The following is a list of studies excluded at the full-paper screening stage of the review, along with the primary reasons for their exclusion. For simplicity, studies were assigned a single reason for exclusion; however, many studies failed more than one inclusion criterion. Studies listed in submissions from the manufacturer of SonoVue are labelled 'M'. Studies provided in submissions from manufacturers that related solely to clinical applications outside the scope of the current assessment (i.e. anatomy other than the liver) are not listed.

The reasons for study exclusion are coded as follows:

Population: The study did not consider characterisation of FLLs (incidentally detected by unenhanced US or detected by surveillance US in patients with cirrhosis), detection of liver metastases in patients with known primary tumours or assessment of response to treatment/recurrence in patients with liver cancer.

Index test: The study did not assess the effectiveness of CEUS using SonoVue.

Comparator: The study did not compare the effectiveness of CEUS using SonoVue with that of CEMRI and/or CECT.

Reference standard: For test accuracy studies, the study did not use histology following biopsy or surgical excision or clinical/radiological follow-up for a minimum of 6 months for patients who had a negative index test result. For studies on the characterisation of FLLs only (suspected HCC), the EASL/AASLD non-invasive diagnostic criteria (two concordant imaging test results) were also considered an acceptable reference standard.

Outcomes: The study did not report any of the outcomes specified in *Chapter 3*, *Inclusion and exclusion criteria* or, for DTA studies, insufficient data were reported to allow the construction of 2×2 contingency tables (numbers of true-positive, false-negative, false-positive and true-negative test results).

Study design: The study design was not one of those specified in *Chapter 3, Inclusion and exclusion criteria* or the study included < 10 participants in the relevant patient groups.

Duplicate: The study was a duplicate publication.

Authors contacted: The study did not report sufficient information for inclusion assessment and authors were contacted for additional information but no response was received.

- 1. Albrecht T, Hohmann J, Oldenburg A, Skrok J, Wolf KJ. Detection and characterisation of liver metastases. *Eur Radiol* 2004;**14**:P25–33. (**Reference standard**)
- 2. Andreano A, Meneghel E, Bovo G, Ippolito D, Salvioni A, Filice C, *et al.* Contrast-enhanced ultrasound in planning thermal ablation of liver metastases: should the hypervascular halo be included in the ablation volume? *J Ultrasound* 2010:**13**:158–63. (**Outcomes**)
- 3. Aube C, Lebigot J. [Contrast ultrasonography: value in diagnosis and characterisation of hepatic tumors.] *Gastroenterol Clin Biol* 2003;**27**:B63–70. (**Study design**)
- 4. Banghui P, Chiche L, Alkofer B, Salame E, Bouvard N, Lepennec V. Imaging modalities before liver resection for colorectal metastases: which, when and how many? Paper presented at the 9th World

