NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Health Technology Evaluation

Report for Guidance Executive

Review of DG5: SonoVue (sulphur hexafluoride microbubbles) - contrast agent for contrast enhanced ultrasound in liver imaging

This guidance was issued in August 2012

The review date for this guidance is August 2015.

NICE proposes an update of published guidance if the evidence base or clinical environment has changed to an extent that is likely to have a material effect on the recommendations in the existing guidance. Other factors such as the introduction of new technologies relevant to the guidance topic, or newer versions of technologies included in the guidance, will be considered relevant in the review process, but will not in individual cases always be sufficient cause to update existing guidance.

1. Recommendation

Transfer the guidance to the 'static guidance list' and signpost users from the landing page to the evidence which addresses the research recommendations.

That we should consult on the proposal.

A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper.

2. Original objective of guidance

To assess the clinical and cost effectiveness of using the contrast agent, SonoVue, for contrast-enhanced ultrasound imaging of suspected focal liver disease in adults.

3. Current guidance

Adoption recommendations

1.1 Contrast-enhanced ultrasound with SonoVue is recommended for characterising incidentally detected focal liver lesions in adults in whom an unenhanced ultrasound scan is inconclusive. An unenhanced ultrasound scan in which a focal liver lesion is detected, but not characterised, is defined as inconclusive.

1.2 Contrast-enhanced ultrasound with SonoVue is recommended for investigating potential liver metastases in adults:

- if contrast-enhanced computed tomography (CT) is not clinically appropriate, is not accessible or is not acceptable to the person, **and**
- in whom an unenhanced ultrasound scan is unsatisfactory and contrast is needed for further diagnosis.

1.3 Contrast-enhanced ultrasound with SonoVue is recommended for characterising focal liver lesions in adults whose cirrhosis is being monitored:

- if contrast-enhanced magnetic resonance imaging (MRI) is not clinically appropriate, is not accessible or is not acceptable to the person, **and**
- when unenhanced ultrasound scan is inconclusive.

Research recommendations

7.1 Research is recommended on the percentage of unenhanced ultrasound scans that are inconclusive, particularly in people with cirrhosis. Such studies should explicitly define and describe why scans are 'inconclusive'.

7.2 Research is recommended on patient preferences, and their impact on quality of life, for contrast-enhanced ultrasound and other imaging modalities. Ideally such research should compare all appropriate imaging modalities in the same patient group.

4. Rationale

Changes in clinical practice, technology costs or evidence that would lead to a change in the adoption recommendations of the original guidance have not been identified. Evidence directly addressing the research recommendations and supporting the assumptions made in the original guidance was identified (generated by NICE's research facilitation activities). It is therefore proposed that the guidance is placed on the static list.

5. Implications for other guidance producing programmes

No overlaps have been identified.

6. New evidence

The search strategy from the original diagnostics assessment report was re-run on Embase, Medline, Medline in-process & daily update, Cochrane Database of Systematic Reviews, CENTRAL, DARE, DARE/HTA, Web of Science, NHS EED,

HTA Database, HEED, and Science Citation Index. References from January 2011 onwards were reviewed. For some databases, the start date was extended (to pre-date the 2011 search) to ensure that studies with a delay in uploading to databases did not get missed by the search. The following modifications were made to the search strategies

- Conference searching facility from Embase search was omitted
- Inclusion of a new MeSH term which was introduced in 2012 “Neoplasm Micrometastasis”.

Additional searches of clinical trials registries were also carried out and relevant guidance from NICE and other professional bodies was reviewed to determine whether there have been any changes to the diagnostic and care pathways. The company was asked to submit all new literature references relevant to their technology along with updated costs and details of any changes to the technology itself or the market authorisation for use for their technology. Specialist Committee Members for this guidance topic were also consulted and asked to submit any information regarding changes to the technology, the evidence base and clinical practice. The results of the literature search are discussed in the ‘Summary of evidence and implications for review’ section below. See Appendix 2 for further details of ongoing and unpublished studies. In response to the research recommendations in the guidance, NICE facilitated collaborative research to generate evidence addressing the uncertainties which is described in sections 6.4.5 and 6.4.6.

6.1 Technology

6.1.1 SonoVue

Since the publication of diagnostics guidance 5 in August 2012, there have been no new versions of SonoVue developed and there has been a minor change to the cost of SonoVue.

