National Institute for Health and Clinical Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Evidence overview

SonoVue (sulphur hexafluoride microbubbles) – contrast agent for contrast-enhanced ultrasound imaging of the liver

This overview summarises the key issues for the Diagnostics Advisory Committee's consideration. It includes a brief description of the topic, a description of the analytical structure and model, a discussion of the analytical difficulties, and a brief summary of the results. It is not a complete summary of the diagnostics assessment report, and it is assumed that the reader is familiar with that document. This overview contains sections from the original scope and the diagnostics assessment report, as well as referring to specific sections of these documents.

1 Background

1.1 Introduction

SonoVue was referred by the Medical Technologies Advisory Committee for recommendations on its use as a contrast agent in ultrasound for liver imaging. SonoVue, a pharmaceutical agent for diagnostic use only, is a contrast agent involving sulphur hexafluoride microbubbles, and is indicated for contrast-enhanced ultrasound imaging in adults when unenhanced imaging has been inconclusive. Because SonoVue has a marketing authorisation for use in a range of areas [(echocardiography, Doppler imaging of macrovasculature (for example, cerebral arteries) and of microvasculature (for example, breast and liver lesions)], indications to be included in this assessment were discussed at the scoping workshop. Attendees, including clinical experts, advised that NICE guidance on the use of SonoVue would be

most valuable in liver imaging, because practice varies nationally and sufficient data are available to evaluate the use of SonoVue in that setting.

The purpose of this assessment is therefore to evaluate the clinical and cost effectiveness of SonoVue as a contrast agent for contrast-enhanced ultrasound imaging of the liver in adults. Provisional recommendations are to be formed at the Diagnostics Advisory Committee meeting on April 3rd 2012.

1.2 The technology

SonoVue (Bracco UK) is a second generation contrast agent that uses sulphur hexafluoride microbubbles for contrast-enhanced ultrasound 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 has a UK marketing authorisation for diagnostic use only. The summary of product characteristics (SPC) states that SonoVue improves display of the blood vessels in liver lesions during Doppler sonography, allowing more specific characterisation of lesions. The SPC also states that SonoVue should only be used in patients in whom unenhanced ultrasound is inconclusive. SonoVue is a low solubility gas contrast agent that allows imaging at low mechanical index, which leads to effective suppression of the tissue signal.

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.

SonoVue remains within the patient's blood vessels and, depending on the type of lesion, it shows a pattern of uptake similar to that of contrast agents used for imaging blood vessels in computed tomography (CT) or magnetic

resonance imaging (MRI). The contrast agent is broken down by the body after a few minutes. 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).

Alternative technologies

Other similar ultrasound contrast agents [for example, 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 of contrast-enhanced ultrasound imaging of the liver.

Comparators

People with inconclusive unenhanced ultrasound are currently referred for contrast-enhanced CT and/or contrast-enhanced MRI. These are therefore the comparators for this assessment. Contrast-enhanced MRI generally uses gadolinium-based vascular contrast agents, which can differentiate between benign and malignant focal liver lesions based on vascular enhancement patterns in a similar way to contrast-enhanced CT and contrast-enhanced ultrasound. However, contrast-enhanced MRI of the liver can also use hepatocyte-specific contrast agents. These include superparamagnetic iron oxide (SPIO), which is taken up by Kupffer cells. Because malignant lesions are generally deficient in Kupffer cells, particularly when the lesions are hypervascular, or 'combined' vascular, areas with low contrast uptake are likely to be malignant. Another example of a hepatocyte-specific contrast agent is gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA).

CEUS could be included in the diagnostic pathway as a replacement for CECT/CEMRI, or as a triage step to reduce the use of CECT/CEMRI. Further details can be found in section 1.5.

Expert opinion indicated that biopsy would not be performed as the next test when unenhanced ultrasound was inconclusive, therefore biopsy was not considered a relevant comparator in this assessment.

The comparators used in the economic analysis were:

- contrast-enhanced CT
- contrast-enhanced MRI using gadolinium as contrast agent
- contrast-enhanced MRI using SPIO as contrast agent.

1.3 The condition(s)

Primary application of SonoVue

SonoVue is indicated for use only when unenhanced ultrasound is inconclusive. Therefore the External Assessment Group (EAG) considered its primary application to be in the characterisation (investigation) of focal liver lesions. Most people who have had unenhanced ultrasound and who have proceeded to contrast-enhanced ultrasound are likely to have focal liver lesions (seen by unenhanced ultrasound), the nature of which remains uncertain. Detection of focal liver lesions by unenhanced ultrasound may be 'incidental' (detected during abdominal ultrasound for symptoms and/or biochemistry suggestive of liver disease, or for other reasons unrelated to possible liver disease), or the result of routine monitoring in people with cirrhosis. Contrast-enhanced ultrasound may also identify focal liver lesions not detected by unenhanced ultrasound. Other relevant applications include the detection of specific types of malignant focal liver lesion (for example, liver metastases from colorectal carcinoma, recurrent or residual disease following treatment of a known malignancy).

In the context of this evaluation, the term focal liver lesion refers to any focal area of perceived difference seen by imaging and occurring in one specific area of the liver. Focal liver lesions can be broadly classified as benign (for example, haemangioma, focal nodular hyperplasia, focal fatty infiltration or sparing and adenoma) or malignant (for example, primary hepatocellular carcinoma, cholangiocarcinoma or liver metastases). The detection or

exclusion of malignancy is the primary aim of diagnostic imaging. The distinction between benign and malignant determines the prognosis and subsequent treatment strategy. Benign, asymptomatic liver lesions usually do not need treatment. Depending on the type of lesion, the person's condition may be monitored and the lesion rescanned in 6–12 months. Once a malignant lesion is identified it is important to distinguish between primary and secondary cancers because this is likely to affect how the condition is managed. Malignant lesions may be treated with a range of interventions, including chemotherapy, surgery and local ablative therapy.

Indication

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

The assessment focused on those indications in which clinical opinion indicated that the use of contrast-enhanced ultrasound would most likely be of benefit. These were also the indications from which most of the data on test performance were derived (see section 2.1.2). Some studies on the detection of metastases included patients with primary tumours other than colorectal cancer, but these patients were in the minority. No separate data were available for the accuracy in detecting liver metastases from primary tumours other than colorectal cancer. Clinical experts advised that liver metastases from colorectal cancer were the main focus of testing because these are considered most likely to be successfully treated. Therefore, this assessment addresses the clinical and cost effectiveness of using SonoVue for contrast-enhanced ultrasound in the following three specific clinical indications:

- detection of hepatocellular carcinoma through monitoring in patients with cirrhosis
- detection of liver metastases in patients with colorectal cancer
- characterisation of incidentally detected focal liver lesions .

The use of SonoVue for treatment planning and determining treatment response in patients with liver cancers was also assessed as described in the scope. However, the available data, summarised in section 2, did not allow a cost-effectiveness analysis to be conducted for these applications.

Liver malignancy

There are two types of cancer of the liver. A cancer that starts in the liver is known as a primary liver cancer and a cancer that spreads to the liver from another part of the body is known as a secondary liver cancer. Approximately 3200 people in the UK are diagnosed with primary liver cancer each year whereas approximately 90,000 people are diagnosed with secondary liver cancer. As many as 70–75% of focal liver lesions assessed in the NHS may be benign.

Most people with a diagnosis of primary liver cancer (approximately 85%) have a hepatocellular carcinoma. Although primary liver cancer is rare in the UK (age-standardised rates are 4.7 per 100,000 men and 2.9 per 100,000 women), it is the second most rapidly increasing cancer in men and the third in women (increases of 38% and 28% respectively in the past decade).