- Congress of the International Hepato-Pancreato-Biliary Association, Buenos Aires, Argentina, 18–22 April 2010. *HPB* 2010;**12**(Suppl. 1):100. (**Authors contacted**)
- 5. Bartolotta TV, Taibbi A, Galia M, Runza G, Matranga D, Midiri M, *et al.* Characterization of hypoechoic focal hepatic lesions in patients with fatty liver: diagnostic performance and confidence of contrast-enhanced ultrasound. *Eur Radiol* 2007;**17**:650–61. (**Comparator**)
- 6. Bartolotta TV, Sandonato L, Taibbi A, Latteri S, Soresi M, Lombardo G, *et al.* [Focal liver lesions: clinical usefulness of contrast-enhanced ultrasound in the selection of surgical patients.] *Chir Ital* 2009;**61**:295–307. (**Comparator**)
- 7. Bartolotta TV, Taibbi A, Midiri M, La Grutta L, De Maria M, Lagalla R. Characterisation of focal liver lesions undetermined at grey-scale US: contrast-enhanced US versus 64-row MDCT and MRI with liver-specific contrast agent. *Radiol Med* 2010;**115**:714–31. (**Reference standard**)
- 8. Bartolotta TV, Taibbi A, Midiri M, Matranga D, Solbiati L, Lagalla R. Indeterminate focal liver lesions incidentally discovered at gray-scale US: role of contrast-enhanced sonography. *Invest Radiol* 2011;**46**:106–15. (**Reference standard**)
- 9. Bauditz J, Schade T, Wermke W. [Sonographic diagnosis of hilar cholangiocarcinomas by the use of contrast agents.] *Ultraschall Med* 2007;**28**:161–7. (**Index test**)
- 10. Bauditz J, Quinkler M, Beyersdorff D, Wermke W. Improved detection of hepatic metastases of adrenocortical cancer by contrast-enhanced ultrasound. *Oncol Rep* 2008;**19**:1135–9. (**Index test**)
- 11. Bauditz J, Zeitz M, Wermke W. Malignant liver tumors: monitoring of local ablation by contrast enhanced ultrasound and computed tomography. Paper presented at the 61st Annual Meeting of the American Association for the Study of Liver Diseases: the Liver Meeting, Boston, MA, 29 October–2 November 2010. *Hepatology* 2010;**52**:963A. (**Outcomes**)
- 12. Beaton C, Cochlin D, Kumar N. Contrast enhanced ultrasound should be the initial radiological investigation to characterise focal liver lesions. *Eur J Surg Oncol* 2010;**36**:43–6. (**Reference standard, M**)
- 13. Bernardini I, Mucciarini C, Razzini G, Guerzoni R, Blanzieri S, Bellentani S, *et al.* The role of contrast-enhanced ultrasound in detection of liver metastases from colorectal cancer: 2 years update results. Paper presented at the 35th ESMO Congress, Milan, Italy, 8–12 October 2010. *Ann Oncol* 2010;**21**:viii215. (**Population**)
- 14. Bleuzen A, Huang C, Olar M, Tchuenbou J, Tranquart F. Diagnostic accuracy of contrast-enhanced ultrasound in focal lesions of the liver using cadence contrast pulse sequencing. *Ultraschall Med* 2006;**27**:40–8. (**Reference standard**)
- 15. Cantisani V, Ricci P, Erturk M, Pagliara E, Drudi F, Calliada F, *et al.* Detection of hepatic metastases from colorectal cancer: prospective evaluation of gray scale US versus SonoVue low mechanical index real time-enhanced US as compared with multidetector-CT or Gd-BOPTA-MRI. *Ultraschall Med* 2010;**31**:500–5. (**Reference standard, M**)
- 16. Caturelli E, Ghittoni G, Roselli P, Anti M. Sensitivity rates in characterizing hepatocellular carcinomas. AJR Am J Roentgenol 2005;**185**:1079–80. (**Study design**)
- 17. Chami L, Lassau N, Malka D, Ducreux M, Bidault S, Roche A, *et al.* Benefits of contrast-enhanced sonography for the detection of liver lesions: comparison with histologic findings. *AJR Am J Roentgenol* 2008;**190**:683–90. (**Comparator**)
- 18. Chen LD, Xu HX, Xie XY, Lu MD, Xu ZF, Liu GJ, *et al.* Enhancement patterns of intrahepatic cholangiocarcinoma: comparison between contrast-enhanced ultrasound and contrast-enhanced CT. *Br J Radiol* 2008;**81**:881–9. (**Population**)