The indications in the marketing authorisation for SonoVue remain unchanged; however, there have been a number of changes to the contraindications for using SonoVue. The contraindications for pregnant women and breast-feeding women have been removed, and for critically ill patients, the following text regarding the contraindication has been downgraded to a special warning:

“*patients with recent acute coronary syndrome or clinically unstable ischaemic cardiac disease, including: evolving or ongoing myocardial infarction, typical angina at rest within last 7 days, significant worsening of cardiac symptoms within last 7 days, recent coronary artery intervention or other factors suggesting clinical*

instability, (for example, recent deterioration of ECG, laboratory or clinical findings), acute cardiac failure, Class III/IV cardiac failure, or severe rhythm disorders"

6.1.2 Ultrasound machinery and SonoVue dose

The company reports that the technical performance of contrast-enhanced ultrasound (CEUS) examinations has significantly improved with more recent ultrasound technologies, resulting in a better diagnostic performance (better penetration, better tissue subtraction) and a lower dose of contrast agent needed. Although the recommended dose for liver imaging with SonoVue remains at 2.4ml (each reconstituted vial contains 4.8ml), healthcare professionals are tending to reduce the dose by between 0.5ml and 1ml per patient in order to obtain optimal images, with more recent ultrasound technology. The exact dose given may vary depending on clinician preference and patient size; larger patients tend to receive higher doses. If the reduced dose is insufficient for imaging, the CEUS examination will be repeated with a higher dose of SonoVue. Once reconstituted, the chemical and physical stability of SonoVue has been demonstrated for 6 hours; however, to avoid microbiological contamination the product should be used immediately. It is therefore not anticipated that cost savings can be made by using a single vial of SonoVue for more than one patient.

6.2 Additional technologies

6.2.1 Quantified contrast-enhanced ultrasound (CEUS)

Contrast-enhanced ultrasound imaging enables a qualitative assessment of complex anatomy which relies on the user's ability to interpret contrast differences and the pattern of enhancement. Recently, there have been developments in CEUS technology to enable quantitative assessment and thus, allow the level of image enhancement by using SonoVue to be quantified, a technique sometimes referred to as dynamic contrast-enhanced ultrasound (DCE-US). The information acquired during the contrast examination, via cine loop feeds, is fed into imaging software, and the relative enhancement curves are measured to give a quantitative value to enhancement. Egger et al., (2012) compared the ability of different contrast-enhanced imaging technologies to diagnose HCC lesions (median diameter approximately 40mm). No statistical difference was found between diagnoses made by qualatative CEUS using SonoVue, DCE-US (dynamic contrast-enhanced ultrasound) using SonoVue and DCE-CT (dynamic contrast-enhanced computed tomography) (for all comparisons $p<0.05$). The External Assessment Centre found little evidence for using quantified CEUS in the literature and no evidence of current use in the NHS.

6.3 Clinical practice

The World Federation for Ultrasound in Medicine & Biology (WFUMB) and the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) guidelines update (Claudon et al., 2013) recommended similar clinical situations to those described in the recommendations in DG5 for the use of CEUS (using SonoVue and other contract agents not available in the UK).

Several American guidelines have recently suggested that CEUS has limited ability in distinguishing between hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC), and/or small sized lesions (≤2cm). The American Association for the Study of Liver Diseases (AASLD) guideline update (Bruix, 2010) removed the recommendation for the use of CEUS for small nodule characterisation, though it is noted that ultrasound contrast agents are not licensed for use in the liver in the United States.

Evidence from semi-structured interviews of UK radiologists and sonographers indicated that in practice, CEUS is being used as a triage step, to reduce the amount of CT and MRI scans, though further standardisation of diagnostic pathways is required for CEUS to be integrated as a replacement or triage step for CT or MRI (Smith, 2014). The use of CEUS as a triage step was included in the DG5 diagnostic pathway. The EAC identified no other changes to diagnostic and care pathways involving CEUS. This was confirmed by the specialist Committee members (SCMs) involved in the development of DG5.

6.4 New studies

The EAC identified 8 studies relevant to this topic with clinical data available. All studies focused on diagnostic test accuracy (DTA) outcomes. Three studies included focal liver lesions (FLLs) from patients undergoing routine surveillance for cirrhotic liver (2 studies only included malignant lesions), 1 study included FLLs in patients with suspected liver metastases, 4 studies included FLLs found either through surveillance or incidentally (1 study only included malignant lesions).