Primary liver cancer in adults has a poor prognosis because it tends to be diagnosed in the advanced stages. Only about 10% of cases of primary liver cancer are diagnosed in the early stages when surgery may help. The prognosis of primary liver cancer is dependent on the stage of disease (stages 0–4) and underlying liver function. About 20% of people with a primary liver cancer live for at least 1 year after diagnosis. Around 5% live for at least 5 years.

The primary cancers most commonly leading to secondary cancers in the liver originate in the breast, lung and bowel (colorectal). The origin of the primary cancer is important because the cells of the secondary cancer in the liver will be the same as those of the primary cancer, and will be treated according to the cell type of the primary cancer. The prognosis of secondary liver cancer is dependent on the stage of disease (stages 0–4) and the underlying liver function. For example, 25–40% of people with stage 4 colorectal cancer (where the cancer has spread to another part of the body), with a resectable secondary cancer in the liver will live for 5 years after surgery.

1.4 Guidelines

EFSUMB

The European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) produced guidelines and good clinical practice recommendations for contrast-enhanced ultrasound in 2004. The latest version of the guidelines was published in 2008 and is currently being updated.

The EFSUMB guidelines provide information on the typical enhancement patterns associated with various types of benign and malignant liver lesions. Contrast-enhanced ultrasound can provide useful information about the success of percutaneous ablation therapies whereas unenhanced ultrasound cannot. This is because assessment of vascularisation and tissue perfusion is essential to enable differentiation of tissue necrosis from residual tumour.

The 2008 EFSUMB guidelines recommend the use of contrast-enhanced ultrasound for the characterisation of focal liver lesions in a range of indications. Further details can be found in section 3.2 of the diagnostics assessment report.

NICE

The treatment of primary hepatocellular carcinoma has been addressed in published technology appraisals guidance, and NICE has issued interventional procedure guidance on a number of individual interventions for primary hepatocellular carcinoma and liver metastases (see appendix 6 of the diagnostics assessment report). However, expert opinion suggests that practice within the NHS may vary significantly across regions based on clinician preference.

1.5 Diagnostic and care pathways

Diagnostic pathway

Contrast-enhanced ultrasound could be included in the diagnostic pathway as a replacement for contrast-enhanced CT/contrast-enhanced MRI (figure 1), or as a triage step to reduce the use of contrast-enhanced CT/contrast-enhanced MRI (figure 2).

Figure 1 Diagnostic pathway for liver imaging with contrast-enhanced ultrasound as a replacement for contrast-enhanced CT/contrast-enhanced MRI

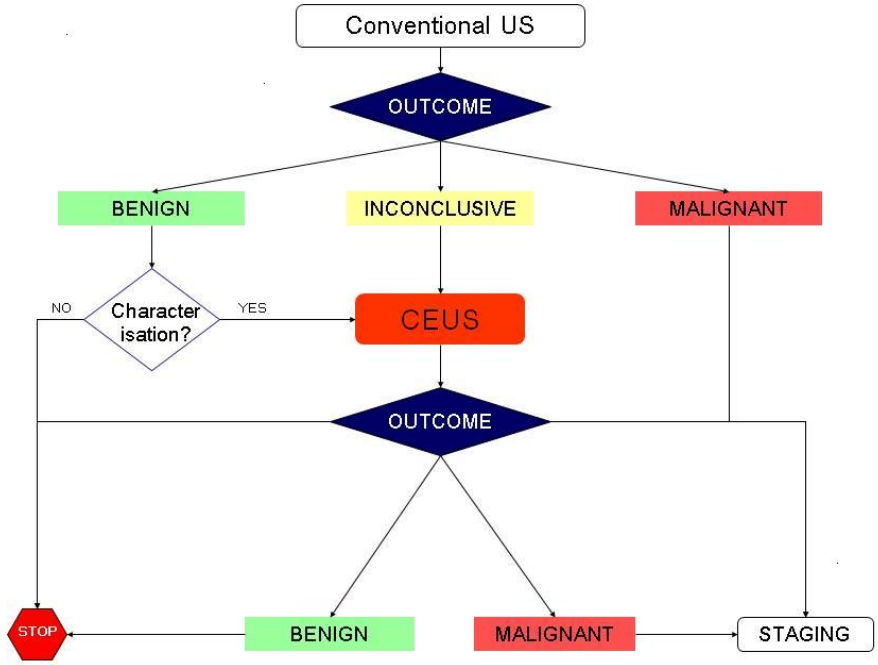
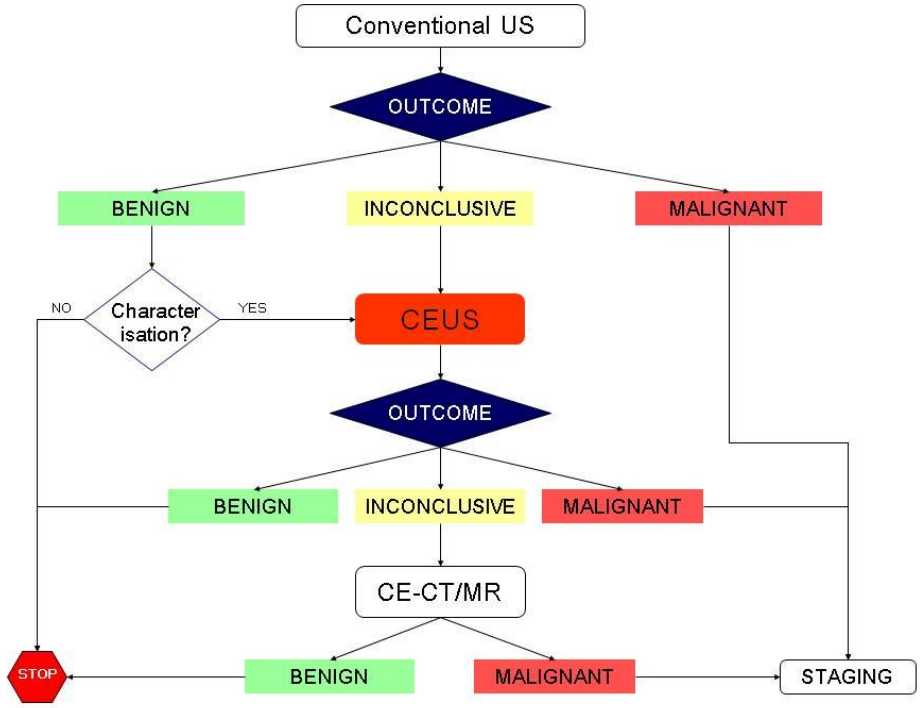


Figure 2 Diagnostic pathway for liver imaging with contrast-enhanced ultrasound as a triage test to reduce the use of contrast-enhanced CT/contrast-enhanced MRI



Care pathway

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. In this case, survival is the key variable of interest when considering the carer pathway. Improvements in survival by any therapeutic option are largely dependent on the disease stage at diagnosis. The earlier the diagnosis is made, the greater is the chance for successful treatment. Detailed care pathways for the three indications considered in this assessment can be found in section 3.4 of the diagnostics assessment report.

2 The evidence

2.1 Clinical effectiveness

A systematic review of the clinical effectiveness of contrast-enhanced ultrasound using SonoVue compared with contrast-enhanced CT and

contrast-enhanced MRI was undertaken by the External Assessment Group (EAG).

Outcomes

Studies reporting the following outcomes were considered relevant:

- effect of testing on treatment plan (for example, surgical or medical management, or palliative care), when information on the appropriateness of the final treatment plan is also reported
- effect of pre-treatment testing on clinical outcome (for example, overall survival, progression-free survival)
- prognosis – the ability of test result to predict clinical outcome (for example, overall survival, progression-free survival, response to treatment)
- test accuracy and number of patients/lesions for which no conclusive diagnostic information could be obtained with contrast-enhanced ultrasound using SonoVue.

