer of SonoVue®.[56, 57]

6.2.2 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 colorectal cancer, and characterisation of incidentally detected focal liver lesions. All three models were based on existing models that had previously informed NICE guidance.[9, #1230] Where needed, we updated and improved these models. The model for incidentally detected liver lesions 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 as high quality as possible. Where 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 focal liver lesions. As a consequence, the estimated cost-effectiveness of CEUS for the surveillance of cirrhosis and the diagnosis of liver metastases from colorectal cancer had to be based on single studies. Scenario analyses were performed using the other 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 for example defined incidentally detected focal liver lesions in different ways. Interestingly, regardless of the variation in composition of the patient populations, there was never an instance where 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. While the pathway may be straightforward for false negatives, as their disease may be correctly diagnosed in a later stage of the initial workup, this is more difficult for false positives. In the liver metastases from colorectal cancer 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 where 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 to CECT and especially CEMRI that it is highly accessible. All patients already receive an un-enhanced ultrasound, and can be immediately diagnosed using CEUS as part of the same examination. A potential benefit of CEUS is, therefore, the potential 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. Though 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 CEMR.

6.3 Uncertainties

6.3.1 Clinical effectiveness

None of the clinical applications of liver imaging considered in this review were 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 un-enhanced US. Although, as noted in section 6.2.1 strengths and limitations of the clinical effectiveness assessment, this review benefits from focussing upon studies which directly compared the performance of SonoVue® CEUS with other imaging modalities, only two studies on the characterisation of FLLs detected on surveillance of cirrhosis patients[10, 52] and two studies on the detection of liver metastases in patients with known primary cancers[12, 15] compared all three imaging modalities under assessment (CEUS, CECT and CEMRI). Most studies which assessed CEMRI used gadolinium-based vascular contrast agent, which has a comparable mode of operation to 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.[10, 12, 14, 15] 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 only reported as conference abstracts,[15, 45-47] which further limited the available data. These factors meant that, as detailed in section 6.1.1 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 un-enhanced US examination has proved inconclusive. In addition to test accuracy, it is therefore particularly important to assess the proportion of patients in whom ultrasound 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 number of participants in whom imaging was inconclusive; three studies indicated that SonoVue® CEUS was inconclusive in slightly fewer patients than CECT (0, 3% and 3% for SonoVue® CEUS compared with 14%, 8% and 6% for CECT).[16, 51, 55] One study reported 11% inconclusive imaging studies for both SonoVue® CEUS and CEMRI.[57] Though 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.

Where 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.[50] 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.[22] This study found 29 cases of adverse events, of which 2 were graded as serious, 1 severe, 3 moderate and 23 mild.[22] There were no fatal adverse events.[22] 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 bradychardia, within 1 min after injection of SonoVue®.[22] 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.[22] None of the studies identified reported any information on patient preferences.

It should be further noted that, whilst 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[60] was identified which reported the effects of imaging with SonoVue® on patient outcomes; the ultimate aim of any research on clinical tests should be to determine impact upon patient management and clinical outcomes. As described in section 6.1.1 statement of principal findings for the clinical effectiveness assessment, this study indicated that the inclusion of CEUS in pre-treatment imaging protocols for patients undergoing RFA for HCC may result in some improved outcomes compared with un-enhanced US. Overall, the effects, if any, of imaging with SonoVue® CEUS upon management and outcome of patients with FLLs remain uncertain.

6.3.2 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 colorectal cancer 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 un-enhanced ultrasound or which may have been identified at this examination, hence it is expected that their complaints worsen and that their lesion will be detected in 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 diagnostics, but would not undergo inappropriate treatment since the correct diagnosis would be determined after additional diagnostic workup. In the liver metastases of colorectal cancer model we examined the extreme situation where all patients who were incorrectly diagnosed with metastases would receive treatments for these metastases. As this involves costs of the treatment as well as reduced quality of life, this has 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 inconclusive un-enhanced ultrasound examinations, or

if the proportion of inconclusive un-enhanced ultrasounds were lower, Gd-CEMRI would be cost-effective compared to CEUS.

7 CONCLUSIONS

7.1 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 un-enhanced US; detection of liver metastases in patients with known primary cancers (CRC); characterisation of incidentally detected FLLs identified by un-enhanced US. However, some caution is required in the interpretation of these findings as studies were generally small and heterogeneous with respect to 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 un-enhanced ultrasound 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 characterisation of incidentally detected FLLs, while it was similar in terms of costs and effects in the detection of liver metastases from colorectal cancer. 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 rapid rule-out of malignancy, equivalent diagnostic performance may be sufficient for SonoVue® CEUS to be preferred over other imaging modalities when un-enhanced 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 un-enhanced US examination. Although this would be unlikely to reduce waiting times (compared to 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, (for example, by avoiding the administration costs of scheduling new appointments).

7.2 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 un-enhanced US; detection of liver metastases in patients with known primary cancers (CRC); characterisation of incidentally detected FLLs identified by un-enhanced US; determination of treatment response in patients with liver cancers. However, data were relatively sparse and studies were heterogeneous with respect to 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 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 of patients' preferences. Further investigation of the potential role of CEMRI using both vascular and hepatocyte-specific, or 'combined' contrast agents may also be warranted. QUADAS-2 assessment highlighted limitations in the reporting of many studies included in our review; future studies should follow the STARD guidelines for reporting test accuracy studies.[105, 106]

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, which reported data on patient outcomes, considered the impact of using SonoVue® CEUS for pre-treatment assessment upon clinical outcomes following treatment. This study had a number of methodological limitations and found significant effects of SonoVue® CEUS only in secondary outcomes. The ideal study to address questions of clinical effectiveness would be a large multi-centre 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, in order to minimise performance bias. Long-term, observational studies assessing the clinical consequences of incorrect initial diagnoses may also be informative.

8 REFERENCES

[1] Centre for Reviews and Dissemination. *Systematic reviews: CRD's guidance for undertaking reviews in health care [Internet]*. York: University of York, 2009 [cited 7.6.11] Available from: http://www.york.ac.uk/inst/crd/systematic_reviews_book.htm

[2] Cochrane Diagnostic Test Accuracy Working Group. *Handbook for DTA Reviews [internet]*: Cochrane Collaboration, 2011 [cited 12.1.11] Available from: http://srdta.cochrane.org/handbook-dta-reviews

[3] Whiting P, Westwood M, Beynon R, Burke M, Sterne JA, Glanville J. Inclusion of methodological filters in searches for diagnostic test accuracy studies misses relevant studies. *J Clin Epidemiol* 2011;64(6):602-7.

[4] National Institute for Health and Clinical Excellence. *Diagnostics Assessment Programme: interim methods statement (version 2) [Internet]*. London: NICE, 2010 [cited 12.1.11]. 46p. Available from: http://www.nice.org.uk/media/164/3C/DAPInterimMethodsStatementProgramme.pdf

[5] Whiting P, Rutjes AW, westwood M, Mallet S, Deeks JJ, Reitsma JB, et al. The development of QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;155(8):529-36.

[6] Higgins JPT, Green S, eds. *Cochrane handbook for systematic reviews of interventions [Internet]*. Version 5.1.0 [updated March 2011]: The Cochrane Collaboration, 2011 [cited 23.03.11]. Available from: http://www.cochrane-handbook.org/

[7] Zamora J, Abraira V, Muriel A, Khan K, Coomarasamy A. Meta-DiSc: a software for meta-analysis of test accuracy data. *BMC Med Res Methodol* 2006;6:31.

[8] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21(11):1539-58.

[9] 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):1-206.

[10] 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(3):599-609.

[11] Brush J, Boyd K, Chappell F, Crawford F, Dozier M, Fenwick E, et al. The value of FDG positron emission tomography/computerised tomography (PET/CT) in pre-operative staging of colorectal cancer: a systematic review and economic evaluation. *Health Technol Assess* 2011;15(35):1-192, iii-iv.

[12] Mainenti PP, Mancini M, Mainolfi C, Camera L, Maurea S, Manchia A, et al. Detection of colo-rectal 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(5):511-521.

[13] 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(1):28-44.

[14] Blondin D, Erhardt A, Crynen K, Sagir A, Scherer A, Kropil P, et al. [Diagnosis of focal liver lesions in cirrhotic patients: comparison of contrast-enhanced ultrasound using sulphur hexafluoride (SF6) microbubbles and MRI using Gd-EOB-DTPA]. *Z Gastroenterol* 2011;49(1):23-9.

[15] Jonas E, Nilsson H, Larsson J, Freedman J. Detection of colorectal cancer liver metastases: an assessment of four imaging modalities. Paper presented at the 9th Congress of the European-African HPBA (E-AHPBA);12-16 Apr; Cape Town, South Africa. *HPB* 2011;13:24.

[16] Clevert DA, Jung EM, Stock KF, Weckbach S, Feuerbach S, Reiser M, et al. Evaluation of malignant liver tumors: biphasic MS-CT versus quantitative contrast harmonic imaging ultrasound. *Z Gastroenterol* 2009;47(12):1195-1202.

[17] Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology* 2005;42(5):1208-36.

[18] Ryder S, Hepatocellular UK Group. *UK Guidelines for the management of suspected hepatocellular carcinoma (HCC) in adults (revised edition)*. Nottingham: Nottingham University Hospitals NHS Trust, 2009. 57p.

[19] Office for National Statistics. *Cancer statistics registrations: registrations of cancer diagnosed in 1999, England (Series MB1 no. 30)*. London: ONS, 2002.

[20] Cancer Research UK. Cancer incidence for common cancers - UK statistics [Internet]. London: Cancer Research UK, 2011 [cited 14.9.11]. Available from: http://info.cancerresearchuk.org/cancerstats/incidence/commoncancers/

[21] Cabassa P, Bipat S, Longaretti L, Morone M, Maroldi R. Liver metastases: sulphur hexafluoride-enhanced ultrasonography for lesion detection: a systematic review. *Ultrasound Med Biol* 2010;36(10):1561-7.

[22] Piscaglia F, Bolondi L. The safety of Sonovue in abdominal applications: Retrospective analysis of 23188 investigations. *Ultrasound Med Biol* 2006;32(9):1369-1375.

[23] Ward J, Guthrie JA, Scott DJ, Atchley J, Wilson D, Davies MH, et al. Hepatocellular carcinoma in the cirrhotic liver: double-contrast MR imaging for diagnosis. *Radiology* 2000;216(1):154-62.

[24] Lutz AM, Willmann JK, Goepfert K, Marincek B, Weishaupt D. Hepatocellular carcinoma in cirrhosis: enhancement patterns at dynamic gadolinium- and superparamagnetic iron oxide-enhanced T1-weighted MR imaging. *Radiology* 2005;237(2):520-8.

[25] Lee NK, Kim S, Lee JW, Lee SH, Kang DH, Kim GH, et al. Biliary MR imaging with Gd-EOB-DTPA and its clinical applications. *Radiographics* 2009;29(6):1707-24.

[26] Guang Y, Xie L, Ding H, Cai A, Huang Y. Diagnosis value of focal liver lesions with SonoVue-enhanced ultrasound compared with contrast-enhanced computed tomography and contrast-enhanced MRI: a meta-analysis. *J Cancer Res Clin Oncol* 2011.

[27] Schwartz J, Kruskal J. Approach to the patient with a focal liver lesion. In: Basow D, editor. *UpToDate*. Waltham, MA: UpToDate, 2011.

[28] National Institute for Health and Clinical Excellence. *Colorectal cancer: the diagnosis and management of colorectal cancer. Full guideline [Internet]*. London: NICE, 2011 [cited 23.1.12]. 186p. Available from: http://www.nice.org.uk/nicemedia/live/13597/56957/56957.pdf

[29] Garden OJ, Rees M, Poston GJ, Mirza D, Saunders M, Ledermann J, et al. Guidelines for resection of colorectal cancer liver metastases. *Gut* 2006;55 Suppl 3:iii1-8.

[30] Westwood M, Al M, Burgers L, Redekop W, Lhachimi S, Armstrong N, et al. *Computed tomography (CT) scanners for cardiac imaging – Somatom Definition Flash, Aquilion One, Brilliance iCT and Discovery CT750 HD: a Diagnostic Assessment Report [Internet]*. York: Kleijnen Systematic Reviews Ltd., 2011 [cited 14.9.11]. 336p. Available from: http://guidance.nice.org.uk/nicemedia/live/13243/56230/56230.pdf

[31] McGowan J, Sampson M, Lefebvre C. An evidence based checklist for the peer review of electronic search strategies (PRESS EBC). *Evid Based Libr Inf Pract* 2010;5(1):1-6.

[32] Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol* 2003;3:25.

[33] Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM, Kleijnen J. A systematic review of sources of variation and bias in studies of diagnostic accuracy. *Ann Intern Med* 2004;140:189-202.

[34] Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM, Kleijnen J. A systematic review finds that diagnostic reviews fail to incorporate quality despite available tools. *J Clin Epidemiol* 2005;58(1):1-12.

[35] Reitsma JB, Glas AS, Rutjes AWS, Scholten RJPM, Bossuyt PMM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol* 2005;58:982-90.

[36] Harbord RM, Deek JJ, Egger M, Whiting P, Sterne JA. A unification of models for meta-analysis of diagnostic accuracy studies. *Biostatistics* 2007;8(2):239-51.

[37] Harbord RM, Whiting P, Sterne JA, Egger M, Deeks JJ, Shang A, et al. An empirical comparison of methods for meta-analysis of diagnostic accuracy showed hierarchical models are necessary. *J Clin Epidemiol* 2008;61(11):1095-103.

[38] Bohata S, Pavlik T, Chlumska D, Valek V. [Contribution of the contrast enhanced ultrasound in the differential diagnosis of the focal lesions]. *Ceska Radiol* 2010;64(1):11-19.

[39] Chen M-h, Wu W, Yang W, Gao W, Dai Y, Yin S-s, et al. [Application of contrast-enhanced ultrasonography in selecting indication of radiofrequency ablation among hepatocellular carcinoma patients]. *Zhonghua Yi Xue Za Zhi* 2005;85(49):3491-4.

[40] Passamonti M, Vercelli A, Azzaretti A, Rodolico G, Calliada F. Characterization of focal liver lesions with a new ultrasound contrast agent using continuous low acoustic power imaging: comparison with contrast enhanced spiral CT. *Radiol Med* 2005;109(4):358-69.

[41] 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? Abstract MO-113. Paper presented at the 9th World Congress of the International Hepato-Pancreato-Biliary Association; 18-22 Apr; Buenos Aires, Argentina. *HPB* 2010;12(Suppl 1):100.

[42] 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); 12-16 Apr; Cape Town, South Africa. *HPB* 2011;13:25-26.

[43] 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; 18-22 Apr; Buenos Aires, Argentina. *HPB* 2010;12:269.