Of the 8 studies, 2 used CECT as a comparator and the remaining 6 studies used both CECT and CEMRI as comparators. Where reported, the contrast agent was iodine-based for CECT and gadolinium for CEMRI. Results from these studies are described below, divided by patient group.

6.4.1 Focal liver lesions detected through cirrhotic liver surveillance

Three studies were identified which report the diagnostic accuracy of CEUS in focal liver lesions detected in patients with cirrhosis. Results from these studies are presented in Table 1. In summary:

- One study reported percentage agreement between CEUS and CECT (59%) and CEUS and CEMRI (81%) and CECT and CEMRI (80%)
- One study reported CEUS sensitivity of 69% (95% CI 59–79%)
- One study reported low sensitivity values for all 3 imaging techniques, CEUS (39.1%), CECT (34.8%) and CEMRI (36%). This study was in small to medium sized lesions (10-20mm). The reference standard in this study was based on histology, interval growth and recurrence after primary treatment and was poorly described which may account for the low sensitivities.

Table 1. Summary of results from studies in patients with FLL's detected during routine surveillance for cirrhosis

Study	Population	Comparator	Sensitivity	Specificity
Furlan et al., (2012)	Lesions (n=96) from patients with cirrhosis (n=91)	CECT and CEMRI	DTA not presented. Agreement between modalities were: CEUS and CECT – 59% CEUS and CEMRI – 81% CECT and CEMRI – 80%	N/A
Manini et al., (2014)	De novo liver nodules (n=119) from patients with cirrhosis (n=98)	CECT and CEMRI	69% (95% CI 59–79%),	100% (95% CI 85–100%)
Quaia et al., (2013)	Nodules (n=46) from patients with cirrhosis (n=42)	CECT and CEMRI	CEUS – 39.1% CECT – 34.8% CEMRI – 63%	N/A – only HCC patients

6.4.2 Focal liver lesions in patients with suspected liver metastases

One study was identified which reported the diagnostic accuracy of CEUS in focal liver lesions detected in patients with suspected liver metastases. Results from the studies are presented in Table 2. In summary:

- One new study reported a sensitivity of 81% in detecting liver metastases compared to 79% to 100% reported from a systematic review in the original DAR.

Table 2. Summary of results from studies in patients with FLL's with suspected liver metastases

Study	Population	Comparator	Sensitivity	Specificity
Rojas Limpe et al., (2014)	Patients with colorectal carcinoma (n=51) with suspected liver metastases	CECT and CEMRI	CEUS – 81% CECT – 82% CEMRI – 91%	N/A

6.4.3 Focal liver lesions found either through surveillance or incidentally

Four studies were identified which reported the diagnostic accuracy of CEUS in focal liver lesions detected incidentally or through surveillance. Results from the studies are presented in Table 3. In summary:

- Three new studies reported sensitivities ranging from 83.3% to 97% in detecting liver malignancies in FLL's detected incidentally or through surveillance compared to a pooled estimate of a 95% sensitivity in the original assessment.

- The 4th study (Wang et al., 2014) reported numbers misdiagnosed or not identified by CEUS (6/38).

Table 3. Summary of results from studies in patients with FLL's detected incidentally or through surveillance

Study	Population	Comparator	Sensitivity	Specificity
Egger et al., (2012)	Lesions (n=19) from HCC patients with cirrhosis (n=19)	CECT	CEUS – 84% CECT – 100%	N/A

Study	Population	Comparator	Sensitivity	Specificity
Ryu et al., (2014)	Lesions (n=50) from HCC patients with cirrhosis (n=19)	CECT CEMRI	CEUS – 83.3% CECT – 95% CEMRI – 94.6%	CEUS – 87.5% CECT – 87.5% CEMRI – 83.3%
Sawatzki et al., (2013)	Lesions (n=112)	CECT CEMRI	CEUS – 96-97%	CEUS – 83-90%
Wang et al., (2014)	Lesions (n=38) patients (n=29)	CECT	N/A	N/A

6.4.4 Identification of diagnostic pathways

One study (Smith et al., 2014) used a series of semi-structured interviews with seven UK radiologists and sonographers to identify the diagnostic pathways followed by patients with potential liver lesions. The study found large reported variations in clinical practice. Clinicians suggested the patient preference would be for CEUS, because of fewer side effects and less anxiety. Anxiety was reduced because CEUS results are often provided at the time of scan, particularly if benign. The process is seen as less formal as the clinician is in the room with the patient during the scan and claustrophobic feelings induced by being inside a body-scanner do not occur. The interviews indicated that, in practice, CEUS is being used as a triage step to reduce the number of CT or MRI scans. The study's findings suggested that further standardisation of the diagnostic pathways for the characterisation of focal liver lesions is required to introduce CEUS as a replacement or triage step for CT or MRI.