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

- additional focal liver lesions detected by contrast-enhanced ultrasound, over and above those seen on unenhanced ultrasound
- adverse events associated with testing (for example, claustrophobia, reaction to contrast media)
- acceptability of tests to patients or surrogate measures of acceptability (for example, waiting time and associated anxiety).

Radiation exposure was not considered a relevant outcome because the population is mostly older adults in whom additional incident cancers as a result of imaging are likely to be minimal.

Results of the systematic review

Based on the searches, 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. 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 contrast-enhanced ultrasound with SonoVue for the characterisation of focal liver lesions detected during routine monitoring in patients with cirrhosis
- four assessed the performance of contrast-enhanced ultrasound with SonoVue for the detection of liver metastases in patients with known primary cancers (colorectal cancer)
- six concerned the use of contrast-enhanced ultrasound with SonoVue for the characterisation of incidentally detected focal liver lesions
- three considered the use of contrast-enhanced ultrasound with SonoVue to assess response to treatment in patients with liver cancer.

The remaining study was a controlled trial which compared assessment with conventional imaging (contrast-enhanced CT or contrast-enhanced MRI) plus unenhanced ultrasound with assessment with conventional imaging (contrast-enhanced CT or contrast-enhanced MRI) plus contrast-enhanced ultrasound with SonoVue before radiofrequency ablation. This study reported the following patient-relevant outcomes: successful ablation, tumour progression, incidence of new hepatocellular carcinoma, incidence of repeat radiofrequency ablation, local progression-free survival, new tumour-free survival and complications after therapy.

Only one of the studies of test accuracy included in this review reported any information on adverse events related to testing. In this study there were no adverse events associated with contrast-enhanced ultrasound with SonoVue, but there was no information about the comparator (contrast-enhanced MRI with gadolinium). A large, retrospective safety study of contrast-enhanced ultrasound with SonoVue in abdominal imaging did not meet the inclusion criteria for this review but reported data from 23,188 investigations in 29

centres in Italy. This study found 29 incidents of adverse events, of which 2 were graded as serious, 1 severe, 3 moderate and 23 mild. There were no fatal adverse events. Most non-serious adverse events resolved without intervention.

All included studies were published in 2006 or later. Of the 21 included studies, 16 were conducted in Europe (most in Italy or Spain) and the remaining 5 studies were conducted in China (including two Chinese language publications). Two studies reported funding from the manufacturer of SonoVue and 13 studies did not report any information on funding sources.

Presentation of test accuracy results

The results of test accuracy studies were summarised according to the clinical indication for imaging (characterisation of focal liver lesions detected during routine monitoring in patients with cirrhosis , detection of liver metastases in patients with known primary malignancy, characterisation of incidentally detected focal liver lesions, assessment of response to treatment in known liver malignancy) and further stratified by target condition (hepatocellular carcinoma, liver metastases, or 'any liver malignancy') and/or comparator test(s) (contrast-enhanced CT, contrast-enhanced MRI, both). 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 for contrast-enhanced ultrasound with SonoVue, comparator(s) and target condition. When multiple data sets were reported (for example, for per patient and per lesion data, different diagnostic criteria, different lesion sizes) these were extracted in full. Data on the numbers of tests with no conclusive diagnostic information were also included. No study reported data on patient preferences.

Test accuracy and quality of the studies in relation to each clinical indication assessed are summarised below. Further details can be found in section 4.6 of the diagnostics assessment report.

Accuracy data from studies of contrast-enhanced ultrasound with SonoVue for the characterisation of focal liver lesions detected during monitoring in patients with cirrhosis

Studies conducted in patients with cirrhosis during routine monitoring all concerned the differentiation of hepatocellular carcinoma from other lesion types in small to medium (< 30 mm) focal liver lesions. The definition of a positive test for hepatocellular carcinoma varied across studies. Studies assessing contrast-enhanced MRI used three contrast agents: gadolinium (a vascular contrast agent), SPIO (a hepatocyte-specific contrast agent), Gd-EOB-DTPA (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. When the definition of hepatocellular carcinoma given in the EFSUMB guidelines (arterial phase enhancement followed by portal-venous washout) was used, estimates of the sensitivity and specificity of each of the imaging modalities varied across studies. There was some evidence, from one study comparing contrast-enhanced ultrasound and contrast-enhanced MRI using gadolinium, that these imaging techniques may be better at ruling out hepatocellular carcinoma in focal liver lesions between 11 and 30 mm (sensitivities were 92% and 95% respectively) than in small focal liver lesions ≤ 10 mm (sensitivities 27% and 73% respectively), but this study did not use the EFSUMB definition of hepatocellular carcinoma. It is therefore possible that some of the variation in sensitivity estimates in studies of focal liver lesions < 30 mm may be a result of differences in the size distribution of focal liver lesions included. There was also some evidence from two studies that combined contrast-enhanced ultrasound and contrast-enhanced CT or all three imaging modalities, and considered any positive imaging result as 'test positive', that combined imaging may increase sensitivity. Inconsistent estimates of sensitivity mean that it is unclear whether contrast-enhanced ultrasound alone can rule out hepatocellular carcinoma in focal liver lesions < 30 mm. Contrast-enhanced ultrasound alone may be adequate to rule out hepatocellular carcinoma for focal liver lesions between 11 and 30 mm.

Table 1 QUADAS-2 results for studies of the accuracy of contrast-enhanced ultrasound with SonoVue for the characterisation of focal liver lesions detected during monitoring in patients with cirrhosis

Study	Risk of bias					Applicability concerns
	Patient selection	Index test	Comparator test	Reference standard	Flow and timing	Patient selection
Blondin 2011	High	Unclear	Unclear	Low	Low	High
Dai 2008	Low	Low	Low	Unclear	Low	Low
Forner 2008	Unclear	Unclear	Low	Unclear	Unclear	Unclear
Giorgio 2007	Low	Low	Low	Low	Low	Unclear
Leoni 2010	High	Low	Low	High	High	Unclear
Quaia 2009	High	Low	Low	Unclear	High	Unclear
Sangiovanni 2010	High	Unclear	Unclear	Low	Low	Unclear

Accuracy data from studies of contrast-enhanced ultrasound with SonoVue for the detection of liver metastases in patients with known primary malignancy

Studies of the diagnosis of liver metastases using imaging with vascular contrast media (contrast-enhanced ultrasound, contrast-enhanced CT and contrast-enhanced MRI with gadolinium), in which definitions of a positive imaging test were reported, gave various descriptions of peripheral rim enhancement as the criteria for liver metastases. Two studies also reported data for contrast-enhanced MRI with SPIO. There was no evidence for any consistent 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 colorectal cancer and more than 95% for both contrast-enhanced ultrasound and contrast-enhanced CT in a second study of patients with various primary cancers (mostly colorectal cancer). The only previous systematic review of contrast-enhanced ultrasound with SonoVue for the diagnosis of liver metastases did not include any comparator tests and reported sensitivities ranging from 79% to 100%. The limited data available indicate that contrast-

enhanced ultrasound alone may be adequate to rule out liver metastases in patients with known primary malignancies.