- 19. Chen MH, Dai Y, Yan K, Fan ZH, Yin SS, Yang W, et al. The role of contrast-enhanced ultrasound on the diagnosis of small hepatocellular carcinoma (≤3 cm) in patients with cirrhosis. *Hepatol Res* 2006;**35**:281–8. (**Population**)
- 20. Chen MH, Yang W, Yan K, Dai Y, Wu W, Fan ZH, et al. The role of contrast-enhanced ultrasound in planning treatment protocols for hepatocellular carcinoma before radiofrequency ablation. *Clin Radiol* 2007;**62**:752–60. (**Duplicate**)
- 21. Chiesara F, Baccini F, Merola E, Rinzivillo M, Panzuto F, Capurso G, et al. Contrast enhanced ultrasonography (CEUS) and quantitative perfusion analysis in the assessment of neuroendocrine liver metastases. *Gastroenterology* 2011;**140**:S875. (**Population**)
- 22. Cijevschi Prelipcean C, Pintilei I, Nedelciuc O, Chirita D, Dranga M, Mihai C. Liver tumors: the vascularisation pattern assessed by contrast-enhanced ultrasound. Paper presented at the 21st Conference of the Asian Pacific Association for the Study of the Liver (APASL), Bangkok, Thailand, 17–20 February 2011. *Hepatol Int* 2011;**5**:480–1. (**Reference standard**)
- 23. Cokkinos DD, Blomley MJ, Harvey CJ, Lim A, Cunningham C, Cosgrove DO. Can contrast-enhanced ultrasonography characterize focal liver lesions and differentiate between benign and malignant, thus providing a one-stop imaging service for patients? *J Ultrasound* 2007;**10**:186–93. (**Outcomes**)
- 24. Dai Y, Chen MH, Yin SS, Yan K, Fan ZH, Wu W, *et al.* Focal liver lesions: can SonoVue-enhanced ultrasound be used to differentiate malignant from benign lesions? *Invest Radiol* 2007;**42**:596–603. (**Comparator**)
- 25. De Sanctis R, Quadrini S, Tedeschi M, Stumbo L, Gori B, Del Signore E, *et al.* Early response evaluation of antiangiogenic therapy: use of contrast-enhanced ultrasonography (CE-US) in hepatocellular carcinoma. *Ann Oncol* 2009;**20**:92. (**Study design**)
- 26. Dietrich CF, Kratzer W, Strobel D, Danse E, Fessl R, Bunk A, et al. Assessment of metastatic liver disease in patients with primary extrahepatic tumors by contrast-enhanced sonography versus CT & MRI. World J Gastroenterol 2006;**12**:1699–705. (**Reference standard**)
- 27. Ding H, Wang WP, Huang BJ, Wei RX, He NA, Qi Q, *et al.* Imaging of focal liver lesions: low-mechanical-index real-time ultrasonography with SonoVue. *J Ultrasound Med* 2005;**24**:285–97. (**Comparator**)
- 28. D'Onofrio M, Rozzanigo U, Caffarri S, Zogno A, Procacci C. Contrast-enhanced US of hepatocellular carcinoma. *Radiol Med* 2004;**107**:293–303. (**Population**)
- 29. D'Onofrio M, Martone E, Faccioli N, Zamboni G, Malago R, Mucelli RP. Focal liver lesions: sinusoidal phase of CEUS. *Abdom Imaging* 2006;**31**:529–36. (**Reference standard**)
- 30. D'Onofrio M, Faccioli N, Zamboni G, Malago R, Caffarri S, Fattovich G, *et al.* Focal liver lesions in cirrhosis: value of contrast-enhanced ultrasonography compared with Doppler ultrasound and alpha-fetoprotein levels. *Radiol Med* 2008;**113**:978–91. (**Reference standard**)
- 31. Dumitru E, Dumitru IM, Alexandrescu L, Rugina S. Contrast enhanced ultrasonography (CEUS) helps characterization of focal liver lesions in HIV positive patients. Paper presented at the 21st Conference of the Asian Pacific Association for the Study of the Liver (APASL), Bangkok, Thailand, 17–20 February 2011. *Hepatol Int* 2011;5:482. (Comparator)
- 32. Ercolani G, Zanello M, Rojas L, Ravaioli M, Cescon M, Gaudio MD, *et al.* A prospective comparative evaluation of pre-and intraoperative imaging techniques in chemo-pretreated or not pretreated patients with colorectal liver metastases. Paper presented at the 9th Congress of the European-African HPBA (E-AHPBA), Cape Town, South Africa, 12–16 April 2011. *HPB* 2011;**13**:25–6. (**Authors contacted**)