6.4.5 Patient preferences for scanning modalities

One study (Whitty, 2015) investigated patient preferences for scanning modalities used in diagnosing focal liver lesions using a discrete choice experiment. A sample of the general population was selected to represent, as closely as possible, the demographics of patients with liver conditions in the UK. This did not exactly match the research recommendation which stated that research should "compare all appropriate imaging modalities in the same patient group".

The study found that patients would on average prefer CEUS over CEMRI/CECT, because of the shorter waiting times, the ultrasound scanning process (handheld scanner as opposed to body scanner) and the lack of side effects.

Despite the current limited patient choice of imaging technologies, patient preferences may help facilitate clinician decisions and patient-clinician interaction. However, the substantial variation observed in respondent preferences, highlights the need to discuss the comparative advantages of different imaging technologies with individual patients if a choice of different technologies is available

6.4.6 Proportion of inconclusive US scans

In the original diagnostics assessment for DG5 there was uncertainty around the figure used in the model for the percentage of inconclusive unenhanced ultrasound scans (43%).Willits et al., (2015) performed a retrospective review of Radiology Information System records of patients who had a general ultrasound examination of the abdomen or a specific scan of the liver. The study aimed to estimate the probability that an unenhanced ultrasound scan report mentioned an uncharacterized focal liver lesion, given that one or more focal liver lesions were detected during the scan. NICE defined an inconclusive scan as 'an unenhanced ultrasound scan in which a FLL is detected, but not characterised'.

When cycts were excluded from the analysis the study reported that around 28% of scans of livers with identified FLLs in the GP cohort and around 43% in the outpatient cohort were described as inconclusive by the operator. Subgroup analysis showed cirrhotic livers were more than twice as likely (odds ratio 2.4) to show an inconclusive scan compared to non-cirrhotic livers. This is likely to be because cirrhotic livers have features which cause distortion of ultrasound attenuation. The authors suggested that these groups will often require additional imaging modality to provide a diagnosis and CEUS is likely to be a useful option for this.

7. Summary of new evidence and implications for review

Since the publication of diagnostics guidance 5, no significant changes have occurred to the SonoVue product. A potential alternative technology was identified, Quantified CEUS, but there is little evidence for its use in the literature and no evidence of current use in the NHS.

A number of international guidelines have been updated, but none have an impact on the clinical pathway in the UK. A large amount of variation in the clinical pathway in the UK was reported in 1 study however (Smith et al, 2014).

All new clinical effectiveness studies identified were diagnostic accuracy studies. A number of studies used different reference standard than those defined in the original scope. Of the studies, the majority reported sensitivity and specificity

estimates which are broadly in line with those reported in the studies from the original review. Given that the new accuracy data are comparable to those in the original review, they are therefore unlikely to have any material effect on the existing guidance recommendations.

A number of studies have been published that are relevant to the research recommendations in diagnostics guidance 5. Willits et al., (2015) relates to research recommendation 7.1, and Smith et al., (2014) and Whitty, (2015) relate to research recommendation 7.2. Willits et al., (2015) reported the proportion of ultrasound scans that were inconclusive, as there was considerable uncertainty around the figure in the original DAR (43%) which could greatly affect the cost-effectiveness of SonoVue. When cysts were excluded from the analysis the study reported that around 28% of scans (GP cohort) and around 43% (outpatient cohort) were described as inconclusive. Subgroup analysis showed cirrhotic livers were more than twice as likely (odds ratio 2.4) to show an inconclusive scan compared to non-cirrhotic livers. This study demonstrates that the figure of 43% inconclusive ultrasound scans used in the diagnostics assessment for DG5 was a reasonable estimate and supports the assumptions made in the cost-effectiveness analyses. Smith et al., (2014) used structured interviews to investigate the patient experience of the diagnostic pathway for people with liver lesions. It reported considerable variation in practice and clinicians suggested a patient preference for CEUS over other imaging modalities. The second study, Whitty et al, (2015), explored patient preferences using a discrete choice experiment. It reported that given a choice, patients would prefer CEUS over CECT and CEMRI.