Table 2 QUADAS-2 results for studies of the accuracy of contrast-enhanced ultrasound with SonoVue for the detection of liver metastases in patients with known primary malignancy

Study	Risk of bias					Applicability concerns
	Patient selection	Index test	Comparator test	Reference standard	Flow and timing	Patient selection
Clevert 2009	Low	Low	Low	Unclear	High	Unclear
Flor 2010 (abstract only)	Unclear	Unclear	No comparator	Unclear	Unclear	Low
Jonas 2011 (abstract only)	High	Unclear	Unclear	Unclear	Unclear	High
Mainenti 2010	Low	Low	Low	Unclear	Low	Unclear

Accuracy data from studies of contrast-enhanced ultrasound with SonoVue for the characterisation of incidentally detected focal liver lesions

The primary outcome measure reported by studies conducted in patients with incidentally detected focal liver lesions was test accuracy for the differentiation of malignant from benign liver lesions. Studies consistently used definitions of the imaging criteria for hepatocellular carcinoma and liver metastases which were similar to those reported in the EFSUMB guidelines on the use of contrast-enhanced ultrasound. All studies reported no significant difference in the accuracy of contrast-enhanced ultrasound and contrast-enhanced CT or contrast-enhanced MRI for the characterisation of focal liver lesions. All but one study reported data for one lesion per patient. 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 contrast-enhanced ultrasound and contrast-enhanced CT. The pooled estimates of specificity were 94% and 93%, respectively, based on data from four studies. The single study comparing contrast-enhanced ultrasound with contrast-enhanced MRI used gadolinium for MRI in all patients, with the addition of SPIO in an unspecified

number. This study 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 contrast-enhanced ultrasound and contrast-enhanced CT did not increase sensitivity when a positive result on either modality was treated as 'test positive'. This, combined with the high estimates of sensitivity, indicates that contrast-enhanced ultrasound alone may be adequate to rule out liver malignancy in patients with incidentally detected focal liver lesions.

The systematic review identified a number of studies on the detection of any liver malignancy in patients with incidentally detected focal liver lesions, which used similar criteria to define a positive test. Therefore, it was possible to combine these studies to provide pooled estimates and a summary receiver operating characteristic curve of test accuracy for the different imaging modalities. The results are summarised in figures 4, 5 and 6 of the diagnostics assessment report.

Table 3 QUADAS-2 results for studies of the accuracy of contrast-enhanced ultrasound with SonoVue for the characterisation of incidentally detected focal liver lesions

Study	**Risk of bias**					**Applicability concerns**
	Patient selection	**Index test**	**Comparator test**	**Reference standard**	**Flow and timing**	**Patient selection**
Catala 2007	High	Low	Low	Unclear	High	Unclear
Gierblinski 2008	High	Unclear	No comparator	Low	Unclear	Unclear
Li 2007	Unclear	Low	Low	Unclear	Low	Unclear
Seitz 2009	High	Unclear	Unclear	Unclear	Unclear	Unclear
Seitz 2010	High	Unclear	Unclear	Unclear	Unclear	Unclear
Solbiati 2006 (abstract only)	High	Unclear	Unclear	High	High	Unclear

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

Three studies reported comparisons of contrast-enhanced ultrasound with SonoVue and other imaging modalities for the assessment of treatment success (complete response) in patients with malignant liver lesions (mainly hepatocellular carcinoma). Two were Chinese language publications and the other was only published as a conference abstract.

The two Chinese language publications compared imaging modalities for the assessment of response to treatment (cryosurgery and non-surgical treatment) in patients with hepatocellular carcinoma. They reported per lesion sensitivity estimates of more than 95% and specificity estimates of more than 80% for complete response, using contrast-enhanced ultrasound, contrast-enhanced CT and contrast-enhanced MRI with gadolinium. These very limited data indicate that contrast-enhanced ultrasound may provide information on response in patients treated for hepatocellular carcinoma. However, these data may not be directly applicable to UK clinical practice. The EAG suggests that further studies, ideally conducted in a UK setting, are needed to confirm these findings.

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

One controlled clinical trial indicated that contrast-enhanced ultrasound before treatment for patients undergoing radiofrequency ablation for hepatocellular carcinoma may result in a reduced incidence of disease progression, new hepatocellular carcinoma and repeat radiofrequency ablation, and increased time without local progression and new tumours, compared with unenhanced ultrasound. However, this non-randomised study was considered to have ‘risk of bias’ in a number of areas and no difference was found in the primary outcome (successful ablation). The EAG suggests that high quality randomised controlled trials are needed to determine the relative effectiveness of different imaging strategies for treatment planning.

2.2 Cost effectiveness

Systematic review of cost-effectiveness evidence

Four studies were identified that met the inclusion criteria for an economic analysis related to use of SonoVue in contrast-enhanced ultrasound.

Although all the studies were of reasonably good quality, they did not fully address the cost effectiveness of SonoVue as defined in this assessment. 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. (2011) was the only study that modelled disease management and reported health outcomes relevant to this assessment, but the follow-up was only 24 months. Further details can be found in section 5.2 of the diagnostics assessment report.

Economic analysis conducted by the EAG

The EAG conducted an economic analysis of contrast-enhanced ultrasound using SonoVue for assessing focal liver lesions in adults, in whom unenhanced ultrasound or other liver imaging is inconclusive. Three separate models were used for three clinical applications for which the most data on test performance were available and experts suggested there was most likely to be clinical benefit:

- cirrhosis surveillance
- liver metastases in colorectal cancer
- investigation of incidentally detected focal liver lesions.

In each model, contrast-enhanced ultrasound was compared with contrast-enhanced CT, contrast-enhanced MRI using gadolinium and/or contrast-enhanced MRI using SPIO. Average costs, expected life years and expected quality-adjusted life years (QALYs) per patient were calculated for each comparator, when evidence on test performance was available.

Costs of contrast-enhanced and unenhanced ultrasound were based on expert opinion of clinicians and the manufacturer of SonoVue. The costs of using the contrast agent, including cannulation, were assumed to be £48.70 (estimate supplied by the manufacturer and agreed by clinicians). In addition, contrast-enhanced ultrasound was expected to take longer than the unenhanced ultrasound. Therefore, the EAG used the difference between the reference costs of an ultrasound taking less than 20 minutes (£55) and an ultrasound taking more than 20 minutes (£71) as the additional time costs of contrast-enhanced ultrasound. The total additional cost was therefore estimated to be £65. This assumes that contrast-enhanced ultrasound is performed in the same appointment as the unenhanced scan.

The costs of the other diagnostic tests, the outpatient appointment, orthotopic liver transplantation and resection were based on 2011 NHS reference costs.

Cirrhosis surveillance model

Model description

The model was a modified version of a model produced by the Peninsula Technology Assessment Group (the PenTAG cirrhosis surveillance model). The population consisted of people with a diagnosis of compensated cirrhosis deemed eligible to enter a surveillance programme [aged 70 years or younger 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 was a probabilistic state-transition (Markov) cohort model constructed using Excel. The time horizon was lifetime and the cycle duration was 1 month. Patients in the model can develop hepatocellular carcinoma. In the base-case analysis monitoring takes place every 6 months, and stops for people who reach 70 years. 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. (2010). It was assumed that large (> 5 cm) tumours are always detected during monitoring. If the

tumour is not detected (false negative), it grows and might be detected 6 months later during the next monitoring, or when it becomes symptomatic. It is assumed that false positives (misdiagnoses of hepatocellular carcinoma) are rapidly discovered before treatment. The treatments considered in the model are liver transplantation and liver resection.

Test accuracy data used in the model

It was assumed that the first test used for monitoring was unenhanced ultrasound. The test performance of unenhanced ultrasound used in the model is shown in table 4 and was based on the study by Bennett et al. (2002) as used in the HTA report by Thompson Coon et al. (2007). 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 4 Test performance of unehanced ultrasound used in the cirrhosis surveillance model (based on Bennett et al. 2002)[a]

Tumour size	True positive	False negative	False positive	True negative	Sensitivity
Small	3	25	6	118	0.11
Medium	2	5	0	2	0.29
Large	3	1	0	0	0.75
[a]The false-positive rate was 0.04.					