[44] 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(4):706A-707A.

[45] Flor N, Serantoni S, Barbosa Da Silva F, Impellizzeri E, Danaro M, Cornalba G, et al. B-582: Characterization of small indeterminate focal liver lesions at multiphasic MDCT in patients with known primary cancer: US and contrast-enhanced ultrasound as problem-solving approach? In: European Congress of Radiology 2009; 6-10 Mar; Vienna, Austria, 2009.

[46] Luttich A, Puig J, Martín J, Darnell A, Malet A, Veintemillas M. B-736: Can the response to radiofrequency ablation of hepatocarcinoma be adequately measured by means of contrast-enhanced US and dynamic MRI? In: European Congress of Radiology; 3-7 Mar; Vienna, Austria, 2006.

[47] Solbiati L. D-55: Diagnostic performance and cost-effectiveness of contrast-enhanced ultrasound in the characterization of focal liver lesions. In: European Congress of Radiology; 3-7 Mar; Vienna, Austria, 2006.

[48] Dai Y, Chen MH, Fan ZH, Yan K, Yin SS, Zhang XP. Diagnosis of small hepatic nodules detected by surveillance ultrasound in patients with cirrhosis: Comparison between contrast-enhanced ultrasound and contrast-enhanced helical computed tomography. *Hepatol Res* 2008;38(3):281-290.

[49] 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(1):97-104.

[50] Giorgio A, De Stefano G, Coppola C, Ferraioli G, Esposito V, Di Sarno A, et al. Contrast-enhanced sonography in the characterization of small hepatocellular carcinomas in cirrhotic patients: comparison with contrast-enhanced ultrafast magnetic resonance imaging. *Anticancer Res* 2007;27(6 C):4263-4269.

[51] Quaia E, Alaimo V, Baratella E, Medeot A, Midiri M, Cova MA. The added diagnostic value of 64-row multidetector CT combined with contrast-enhanced US in the evaluation of hepatocellular nodule vascularity: implications in the diagnosis of malignancy in patients with liver cirrhosis. *Eur Radiol* 2009;19(3):651-663.

[52] Sangiovanni A, Manini MA, Iavarone M, Romeo R, Forzenigo LV, Fraquelli M, et al. The diagnostic and economic impact of contrast imaging techniques in the diagnosis of small hepatocellular carcinoma in cirrhosis. *Gut* 2010;59(5):638-644.

[53] Catala V, Nicolau C, Vilana R, Pages M, Bianchi L, Sanchez M, et al. Characterization of focal liver lesions: comparative study of contrast-enhanced ultrasound versus spiral computed tomography. *Eur Radiol* 2007;17(4):1066-1073.

[54] Gierblinski IW, Wocial T, Jarosz D. [In which cases can contrast-enhanced ultrasound replace fine needle aspiration biopsy? Clinical feasibility study]. *Nowotwory* 2008;58(3):238-245.

[55] Li R, Guo Y, Hua X, He Y, Ding J, Guo A, et al. Characterization of focal liver lesions: Comparison of pulse-inversion harmonic contrast-enhanced sonography with contrast-enhanced CT. *J Clin Ultrasound* 2007;35(3):109-117.

[56] 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 Dreilandertreffen 2008, Davos. *Ultraschall Med* 2009;30(4):383-9.

[57] 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(5):492-9.

[58] Feng XY, Sun XY, Tan BB, Qian GJ, Wu MC. [Evaluation of enhanced ultrasonography for hepatic carcinoma with cryosurgery]. *J Interv Radiol* 2007;16(4):246-248.

[59] Zhou P, Liu X-Y, Li R-Z, Nie W-P, Liu S. [Comparison of treatment response in primary hepatocellular carcinomas with contrast-enhanced ultrasonography and contrast-enhanced helical CT]. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* 2007;32(4):690-4.

[60] Chen MH, Wu W, Yang W, Dai Y, Gao W, Yin SS, et al. The use of contrast-enhanced ultrasonography in the selection of patients with hepatocellular carcinoma for radio frequency ablation therapy. *J Ultrasound Med* 2007;26(8):1055-1063.

[61] 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(8):752-760.

[62] Sangiovanni A, Manini MA, Romeo R, Iavarone M, Fraquelli M, Forzenigo LV, et al. Prospective validation of AASLD guidelines for the early diagnosis of hepatocellular carcinoma in cirrhotic patients. *Hepatology* 2007;46(4 Suppl 1):241A-242A.

[63] 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(4):186-193.

[64] Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996;313(7052):275-83.

[65] 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(6):810-20.

[66] 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.

[67] Sirli R, Sporea I, Martie A, Popescu A, Danila M. Contrast enhanced ultrasound in focal liver lesions: a cost efficiency study. *Med Ultrason* 2010;12(4):280-5.

[68] Zaim R, Taimr P, Redekop W, Uyl-de Groot C. *Economic evaluation of contrast-enhanced ultrasound (CEUS) in the characterization of focal liver lesions (FLL) in the Netherlands*. Rotterdam, Netherlands: Institute for Medical Technology Assessment, Department of Health Policy and Management, Erasmus University; Department of Gastroenterology and Hepatology, Erasmus MC University Hospital, 2011. 25p.

[69] Bennett GL, Krinsky GA, Abitbol RJ, Kim SY, Theise ND, Teperman LW. Sonographic detection of hepatocellular carcinoma and dysplastic nodules in cirrhosis: correlation of pretransplantation sonography and liver explant pathology in 200 patients. *AJR Am J Roentgenol* 2002;179(1):75-80.

[70] Roberts SE, Goldacre MJ, Yeates D. Trends in mortality after hospital admission for liver cirrhosis in an English population from 1968 to 1999. *Gut* 2005;54(11):1615-21.

[71] Fattovich G, Giustina G, Schalm SW, Hadziyannis S, Sanchez-Tapias J, Almasio P, et al. Occurrence of hepatocellular carcinoma and decompensation in western European patients with cirrhosis type B. The EUROHEP Study Group on Hepatitis B Virus and Cirrhosis. *Hepatology* 1995;21(1):77-82.

[72] Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997;112(2):463-72.

[73] Office for National Statistics. Mortality Statistics: Deaths registered in England and Wales (Series DR), 2010 [Internet]. Newport: Office for National Statistics 2011 [cited 5.1.12]. Available from: http://www.ons.gov.uk/ons/rel/vsob1/mortality-statistics--deaths-registered-in-england-and-wales--series-dr-/2010/index.html

[74] Fattovich G, Pantalena M, Zagni I, Realdi G, Schalm SW, Christensen E, et al. Effect of hepatitis B and C virus infections on the natural history of compensated cirrhosis: a cohort study of 297 patients. *Am J Gastroenterol* 2002;97(11):2886-95.

[75] Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 2004;127(5 Suppl 1):S35-50.

[76] Taouli B, Goh JS, Lu Y, Qayyum A, Yeh BM, Merriman RB, et al. Growth rate of hepatocellular carcinoma: evaluation with serial computed tomography or magnetic resonance imaging. *J Comput Assist Tomogr* 2005;29(4):425-9.

[77] Trevisani F, D'Intino PE, Morselli-Labate AM, Mazzella G, Accogli E, Caraceni P, et al. Serum alpha-fetoprotein for diagnosis of hepatocellular carcinoma in patients with chronic liver disease: influence of HBsAg and anti-HCV status. *J Hepatol* 2001;34(4):570-5.

[78] UK Transplant. *Liver transplant services: donor organ use – protocols and guidelines for adults undergoing cadaveric liver transplantation [Internet]*. Bristol: UK Transplant, 2005 [cited 23.1.12] Available from: http://www.uktransplant.org.uk/ukt/about_transplants/organ_allocation/liver/national_protocols_and_guidelines/protocols_and_guidelines/adults.jsp

[79] Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. *Hepatology* 1999;30(6):1434-40.

[80] Greten TF, Papendorf F, Bleck JS, Kirchhoff T, Wohlberedt T, Kubicka S, et al. Survival rate in patients with hepatocellular carcinoma: a retrospective analysis of 389 patients. *Br J Cancer* 2005;92(10):1862-8.

[81] Department of Health. *NHS Reference Costs 2009-2010 [Internet]*. London: Department of Health, 2011 [cited .5.1.12] Available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_123459

[82] Personal Social Services Research Unit. *Unit Costs of Health and Social Care*. Canterbury: University of Kent, 2011 [cited 17.1.12]. 236p. Available from: http://www.pssru.ac.uk/pdf/uc/uc2011/uc2011.pdf

[83] Chong CA, Gulamhussein A, Heathcote EJ, Lilly L, Sherman M, Naglie G, et al. Health-state utilities and quality of life in hepatitis C patients. *Am J Gastroenterol* 2003;98(3):630-8.

[84] Ratcliffe J, Longworth L, Young T, Bryan S, Burroughs A, Buxton M. Assessing health-related quality of life pre- and post-liver transplantation: a prospective multicenter study. *Liver Transpl* 2002;8(3):263-70.

[85] Saunders TH, Mendes Ribeiro HK, Gleeson FV. New techniques for imaging colorectal cancer: the use of MRI, PET and radioimmunoscintigraphy for primary staging and follow-up. *Br Med Bull* 2002;64:81-99.

[86] Lejeune C, Bismuth MJ, Conroy T, Zanni C, Bey P, Bedenne L, et al. Use of a decision analysis model to assess the cost-effectiveness of 18F-FDG PET in the management of metachronous liver metastases of colorectal cancer. *J Nucl Med* 2005;46(12):2020-8.

[87] Medical Services Advisory Committee. *Positron emission tomography for recurrent colorectal cancer: assessment report (MSAC reference 35a) [Internet]*. Canberra, Australia: Medical Services Advisory Committee, August 2007, 2008 [cited 5.1.12]. 159p. Available from: http://www.msac.gov.au/internet/msac/publishing.nsf/Content/8FD1D98FE64C8A2FCA2575AD0082FD8F/$File/MSAC35a_PET_CRC_print250608new.pdf

[88] American Cancer Society. *Colorectal cancer: facts and figures. Special edition [Internet]*. Atlanta, USA: American Cancer Society, 2005 [cited 5.1.12]. 24p. Available from: http://www.cancer.org/acs/groups/content/@nho/documents/document/caff2005cr4pwsecuredpdf.pdf

[89] Colon and Rectum. In: Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, editors. *AJCC Cancer Staging Manual*. 7th ed. New York: Springer, 2009: 143-164.

[90] Office for National Statistics. UK Interim Life Tables, 1980-82 to 2008-10 [Internet]. Newport: Office for National Statistics 2011 [cited 5.1.12]. Available from: http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Life+Tables

[91] Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier AM. Epidemiology and management of liver metastases from colorectal cancer. *Ann Surg* 2006;244(2):254-9.

[92] Joint Formulary Committee. *British National Formulary. 58*. London: BMJ Group and Pharmaceutical Press, 2009.

[93] Information Services Division, NHS National Services Scotland. Costs Book 2009 [Internet]. Edinburgh: NHS National Services Scotland, 2009 [cited 20.11.09]. Available from: http://www.isdscotlandarchive.scot.nhs.uk/isd/6480.html

[94] Cancer Research UK. Treating bowel cancer [Internet]. [cited 5.1.12]. Available from: http://cancerhelp.cancerresearchuk.org/type/bowel-cancer/treatment/

[95] Guest JF, Ruiz FJ, Greener MJ, Trotman IF. Palliative care treatment patterns and associated costs of healthcare resource use for specific advanced cancer patients in the UK. *Eur J Cancer Care* 2006;15(1):65-73.

[96] Kind P, Hardman G, Macran S. *UK population norms for EQ-5D. CHE Discussion Paper 172 [Internet]*. York: Centre for Health Economics, University of York, [cited 5.1.12]. 98p. Available from: www.york.ac.uk/media/che/documents/papers/discussionpapers/CHE%20Discussion%20Paper%20172.pdf

[97] Ramsey SD, Andersen MR, Etzioni R, Moinpour C, Peacock S, Potosky A, et al. Quality of life in survivors of colorectal carcinoma. *Cancer* 2000;88(6):1294-303.

[98] Langenhoff BS, Krabbe PF, Peerenboom L, Wobbes T, Ruers TJ. Quality of life after surgical treatment of colorectal liver metastases. *Br J Surg* 2006;93(8):1007-14.

[99] Tengs TO, Wallace A. One thousand health-related quality-of-life estimates. *Med Care* 2000;38(6):583-637.

[100] 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(2):106-115.

[101] 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(6):854-861.

[102] Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. *J Clin Epidemiol.* 2005;58:882-93.

[103] 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(5):500-5.

[104] Zhou X, McClish D, Obuchowski N. *Statistical methods in diagnostic medicine*. New York: Wiley Interscience, 2002.

[105] Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *BMJ* 2003;326(7379):41-4.

[106] Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. *Ann Intern Med* 2003;138(1):W1-12.