- 33. Fan ZH, Chen MH, Dai Y, Wang YB, Yan K, Wu W, et al. Evaluation of primary malignancies of the liver using contrast-enhanced sonography: correlation with pathology. AJR Am J Roentgenol 2006;**186**:1512–19. (**Outcomes**)
- 34. Fracanzani AL, Maraschi A, Burdick L, Bertelli C, Fatta E, Bonelli N, *et al.* Contrast-enhanced ultrasonography (CEUS) and spiral computed tomography (CT) in the assessment of efficacy of percutaneous ablation treatments of hepatocellular carcinoma in cirrhosis. *J Hepatol* 2008;**48**:S145. (**Reference standard**)
- 35. Frieser M, Kiesel J, Lindner A, Bernatik T, Haensler JM, Janka R, *et al.* Efficacy of contrast-enhanced US versus CT or MRI for the therapeutic control of percutaneous radio-frequency ablation in the case of hepatic malignancies. *Ultraschall Med* 2011;**32**:148–53. (**Reference standard**)
- 36. Gaiani S, Celli N, Piscaglia F, Cecilioni L, Losinno F, Giangregorio F, *et al.* Usefulness of contrast-enhanced perfusional sonography in the assessment of hepatocellular carcinoma hypervascular at spiral computed tomography. *J Hepatol* 2004;**41**:421–6. (**Outcomes**)
- 37. Galassi M, Granito A, Piscaglia F, Borghi A, Lucidi V, Golfieri R, et al. Impact of gadoxetic acid (Gd-EOB-DTPA)-enhanced MR on the non-invasive diagnosis of small hepatocellular carcinoma. Paper presented at the Italian Association for the Study of the Liver (AISF) Annual Meeting, Rome, Italy, 24–25 February 2011. *Dig Liver Dis* 2011;**43**:S82. (**Outcomes**)
- 38. Gallotti A, D'Onofrio M, Ruzzenente A, Martone E, De Robertis R, Guglielmi A, et al. Contrastenhanced ultrasonography (CEUS) immediately after percutaneous ablation of hepatocellular carcinoma. *Radiol Med* 2009;**114**:1094–105. (**Reference standard**)
- 39. Gheorghe L, Carabelea A, Vadan R, Becheanu G. QUIZ HQ 54. Contrast-enhanced ultrasound (CEUS) for the detection and assessment of treatment efficacy in focal liver lesions. *J Gastrointestin Liver Dis* 2009;**18**:473–4. (**Study design**)
- 40. Giangregorio F, Comparato G, Marinone MG, Di Stasi M, Sbolli G, Aragona G, et al. Imaging detection of new HCCs in cirrhotic patients treated with different techniques: comparison of conventional US, spiral CT, and 3-dimensional contrast-enhanced US with the navigator technique (Nav 3D CEUS). J Ultrasound 2009;12:12–21. (Reference standard)
- 41. Giangregorio F, Aragona G, Marinone G, Comparato G, Fanigliulo L, Di Stasi M, *et al.* Contrastenhanced US (CEUS) in early evaluation of non-surgical treatment of HCC can change the patient's follow-up and survival. Paper presented at the 45th Annual Meeting of the European Association for the Study of the Liver (EASL) International Liver Congress, Vienna, Austria, 14–18 April 2010. *J Hepatol* 2010;**52**:S90–1. (**Outcomes**)
- 42. Giangregorio F, Marinone M, Aragona G, Comparato G, Fanigliulo L, Sbolli G, et al. Echographic detection of hepatocellular carcinoma (HCC) during followup in cirrhotic patients with previous HCC: comparison among US, CT and a new panoramic 3-dimensional contrast-enhanced US with navigator system (3-D NAV CEUS). Paper presented at the 16th National Congress of Digestive Diseases Italian Federation of Societies of Digestive Diseases (FISMAD), Verona, Italy, 6–9 March 2010. *Dig Liver Dis* 2010;**42**:S77. (**Reference standard**)
- 43. Giangregorio F. Contrast-enhanced ultrasound (CEUS) for echographic detection of hepato cellular carcinoma in cirrhotic patients previously treated with multiple techniques: comparison of conventional US, spiral CT and 3-dimensional CEUS with navigator technique (3DNav CEUS). *Cancers* 2011;**3**:1763–76. (**Reference standard**)
- 44. Giesel FL, Delorme S, Sibbel R, Kauczor HU, Krix M. [Contrast-enhanced ultrasound for the characterization of incidental liver lesions an economical evaluation in comparison with multiphase computed tomography.] *Ultraschall Med* 2009;**30**:259–68. (**Study design, M**)
- 45. Giorgio A, Di Sarno A, Nunzia F, De Stefano G, Scognamiglio U, Coppola C, *et al.* Value of contrast enhanced ultrasound in the characterization of small nodular lesions in cirrhotic livers. Paper