There have been minimal changes to the costs of SonoVue and these would not impact its cost-effectiveness.

In conclusion, the evidence base and clinical environment has not changed to an extent that is likely to have a material effect on the adoption recommendations in the existing guidance; it is therefore suggested that the guidance is transferred to the static list. The evidence base on the uncertainties described in the research recommendations was increased as a result of collaborative research facilitated by NICE, and confirmed the assumptions made which led to the adoption recommendations. It is proposed to signpost users to the relevant evidence from the guidance landing page.

8. Implementation

No relevant Implementation data were found, however, a large amount of variation in the clinical pathway in the UK was reported in 1 study (Smith et al, 2014).

9. Equality issues

At the time of the assessment of the original guidance the Committee considered possible equality impacts. It noted that although obesity may be a general barrier to the use of ultrasound in some people, its impact on image quality on an individual basis is unpredictable. The Committee concluded that the recommendations would be unlikely to disadvantage those with obesity or protected groups.

GE paper sign off: Carla Deakin, Associate Director, 1 October 2015

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Appendix 1 – explanation of options

If the published Diagnostics Guidance needs updating NICE must select one of the options in the table below:

Options	**Consequence**	**Selected – 'Yes/No'**
Standard update of the guidance	A standard update of the Diagnostics Guidance will be planned into NICE's work programme.	No
Accelerated update of the guidance	An accelerated update of the Diagnostics Guidance will be planned into NICE's work programme. Accelerated updates are only undertaken in circumstances where the new evidence is likely to result in minimal changes to the decision problem, and the subsequent assessment will require less time to complete than a standard update or assessment.	No
Update of the guidance within another piece of NICE guidance	The guidance is updated according to the processes and timetable of that programme.	No

If the published Diagnostics Guidance does not need updating NICE must select one of the options in the table below:

Options	**Consequences**	**Selected – 'Yes/No'**
Transfer the guidance to the 'static guidance list'	The guidance remains valid and is designated as static guidance. Literature searches are carried out every 5 years to check whether any of the Diagnostics Guidance on the static list should be flagged for review.	Yes
Produce a technical supplement	A technical supplement describing newer versions of the technologies is planned into NICE's work programme.	No
Defer the decision to review the guidance to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
Withdraw the guidance	The Diagnostics Guidance is no longer valid and is withdrawn.	No

Appendix 2 – supporting information

Relevant Institute work

As focal liver lesions 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) there are many pieces of NICE guidance which could be considered relevant. The most relevant NICE guidance are listed below in order of publication date:

Published

Suspected cancer: recognition and referral (2015) NICE guideline 12

Hepatitis B (chronic) (2013) NICE guideline CG165

Alcohol-use disorders: Diagnosis and clinical management of alcohol-related physical complications (2010) NICE guideline CG100

Colorectal cancer (2011) NICE guideline CG131

Alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence (2011) NICE guideline CG115

Metastatic malignant disease of unknown primary origin (2010) NICE guideline CG104

Bladder cancer: diagnosis and management (2015) NICE guideline 2

Advanced breast cancer (update): Diagnosis and treatment (2009) NICE guideline CG81

Early and locally advanced breast cancer: Diagnosis and treatment (2009) NICE guideline CG80

Lung cancer: The diagnosis and treatment of lung cancer (2011) NICE guideline CG121

Ovarian cancer: The recognition and initial management of ovarian cancer (2011) NICE guideline CG122

Prostate cancer: diagnosis and treatment (2014) NICE guideline CG175

Melanoma: assessment and management (2015) NICE guideline 14

In progress

Liver disease (non-alcoholic fatty [NAFLD]). NICE guideline. Publication expected July 2016

Assessment and Management of Cirrhosis. NICE guideline. Publication expected June 2016

Referred - QSs and CGs

None identified

Suspended/terminated

None identified

Details of new technologies

Device (manufacturer)	Details (phase of development, expected launch date,)
None found	N/A

Registered and unpublished trials

Trial name and registration number	Details
None Found	N/A

Additional information

None found.

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