APPENDICES

Appendix 1: Literature search strategies

Clinical Effectiveness search strategies

Embase (OvidSP): 2000-2011/wk 39
Searched 6.10.11

1 metastasis/ (154939)
2 (Metasta$ or meta-sta$).ti,ab,ot,hw. (394219)
3 or/1-2 (394219)
4 (liver or hepato$ or hepatic$).ti,ab,ot,hw. (999970)
5 3 and 4 (64975)
6 exp liver tumor/ (134843)
7 FLL.ti,ab,ot. (104)
8 FLLs.ti,ab,ot. (41)
9 bile duct carcinoma/ (9888)
10 ((liver$ or hepat$) adj3 (cancer$ or met$ or malignan$ or carcinoma$ or tumo?r$ or neoplas$ or adeno$ or angiom$ or sarcoma$ or angiosarcoma$)).ti,ab,ot,hw. (210520)
11 (hepatoma$ or h?emangiosarcoma$ or h?emangio-sarcoma$).ti,ab,ot,hw. (24960)
12 (Focal liver lesion$ 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$)).ti,ab,ot,hw. (845)
13 (BFLL or BFLLS).ti,ab,ot. (5)
14 (HCC or HCCs).ti,ab,ot. (25130)
15 (Cholangiocarcinoma$ 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$)).ti,ab,ot,hw. (18232)
17 or/5-16 (252012)
18 Echography/ or Echotomography/ (186679)
19 ((ultrasonic$ 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$).ti,ot,ab,hw. (413388)
21 or/18-20 (413388)
22 Sulfur hexafluoride/ (1199)
23 (hexafluoruro-sulfurico or SF6 or SF-6 or sulphur hexa-fluoride$ 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 (23736)
36 bile duct carcinoma/di (2943)
37 metastasis/di (11811)
38 or/35-37 (36762)
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/ (3084529)
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. (4773759)
45 or/43-44 (4773759)
46 exp human/ or human experiment/ (12541220)
47 45 not (45 and 46) (3833028)
48 42 not 47 (578)

Medline (OvidSP): 2000-2011/09/wk 4
Searched 6.10.11

1 neoplasm metastasis/ or neoplasm seeding/ or neoplasms, unknown primary/ (79582)
2 (Metasta$ or meta-sta$).ti,ab,ot,hw. (311666)
3 or/1-2 (313877)
4 (liver or hepato$ or hepatic$).ti,ab,ot,hw. (871423)
5 3 and 4 (46193)
6 exp Liver Neoplasms/ (112995)
7 exp Bile Duct Neoplasms/ (11958)
8 Carcinoma, Hepatocellular/ (51056)
9 (FLL or FLLs).ti,ab,ot. (95)
10 Cholangiocarcinoma/ (4146)
11 ((liver$ or hepat$) adj3 (cancer$ or met$ or malignan$ or carcinoma$ or tumo?r$ or neoplas$ or adeno$ or angiom$ or sarcoma$ or angiosarcoma$)).ti,ab,ot,hw. (169576)
12 (hepatoma$ or h?emangiosarcoma$ or h?emangio-sarcoma$).ti,ab,ot,hw. (27800)
13 (Focal liver lesion$ 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$)).ti,ab,ot,hw. (712)
14 (BFLL or BFLLS).ti,ab,ot. (3)
15 (HCC or HCCs).ti,ab,ot. (18801)
16 (Cholangiocarcinoma$ 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$)).ti,ab,ot,hw. (14499)
18 or/5-17 (200072)
19 ultrasonography/ or ultrasonography, doppler/ or exp ultrasonography, doppler, duplex/ or exp ultrasonography, doppler, pulsed/ (89811)
20 ((ultrasonic$ 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$).ti,ot,ab,hw. (276299)
22 or/19-21 (280667)
23 Sulfur Hexafluoride/ (1489)
24 (hexafluoruro-sulfurico or SF6 or SF-6 or sulphur hexa-fluoride$ 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/) (3606824)
48 46 not 47 (342)

Medline In-Process Citations (OvidSP): 2000-2011/10/05
Medline Daily Update (OvidSP): 2000-2011/10/05
Searched 6.10.11

1 neoplasm metastasis/ or neoplasm seeding/ or neoplasms, unknown primary/ (66)
2 (Metasta$ or meta-sta$).ti,ab,ot,hw. (12580)
3 or/1-2 (12581)
4 (liver or hepato$ or hepatic$).ti,ab,ot,hw. (21219)
5 3 and 4 (1428)
6 exp Liver Neoplasms/ (134)
7 exp Bile Duct Neoplasms/ (6)
8 Carcinoma, Hepatocellular/ (99)
9 (FLL or FLLs).ti,ab,ot. (21)
10 Cholangiocarcinoma/ (7)
11 ((liver$ or hepat$) adj3 (cancer$ or met$ or malignan$ or carcinoma$ or tumo?r$ or neoplas$ or adeno$ or angiom$ 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 tumo?r$ or neoplas$ or adeno$ or angiom$ or sarcoma$ or angiosarcoma$)).ti,ab,ot,hw. (22)
14 (BFLL or BFLLS).ti,ab,ot. (0)
15 (HCC or HCCs).ti,ab,ot. (1356)
16 (Cholangiocarcinoma$ or Cholangio-carcinoma$).ti,ab,ot,hw. (319)
17 (Bile duct$ adj3 (cancer$ or met$ or malignan$ or lesion$ or carcinoma$ or tumo?r$ or neoplas$ or adeno$ or angiom$ 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$).ti,ot,ab,hw. (11431)
22 or/19-21 (11432)
23 Sulfur Hexafluoride/ (0)
24 (hexafluoruro-sulfurico or SF6 or SF-6 or sulphur hexa-fluoride$ 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 (CDSR) (Wiley): Issue 10:2011
Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): Issue 4:2011
http://www.thecochranelibrary.com/
Search limited to 2000-2011
Searched 6.10.11

#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 10876
#5 (#1 OR #2 OR #3 OR #4) 10908
#6 (liver or hepato* or hepatic*):ti,ab,kw 30235
#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 14089
#26 (#20 OR #21 OR #22 OR #23 OR #24 OR #25) 14122
#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 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 (DARE) via Cochrane Library (Wiley): 2000-2011/10/07
Health Technology Assessment Database (HTA) via Cochrane Library (Wiley): 2000-2011/10/07
http://www.thecochranelibrary.com/
Search limited to 2000-2011
Searched 6.10.11

#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 10876
#5 (#1 OR #2 OR #3 OR #4) 10908
#6 (liver or hepato* or hepatic*):ti,ab,kw 30235
#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 14089
#26 (#20 OR #21 OR #22 OR #23 OR #24 OR #25) 14122
#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 (DARE) (Internet) (Top-up search for currency)
Health Technology Assessment Database (HTA) (Internet) (Top-up search for currency)
Records added to CRD databases between 2011/01/01-2011/10/06
http://www.york.ac.uk/inst/crd/
Searched 7.10.11

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*) 17021
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 (SCI) (Web of Knowledge): 2000-2011/
Search limited to 2000-2011/10/06
Searched 7.10.11

 # 25 416 #23 not #24
Databases=SCI-EXPANDED Timespan=2000-2011
Lemmatization=On
# 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 1,281 #21 OR #14
# 21 1,273 #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 3,932 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
# 11 166,385TS=(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 9,832 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 4,831 TS=(Cholangiocarcinoma* or Cholangio-carcinoma*)
# 6 1,966 TI=(BFLL or BFLLS or HCC or HCCs)
# 5 1,584 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*)

3 230,065TS=((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 7.10.11

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**

mRCT – metaRegister of Controlled Trials (Internet)
http://www.controlled-trials.com/
Searched 7.10.11

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	1

haemangio-sarcoma)	
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**

WHO International Clinical Trials Registry Platform (ICTRP) (Internet)
http://www.who.int/ictrp/en/
Searched 7.10.11

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 Registry (EU CTR) (Internet)
https://www.clinicaltrialsregister.eu/ctr-search/
Searched 10.10.11

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 & Biology conference) (Internet): 2011 only
Searched 10.11.11 (2011 abstracts); 21.11.11 (2007-2008 abstracts)

2011 = **http://www.wfumb2011.org/index.php?pid=70** Searched title+abstract
2010 = Unable to access

2009 = Unable to access
2008 = **https://www.thieme-connect.com/ejournals/toc/ultraschall/33697/grouping/54161**
Searched title
2007 = **http://www.interplan.de/pages/euroson2007/front_content.php?idcat=82**
Searched title+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): 2006-2011
Searched 10.11.11

2011 = **http://www.myesr.org/cms/website.php?id=/en/past_congresses/ecr_2011/ecr_2011_book_of_abstracts.htm**
2010 = **http://www.myesr.org/cms/website.php?id=/en/ecr_2010/book_of_abstracts.htm**
2009 = **http://www.myesr.org/cms/website.php?id=/en/ecr_2009/ecr_2009_book_of_abstracts.htm**
2008 = **http://www.abstractsonline.com/viewer/?mkey={9AF35541-5128-444B-9D15-447022358A3F}**
2007 = **http://www.abstractsonline.com/viewer/?mkey={9A26688A-5BBE-4366-AE14-5AC99DF8F8E4}**
2006 = **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**	**27**	**34**	**32**
TOTAL	**137**					

Radiological Society of North America (RSNA) conference (Internet): 2006-2010

Searched 10.11.11

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**	**126**	**124**
TOTAL	**415**				

Cost -Effectiveness searches

Medline (OvidSP): 2000-2011/09/wk 2
Searched 11.10.11

1 neoplasm metastasis/ or neoplasm seeding/ or neoplasms, unknown primary/ (79582)
2 (Metasta$ or meta-sta$).ti,ab,ot,hw. (311666)
3 or/1-2 (313877)
4 (liver or hepato$ or hepatic$).ti,ab,ot,hw. (871423)
5 3 and 4 (46193)
6 exp Liver Neoplasms/ (112995)
7 exp Bile Duct Neoplasms/ (11958)
8 Carcinoma, Hepatocellular/ (51056)
9 (FLL or FLLs).ti,ab,ot. (95)
10 Cholangiocarcinoma/ (4146)
11 ((liver$ or hepat$) adj3 (cancer$ or met$ or malignan$ or carcinoma$ or tumo?r$ or neoplas$ or adeno$ or angiom$ or sarcoma$ or angiosarcoma$)).ti,ab,ot,hw. (169576)
12 (hepatoma$ or h?emangiosarcoma$ or h?emangio-sarcoma$).ti,ab,ot,hw. (27800)
13 (Focal liver lesion$ 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$)).ti,ab,ot,hw. (712)
14 (BFLL or BFLLS).ti,ab,ot. (3)
15 (HCC or HCCs).ti,ab,ot. (18801)
16 (Cholangiocarcinoma$ 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$)).ti,ab,ot,hw. (14499)
18 or/5-17 (200072)
19 tomography, emission-computed/ or exp tomography, x-ray computed/ (278220)
20 exp Ultrasonography/ (220625)
21 exp Tomography/ (530496)
22 exp Magnetic Resonance Imaging/ (259244)
23 exp Tomography, Emission-Computed/ (65860)
24 Fluorodeoxyglucose F18/du (11296)
25 (MSCT or MDST or MRI or FDGPET or FDG-PET or MDCT or IOUS or MRI or FMRI or NMRI or FNMRI).ti,ab,ot. (131472)
26 (pet or petscan$ or positron).ti,ot,ab,hw. (55858)
27 (CAT or CTA or CT or cine-ct).ti,ab,ot. (241703)
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$)).ti,ab,ot,hw. (473823)
31 (electron beam adj4 (scan$ 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. (36261)
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$).ti,ot,ab,hw. (629456)
36 "ultrasound without contrast".ti,ot,ab,hw. (1)
37 ("ultrasonography without contrast" or "ultrasonograph without contrast").ti,ot,ab,hw. (0)
38 ((Un-enhanced or Unenhanced) adj4 (sonogra$ 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. (38028)
40 or/19-39 (1087651)
41 18 and 40 (29857)
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 (30149)
51 economics/ (26431)
52 exp "costs and cost analysis"/ (160527)
53 economics, dental/ (1886)
54 exp "economics, hospital"/ (17621)
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$).ti,ab. (348545)
59 (expenditure$ not energy).ti,ab. (14733)
60 (value adj1 money).ti,ab. (20)
61 budget$.ti,ab. (14850)
62 or/51-61 (463424)
63 ((energy or oxygen) adj cost).ti,ab. (2377)
64 (metabolic adj cost).ti,ab. (624)
65 ((energy or oxygen) adj expenditure).ti,ab. (13655)
66 or/63-65 (16028)
67 62 not 66 (459787)
68 letter.pt. (728700)
69 editorial.pt. (285457)
70 historical article.pt. (282970)
71 or/68-70 (1283982)
72 67 not 71 (434958)
73 animals/ not (animals/ and humans/) (3606824)
74 72 not 73 (409921)
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 [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

Medline In-Process Citations (OvidSP): 2000-2011/10/10
Medline Daily Update (OvidSP): 2000-2011/10/10
Searched 11.10.11

1 neoplasm metastasis/ or neoplasm seeding/ or neoplasms, unknown primary/ (84)
2 (Metasta$ or meta-sta$).ti,ab,ot,hw. (12775)
3 or/1-2 (12776)
4 (liver or hepato$ or hepatic$).ti,ab,ot,hw. (21579)

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. (10016)
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$)).ti,ab,ot,hw. (10787)
31 (electron beam adj4 (scan$ 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$).ti,ot,ab,hw. (21818)
36 "ultrasound without contrast".ti,ot,ab,hw. (0)
37 ("ultrasonography without contrast" or "ultrasonograph without contrast").ti,ot,ab,hw. (1)
38 ((Un-enhanced or Unenhanced) adj4 (sonogra$ 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 (38105)
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$).ti,ab. (24833)
59 (expenditure$ not energy).ti,ab. (706)
60 (value adj1 money).ti,ab. (2)
61 budget$.ti,ab. (1368)
62 or/51-61 (26315)
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 (26100)
68 letter.pt. (17183)
69 editorial.pt. (10629)
70 historical article.pt. (603)
71 or/68-70 (28394)
72 67 not 71 (25702)
73 animals/ not (animals/ and humans/) (2838)
74 72 not 73 (25645)
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 [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

Embase (OvidSP): 2000-2011/wk 40
Searched 12.10.11

1 metastasis/ (155985)
2 (Metasta$ or meta-sta$).ti,ab,ot,hw. (396806)
3 or/1-2 (396806)
4 (liver or hepato$ or hepatic$).ti,ab,ot,hw. (1004150)
5 3 and 4 (65370)
6 exp liver tumor/ (135580)
7 FLL.ti,ab,ot. (107)
8 FLLs.ti,ab,ot. (43)
9 bile duct carcinoma/ (9937)
10 ((liver$ or hepat$) adj3 (cancer$ or met$ or malignan$ or carcinoma$ or tumo?r$ or neoplas$ or adeno$ or angiom$ or sarcoma$ or angiosarcoma$)).ti,ab,ot,hw. (211624)
11 (hepatoma$ or h?emangiosarcoma$ or h?emangio-sarcoma$).ti,ab,ot,hw. (25072)

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$)).ti,ab,ot,hw. (854)
13 (BFLL or BFLLS).ti,ab,ot. (5)
14 (HCC or HCCs).ti,ab,ot. (25363)
15 (Cholangiocarcinoma$ 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$)).ti,ab,ot,hw. (18319)
17 or/5-16 (253318)
18 exp Tomography/ (524140)
19 exp Echography/ (399873)
20 exp Nuclear-Magnetic-Resonance-Imaging/ (385701)
21 Fluorodeoxyglucose-F-18/du (0)
22 (MSCT or MDST or MRI or FDGPET or FDG-PET or MDCT or IOUS or MRI or FMRI or NMRI or FNMRI).ti,ab,ot. (175669)
23 (pet or petscan$ or positron).ti,ot,ab,hw. (88701)
24 (CAT or CTA or CT or cine-ct).ti,ab,ot. (295625)
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$)).ti,ab,ot,hw. (554605)
28 (electron beam adj4 (scan$ 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. (41562)
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$).ti,ot,ab,hw. (906553)
33 "ultrasound without contrast".ti,ot,ab,hw. (2)
34 ("ultrasonography without contrast" or "ultrasonograph without contrast").ti,ot,ab,hw. (0)
35 ((Un-enhanced or Unenhanced) adj4 (sonogra$ 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$)).ti,ot,ab,hw. (412)
36 Positron emission tomogra$.ti,ot,ab,hw. (67261)
37 or/18-36 (1418654)
38 17 and 37 (42839)
39 health-economics/ (30583)
40 exp economic-evaluation/ (172264)
41 exp health-care-cost/ (165499)
42 exp pharmacoeconomics/ (140625)
43 or/39-42 (395230)
44 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (448361)
45 (expenditure$ not energy).ti,ab. (17805)
46 (value adj2 money).ti,ab. (974)
47 budget$.ti,ab. (18892)
48 or/44-47 (467436)
49 43 or 48 (700900)
50 letter.pt. (742741)
51 editorial.pt. (383238)
52 note.pt. (452797)