Additional imaging takes place when unenhanced ultrasound is inconclusive. About 43% of unenhanced ultrasounds were estimated to be inconclusive, based on information provided by the manufacturer of SonoVue during the scoping phase. The systematic review identified seven studies that compared contrast-enhanced ultrasound with at least one of the comparators (contrast-enhanced CT, contrast-enhanced MRI with gadolinium or contrast-enhanced MRI with SPIO) for the characterisation of focal liver lesions detected during routine monitoring in patients with cirrhosis.

In the base-case analysis, the probability of detecting hepatocellular carcinoma and the proportion of people with a false-positive test result were taken from Leoni et al (2010). Data from this study were used because

diagnostic criteria matched the EFSUMB guidance on the use of contrast-enhanced ultrasound and the performance of contrast-enhanced ultrasound, contrast-enhanced CT and contrast-enhanced MRI with gadolinium was reported in the same population. Most other studies compared contrast-enhanced ultrasound with either contrast-enhanced CT or contrast-enhanced MRI. A potential disadvantage of using data from Leoni et al. (2010) was the sub-optimal reference standard (concordance between at least two imaging tests) used for most patients. Leoni et al. (2010) also reported accuracy data for contrast-enhanced MRI with SPIO, which were not incorporated in the base-case analysis. The study included patients with liver lesions between 1 and 3 cm. In the base-case analysis the EAG 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 hepatocellular carcinomas was assumed to be 100% for all confirmatory imaging tests, and this assumption was agreed by the clinical experts.

Table 5[a] Test performance of confirmatory imaging used in the cirrhosis surveillance model (based on Leoni et al. 2010)

Test	True positive	False negative	False positive	True negative	Sensitivity for detecting small and medium tumours
Contrast-enhanced ultrasound	37	18	2	18	0.67
Contrast-enhanced CT	37	18	2	18	0.67
Contrast-enhanced MRI with gadolinium	45	10	1	19	0.82

[a]False positive rates were 0.03, 0.03 and 0.01 for contrast-enhanced ultrasound, contrast-enhanced CT and contrast-enhanced MRI with gadolinium respectively.

Base-case cost effectiveness results

Contrast-enhanced ultrasound had the lowest discounted lifetime costs per patient (£35,744), followed by contrast-enhanced CT (£36,124) and contrast-enhanced MRI with gadolinium (£36,807). Compared with contrast-enhanced ultrasound, contrast-enhanced CT was as effective but more costly, and was thus considered to be dominated by contrast-enhanced ultrasound (table 6). Contrast-enhanced MRI with gadolinium cost £1063 more per patient than contrast-enhanced ultrasound, but also yielded 0.022 more QALYs, resulting in an incremental cost-effectiveness ratio (ICER) of £48,454 per QALY gained. As this is above an ICER of £30,000 per QALY gained, contrast-enhanced MRI with gadolinium was not deemed cost effective compared with contrast-enhanced ultrasound.

Table 6 Base-case cost-effectiveness results for cirrhosis surveillance

Test	**Cost**	**QALY**	**Compared with contrast-enhanced ultrasound (and to next cost-effective test)**		
			Incremental cost	**Incremental QALY**	**Incremental cost/QALY**
Contrast-enhanced ultrasound	£35,744	10.153			
Contrast-enhanced CT	£36,124	10.153	£379	0.000	Dominated
Contrast-enhanced MRI with gadolinium	£36,807	10.175	£1063	0.022	£48,454

Additional analyses

Additional analyses are shown in table 7.

Table 7 Sensitivity and scenario analyses for cirrhosis surveillance

Analysis	Comparator	Compared with contrast-enhanced ultrasound		
		Incremental cost	Incremental QALY	Incremental cost/QALY
Base-case analysis				
	CECT	£379	0.000	Dominated
	Gd-CEMRI	£1063	0.022	£48,454
Sensitivity analysis				
Imaging used as confirmatory test after all positive unenhanced ultrasounds	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. 2008 used as source for accuracy data	CECT	129	-0.004	Dominated
Quaia et al. 2009 used as source for accuracy data	CECT	288	-0.005	Dominated
Blondin et al.2011 used as source for accuracy data	Gd-CEMRI	1044	0.004	297,695
Giorgio et al. 2007 used as source for accuracy data	Gd-CEMRI	1210	0.018	68,940

In probabilistic sensitivity analysis with over 5000 replications, contrast-enhanced ultrasound had the highest probability of being cost effective below £55,000 per QALY gained. Above this level, contrast-enhanced MRI with gadolinium had the highest probability of being cost effective. At a value of £20,000 per QALY gained the probability that contrast-enhanced ultrasound, contrast-enhanced CT or contrast-enhanced MRI with gadolinium was cost effective is 99%, 0% and 1% respectively.

Liver metastases from colorectal cancer model

Model description

The model was a modified version of the model developed by Brush et al. (2011). The model was adapted to assess the cost effectiveness of contrast-enhanced ultrasound compared with contrast-enhanced CT and contrast-enhanced MRI in detecting metastases from colorectal cancer after an inconclusive unenhanced ultrasound scan. The population consisted of patients who had previously had surgery for primary colorectal cancer and who, during routine follow-up, were identified as potentially having a metastatic recurrence. The model was a decision tree combined with a probabilistic state transition (Markov) cohort model. The time horizon was lifetime and the cycle duration was 1 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. (2010). 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 a poorer prognosis only in the first year. In the base-case analysis, patients who are inaccurately diagnosed as having metastases (false positives) receive biopsy and the incorrect diagnosis is discovered. They are, therefore, not unnecessarily treated. In line with Brush et al. (2011), it was assumed that all patients with metastases at a single site will receive preoperative chemotherapy and surgery for metastases, and those patients with metastases at multiple sites are assumed to be non-curable and will receive either preoperative chemotherapy followed by surgery and palliative care, or chemotherapy and palliative care.

Test accuracy data used in the model

The systematic review identified two studies that assessed the accuracy of contrast-enhanced ultrasound compared with contrast-enhanced CT and/or contrast-enhanced MRI with gadolinium and/or contrast-enhanced MRI with SPIO in detecting liver metastases in people with colorectal cancer after inconclusive unenhanced ultrasound. The test performance used in the base

case was that in the study of Mainenti et al. (2010) because this study compared all three alternative tests (contrast-enhanced CT, contrast-enhanced MRI with gadolinium, contrast-enhanced MRI with SPIO) with contrast-enhanced ultrasound. In this study, based on a total of 34 patients, sensitivity was 83% for all comparators. Specificity was lowest for contrast-enhanced ultrasound (86%), followed by contrast-enhanced CT (96%), contrast-enhanced MRI with SPIO (96%) and contrast-enhanced MRI with gadolinium (100%) (table 8).

Table 8 Test performance of imaging used in the liver metastases model (based on Mainenti et al. 2010)

Test	True positive	False negative	False positive	True negative	Sensitivity	Specificity
Contrast-enhanced ultrasound	5	1	4	24	0.83	0.86
Contrast-enhanced CT	5	1	1	27	0.83	0.96
Contrast-enhanced MRI with gadolinium	5	1	0	28	0.83	0.96
Contrast-enhanced MRI with SPIO	5	1	1	27	0.83	1.00

Base-case cost effectiveness results

In the base-case analysis (table 9), using the different imaging techniques to detect liver metastases from colorectal cancer resulted in equal expected lifetime QALYs (8.364). Contrast-enhanced CT was the least costly test, with expected lifetime costs of £7510 per patient. Contrast-enhanced ultrasound was only slightly (£1) more costly with expected lifetime cost of £7511 per patient. Contrast-enhanced MRI with gadolinium (£7688) and contrast-enhanced MRI with SPIO (£7722) were both more costly than, and thus dominated by, contrast-enhanced CT and contrast-enhanced ultrasound. Although technically contrast-enhanced CT dominates contrast-enhanced

ultrasound, their effectiveness is equal and their expected costs are extremely close.