- presented at the 45th Annual Meeting of the European Association for the Study of the Liver (EASL) International Liver Congress, Vienna, Austria, 14–18 April 2010. *J Hepatol* 2010;**52**:S219. (**Comparator**)
- 46. Giorgio A, Di Sarno A, Farella N, De Stefano G, Scognamiglio U, Coppola C, et al. Small nodular lesions in cirrhotic livers: characterization with contrast enhanced ultrasound. Paper presented at the 43rd Annual Meeting of the Italian Association for the Study of the Liver (AISF), Rome; Italy, 25–26 February 2010. *Dig Liver Dis* 2010;**42**:S23–4. (**Comparator**)
- 47. Giorgio A. Diagnostic algorithm of hepatocellular carcinoma on cirrhosis: CEUS or no CEUS, that is the problem. *Dig Liver Dis* 2011;**43**:499. (**Study design**)
- 48. Gomez Rodriguez RA, Artaza Varasa T, Gonzalez de Frutos C, Sanchez Ruano JJ, Repiso Ortega A, Perez-Grueso Macias MJ, *et al.* [Value of contrast-enhanced ultrasound in the diagnosis of hepatocarcinoma in focal lesions detected in patients with liver disease.] *Gastroenterol Hepatol* 2007;**30**:381–6. (**Reference standard**)
- 49. Guo J, Liang Y, Yan JY, Liu Y. [Clinical value of real time contrast-enhanced ultrasound in differentiating benign and malignant liver lesions.] *Chin J Med Imaging Technol* 2008;**24**:1434–7. (**Comparator**)
- 50. Hanle MM, Thiel R, Saur G, Mason RA, Pauls S, Kratzer W. Screening for liver metastases in women with mammary carcinoma: comparison of contrast-enhanced ultrasound and magnetic resonance imaging. *Clin Imaging* 2011;**35**:366–70. (**Outcomes**)
- 51. Hohmann J, Skrok J, Puls R, Albrecht T. [Characterization of focal liver lesions with contrast-enhanced low MI real time ultrasound and SonoVue.] *Rofo* 2003;**175**:835–43. (**Reference standard**)
- 52. Iavarone M, Sangiovanni A, Forzenigo LV, Massironi S, Fraquelli M, Aghemo A, *et al.* Diagnosis of hepatocellular carcinoma in cirrhosis by dynamic contrast imaging: the importance of tumor cell differentiation. *Hepatology* 2010;**52**:1723–30. (**Outcomes**)
- 53. Ignee A, Livraghi T, Tranquart F, Bolondi L, Dietrich CF, Albrecht T. Revised detection of liver lesions by ultrasound-contrast medium of the second generation, compared to conventional sonography. *Endosk Heut*e 2009;**22**:105–9. (**Reference standard**)
- 54. Jang HJ, Kim TK, Wilson SR. Small nodules (1–2 cm) in liver cirrhosis: characterization with contrast-enhanced ultrasound. *Eur J Radiol* 2009;**72**:418–24. (**Index test**)
- 55. Janica JR, Lebkowska U, Ustymowicz A, Augustynowicz A, Kamocki Z, Werel D, *et al.* Contrastenhanced ultrasonography in diagnosing liver metastases. *Med Sci Monit* 2007;**13**(Suppl. 1):111–15. (**Reference standard**)
- 56. Jung EM, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, *et al.* Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: a prospective controlled two-center study. *World J Gastroenterol* 2007;**13**:6356–64. (**Comparator**)
- 57. Jung EM, Schreyer AG, Schacherer D, Menzel C, Farkas S, Loss M, et al. New real-time image fusion technique for characterization of tumor vascularisation and tumor perfusion of liver tumors with contrast-enhanced ultrasound, spiral CT or MRI: first results. *Clin Hemorheol Microcirc* 2009;**43**:57–69. (Index test)
- 58. Kisaka Y, Hirooka M, Kumagi T, Uehara T, Hiasa Y, Kumano S, *et al.* Usefulness of contrast-enhanced ultrasonography with abdominal virtual ultrasonography in assessing therapeutic response in hepatocellular carcinoma treated with radiofrequency ablation. *Liver Int* 2006;**26**:1241–7. (**Index test**)