53 or/50-52 (1578776)
54 49 not 53 (628549)
55 (metabolic adj cost).ti,ab. (670)
56 ((energy or oxygen) adj cost).ti,ab. (2591)
57 ((energy or oxygen) adj expenditure).ti,ab. (15505)
58 or/55-57 (18084)
59 54 not 58 (624471)
60 exp animal/ (1655604)
61 exp animal-experiment/ (1467831)
62 nonhuman/ (3718682)
63 (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. (4119669)
64 or/60-63 (5951308)
65 exp human/ (12628304)
66 exp human-experiment/ (293772)
67 65 or 66 (12629688)
68 64 not (64 and 67) (4686921)
69 59 not 68 (579765)
70 38 and 69 (895)
71 limit 70 to yr="2000 -Current" (667)
72 limit 71 to embase (604)

Economics filter:
Centre for Reviews and Dissemination. NHS EED Economics Filter: Embase (Ovid) weekly search [Internet]. York: Centre for Reviews and Dissemination; 2010 [cited 11.10.11]. Available from: http://www.york.ac.uk/inst/crd/intertasc/nhs_eed_strategies.html

NHS Economic Evaluation Database (NHS EED) (Wiley)
Search limited to 2000-2011
Searched 12.10.11

#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 10876
#5 (#1 OR #2 OR #3 OR #4) 10908
#6 (liver or hepato* or hepatic*):ti,ab,kw 30235
#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 angiogra* or xray* or x-ray*)):ti,ab,kw 8723
#34 ((electron NEXT beam) near/4 (scan* or imag* or tomogra* or angiogra* or angiogra* 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 21304
#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) 31232
#44 (#20 AND #43), from 2000 to 2011 27 (limited to NHS EED only)

NHS Economic Evaluation Database (NHS EED) (Internet)
Top-up search to supplement search of NHS EED via Cochrane Library (Wiley)
Records added to CRD databases between 2011/01/01-2011/10/12
http://www.york.ac.uk/inst/crd/
Searched 12.10.11

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 Economics Evaluation Database (HEED) (Internet): up to 2011/10/12

http://onlinelibrary.wiley.com/book/10.1002/9780470510933
Searched 12.10.11

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): 2000-2011/10/07
Searched 12.10.11

 # 34 432 #8 AND #22 AND #33
Databases=SCI-EXPANDED Timespan=2000-2011
Lemmatization=On
# 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 4,365 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 9,239 TS=(expenditure* not energy)
# 23 435,234TS=(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*))
# 19 318,584TS=(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 3,837 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 1,747 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*))
# 14 153,267TS=((nmr or comput* or mr) near/4 (scan* or imag* or tomogra* or angiogra* or angio-gra* or xray* or x-ray*))
# 13 1,863 TS=(64slice* or 64-slice* or 64row* or 64-row* or 64-detect*)
# 12 143 TS=(3dcta or 3d-cta)
# 11 161,518TS=(CAT or CTA or CT or cine-ct)
# 10 82,730 TS=(pet or petscan* or positron)
# 9 133,925TS=(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 9,838 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 4,832 TS=(Cholangiocarcinoma* or Cholangio-carcinoma*)
# 5 1,970 TI=(BFLL or BFLLS or HCC or HCCs OR FLL or FLLs)
# 4 1,584 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*)
# 2 230,112TS=((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*))
Databases=SCI-EXPANDED Timespan=2000-2011
# 1 24,461 TS=((Metasta* or meta-sta*) AND (liver or hepato* or hepatic*))

Additional NHS EED search - NHS Economic Evaluation Database (NHS EED) (Wiley)
Search limited to 2000-2011
Searched 21.10.11

#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 10876
#5 (#1 OR #2 OR #3 OR #4) 10908
#6 (liver or hepato* or hepatic*):ti,ab,kw 30235
#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

GIN: International Guidelines Library
http://www.g-i-n.net
2000-2011/11/09
Searched 9.11.11

Limited to 2000-2011.

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 (prior to deduplication)	**137**	-
Total (after to deduplication)	**114**	-

National Guidelines Clearinghouse (Internet)
http://www.guideline.gov/
Limited: 2000-2011/11/09
Searched 10.11.11

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 Clinical Excellence (NICE) Guidance (Internet)
http://guidance.nice.org.uk/
Searched 10.11.11

Browsed: Liver Neoplasms = **11**

TRIP database (Internet)
http://www.tripdatabase.com/
Searched 10.11.11

Limited to Guidelines only; 2000-2011

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)	3

from:2000 to:2011	
(title:bile duct) (not Liver or hepato* or hepatic) from:2000 to:2011	2
Total	**101**

Health Technology Assessment Database (HTA) (Internet)
http://www.york.ac.uk/inst/crd/
Search limited to 2000-2011
Searched 10.11.11

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 which 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 weren't 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 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 ≥10% of patients → high risk of bias

Concerns regarding applicability

Included patients were adults with FLLs with uncertain diagnosis on standard ultrasound 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 ultrasound or other imaging, where 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 pre-specify the threshold for a positive result?

The same criteria applied to each of the 3 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 pre-specify the threshold for a positive result?
The same criteria applied to each of the 3 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 ≥90% of test results were confirmed using the reference standard specified by the inclusion criteria (pathology for test +ve and pathology or minimum 6 months follow-up for test -ve) → 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 +ve and pathology or minimum 6 months follow-up for test -ve) → 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 ≤ 1 month in order to be judged as "adequate" and follow-up had to be ≥6 months in order to be judged as "adequate".
"no" but 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 ≥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 ≤ 1 month in order to be judged as "adequate" and follow-up had to be ≥6 months in order to be judged as "adequate".
"no" but 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 ≥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 ≤ 1 month in order to be judged as "adequate"
"no" but 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 ≥10% of patients → high risk of bias

Question 4: Did all patients receive a reference standard?

"no" but for <10% of patients or "yes" → low risk of bias
"unclear" → unclear risk of bias
"no" for ≥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" but 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 ≥10% of test positive or test negative patients → high risk of bias

Question 6: Were all patients included in the analysis?

"no" but for <10% of patients or "yes" → low risk of bias
"unclear" → unclear risk of bias
"no" for ≥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 in order for the domain to be judged as having a low risk of bias.

Appendix 3: Quality assessment - QUADAS-2 results

Completed QUADAS-2 assessments for all included studies:

STUDY ID: Blondin 2011[14]

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Describe methods of patient selection:
retrospective selection of patients liver cirrhosis from a database (radiological information system) of patients who underwent CEMRI (Promovist) and CEUS (Sonovue)

- ❖ Was a consecutive or random sample of patients enrolled? no
- ❖ Was a case-control design avoided?
- ❖ Did the study avoid inappropriate exclusions? unclear

Could the selection of patients have introduced bias? RISK: HIGH

B. Concerns regarding applicability

Describe included patients (prior testing, presentation, intended use of index test and setting):
Patients with liver cirrhosis and FLL diagnosed via CEUS and CEMRI.

Is there concern that the included patients do not match the review question? CONCERN: HIGH

DOMAIN 2a: INDEX TEST

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 max. 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 pre-specified? Yes

Could the conduct or interpretation of the index test have introduced bias? RISK: UNCLEAR

DOMAIN 2b: COMPARATOR TEST

Risk of Bias

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

- ❖ Were the comparator test results interpreted without knowledge of the results of the reference standard? unclear
- ❖ Were the comparator test results interpreted without unclear

knowledge of the index test?

- ❖ If a threshold was used, was it pre-specified? 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 done in all FLL, 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 between index, comparator(s) and reference standard:
Time between index, and comparator test and reference standard were not reported. Time between index and comparator test was max 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**

STUDY ID: Catala 2007[53]

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Describe methods of patient selection:
Patients ≥18 yrs with FLL detected on standard US. 213 patients assessed for inclusion, 77 enrolled.
Excluded if pregnant or nursing, if more than one month between CEUS and SCT (unclear if these patients may be systematically different), 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

Could the selection of patients have introduced bias? RISK: HIGH

B. Concerns regarding applicability

Describe included patients (prior testing, presentation, intended use of index test and setting):
Adult patients with FLL detected at standard ultrasound. Not clear if standard ultrasound was diagnostic

Is there concern that the included patients do not match the review question? CONCERN: UNCLEAR

DOMAIN 2a: INDEX TEST

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 pre-specified? Yes

Could the conduct or interpretation of the index test have introduced bias? RISK: LOW

DOMAIN 2b: COMPARATOR TEST

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 pre-specified? 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:
All index test positive FLLs were confirmed pathologically following biopsy or surgery. Index test negative lesions were confirmed by NRI 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**

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):
213 patients were originally recruited. 77 were included in the analysis. Patients were excluded if more than one month between CEUS and SCT, or if positive lesions not confirmed by pathology.
Describe the time interval and any interventions between index, comparator(s) and reference standard:
Time between index test and comparator one month or less, 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**

STUDY ID: Clevert 2009[16]

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 >5cm; number of lesions >5; strong allergic reactions; liver of kidney disease with confirmed elevation of laboratory parameters; acute heart failure; acute myocardial infarction; subcutaneous emphysema; meteorism; tachypnea; aerobilia.
The majority of test positive patients were diagnosed with liver metastases, but prior investigations and diagnostic status with respect to primary tumours was 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 (prior testing, presentation, intended use of index test and setting):
Prior investigations and diagnostic status with respect to primary tumours was unclear.

Is there concern that the included patients do not match the review question? CONCERN: UNCLEAR

DOMAIN 2a: INDEX TEST

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 pre-specified? Yes

Could the conduct or interpretation of the index test have introduced bias? RISK: LOW

DOMAIN 2b: COMPARATOR TEST

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 pre-specified? 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**

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):
100 patients, with one lesion per patient. Positive tests were confirmed histologically and negative tests by imaging follow-up over 2 years. 21 patients were excluded from the CT analysis (8 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**

STUDY ID: Dai 2008[48]

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 (prior testing, presentation, intended use of index test and setting):
Adult patients with cirrhosis and indeterminate FLL detected at surveillance ultrasound.

Is there concern that the included patients do not match the review question? CONCERN: LOW

DOMAIN 2a: INDEX TEST

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 pre-specified? Yes

Could the conduct or interpretation of the index test have introduced bias? RISK: LOW

DOMAIN 2b: COMPARATOR TEST

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 pre-specified? 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:
All patients underwent biopsy (malignant and benign FLL) within 15 days after CEUS; a negative biopsy was followed for at least 6 months including US, CT and test 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 2x2 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**

STUDY ID: Feng 2007[58]

Chinese language

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 3 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 (prior 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

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 pre-specified? Yes

Could the conduct or interpretation of the index test have introduced bias? RISK: UNCLEAR

DOMAIN 2b: COMPARATOR TEST

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 pre-specified? 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

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 2x2 table (s):
All patients underwent imaging tests within two week 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

Could the patient flow have introduced bias? **RISK: UNCLEAR**

STUDY ID: Flor 2010[45] (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 (<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 (prior testing, presentation, intended use of index test and setting):
Patients with known primary cancer and indeterminate liver lesions (<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

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 pre-specified? Unclear

Could the conduct or interpretation of the index test have introduced bias? RISK: UNCLEAR

DOMAIN 2b: COMPARATOR TEST

Risk of Bias

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

- ❖ 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 pre-specified?

Could the conduct or interpretation of the comparator test have introduced bias? RISK: NA

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

Describe the reference standard and how it was conducted and interpreted:
Biopsy or 3-6 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? — NA

Could methods used to conduct or interpret the reference standard have introduced bias? 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 2x2 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:
Times 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? — NA
- ❖ Was there an appropriate interval between index test and comparator test? — NA
- ❖ 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

STUDY ID: Forner 2008[49]

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 (prior testing, presentation, intended use of index test and setting):
Adult patients with cirrhosis and new FLL detected at surveillance ultrasound. Diagnostic status following conventional ultrasound was not specified.

Is there concern that the included patients do not match the review question? CONCERN: UNCLEAR

DOMAIN 2a: INDEX TEST

Risk of Bias

Describe how the index test and any comparator tests were conducted and interpreted:
Interpreted by 2 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 pre-specified? Yes

Could the conduct or interpretation of the index test have introduced bias? RISK: UNCLEAR

DOMAIN 2b: COMPARATOR TEST

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 pre-specified? 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:
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**

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):
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**

STUDY ID: Gierbliński 2008[54]

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 un-enhanced US and/or CT. Patients with current or previous malignancy, 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 (prior testing, presentation, intended use of index test and setting):
Adult patients incidentally detected FLL in whom US and/or CT were 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

Risk of Bias

Describe how the index test and any comparator tests were conducted and interpreted:
Interpreted by 2 experienced gastroenterologists, blinding un-specified.

- ❖ 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 pre-specified? Yes

Could the conduct or interpretation of the index test have introduced bias? RISK: UNCLEAR

DOMAIN 2b: COMPARATOR TEST

Risk of Bias

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

- ❖ 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 pre-specified?

Could the conduct or interpretation of the comparator test have introduced bias? RISK: NA

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

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? NA

Could methods used to conduct or interpret the reference standard have introduced bias? 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):
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 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? NA
- ❖ Was there an appropriate interval between index test and comparator test? NA
- ❖ 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

STUDY ID: Georgio 2007[50]

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 (≤30 mm) detected on US. Patients with a history of heart disease excluded (due to 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 (prior testing, presentation, intended use of index test and setting):
Adult patients with cirrhosis and single FLL detected at US. Diagnostic status following conventional ultrasound was not specified.

Is there concern that the included patients do not match the review question? CONCERN: UNCLEAR

DOMAIN 2a: INDEX TEST

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 pre-specified? Yes

Could the conduct or interpretation of the index test have introduced bias? RISK: LOW

DOMAIN 2b: COMPARATOR TEST

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 pre-specified? 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:
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**

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):
73 patients all received 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**

STUDY ID: Jonas 2011[15] (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-pre-operative work-up.
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 extra-hepatic 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

Could the selection of patients have introduced bias? RISK: HIGH

B. Concerns regarding applicability

Describe included patients (prior testing, presentation, intended use of index test and setting):
Adult patients with CRC liver metastases. Initial diagnostic status unclear (see previous note).