Table 9 Base-case cost-effectiveness results for liver metastases from colorectal cancer

Test	Cost	QALY	Compared to CEUS			Compared with next cost-effective test			
			Incr. cost	Incr. QALY	Incr. cost/ QALY	Comparator	Incr. cost	Incr. QALY	Incr. cost/ QALY
Contrast-enhanced ultrasound	7511	8.364							
Contrast-enhanced CT	7510	8.364	-1	0.000	Dominant	Contrast-enhanced ultrasound	-1	0.000	Dominant
Contrast-enhanced MRI with gadolinium	7688	8.364	177	0.000	Dominated	Contrast-enhanced CT	178	0.000	Dominated
Contrast-enhanced MRI with SPIO	7722	8.364	211	0.000	Dominated	Contrast-enhanced CT	212	0.000	Dominated

Additional analyses

Additional analyses are shown in tables 10 to 13.

Table 10 Sensitivity analysis for liver metastases model assuming no biopsy if test is positive

Test	Cost	QALY	Compared with contrast-enhanced ultrasound			Compared with next cost-effective test			
			Incr. cost	Incr. QALY	Incr. cost/ QALY	Comparator	Incr. cost	Incr. QALY	Incr. cost/ QALY
CEUS	8335	8.343							
CECT	7321	8.359	-1015	0.016	Dominant	CEUS	-1,015	0.016	Dominant
Gd-CEMRI	7158	8.364	-1177	0.021	Dominant	CECT	-162	0.005	Dominant
SPIO-CEMRI	7537	8.359	-798	0.016	Dominant	Gd-CEMRI	-379	0.005	Dominated

If contrast-enhanced ultrasound is combined with biopsy (see table 9), and contrast-enhanced CT, contrast-enhanced MRI with gadolinium and contrast-enhanced MRI with SPIO are not be followed by biopsy (see table 10), then contrast-enhanced ultrasound and contrast-enhanced MRI with gadolinium are most effective, both yielding 8.364 QALYS. However, contrast-enhanced ultrasound is more costly than, and thus dominated by, contrast-enhanced MRI with gadolinium. Contrast-enhanced CT and contrast-enhanced MRI with SPIO are dominated by contrast-enhanced MRI with gadolinium.

Table 11 Sensitivity analysis for liver metastases model assuming 80% of patients have metastases (40% used in the base case)

Test	Cost	QALY	Compared with contrast-enhanced ultrasound			Compared with next cost-effective test			
			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

Table 12 Scenario analysis for liver metastases model with Jonas et al. (2011) as source for accuracy data

Test	Cost	QALY	Compared with contrast-enhanced ultrasound			Compared with next cost-effective test			
			Incr. cost	Incr. QALY	Incr. cost/ QALY	Comparator	Incr. cost	Incr. QALY	Incr. cost/ QALY
CEUS	7468	8369							
CECT	7475	8364	7	-0.005	Dominated	CEUS			Dominated
SPIO-CEMRI	8055	8382	587	0.014	43,318	CEUS	587	0.014	43,318

Table 13 Scenario analysis for liver metastases model with Clevert et al. (2009) as source for accuracy data

Test	Cost	QALY	Compared with contrast-enhanced ultrasound			Compared with next cost-effective test			
			Incr. cost	Incr. QALY	Incr. cost/ QALY	Comparator	Incr. cost	Incr. QALY	Incr. cost/ QALY
CEUS	7821	8384							
CECT	8121	8382	300	-0,002	Dominated	CEUS	300	-0,002	Dominated

In probabilistic sensitivity analysis with 5000 replications contrast-enhanced ultrasound and contrast-enhanced CT had a similar probability of being cost effective at all ICERs assessed. Contrast-enhanced ultrasound had a slightly higher probability of being cost effective up to a value of £20,000 per QALY gained, after which contrast-enhanced CT had a higher probability of being cost effective. At £20,000 per QALY gained, contrast-enhanced CT had the highest probability of being cost effective (48%), followed by contrast-enhanced ultrasound (47%), contrast-enhanced MRI with gadolinium (3%) and contrast-enhanced MRI with SPIO (2%).

Investigation of incidentally detected focal liver lesions

Model description

People with incidentally detected focal liver lesions can have a variety of conditions, ranging from malignant lesions such as hepatocellular carcinoma and metastases to different types of benign lesions. The prognosis and costs for patients diagnosed with hepatocellular carcinoma were modelled using the cirrhosis surveillance model, whereas the prognosis and costs for patients with liver metastases were modelled using the liver metastases model. The model used for the investigation of incidentally detected focal liver lesions was a decision analytic model with a lifetime time horizon. The diagnostic accuracy results used for the three tests were very similar. For different reasons, it was assumed that patients with an incorrect test result (false-positive and false-negative results) would have their condition correctly identified within 1 year. This was a conservative assumption biased against contrast-enhanced ultrasound. The costs, life-years and QALYs for patients with a malignancy other than hepatocellular carcinoma or metastases were assumed to be equal to those in patients with hepatocellular carcinoma. These other types of malignant lesions (for example, lymphoma) were infrequently seen among people with an incidentally detected focal liver lesion and the studies comparing contrast-enhanced ultrasound with contrast-enhanced CT or contrast-enhanced MRI provided little information about these lesions. Given the heterogeneity in costs and QALYs within this group (and even among patients with the same malignancy), the EAG chose to set the base-case

values to the costs and QALYs of patients with hepatocellular carcinoma and emphasised that this was an assumption. However, it was known in advance that the costs and QALYs for these patients would have limited effect on the cost effectiveness of contrast-enhanced ultrasound because the sensitivity of contrast-enhanced ultrasound was very similar to that of the comparators and the prior probability of other malignancies was small. The impact of this false-negative effect was therefore examined using sensitivity analysis.

Test accuracy data used in the model

Several studies have compared contrast-enhanced ultrasound with contrast-enhanced CT or contrast-enhanced MRI for characterising incidentally detected focal liver lesions. Three different types of diagnostic outcomes have been studied: diagnosis of any malignancy, diagnosis of hepatocellular carcinoma and diagnosis of metastases. Of these three, the most common outcome is diagnosis of any malignancy. In addition, while most of the studies compared contrast-enhanced ultrasound with contrast-enhanced CT, only one of these compared contrast enhanced ultrasound with contrast-enhanced MRI. These two factors (majority of data on any malignancy and only one study comparing contrast-enhanced ultrasound with contrast-enhanced MRI) made it impossible to combine all results into one analysis without important assumptions (listed in section 5.3.3 of the diagnostics assessment report). This issue was resolved by using the test performance results in various ways.

The approach used in the base-case was to take the results from the meta-analysis of four studies that compared contrast-enhanced ultrasound with contrast-enhanced CT for the differentiation of malignant and benign lesions. Table 14 illustrates the similar performance of the two tests. The confidence intervals shown were calculated using the exact method.

Table 14 Sensitivity and specificity of contrast-enhanced ultrasound and contrast-enhanced CT for characterising any malignancy in incidentally detected focal liver lesions

	Estimate	95% confidence interval (exact method)
Sensitivity of contrast-enhanced ultrasound	95.1%	93.3% to 96.6%
Sensitivity of contrast-enhanced CT	94.6%	92.7% to 96.1%
Specificity of contrast-enhanced ultrasound	93.8%	90.4% to 96.3%
Specificity of contrast-enhanced CT	93.1%	89.6% to 95.8%

In addition to using the sensitivity and specificity values from the meta-analysis, the EAG used the results from the individual studies in sensitivity analysis.

Only one study compared the test accuracy of contrast-enhanced ultrasound with MRI. This study reported that all patients in a subgroup had contrast-enhanced MRI with gadolinium, and that a subset of these patients also had MRI with SPIO contrast agent. It was difficult to determine the accuracy of MRI with the two different contrast agents and therefore sections relating to the use of MRI in the characterisation of incidentally detected focal liver lesions refer to contrast-enhanced MRI.