Is there concern that the included patients do not match the review question? CONCERN: HIGH

DOMAIN 2a: INDEX TEST

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 pre-specified? Unclear

Could the conduct or interpretation of the index test have introduced bias? RISK: UNCLEAR

DOMAIN 2b: COMPARATOR TEST

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 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 pre-specified? 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:
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**

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):
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 2x2 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 test 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**

STUDY ID: Leoni 2010[10]

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Describe methods of patient selection:
Prospective consecutive cohort of cirrhotic patients with 1-3 hepatic nodule 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 pre-treated, those with contra-indications to imaging, and patients with neoplastic portal thrombosis or extra-hepatic 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 (prior testing, presentation, intended use of index test and setting):
Diagnostic status following un-enhanced imaging unclear.

Is there concern that the included patients do not match the review question? CONCERN: UNCLEAR

DOMAIN 2a: INDEX TEST

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 pre-specified? Yes

Could the conduct or interpretation of the index test have introduced bias? RISK: LOW

DOMAIN 2b: COMPARATOR TEST

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 comparator test results interpreted without knowledge of the index test? Yes
- ❖ If a threshold was used, was it pre-specified? 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:
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**

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):
Prospective cohort of 60 (75 nodules) cirrhotic patients with at least 1-3 hepatic nodules (1-3 cm) on US. Positive nodules confirmed by two concordant imaging test results, fine needle biopsy or follow-up at 3 month intervals. Negative nodules confirmed by fine needle biopsy or follow-up at 3 month intervals. 7 Nodules (<10%) were not examined by SPIO-MRI and were excluded from the analysis of the performance of this test.
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**

STUDY ID: Li 2007[55]

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Describe methods of patient selection:
Prospective cohort of 109 patients examined with un-enhanced US and un-enhanced 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 (prior 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

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 pre-specified? Yes

Could the conduct or interpretation of the index test have introduced bias? RISK: LOW

DOMAIN 2b: COMPARATOR TEST

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 pre-specified? 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**

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):
109 patients, one lesion per patient. All patients appear to have received index test, comparator and reference standard. Reference standard was histology in all patients. Seven lesions could not be visualised by CECT and 3 could not be visualised by CEUS. For our analysis, non-visualised lesions were classified as negative (FN or TN according to final diagnosis).
Describe the time interval and any interventions between index, comparator(s) and reference standard:
Reference standard was performed within two weeks of 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**

STUDY ID: Lüttich 2006[46] (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 (prior 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

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 pre-specified? Unclear

Could the conduct or interpretation of the index test have introduced bias? RISK: UNCLEAR

DOMAIN 2b: COMPARATOR TEST

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 pre-specified? 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: 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

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 2x2 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

Could the patient flow have introduced bias? **RISK: UNCLEAR**

STUDY ID: Mainenti 2010[12]

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Describe methods of patient selection:
Prospective cohort of 34 consecutive patients with histologically proven colorectal carcinoma, 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 (prior testing, presentation, intended use of index test and setting):
Diagnostic status following un-enhanced imaging unclear.

Is there concern that the included patients do not match the review question? CONCERN: UNCLEAR

DOMAIN 2a: INDEX TEST

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 pre-specified? Yes

Could the conduct or interpretation of the index test have introduced bias? RISK: LOW

DOMAIN 2b: COMPARATOR TEST

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 pre-specified? 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**

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):
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 month, either to confirm negative tests or to detect newly developed metastasis.
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 4-8 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**

STUDY ID: Quaia 2009[51]

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 ≤3 cm that underwent biopsy after CT were included.
Nodules with peripheral enhancement at CECT were excluded due to 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 (prior testing, presentation, intended use of index test and setting):
Diagnostic status following un-enhanced imaging unclear.

Is there concern that the included patients do not match the review question? CONCERN: UNCLEAR

DOMAIN 2a: INDEX TEST

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 pre-specified? Yes

Could the conduct or interpretation of the index test have introduced bias? RISK: LOW

DOMAIN 2b: COMPARATOR TEST

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 pre-specified? 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**

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):
Prospective cohort of 180 (195 nodules) cirrhotic patients with at least one hepatic nodule on US surveillance.
74 nodules were excluded because of a lack of histological diagnosis (n=60), technical inadequacy of CT (n=10), 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**

STUDY ID: Sangiovanni 2010[52, 62]

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 1-2 cm nodules were included in the analysis.
Patients with a pre-existing liver nodule, with 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

Could the selection of patients have introduced bias? RISK: HIGH

B. Concerns regarding applicability

Describe included patients (prior testing, presentation, intended use of index test and setting):
Diagnostic status following un-enhanced imaging unclear.

Is there concern that the included patients do not match the review question? CONCERN: UNCLEAR

DOMAIN 2a: INDEX TEST

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 pre-specified? Yes

Could the conduct or interpretation of the index test have introduced bias? RISK: UNCLEAR

DOMAIN 2b: COMPARATOR TEST

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 pre-specified? 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:
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**

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):
Prospective cohort of 64 (67 nodules) cirrhotic patients with at least one hepatic nodule on 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**

STUDY ID: Seitz 2009[56]

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 FLL 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; 2x2 data with an appropriate reference standard were only extractable 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 wells as malignant tumours with infiltration into hepatic vessels were excluded; patients who were critically ill or suffered from pulmonary hypertension or unstable angina as well as pregnant and nursing women 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

Could the selection of patients have introduced bias? RISK: HIGH

B. Concerns regarding applicability

Describe included patients (prior testing, presentation, intended use of index test and setting):
Patients with newly detected FLL on US; primary diseases not specified

Is there concern that the included patients do not match the review question? CONCERN: UNCLEAR

DOMAIN 2a: INDEX TEST

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 done by the local investigators; Us investigator not blinded to the results of the preceding CT in 8 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 pre-specified? Yes

Could the conduct or interpretation of the index test have introduced bias? RISK: UNCLEAR

DOMAIN 2b: COMPARATOR TEST

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 patient's 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 pre-specified? — 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: Subgroup B: diagnosis was based on US guided FNB; no definitive diagnosis could be obtained in 4 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**

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): 4 patients with inconclusive histology were excluded from analyses (<10% of patients). **Describe the time interval and any interventions between index, comparator(s) and reference standard:** Times between index and comparator test 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**

STUDY ID: Seitz 2010[57]

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 FLL 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; 2x2 data with an appropriate reference standard were only extractable 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 wells 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

Could the selection of patients have introduced bias? RISK: HIGH

B. Concerns regarding applicability

Describe included patients (prior testing, presentation, intended use of index test and setting):
Patients with newly detected FLL on US; primary diseases not specified

Is there concern that the included patients do not match the review question? CONCERN: UNCLEAR

DOMAIN 2a: INDEX TEST

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 done 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 pre-specified? Yes

Could the conduct or interpretation of the index test have introduced bias? RISK: UNCLEAR

DOMAIN 2b: COMPARATOR TEST

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 patient's 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 pre-specified? 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:
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? **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 2x2 table (s):
2 patients with inconclusive histology were excluded from analyses (<10% of patients).
Describe the time interval and any interventions between index, comparator(s) and reference standard:
Times between index and comparator test 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**

STUDY ID: Solbiati 2006[47] (abstract only)

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Describe methods of patient selection:
Retrospective cohort of patients with incidentally detected FLLs un un-enhanced 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 (prior testing, presentation, intended use of index test and setting):
Diagnostic status following un-enhanced imaging unclear.

Is there concern that the included patients do not match the review question? CONCERN: UNCLEAR

DOMAIN 2a: INDEX TEST

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 pre-specified? Unclear

Could the conduct or interpretation of the index test have introduced bias? RISK: UNCLEAR

DOMAIN 2b: COMPARATOR TEST

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 pre-specified? 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 fine-needle biopsy 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**

STUDY ID: Zhou 2007[59]

Chinese language

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

Could the selection of patients have introduced bias? RISK: UNCLEAR

B. Concerns regarding applicability

Describe included patients (prior 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

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 pre-specified? Yes

Could the conduct or interpretation of the index test have introduced bias? RISK: UNCLEAR

DOMAIN 2b: COMPARATOR TEST

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 pre-specified? 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. Three months 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**

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 underwent both imaging tests within one week of treatment. Patients with a positive response on imaging were followed up for three months. Patients with a negative response on imaging (residual tumour detected) were confirmed by fine needle biopsy.
Describe the time interval and any interventions between index, comparator(s) and reference standard:
See above. Note: Three months 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**

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 ID	SonoVue® CEUS details	Comparator test(s) details	Reference standard details
Blondin 2011[14]	Aplio 80 scanner (Toshiba Medical Systems, Neuss, Germany) real time B-mode sonography, low MI (0.2-0.4) CEUS was carried out after administration of a 2.4 ml bolus SonoVue® (Nycomed, Germany) into the antecubital vein. Images were interpreted by a internist and a radiologist, both were blinded.	1.5 Tesla MRT (Magneton Avanto, Siemens Medical Solutions, Germany) The contrast agent used was Gd-EOB-DTBA (Primovist®, Bayer Schwering Pharma, Germany), injected at 2 ml/ s via the antecubital vein. Axial T1 and T2- weighted imaging, contrast enhancement in the arterial (after 20 s), venous (after 60 s) and equilibrium phase (after 180 s) as well as the late phase (after 15 min, consisting of a coronal and axial T1) were used for analysis. Images were interpreted by two independent blinded radiologists	Histology after biopsy or surgery in all lesions
Catala 2007[53]	Sequoia 512 scanner (Acuson, Mountain View, CA). CEUS used specific software Coherent Contrast Imaging with the same convex array probe as baseline US. Baseline US of the liver (to identify FLLs) in the fundamental mode, using a grayscale and a multifrequency 4× C1 convex array probe.	SCT scanner (Somatom Plus 4, Siemens Medical Systems, Erlangen, Germany). 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 s. acquisition of the arterial phase started 6 s after the automatic detection of peak	All malignant lesions were histologically confirmed: biopsy (n = 52); partial hepatic resection (n = 3); explanation (n = 2). For benign FLL, the final diagnosis was obtained by biopsy (n=2); MRI and follow-up ≥12 months (n=18).

Study ID	SonoVue® CEUS details	Comparator test(s) details	Reference standard details
	CEUS was carried out after administration of a 2.4 ml bolus SonoVue® (Bracco, Italy) followed by 5 ml saline flush. Enhancement patterns were studied up to 3.5 min, including the arterial (0–49 s), portal (50–120 s), and late phases (>120 s). Settings were: insonating frequency, 3 MHz; acoustic power −75 to −90 dB; frame rate, 17–20; double focus; low mechanical index (<0.2). Images were interpreted by two independent radiologists with more than five years experience of liver CEUS; 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	aortic enhancement, portal and late venous phases were scanned 70 and 180 s after start of injection of the contrast agent. The contrast agent used was 100 ml Iopromide, 300 mg I/ml, (Ultravist, Schering AG, Berlin, Germany) via the antecubital vein at 4 ml/s. Images were interpreted by two independent radiologists with more than five 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	
Chen 2007[60] related publication[61]	Esaote Technos DU8 (Esaote SpA, Italy) or Philips iU22 (Philips Medical Systems, USA), using 2.5-5 MHz probes. CEUS was carried out after administration of 2.4 ml intravenous bolus SonoVue® (Bracco, Italy) injected over 2 to 3 s; low mechanical index (0.04-0.1).	US without contrast. CT or MRI was performed within one week before RFA in both groups. CT examinations were performed with GE LightSpeed 64 slice spiral CT. MRI was performed with GE EchoSpeed 1.5 T. Images were assessed by three	Reference standard NA (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 4-6 months in the second year. RFA was considered successful if there was no contrast enhancement in or

Study ID	SonoVue® CEUS details	Comparator test(s) details	Reference standard details
	CT or MRI was performed within one week before RFA in both groups. CT examinations were performed with GE LightSpeed 64 slice spiral CT. MRI was performed with GE EchoSpeed 1.5 T. Images were assessed by three experienced radiologists	experienced radiologists	around the tumour, the margins of the ablation zone were clear and smooth, the ablation zone extended beyond the tumour borders.
Clevert 2009 [16]	Multi-frequency curved array transducer, 2.5-4 MHz (Logic 9, GE Healthcare). Transmitted energy reduced to <30%, with a low mechanical index (0.15). After B scan analysis of vascularisation with power Doppler US, CEUS used iv administration as a 2.4 ml bolus SonoVue® (Bracco, Italy), followed by a 10 ml bolus of saline. Scanning was carried out during the arterial phase (<30 s), the portal venous phase (40-120 s) and the late phase (>120 s). CEUS was performed by two blinded radiologists with more than seven years of clinical ultrasound experience. Interpretation was by consensus.	Biphasic contrast-enhanced CT using a 16- or 64-slice scanner (Somatom Sensation 16 or 64, Siemens Medical Systems, Forchheim, Germany). Image volume included the whole liver. Un-enhanced axial sections were not performed. Contrast agent 120 ml Solutrast® (Bracco, Milan, Italy), iodine concentration 300 mg/ml, administered as an intravenous bolus (flow rate 5 ml/s), followed by 50 ml saline. The appropriate can 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 (3mm) maximum intensity projections in	Malignant liver lesions were confirmed by biopsy. For haemangioma, US follow-up for 2 years and MRI or multi-phase CT follow-up for one year were used to confirm diagnosis. No details of who interpreted the reference standard examinations were reported.

Study ID	SonoVue® CEUS details	Comparator test(s) details	Reference standard details
		axial and coronal planes. CT examinations were performed by two blinded, experienced radiologists.	
Dai 2008[48]	Technos MPX scanner (Esaote, Biomedica, Genoa, Italy). Baseline US of the liver (to identify FLLs), using 3.5 MHz convex probe. CEUS was carried out after iv administration as a 2.4 ml bolus within 2-3 s. SonoVue® (Bracco, Italy), continuous observation for 6 min from injection time using the same convex probe as baseline US; low mechanical index (0.05-0.06). 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.	SCT scanner (Somatom Plus 4, Siemens Medical Systems, Erlangen, Germany). 5mm collimation and 7.5 mm/s table speed. CT images obtained before and 25 s (arterial phase), 60 s (portal venous phase), and 2-4 min (late phase) after the start of contrast injection. The contrast agent used was 100ml Omnipaque (Amersham Health Princeton, USA), 300 mg/ml iodine, at a rate of 3.5 ml/s. 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.	Histopathology in all patients. Ultrasound-guided biopsy with 2-3 fold aspiration of each nodule using an 18-gauge needle. Histopathological diagnoses were made in consensus by two pathologists with more than 20 years experience. Negative biopsies were confirmed by further follow-up for a minimum of 6 months.
Feng 2007[58] Chinese language	US and CEUS using Siemens Acuson Sequoia 512. CEUS was carried out following injection of 2 ml SonoVue® (Bracco, Italy); low mechanical index (0.19). Imaging was conducted between 1 week and 3 months after cryosurgery, and all	CECT or CEMRI, no details reported. Imaging was conducted between 1 week and 3 months after cryosurgery, and all imaging tests were conducted within two weeks of each other. No details of who interpreted CECT and	Histopathological diagnosis, no further details reported.

Study ID	SonoVue® CEUS details	Comparator test(s) details	Reference standard details
	imaging tests were conducted within two weeks of each other. No details of who interpreted CEUS were reported.	CEMRI were reported.	
Flor 2010[45] (abstract only)	US and CEUS using Logic 9 (General Electrics). CEUS performed after bolus injection of 4.8 ml SonoVue® (Bracco, Italy); low mechanical index (<0.2). No details of interpretation were reported.	None	Biopsy or follow-up at 3-6 months. No further details were reported.
Forner 2008[49]	US used Sequoia 512 scanner (Acuson, Mountain View, CA, USA). Baseline US of the liver (to identify FLLs), using a multi-frequency 4C1 convex and 4V1 sectorial array probe. CEUS was carried out after administration of 2.4 ml bolus SonoVue® (Bracco, Italy), observation for up to 3.5 min from injection time, including arterial, portal and late phases. CEUS used contrast coherent imaging (CCI, Siemens) and the 4C1 convex array probe; low mechanical index (<0.2). Enhancement patterns were studied during the vascular phase up to 3.5	Symphony 1.5-T system (Siemens Medical Systema, Erlangen, Germany), using a phased-array torso coil. Transverse T1-weighted and T2-weighted MRI and multi-phasic contrast-enhanced dynamic breath-hold 3D MRI of the whole liver with fat suppression. The contrast agent used was gadolinium (gadodiamide 0.5mmol/L, Ominscan-Amersham), injected at 0.2 ml/kg and 2 ml/s. Bolus tracking was used to obtain arterial phase (20 s after injection), portal venous phase (60-65 s after injection), and late phase (100-110 s after injection) images.	All imaging positive nodules were confirmed with FNB using a 20-guage or 18-guage needle and multiple passages. Specimens were routinely processed and stained with hematoxylin-eosin. 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).

Study ID	SonoVue® CEUS details	Comparator test(s) details	Reference standard details
	minutes, including the arterial (0-49 seconds), portal (50-179 seconds), and late phase (>180 seconds). Images were recorded blindly and reviewed by at least two radiologists. Doubtful images were interpreted by consensus.	Images were interpreted by 2 radiologists, experienced in liver MRI, who were unaware of biopsy results.	
Gierbliński 2008[54]	Baseline US/ CT not specified. CEUS was carried out after administration of 2.4 ml bolus (86 patients) or 4.8 ml bolus (14 patients) SonoVue® (Bracco, Italy), followed by 10 ml 0.9% saline; Low MI < 0.09. Philips HDI 5000 SonoCT (Philips Medical Sustemas, Bothwell, WA, USA), using a 2-5 MHz curved linear-array transducer. Imaging duration was 4 min: arterial phase 15-30 s after injection, portal phase 35-90 s after injection, and late venous phase 90-240 s after injection. Images were interpreted by gastroenterologists with 2 years experience of CEUS, who were blind to initial US and CT results.	None	FNB in all patients with a 20-guage Chiba aspirating needle or 19-guage trucut biopsy; this diagnosis was considered final if the lesion was positive. Negative biopsies were confirmed by clinical and imaging follow-up (median 10 months). Biopsies were assessed by a pathologist blinded to CEUS results and follow-up imaging was evaluated by blinded examiners.
Giorgio 2007[50]	All abdominal US scans were performed with Prosound SSD-5500 PHD Extended (Aloka, Tokyo, Japan), using a 3-6 MHz	1.5-T Symphony system (Siemens Medical Systems, Enlargen, Germany).	Ultrasound-guided fine needle biopsy in all patients, using a 19-guage modified Menghini cutting needle.

Study ID	SonoVue® CEUS details	Comparator test(s) details	Reference standard details
	convex array broad-band probe. CEUS was carried out after administration of 2.4 ml bolus SonoVue® (Bracco, Italy), followed by a 5 ml saline flush; low mechanical index (0.11). The scan lasted up to 5 min and the whole vascular phase was observed: arterial (15-30 s after injection), portal (30-60 s after injection), sinusoidal (60-20 s after injection). One operator with over 20 years experience of CEUS performed all studies the day before MRI studies.	Three contiguous sets of T1-weighted, in phase, breath-hold, spoiled gradient echo images. The contrast agent used was 20 ml bolus gadobenate dimeglumine (MultiHance, Bracco Diagnostics, Italy), injection rate 3.0 ml/s, followed by 40 ml saline. Evaluation of arterial, portal and delayed phases was obtained through the whole liver at 22, 48 and 90 s after injection start. Images were interpreted by one experienced radiologist who was unaware of CEUS results.	Biopsy was performed the day after both imaging investigations were complete.
Jonas 2011[15] (abstract only)	SonoVue® CEUS, no further details reported.	MRI with hepatocyte-specific contrast (Primovist®), no further details reported. Triple-phase contrast-enhanced abdominal CECT, no further details reported.	All patients underwent intra-operative US and imaging (CEUS, CECT or CEMRI) follow-up at 3, 6, 12, 24 and 36 months. Histology was used to confirm all resected metastases detected on pre-operative imaging. No further details reported.
Leoni 2010[10]	Technos MPX scanner (Esaote, Genova, Italy) for un-enhanced US. CEUS (device: Esatune, CnTI or Technos MPX, Esaote, Italy) was conducted after administration of SonoVue® (Bracco,	Helical MDCT with Emotion 6 (Siemens Medical Systems, Erlangen, Germany). Un-enhanced and contrast-enhanced images for arterial, portal venous and delayed phases.	Two or more contrast imaging techniques positive was treated as a correct positive diagnosis which did not require further confirmation (EASL and AASLD guidelines for non-invasive diagnosis).

Study ID	SonoVue® CEUS details	Comparator test(s) details	Reference standard details
	Italy), dose not reported; low mechanical index (0.04 to 0.07). The examination was assessed in both the arterial and late phases, (up to 3 min. recorded). Images were interpreted by an operator with at least three years experience of CEUS, immediately after the examination by the same operator.	The contrast agent used was an intravenous bolus injection of 2 ml/kg of non-ionic contrast (Iomeron350, Bracco, Italy) at 4 ml/s. Scans started 5s (arterial phase) after reaching the threshold, 70s (portal venous phase), and 170s (delayed phase). MRI performed with 1.5 T system (Signa, GE Medical Systems, WI, USA) using a body-phased array multi-coil. Un-enhanced sequences were breath-hold T1-weighted. Contrast-enhanced images acquired after injection of ferucarbutan (Resovist, Shering, Germany) 10μmol/kg bolus, followed by 10 ml saline flush. Two sets of SPIO-enhanced images (10 and 20 min after contrast injection) using breath-hold T2-seighted sequences with fat saturation. Dynamic 3D MRI performed after administration of gadolinium (gadopentetate dimeglumine, Magnevist, Germany) 0.2 ml/kg injection at 2 ml/s followed by a 20 ml saline flush. The time delay for the arterial, portal venous and delayed phases was 18, 80 and 180 s, respectively.	Patients with no or one positive contrast-enhanced imaging test were confirmed using US-guided FNB (19G modified Menghini needle, hematoxylin and eosin stain), or follow-up (US or CT) at three month intervals). Diagnosis of HCC was made according to the International Working Party criteria.

Study ID	SonoVue® CEUS details	Comparator test(s) details	Reference standard details
		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.	
Li 2007[55]	HDI 5000 scanner (Philips Ultrasound, Bothwell, WA, USA) used for baseline US and CEUS. In patients with more than 1 FLL detected at baseline US, only the largest lesion was subjected to CEUS. CEUS was carried out after administration of 2.4 ml bolus injection SonoVue® (Bracco, Italy) 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. Scans covered the entire vascular phase (up to 5 min): arterial phase (0-40 s), portal venous phase (41-100 s), late phase (101-300 s). Images were interpreted in consensus by 2 sonologists who were unaware of CECT results.	A 3 phase contrast enhanced protocol was used: Unenhanced CT scan, followed by intravenous infusion of 100-120 (ml 4 ml/s) contrast media, non-ionic, iodine containing (Ultravist 370, Schering, Germany). Scans were obtained in the arterial, portal venous and late phases, with bolus test trigger. Data obtained through the whole liver in a craniocaudal direction, during a single breath-hold helical acquisition (6-8 s). Images were interpreted by two Radiologists who were blinded to the results of CEUS.	Histopathology following surgical resection or FNB with an 18-guage needle, within 2 weeks after CEUS and CECT.
Lüttich 2006[46] (abstract only)	CEUS using sulphur hexafluoride, 4 weeks after treatment (RFA).	Gadolinium-enhanced CEMRI, 4 weeks after treatment (RFA).	All patients were biopsied after CEUS. No further details reported.

Study ID	SonoVue® CEUS details	Comparator test(s) details	Reference standard details
	No further details reported.	No further details reported.	
Mainenti 2010[12]	HDI 5000 scanner (Philips Ultrasound, Bothwell, WA, USA) with a large band frequency covex transducer (3.5-7.5 MHz) used for baseline US and CEUS. CEUS was carried out after administration of 5 ml injection SonoVue® (Bracco, Italy) to the cubital vein, followed by a 10ml saline flush; pulse inversion harmonic imaging and low mechanical index (<0.09). Scans covered the arterial phase (25 s), portal venous phase (70 s), delayed phases (300 s). Images were interpreted by two observers with >10 years experience each, who were blinded to the results of other tests. Where there was disagreement, the final decision was made by a consensus panel of the original two plus one addition observer.	Four-slice MDCT (Aquilion 4, Toshiba Medical System Corporation, Japan) Scans acquired from the diaphragm to the pubic symphysis. Parameters: 4x3 mm beam collimation, pitch 5.5, 120 kV, 300mA, rotation time 0.5 s, effective slice thickness 3mm. Contrast-enhanced imaging was performed 75 s after intravenous bolus (3 ml/s) of 150 cc iodinated non-ionic contrast, iopromide (Ultravist, 370 mg iodine per ml, Schering, Germany). 1.5T MRI system (Gyroscan Intera 1.5 T, Philips Medical Systems, Holland), with a phased-array body coil. Transverse breath-hold T1-weighted and T2-weighted with and without fat saturation. Extra-cellular enhanced CEMRI performed after bolus injection of 0.1 mmol/kg gadopentetate dimeglumine (Magnevist, Berlex Laboratories) at a rate of 3 ml/s. followed by a 20 ml saline flush. Images were acquired during the arterial (25 s), portal (60 s) and equilibrium (180 s) phases.	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. All patients were followed up by MDCT (same technique as described) at 6 and 12 months, either to assess the size of as benign classified FLL or to assess the development of new Metastases. 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.

Study ID	SonoVue® CEUS details	Comparator test(s) details	Reference standard details
		Intra-cellular enhanced CEMRI performed after intravenous injection of 0.12-0.7 mmol/kg Ferucarbotran (Resovist, Schering, Germany). Images were obtained 15 min from the end of injection, repeating the transverse breath-hold T2-weighted with and without fat saturation. All images (both CT and MRI) were interpreted by two observers with >10 years experience each, who were blinded to the results of other tests. Where there was disagreement, the final decision was made by a consensus panel of the original two plus one addition observer. Imaging tests (including CEUS) were performed randomly over a 4-8 day period.	
Quaia 2009[51]	Sequoia, Acuson (Siemens, CA, USA), using a convex array 2-4 MHz 4C1 transducer used for baseline gray-scale and colour or power Doppler un-enhanced US, followed by CEUS, in both participating centres. CEUS was carried out after administration of 2.4 ml bolus injection SonoVue® (Bracco, Italy), followed by a 10ml saline flush; low mechanical index (0.09-0.14),	64-row MDCT systems (Aquilion, Toshiba, Japan, or Brilliance, Philips, USA). CT performed 2-30 days after CEUS. 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; 120 kV; 180-250 mA; field of	US-guided biopsy, using an 18-20-gauge modified Menghini needle. Samples stained with hematoxylin/eosin and the Masson trichrome method. Biopsy performed within 15 days after CT. A senior pathologist from each centre made the diagnosis.

Study ID	SonoVue® CEUS details	Comparator test(s) details	Reference standard details
	dynamic range 65 dB, temporal resolution between frames 75-100 ms (10-13 frames per s). Each nodule was examined. Scans covered the arterial phase (10-40 s), portal venous phase (45-90 s), delayed sinusoidal phase (100 s to micro-bubble disappearance). Images were reviewed independently by 2 Radiologists with 2-8 years experience in liver imaging, who were blinded to clinical history, biopsy results and other imaging results.	view 40 cm. Un-enhanced CT, followed by CECT. Contrast-enhanced imaging performed 8 s after 2 ml/kg intravenous bolus iodinated contrast, Iomeron 400 (Bracco, Italy); 400 mg iodine per ml, 5 ml/s, followed by 50 ml saline flush. The arterial phase started 18 s after threshold was reached, portal venous phase 70-80 s after start of contrast injection, and delayed equilibrium phase 180-210 s after start of contrast injection. Images were reviewed in the same way as for CEUS.	
Sangiovani 2010[52,#908]	iU22 system (Philips Ultrasound, USA), using a multi-frequency 2-5 MHz convex transducer, for both baseline grey-scale ultrasound of the upper abdomen and CEUS. CEUS was carried out after administration of 2.4 ml bolus injection SonoVue® (Bracco, Italy), followed by a 10 ml saline flush; Low mechanical index (<0.1). Scans covered the entire vascular phase (3 min): arterial phase (0-35 s), portal phase (35-120 s), late phase (120-180 s).	64-MDCT Definition (Siemens, Erlangen, Germany). Technical parameters: 2.5 mm slice thickness; rotation time 0.5 s. The contrast agent used was 1.5 mg/kg of iodinated medium Iomeron 400 (Bracco, Italy), injected at a rate of 4 ml/s. Acquisition time, from the start of contrast injection was 40 s for arterial phase, 80 s for portal venous phase, and 180 s for delayed phase.	Histology following FNB using a 21-gauge trenchant needle, carried out within 2 months of detection of nodule. Formalin-fixed paraffin-embedded liver sections were examined by an experienced liver pathologist who was unaware of the results of clinical and imaging examinations. Benign FLL were followed up by imaging: by US every 3 and by CT/MRI every 6 months.