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), whereas in another it was 74% (Catala 2007). In the final scope for this assessment, it was stated that expert opinion had suggested that as many as 70–75% of focal liver lesions assessed in the NHS may be benign. This percentage might be higher if the population were to be limited to people with incidentally detected focal liver lesions. The clinicians surveyed during this assessment were of the opinion that the likelihood of

malignancy was rather low in this population. As a consequence, the EAG used a low probability of malignancy in the base-case scenario. The values shown in table 15 were based on the results of Bartolotta et al. (2011), who reported a low probability of 4.3%. Because Bartolotta et al. (2011)did not include any patients with hepatocellular carcinoma in their study, the EAG increased this to 0.05 to introduce a small chance that a patient with hepatocellular carcinoma would appear on occasion.

Table 15 Probabilities of the different types of lesions at time of assessment of incidentally detected focal liver lesions

Type of lesion	Prior probability (prevalance)
Metastases	0.0211
Hepatocellular carcinoma	0.0141
Cholangiocarcinoma	0.0070
Other malignancy	0.0004
Haemangioma	0.4996
Focal nodular hyperplasia	0.3169
Hepatocellular adenoma	0.0141
Focal fatty sparing	0.0704
Other benign	0.0563
Probability of malignant lesion	0.0426
Probability of benign lesion	0.9574

Base-case cost effectiveness results

The results from the base-case analysis are shown in table 16. As expected, the lower costs of contrast-enhanced ultrasound combined with the slightly better test performance meant that contrast-enhanced ultrasound dominated both contrast-enhanced CT and contrast-enhanced MRI. The main factor in these calculations was the cost of the tests. In the comparison of contrast-enhanced ultrasound and contrast-enhanced CT, contrast-enhanced ultrasound cost £73.50 and contrast-enhanced CT £125. In the comparison of contrast-enhanced ultrasound and contrast-enhanced MRI, contrast-enhanced ultrasound cost £112.60 and contrast-enhanced MRI £242 (per patient costs including cost of the test and additional costs due to false positives).

Table 16 Base-case cost-effectiveness results for incidentally detected focal liver lesions

	Incremental costs (SE)	Incremental QALYS (SE)	ICER
Contrast-enhanced ultrasound vs. contrast-enhanced CT	-£52	0.0002	Dominant
Contrast-enhanced ultrasound vs. contrast-enhanced MRI	-£131	0.0026	Dominant

Additional analyses

Although 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 contrast-enhanced ultrasound compared with contrast-enhanced CT or contrast-enhanced MRI. The most critical factor in the analyses related to the costs of the tests. The impact of any other factors (for example, prior probabilities of a particular diagnosis and costs of treatment) was minimal because the accuracy of the tests was so similar.

Probabilistic sensitivity analyses showed that the probability of contrast-enhanced ultrasound being cost effective compared with contrast-enhanced CT and contrast-enhanced MRI was greater than 95% at values of £20,000 per QALY gained.

3 Issues for consideration

Focus of the evaluation

The assessment addresses the clinical and cost effectiveness of contrast-enhanced ultrasound with SonoVue for liver imaging after an inconclusive ultrasound scan, in the following three specific clinical indications:

- detection of hepatocellular carcinoma by monitoring in patients with cirrhosis

- detection of liver metastases in patients with colorectal cancer (expert opinion indicated that the data for diagnostic accuracy are equally applicable to liver metastases from other primary cancers. However, how the metastases are treated may vary)
- characterisation of incidentally detected focal liver lesions (expert opinion suggested that this is likely to be the main application of contrast-enhanced ultrasound in liver imaging).

The use of SonoVue in treatment planning and the determination of treatment response in patients with liver cancers were also assessed in accordance with the scope. However, the available data, summarised in section 2, did not allow a cost-effectiveness analysis to be conducted for these clinical applications, and therefore these applications will not be considered by the Committee for recommendations.

Systematic review of clinical effectiveness

Quality of included studies

Of the 21 studies included in the systematic review, 20 were studies of diagnostic test accuracy. Most of the 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. '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 (for example, exclusion of patients with a low probability of malignancy). 'High' risk of bias ratings for the 'flow and timing' domain arose from exclusion of more than 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.

Applicability of accuracy data

The clinical applicability of accuracy data included in the systematic review may have some limitations. The inclusion criteria for this assessment specified that contrast-enhanced ultrasound with SonoVue should be used for the characterisation of focal liver lesions when unenhanced ultrasound was inconclusive. Although all study participants had focal liver lesions detected by imaging before contrast-enhanced ultrasound with SonoVue, only one study explicitly stated that unenhanced ultrasound was inconclusive. Perhaps more importantly, the prevalence of malignancy appeared high in studies assessing the accuracy of contrast-enhanced ultrasound and other imaging modalities for the characterisation of incidentally detected focal liver lesions. These study populations may not be representative of the population with incidentally detected focal liver lesions seen in clinical practice. With regards to moitoring patients with colorectal cancer, Inconsistent estimates of sensitivity mean that it is unclear whether contrast-enhanced ultrasound alone can rule out hepatocellular carcinoma in focal liver lesions < 30 mm. Contrast-enhanced ultrasound alone may be adequate to rule out hepatocellular carcinoma for focal liver lesions between 11 and 30 mm.

SonoVue safety data

Only one of the test accuracy studies included in the systematic review reported any information on adverse events related to testing. There were no adverse events associated with contrast-enhanced ultrasound with SonoVue, but there was no information about the comparator (contrast-enhanced MRI with gadolinium). A large, retrospective safety study of contrast-enhanced ultrasound with SonoVue in abdominal imaging did not meet the inclusion criteria for the systematic review, but reported data from 23,188 investigations in 29 centres in Italy. This study found 29 cases of adverse events, of which 2 were graded as serious, 1 severe, 3 moderate and 23 mild. There were no fatal adverse events. Most non-serious adverse events resolved without intervention.

Cost effectiveness

Detection of hepatocellular carcinoma by monitoring in patients with cirrhosis

Contrast-enhanced ultrasound is considered the most cost-effective option after inconclusive unenhanced ultrasound. Probabilistic sensitivity analysis revealed that there was little uncertainty about the cost effectiveness of contrast-enhanced ultrasound compared with the other tests. The base-case results were based on one source for accuracy (Leoni et al. 2010). Using the two other studies that compared contrast-enhanced ultrasound and contrast-enhanced CT the dominance of contrast-enhanced ultrasound over contrast-enhanced CT was maintained, with even lower effectiveness of contrast-enhanced CT. Compared with contrast-enhanced MRI with gadolinium, contrast-enhanced ultrasound was cost effective in most sensitivity analyses, except when all positive unenhanced ultrasound examinations were subject to confirmatory testing instead of the inconclusive ultrasounds only, and when the proportion of patients having an inconclusive ultrasound was considerably lower (20% instead of 43%). These two analyses resulted in ICERs for contrast-enhanced MRI with gadolinium compared with contrast-enhanced ultrasound of £12,806 and £16,121 respectively. Expert opinion indicates that confirmatory testing for all positive unenhanced ultrasound scans is not reflective of current clinical practice. It is thought that the percentage of patients with an inconclusive ultrasound scan is more likely to be nearer 20% (and may be as low as 10–15%). The 43% figure used in the base-case was supplied by the manufacturer, who has forwarded data supporting their claim. These data have been forwarded to the EAG for review. Therefore, the most appropriate ICER is £16,121 (contrast-enhanced MRI with gadolinium cost an additional £624 and led to 0.024 additional QALYS when compared with contrast-enhanced ultrasound - these additional QALYs may be offset by the reduced patient anxiety associated with SonoVue (see section below on 'accessibility').