Study ID	SonoVue® CEUS details	Comparator test(s) details	Reference standard details
	Examinations were interpreted by two expert echographists who were unaware of biopsy results.	Images were interpreted by one experienced radiologist who was unaware of biopsy results. MRI performed with a 1.5T system (Avanto, Siemens Medical Systems, Erlangen, Germany). All patients underwent transverse T1-weighted and T2-weighted MRI and multi-phasic 3D CEMRI of the whole liver, with fat suppression. Dynamic MRI was performed with a 3 dimensional volumetric interpolated breath hold examination sequence in the axial plane by using the following parameters 4.7/2.3, 10 degree flip angle, 320x157 matrix, slice thickness of 3 mm. The contrast agent used was gadolinium (gadopentate dimeglutamine 0.5 mmol/l Multihance, Bracco, Italy) injected at 0.2ml/kg and 2ml/s. Arterial, portal venous and delayed venous phases acquired at 30 s, 80 s and 180 s from the start of contrast injection. Images were interpreted by one experienced radiologist who was unaware of biopsy results.	

Study ID	SonoVue® CEUS details	Comparator test(s) details	Reference standard details
Seitz 2009[56]	The US device used was not specified (different ´high end' US devices and different contrast software) CEUS was conducted after administration of a 1.2 to 4.8 ml intravenous bolus of SonoVue (Bracco, Milan Italy), followed by a 10 ml saline flush. The dose could be doubled or a second dose could be given. Low mechanical index (<0.4). Imaging lasted up to 5 min: Arterial phase (5-25 sec), portal venous phase (25-60 sec) and late phase (>120 sec). For patients with multiple lesions, the dominant lesion was analyzed; where lesions had different sonomorphology in the late phase each lesion was analysed separately with additional contrast media injection. 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 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 8 cases.	The SCT device used was not specified. Single- or multi-slice CT collimation and reconstructed slice thickness at least 5mm, the liver SCT examination performed as a three-phasic-SCT: native scan application of 140 ml of iodinated contrast media (non-ionic various vendors, iodine concentration > 300 mg/ml; flow > 3ml/sec). Two additional scans, early phase (25 – 30 sec), late phase (60-90 sec) All reporting radiologists had access to the patients' clinical information	Subgroup A: final diagnosis was achieved by SCT or proven clinical data including follow-up. Subgroup B: diagnosis was based on US guided FNB.

Study ID	SonoVue® CEUS details	Comparator test(s) details	Reference standard details
Seitz 2010[57]	The US device used was not specified (different ´high end US devices and different contrast software) CEUS was conducted after administration of a 1.2 to 4.8 ml intravenous bolus of SonoVue (Bracco, Milan Italy), followed by a 10 ml saline flush. The dose could be doubled or a second dose could be given. Low mechanical index (<0.4). Imaging lasted up to 5 min: Arterial phase (5-25 sec), portal venous phase (25-60 sec) and late phase (>120 sec). If multiple lesions, those suspicious for malignancy or if benign the largest lesion was analyzed. Where lesions had with different sonomorphology in the late phase each lesion was analysed separately with additional contrast media injection. 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.	The MRI device used was not specified, MRI device with minimum of 1.5 Tesla T1-weighted localizer. T2 TSE axial. 3D TFE dynamics breath hold native, arterial, portal venous using gadolinium DTPA (Prohance 15 ml, Gadoteridol 78.61 mg/ml), 5-8 mm slice thickness). Resovist® contrast used in 88/269 MRI studies.	Subgroup A: final diagnosis was made by MRI, proven clinical data and follow- up for > 6 months. Subgroup B: diagnosis was based on US guided FNB.
Solbiati 2006[47] (abstract only)	CEUS was performed with contrast specific software (CPS, Acuson-Siemens,	Triphasic, helical CECT.	Where CEUS and CECT results were concordant, this was treated as a correct

Study ID	SonoVue® CEUS details	Comparator test(s) details	Reference standard details
	and CnTI, Esaote) after bolus injection of 2.4 ml SonoVue® (Bracco, Italy); low mechanical index. No details of interpretation were reported.	No further details were reported.	diagnosis which did not require further confirmation (EASL and AASLD guidelines for non-invasive diagnosis). Where there was a discordant result FNB was used as the reference standard. No details of who made the diagnosis were reported.
Zhou 2007[59] Chinese language	Acuson Sequoia 512 (Siemens), with a 2.5-6.0 MHz probe. CEUS was carried out after administration of 2.4 ml bolus injection SonoVue® (Bracco, Italy), followed by a 5 ml saline flush; low mechanical index (0.15 to 0.21). Arterial phase 30 s, portal venous phase 60 s, late phase 180 s. Imaging carried out within 1 week after treatment. No details of who interpreted images were reported.	Somatom balance (Siemens) Iodinated contrast medium (350 mg/ml iodine, Omnipaque, iohexol) was used. Arterial phase 30 s, portal venous phase 60 s, late phase 180 s. Imaging carried out within 1 week after treatment. No details of who interpreted images were reported.	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 were reported.

AASLD: American Association for the Study of Liver Diseases; CECT: contrast-enhanced computed tomography; CEMRI: contrast-enhanced magnetic resonance imaging; CEUS: contrast-enhanced ultrasound; DTPA: diethylene triamine pentaacetic acid; EASL: European Association for the Study of Liver; FLL: focal liver lesion; FNB: fine-needle biopsy; MDCT: multi-detector computed tomography; MRI: magnetic resonance imaging; NA: not applicable; RFA: radiofrequency ablation; SCT: spiral computed tomography; TFE: turbo field echo; TSE: turbo spin echo; US: un-enhanced ultrasound

Inclusion/exclusion criteria and participant characteristics of included studies:

Study ID	Participant number)	Inclusion criteria	Exclusion criteria	Participant characteristics
Blondin 2011[14]	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 male/8 female Chronic liver disease 33 (15 due to viral hepatitis; 13 due to alcohol abuse; 1 due to haemochromatosis; 4 unknown reason, therefore classified as cryptogen) Mean nodule size not specified Final diagnosis: HCC 41; 6 RN
Catala 2007[53]	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 (≥18 years) patients with FLLs detected on US. Only FLLs evaluated with an interval of no more than one month between CEUS and SCT were included. Malignant FLL were only included if confirmed by pathology.	Patients who were pregnant, or nursing.	Mean age 62 ± 11 years 45 male/32 female Chronic liver disease 53 Mean nodule size 3.5 ± 2.2 cm Final diagnosis: HCC 45; Metastases 12; haemangioma 10; FNH 8
Chen 2007[60] related publication[61]	179 patients originally recruited (intervention CEUS 92, comparator US 87). 165 patients who were suitable for RFA (intervention CEUS	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.	Intervention (CEUS) Comparator (US) n=92 n=87 Mean age 67.5 years 66.9 years Male/female 59/33 52/35 TNM stage II/III 55 51 Child-Pugh A 67 65 Mean tumour size 3.6±1.1 3.5±1.1 cm Mean tumour n 1.6±0.7 1.7±0.7

Study ID	Participant number)	Inclusion criteria	Exclusion criteria	Participant characteristics
	83, comparator US 82) were included in the analyses.			CECT n 81 74 CEMRI n 11 13
Clevert 2009[16]	100 consecutive patients with suspected malignant liver lesions (maximum 5 lesions per patient). 21 patients were excluded from the CT analysis, 8 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 ultrasound examination.	Exclusion criteria: tumour lesion >5 cm, number of lesions >5; 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 to 83) 57 male/43 female 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[48]	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 to 80) 59 male/13 female Cirrhosis, without extra-hepatic malignancies 72 Previous treatment for HCC 9 Elevated AFP 9 Mean nodule size 1.5 ± 0.3 cm Final diagnosis (by nodule): HCC 56; RN 47
Feng 2007[58] Chinese language	23 patients with 26 malignant lesions undergoing cryosurgery.	NR	NR	Mean age 57 years (range 45 to 68) 20 male/3 female Initial diagnosis: HCC 21 (23 lesions); M 2 (3 lesions) Mean tumour size 31.5 mm (range 16.7 mm to

Study ID	Participant number)	Inclusion criteria	Exclusion criteria	Participant characteristics
				42.6 mm) Final diagnosis(by lesion): complete treatment response 21; recurrence 5
Flor 2010[45] (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 male/12 female 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; intra-hepatic biliary tract 1; CT artifacts 5.
Forner 2008[49]	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 co-morbidities. Patients with severe clotting alterations or contraindications for CEUS, CEMRI, or fine needle biopsy.	Median age 65 years (range 37 to 83) 53 male/36 female Cirrhosis 89 Median AST 81 UI/l (range 25 to 322) Median ALT 70 UI (range 16 to 537) Median prothrombin ratio 78.5% (range 35 to 100) Median bilirubin 1 mg/dl (range 0.3 to 4.1) Median baseline AFP 8 ng/ml(range 1 to 1154) Median nodule size 14 mm (7-20 mm) Final diagnosis: HCC 60; CCC 1; RN 24; haemangioma 3; FNH 1
Gierbliński 2008[54]	100 patients with 100 incidentally detected FLLs, who were referred for liver biopsy.	Patients with incidentally detected FLL 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.	No details of age and sex of patients reported. Final diagnosis: HCC 9; metastases 14; haemangioma 34; FNH 19; skip area in fatty liver 11; focal steatosis 10; adenoma 1; dysplatic nodule 1; hyper-regenerative nodule 1

Study ID	Participant number)	Inclusion criteria	Exclusion criteria	Participant characteristics
			Patients in whom biopsy was not possible.	
Giorgio 2007[50]	73 patients with cirrhosis and a single FLL detected at surveillance US.	Patients with cirrhosis and a single liver nodule ≤30mm detected on US.	Patients with heart disease (because of rare AE reported for SonoVue®).	Mean age 63 years (range 40 to 84) 49 male/24 female Cirrhosis 73 (HCV-associated 65, alcoholic 2, alcoholic and HCV-associated 2, HBV-associated 3) 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[15] (abstract only)	20 patients CRC and 48 liver lesions.	Patients with CRC liver metastases who underwent complete pre-operative work-up and could be rendered tumour-free by a single-stage surgical intervention.	Patients with concomitant resectable extra-hepatic 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 to 80 mm). All patients had CRC and metastasis was the only diagnosis reported.
Leoni 2010[10]	60 patients with cirrhosis and 75 FLLs (28 newly detected and 32 recurrent).	Adult patients (>18 years) with cirrhosis and 1 to 3 liver nodules between 1 and 3 cm, which were visible on US.	Previous treatment of nodules include in the study Contra-indications to imaging, allergy to contrast agent, claustrophobia, or magnetic or metallic devices in the body. Neoplastic portal thrombosis or extra-hepatic metastases.	Mean age 65 years (range 40 to 83) 52 male/8 female 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 to 2849)

Study ID	Participant number)	Inclusion criteria	Exclusion criteria	Participant characteristics
				AST 96±78 U/l ALT 82±57 U/l ɣ-GT 97±72 U/l Alkaline phosphatise 305±119 U/l Final diagnosis (by lesion): HCC 55; not HCC 20
Li 2007[55]	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 un-enhanced CT.	Not specified.	Mean age 49 ± 12 years (range 18 to 79) 72 Male/37 female Mean nodule size 2.9 ± 1.3 cm (range 0.9 to 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[46] (abstract only)	15 patients with HCC who were being treated by RFA.	NR	NR	No details reported.
Mainenti 2010[12]	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 to 81) 20 male/14 female Metastatic lesion size: 3 to 80 mm Final diagnosis (by lesion): metastases 16; haemangioma 11; cysts 29; focal fatty liver 1
Quaia 2009[51]	180 patients with cirrhosis and 195 nodules detected on surveillance US	Patients with a definite diagnosis of cirrhosis (Child-Pugh class A or B) and at least one hepatocellular	Nodules with peripheral enhancement at CECT were excluded due to high probability of haemangioma diagnosis.	Cirrhosis 180 (HBV 85, HCV 52, HBV and HCV 3, alcohol abuse 40) 106 included patients:

Study ID	Participant number)	Inclusion criteria	Exclusion criteria	Participant characteristics
	were initially recruited (up to two nodules per patient). 106 patients with 121 nodules finally included.	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 were excluded because of a lack of histological diagnosis (n=60), technical inadequacy of CT (n=10), inadequacy of CEUS examination (n=4)	Mean age 70 ± 7 years 68 male/38 female Mean nodule size: 1.9 cm ± 1.1 (range 1-3 cm). Final diagnosis (by nodule): HCC 72; dysplastic nodule 10; RN 15; haemangioma 12; other benign 3; pseudotumour 9
Sangiovani 2010[52,#908]	64 patients with cirrhosis and abnormal US findings on surveillance were originally included, 67 liver nodules. 55	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.	64 patients: Mean age 65 years (44-80) 47 male/17 female Child-Pugh A 63 Child-Pugh B 1 HBV 10

Study ID	Participant number)	Inclusion criteria	Exclusion criteria	Participant characteristics
	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 an echo-coarse US pattern without a well defined nodule.	HCV 40 Alcohol abuse 4 Median AFP 11 ng/ml (range 1-2156) AFP >200 ng/ml 3 Final diagnosis (by nodule for 1-2 cm nodules): HCC 34; CCC 1, low grade dysplastic nodule 3; RN 17
Seitz 2009[56]	267 patients with incidentally detected FLLs: subgroup A (suspected benign lesion): 109 patients, 111 FLL subgroup B (suspected malignant lesion): 158 patients 158 FLL. For patients with multiple FLLs, the dominant lesion (most suspicious for malignancy or	Patients with newly detected FLL 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 wells as malignant tumours with infiltration into hepatic vessels. Patients who were critically ill or suffered from pulmonary hypertension or unstable angina as well as pregnant and nursing women.	Subgroup A + B (not specified by subgroups): Mean age 60.3 years (21 – 89) 121 male/146 female Final diagnosis (subgroup A): HCC 7; metastases 7; haemangioma 48; FNH 31; fatty sparing lesion 5; abscess 4; cyst 3; un-defined 6 Final diagnosis (subgroup B): HCC 40; metastases 56; haemangioma 9; FNH 14; adenoma 2; lymphoma 3; fatty sparing lesion 6; other benign 14; other malignant 10; un-defined 4

Study ID	Participant number)	Inclusion criteria	Exclusion criteria	Participant characteristics
	largest) was analysed.			
Seitz 2010[57]	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 lesion): 185 Subgroup B (suspected malignant lesion): 84	Patients with newly detected FLL on US.	Patients with typical findings of simple cysts, hyper-echoic haemangioma in a non-steatotic liver, or fatty sparing lesions without clinical signs and symptoms and patients with malignant tumours infiltrating hepatic vessels.	Subgroup A: Mean age 49.9 years (range 16 to 82) 58 male/127 female Final diagnosis: metastases 3; haemangioma 122; FNH 43; fatty sparing lesion 2; abscess 1; cyst 4; echinincoccus 2; other benign lesion 2; un-defined 5; drop-outs 5 Subgroup B: Mean age 59.6 years (range 28 to 82) 53 male/31 female 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; angiomyolipoma 1; RN 1; peliosis 1; un-defined 2
Solbiati 2006[47] (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; FNH11; adenoma 4; cyst 3; pseudolesion 13
Zhou 2007[59]	56 patients with 64 HCC lesions, who	Patients with HCC who were undergoing non-surgical	NR	Mean age 42±13.8 years (range 21 to 68) 40 male/16 female

Study ID	Participant number)	Inclusion criteria	Exclusion criteria	Participant characteristics
Chinese language	were undergoing non-surgical treatment	treatment		Mean lesion diameter 3.4±1.6 cm (range 1.0 to 8.0) Treatment: TACE 4; PEI 8; PMCT 11; RFA 5; TACE+PEI 4; TACE+PMCT 3; PEI+PMCT 11; PEI+PMAT+PMCT 10

AFP: alpha-fetoprotein; ALT: alanine aminotransferase; AST: aspartate aminotransrefase; CCC: cholangiocarcinoma; CEUS: contrast enhanced ultrasound; CRC: colorectal cancer; FLL: focal liver lesions; FNH: focal nodular hyperplasia; ɤ-GT: gamma glutamyltransferase; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; MDCT: multi-detector computed tomography; NR: not reported; PEI: percutaneous ethanol injection; PMAT: percutaneous microwave ablation therapy; PMCT: percutaneous microwave coagulation therapy; RFA: radiofrequency ablation; RN: regenerative nodule; SCT: spiral computed tomography; TACE: transarterial chemoembolisation; TNM: Tumour lymphNode Metastasis; US: standard un-enhanced ultrasound

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 reason for their exclusion; for simplicity, studies were assigned a single reason for exclusion, however, many studies failed more than one inclusion criteria. 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 liver) are not listed.

The reasons for study exclusion are coded as follows:

population – The study did not consider characterization of focal liver lesions (incidentally detected by un-enhanced 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 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 six 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 section 4.1, OR, for diagnostic test accuracy studies, insufficient data were reported to allow the construction of 2 x2 contingency tables (numbers of TP, FN, FP, and TN test results).

study design – The study design was not one of those specified in section 4.1, 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-P33. – **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(4):158-163. – **outcomes**

[3] Aube C, Lebigot J. [Contrast ultrasonography: value in diagnosis and characterisation of hepatic tumors]. *Gastroenterol Clin Biol* 2003;27(5 Suppl):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? Abstract MO-113. Paper presented at the 9th World Congress of the International Hepato-Pancreato-Biliary Association; 18-22 Apr; Buenos Aires, Argentina. *HPB* 2010;12(Suppl 1):100. – **authors contacted**

[5] 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(3):295-307. – **comparator**

[6] 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(3):650-61. – **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(5):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(2):106-115. – **reference standard**

[9] Bauditz J, Quinkler M, Beyersdorff D, Wermke W. Improved detection of hepatic metastases of adrenocortical cancer by contrast-enhanced ultrasound. *Oncol Rep* 2008;19(5):1135-1139. – **index test**

[10] Bauditz J, Schade T, Wermke W. [Sonographic diagnosis of hilar cholangiocarcinomas by the use of contrast agents]. *Ultraschall Med* 2007;28(2):161-7. – **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; 29 Oct - 2 Nov; Boston, US. *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(1):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; 8-12 Oct; Milan, Italy. *Ann Oncol* 2010;21:viii215. – **population**

[14] Bleuzen A, Huang C, Olar M, Tchuenbou J, Tranquart F. Diagnostic accuracy of contrast-enhanced ultrasound in focal lesions of the liver using cadence contrast pulse sequencing. *Ultraschall Med* 2006;27(1):40-48. – **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(5):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(4):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(3):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(971):881-889. – **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 (</=3cm) in patients with cirrhosis. *Hepatol Res* 2006;35(4):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(8):752-760. – **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(5):S875-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); 17-20 Feb; Bangkok, Thailand. *Hepatol Int* 2011;5(1):480-481. – **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(4):186-193. – **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(8):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;20:92-92. – **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(11):1699-1705. – **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(3):285-297. – **comparator**

[28] 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(7):978-91. – **reference standard**

[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(5):529-536. – **reference standard**

[30] D'Onofrio M, Rozzanigo U, Caffarri S, Zogno A, Procacci C. Contrast-enhanced US of hepatocellular carcinoma. *Radiol Med* 2004;107(4):293-303. – **population**

[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); 17-20 Feb; Bangkok, Thailand. *Hepatol Int* 2011;5(1):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); 12-16 Apr; Cape Town, South Africa. *HPB* 2011;13:25-26. – **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(6):1512-1519. – **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-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 in Med* 2011;32:148-153. – **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(3):421-426. – **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; 24-25 Feb; Rome, Italy. *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(7):1094-1105. – **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(4):473-4. – **study design**

[40] Giangregorio F. Contrast-enhanced ultrasound (CEUS) for echographic detection of hepato cellular 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(2):1763-1776. – **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; 14-18 Apr; Vienna, Austria. *J Hepatol* 2010;52:S90-S91. – **outcomes**

[42] 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(1):12-21. – **reference standard**

[43] 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); 6-9 Mar; Verona, Italy. *Dig Liver Dis* 2010;42:S77. – **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(3):259-68. – **study design M**

[45] Giorgio A. Diagnostic algorithm of hepatocellular carcinoma on cirrhosis: CEUS or no CEUS, that is the problem. *Dig Liver Dis* 2011;43(6):499. – **study design**

[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); 25-26 Feb; Rome; Italy. *Dig Liver Dis* 2010;42:S23-S24. – **comparator**

[47] 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; 14-18 Apr; Vienna, Austria. *J Hepatol* 2010;52:S219. – **comparator**

[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(7):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(9):1434-1437. – **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(5):366-370. – **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]. *Rofo* 2003;175(6):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(5):1723-1730. – **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(2):105-109. – **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(3):418-424. – **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 1:111-5. – **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(47):6356-6364. – **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(1-2):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(10):1241-1247. – **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(4):A494-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(4):706A-707A. – **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(1):57-65. – **index test**

[62] Konopke R, Bunk A, Kersting S. Contrast-enhanced ultrasonography in patients with colorectal liver metastases after chemotherapy. *Ultraschall Med Suppl* 2008;29(4):S203-S209. – **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(2):201-207. – **comparator**

[64] 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(2):107-13. – **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(3):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(12):1703-1714. – **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(2):302-307. – **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(2):308-313. – **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); 4-9 Jun; Chicago, USA. *J Clin Oncol* 2010;28(15 Suppl 1). – **outcomes**

[70] Leen E. The role of contrast-enhanced ultrasound in the characterisation of focal liver lesions. *Eur Radiol* 2001;11(Suppl 3):E27-E34. – **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(6):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(6):276-285. – **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(11):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(Suppl 2):S371-S374. – **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; 24-25 Feb 2011; Rome, Italy. *Dig Liver Dis* 2011;43:S73-S74. – **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(2):186-188. – **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(18):1879-1882. – **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(5):1214-1222. – **reference standard**

[79] 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(9):1133-1142. – **outcomes**

[80] 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(3):211-221. – c**omparator**

[81] 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; 18-22 Apr; Buenos Aires, Argentina. *HPB* 2010;12:269. – **authors contacted**

[82] 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; 18-22 Apr; Buenos Aires, Argentina. *HPB* 2010;12:100-101. – **outcomes**

[83] Lu Md, Yu Xl, 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(11):1736-1749. – **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(4):A193-A194. – **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, International Liver Congress; 30 Mar - 3 Apr; Berlin, Germany. *J Hepatol* 2011;54:S393-S394. – **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(5):652-662. – **outcomes**

[87] Mucciarini 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); 29 May - 2 Jun; Orlando, USA. *J Clin Oncol* 2009;27(15 Suppl 1):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(2):326-335. – **reference standard**

[89] Nicolau C, Vilana R, Catala V, Bianchi L, Gilabert R, Garcia A, et al. Importance of evaluating all vascular phases on contrast-enhanced sonography in the differentation of benign from malignant focal liver lesions. *AJR Am J Roentgenol* 2006;186(1):158-167. – **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(4):277-284. – **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(5):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(1):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(9):1369-1375. – **study design M**

[94] Piscaglia F, Corradi F, Mancini M, Giangregorio F, Tamberi S, Ugolini G, et al. Real time contrast enhanced ultrasonography in detection of liver metastases from gastrointestinal cancer. *BMC Cancer* 2007;7(171). – **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(5):954-961. – **reference standard**

[96] 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(1):25-36. – **outcomes**

[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(7):739-750. – **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(2):420-430. – **study design**

[99] 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(6):1474-1483. – **reference standard**

[100] 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(7):1599-1609. – **reference standard**

[101] 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**

[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); 14-17 Oct; Perth, USA. *J Med Imaging Radiat Oncol* 2010;54:A123. – **outcomes**

[103] 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(4):420-425. – **reference standard**

[104] 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); 23-30 Mar; Nice, France. *Ann Oncol* 2010;21:i27. – **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(3):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; 20-24 Sep; Berlin, Germany. *Eur J Cancer Suppl* 2009;7(2-3):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(4):447-453. – **reference standard**

[109] Sirli R, Sporea I, Martie A, Popescu A, Danila M. Contrast enhanced ultrasound in focal liver lesions: a cost efficiency study. *Med Ultrason* 2010;12(4):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. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). . 2011 [cited 12.12.11]. Available from: http://ClinicalTrials.gov/show/NCT01329458– **reference standard**

[111] 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(SUPPL.):S19-S23. – **study design**

[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(12 Suppl B):25-30. – **study design**

[113] 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(Suppl 3):E15-E26. – **reference standard**

[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(7):1715-1725. – **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(1):22-25. – **reference standard M**

[116] Sporea I, Badea R, Martie A, Sirli R, Socaciu M, Popescu A, et al. Contrast enhanced ultrasound for the characterization of focal liver lesions. *Med Ultrason* 2011;13(1):38-44. – **outcomes**

[117] Sporea I, Badea R, Popescu A, Martie A, Socaciu M, Sirli 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); 17-20 Feb; Bangkok, Thailand. *Hepatol Int* 2011;5(1):481-482. – **outcomes**

[118] Sporea I, Badea R, Popescu A, Martie AF, Socaciu M, Sirli 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; 7-10 May; Chicago, USA. *Gastroenterology* 2011;140(5 Suppl 1):s926-s927. – **outcomes**

[119] Sporea I, Sirli 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(4):393-8. – **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(5):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(4):376-382. – **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(10):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; 14-18 Apr; Vienna, Austria. *J Hepatol* 2010;52:s235-236. – **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); 5-9 Mar; Turin, Italy. *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(6):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; 30 Oct - 3 Nov; Boston, USA. *Hepatology* 2009;50:1131A. – **reference standard**

[127] 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(1):109-122. – **comparator M**

[128] 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(11):9-15. – **reference standard 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(30):3748-56. – **reference standard**

[130] University Hospital (Tours). Evaluation of contrast-enhanced ultrasound imaging for the early estimate of bevacizumab effect on colorectal cancer liver metastases. NCT00489697. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2009 [cited 12.12.11]. Available from: http://ClinicalTrials.gov/show/NCT00489697– **outcomes**

[131] University Hospital (Tours), Ministry of Health France. Characterization of focal liver lesions by real-time contrast-enhanced ultrasound imaging (CEUS). NCT00243633. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2008 [cited 12.12.11]. Available from: http://ClinicalTrials.gov/show/NCT00243633 – **study design**

[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;40:85-85. – **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(2):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(11):2454-2462. – **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(12):1557-1568. – **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):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(25):2726-2729. – **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(8):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(4):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(10):1511-1519. – **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(6):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(3):752-761. – **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(5):692-695. – **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(6):854-861. – **study design**

[145] 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(6):261-272. – **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(3):349-361. – **reference standard**

[147] 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(21):1375-8. – **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 < or =2 cm. *J Clin Ultrasound* 2008;36(5):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(1):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(1):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(5):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(1-2):109-118. – **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(10):751-763. – **outcomes**

The following is a list of those studies provided in the submission from the manufacturer of SonoVue®, which 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 liver) are not listed:

[1] Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology* 2005;42(5):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(1):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(6):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(1):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(2):236-240.

[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(5):315-321.

[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(3):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(4):379-U1509.

[9] 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(5):492-9.

[10] 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 Dreilandertreffen 2008, Davos. *Ultraschall Med* 2009;30(4):383-9.

Appendix 6: NICE guidance relevant to the treatment of liver malignancies

Cryotherapy for the treatment of metastases. NICE interventional procedure guidance 369 (2010). Available from
http://guidance.nice.org.uk/IPG369

Ex-vivo hepatic resection and reimplantation for liver cancer. NICE interventional procedure guidance 298 (2009). Available from
http://guidance.nice.org.uk/IPG298

Laparoscopic liver resection. NICE interventional procedure guidance 135 (2005). Available from
http://guidance.nice.org.uk/IPG135

Microwave ablation for the treatment of liver metastases. NICE interventional procedure guidance 406 (2011). Available from
http://guidance.nice.org.uk/IPG406

Microwave ablation of hepatocellular carcinoma. NICE interventional procedure guidance 214 (2007). Available from
http://guidance.nice.org.uk/IPG214

Radiofrequency ablation of hepatocellular carcinoma. NICE interventional procedure guidance 2 (2003). Available from
http://guidance.nice.org.uk/IPG2

Radiofrequency-assisted liver resection. NICE interventional procedure guidance 211 (2007). Available from
http://guidance.nice.org.uk/IPG211

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 7: PRISMA check list

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	pg 1
ABSTRACT			
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.	pg 1 and pg 13 to 22
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Section 3.1, pg 24-25 and section 3.3, pg 28
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	pg 23
METHODS			
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 http://www.crd.york.ac.uk/prospero/ NICE http://guidance.nice.org.uk/DT/6
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.	Section 4.1, pg 34 to 36
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.	Section 4.2, pg 36 to 38

Section/topic	#	Checklist item	Reported on page #
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
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).	Section 4.3, pg 38 to 39
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.	Section 4.3, pg 38 to 39
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Section 4.3, pg 39
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Section 4.4, pg 40
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Section 4.5, pg 40 to 41
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Section 4.5, pg 40 to 41
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).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
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.	Section 4.6 pg 41 to 43, Figure 3 pg 44 and Appendix 5
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.	Appendix 4
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).	Appendix 3 and Table 11, pg 89
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 confidence intervals, ideally with a forest plot.	Section 4.6, Tables 4,6,8,10 and 12

Section/topic	#	Checklist item	Reported on page #
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Section 4.6.3 pg 76 and Figures 4 and 5 pg 84
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	pg 76
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Section 6.1.1, pg 147 to 150
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Sections 6.2 and 6.3, pg 151 to 160
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Section 7, pg 161 to 162
FUNDING			
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.	pg 1