Detection of liver metastases in patients with colorectal cancer

Contrast-enhanced ultrasound had similar costs and effects compared with contrast-enhanced CT. Although with a lifetime time horizon the two tests yielded equal QALYs per patient, contrast-enhanced ultrasound cost £1 more than contrast-enhanced CT. Both contrast-enhanced MRI with gadolinium and contrast-enhanced MRI with SPIO were dominated by contrast-enhanced CT in this population because they were more costly and equally effective. Probabilistic sensitivity analysis showed that at a value of £20,000 per QALY gained, contrast-enhanced CT has the highest probability of being cost effective (48%), followed by contrast-enhanced ultrasound (47%), contrast-enhanced MRI with gadolinium (3%) and contrast-enhanced ultrasound MRI with SPIO (2%). However, in this base-case analysis it was assumed that patients who were incorrectly diagnosed with liver metastases would receive biopsy and the incorrect diagnosis would be discovered before treatment. If this is not assumed, and patients could receive unnecessary treatment, the lower specificity of contrast-enhanced ultrasound had larger consequences. Under this assumption, contrast-enhanced ultrasound is both the most costly and the least effective option, and contrast-enhanced MRI with gadolinium dominates all other tests. Expert opinion indicates that although the diagnostic pathway varies depending on the clinical scenario, patients would be very unlikely to receive unnecessary treatment. This is because further tests (histology or further imaging) are likely to be requested by the multidisciplinary team when there is doubt about the diagnosis. However, these may be of the primary cancer and not the liver metastases. If the proportion of patients with metastases were higher (80% rather than 40% as used in the base case), contrast-enhanced ultrasound would dominate the other tests. Garden et al. (2006) suggest that the prevalence of metastases from colorectal cancer is between 60 and 75%. Experts suggest that advances in understanding of tumour biology, greater awareness among clinicians and the NHS Bowel Cancer Screening Programme (which started in July 2006 and achieved nationwide coverage by 2010) is leading to earlier detection of bowel cancers in the disease process. Therefore, the prevalence of metastases may be lower than that suggested by Garden et al. (2006). Based on the two other

studies that reported accuracy data in this population, contrast-enhanced ultrasound dominated contrast-enhanced CT. Contrast-enhanced MRI with gadolinium yielded 0.014 more QALYs, but also cost £587 more than contrast-enhanced ultrasound, resulting in an ICER of 43,318 per QALY gained.

Characterisation of incidentally detected focal liver lesions

In the base-case analysis, no large differences in effectiveness were found between the three imaging strategies (incremental QALYs for contrast-enhanced ultrasound compared with contrast-enhanced CT were 0.00016, and for contrast-enhanced ultrasound compared with contrast-enhanced ultrasound MRI 0.0026). However, there was a difference in costs (contrast-enhanced ultrasound compared with contrast-enhanced CT -£52, and contrast-enhanced ultrasound compared with contrast-enhanced MRI -£131) and this resulted in dominance of contrast enhanced ultrasound with SonoVue. Probabilistic sensitivity analysis revealed that there was little uncertainty about the cost effectiveness of contrast-enhanced ultrasound compared with the other two tests. Additional analyses changed the absolute costs and effectiveness of the different strategies but did not lead to dramatic changes in the incremental costs and effectiveness of contrast-enhanced ultrasound compared with contrast-enhanced CT or contrast-enhanced MRI. 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 vary locally.

General

The main uncertainty surrounding the cost effectiveness of contrast-enhanced ultrasound is what happens when a patient receives an incorrect diagnosis. 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 may have associated risk factors or evidence of liver disease, which may have been the indication for initial testing with unenhanced ultrasound or which may have been identified by further imaging. Hence it is expected that their symptoms will worsen and that their lesion will be detected in a few months. How patients with a false-positive test result are managed might be more complex. The EAG assumed that in all models these patients would receive additional diagnostic tests (with additional costs), but would not undergo inappropriate treatment. In the liver metastases from colorectal cancer model, the EAG examined the extreme situation in which all patients with an incorrect diagnosis of 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.

Accessibility

Besides being less costly, contrast-enhanced ultrasound is more accessible than contrast-enhanced CT and especially contrast-enhanced MRI. All patients already have an unenhanced ultrasound, and can receive an immediate diagnosis using contrast-enhanced ultrasound as part of the same examination. A possible benefit of contrast-enhanced ultrasound is, therefore, reduced patient anxiety 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, because little evidence is available on the effect of anxiety on quality of life. It might be expected that the effects of using contrast-enhanced ultrasound are therefore underestimated. Although the length of wait for other imaging tests is unknown, consideration of this reduced anxiety would only further support the use of contrast-enhanced ultrasound over contrast-enhanced CT or contrast-enhanced MRI.

4 Equality considerations

No potential equality issues have been identified.

5 Implementation issues

Contrast-enhanced ultrasound is much more accessible than contrast-enhanced CT and especially contrast-enhanced MRI. All patients already have an unenhanced ultrasound scan, and can receive an immediate diagnosis using contrast-enhanced ultrasound as part of the same examination.

Many studies emphasised that the participating clinicians had years of experience in the use of contrast-enhanced ultrasound. It is possible that the diagnostic accuracy of contrast-enhanced ultrasound may be poorer if the user has little experience of the technique. However, widespread implementation of contrast-enhanced ultrasound would improve experience and ultimately diagnostic accuracy.

6 Summary

The systematic review did not provide a clear indication that any of the imaging modalities (contrast-enhanced ultrasound, contrast-enhanced CT or contrast-enhanced MRI) 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 the three types of imaging for the characterisation of focal liver lesions. However, reporting quality of the studies included in the systematic review 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.

Three models were used to assess the cost effectiveness of SonoVue as a contrast agent for contrast-enhanced ultrasound in three clinical indications (monitoring of cirrhosis, detecting liver metastases from colorectal cancer and investigating incidentally detected focal liver lesions). The base-case cost-effectiveness analysis of the use of contrast-enhanced ultrasound for people with an inconclusive unenhanced ultrasound scan indicated that the use of contrast-enhanced ultrasound instead of contrast-enhanced MRI was cost

effective in all three clinical indications. The use of contrast-enhanced ultrasound instead of contrast-enhanced CT was cost effective in the monitoring of cirrhosis and the investigation of incidentally detected focal liver lesions, but was similar in terms of costs and effects in the detection of liver metastases from colorectal cancer. The cost-effectiveness results vary depending on the additional analyses performed by the EAG and require the Committee's consideration. It should be noted that reduced patient anxiety associated with a malignant lesion being ruled out sooner as a result of not having to wait too long for another test was not included in the quantitative analysis.

Besides being less costly, contrast-enhanced ultrasound is more accessible than contrast-enhanced CT and especially contrast-enhanced MRI.

This overview was prepared by:

Gurleen Jhuti

Topic Lead

Hanan Bell

Technical Adviser

March 2012

Appendix A: Sources of evidence considered in the preparation of the overview

A. The diagnostics assessment report for this evaluation was prepared by the Kleijnen Systematic Reviews Ltd Assessment Group.

- Westwood M, Joore M, Grutters J. et al. 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. January 2012

B. The following organisations accepted the invitation to participate in this assessment as stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report.

I. Manufacturers/sponsors:

Technology(ies) under consideration

- Bracco UK Ltdo

Comparator(s)

- None

Other

- GE Healthcare

II. Professional/specialist and patient/carer groups:

- Royal College of Nursing
- British Medical Ultrasound Society

- Echocardigraphy Department, Princess Royal University Hospital, London
- Gateshead Health NHS Foundation Trust
- British Liver Trust
- British Society of Gastrointestinal and Abdominal Radiology
- Peterborough City Hospital