- 59. Kobayashi Y, Nakamura S, Toshikuni N, Tanaka H, Matsumoto E, Ohnishi H, *et al.* Contrast-enhanced dynamic ultrasonography (CE-US) differentiates hepatocellular carcinoma from dysplastic nodules: correlation with histological grading. *Gastroenterology* 2004;**126**:A494. (Index test)
- Kono Y, Alton K, Rose SC, Hassanein TI, Mattrey RF. The ability of contrast-enhanced ultrasound (CEUS) to predict final outcome within 1 week after transarterial chemoembolization (TACE) for hepatocellular carcinoma (HCC). Hepatology 2004;40:706–7A. (Index test)
- 61. Kono Y, Lucidarme O, Choi SH, Rose SC, Hassanein TI, Alpert E, *et al.* Contrast-enhanced ultrasound as a predictor of treatment efficacy within 2 weeks after transarterial chemoembolization of hepatocellular carcinoma. *J Vasc Interv Radiol* 2007;**18**:57–65. (**Index test**)
- 62. Konopke R, Kersting S, Saeger HD, Bunk A. [Detection of liver lesions by contrast-enhanced ultrasound: comparison to intraoperative findings.] *Ultraschall Med Suppl* 2005;**26**:107–13. (**Comparator**)
- 63. Konopke R, Kersting S, Bergert H, Bloomenthal A, Gastmeier J, Saeger HD, et al. Contrast-enhanced ultrasonography to detect liver metastases. *Int J Colorectal Dis* 2007;**22**:201–7. (**Comparator**)
- 64. Konopke R, Bunk A, Kersting S. Contrast-enhanced ultrasonography in patients with colorectal liver metastases after chemotherapy. *Ultraschall Med Suppl* 2008;**29**:S203–9. (**Comparator**)
- 65. Laghi F, Catalano O, Maresca M, Sandomenico F, Siani A. Indeterminate, subcentimetric focal liver lesions in cancer patients: additional role of contrast-enhanced ultrasound. *Ultraschall Med* 2010;**31**:283–8. (**Reference standard**)
- 66. Lanka B, Jang HJ, Kim TK, Burns PN, Wilson SR. Impact of contrast-enhanced ultrasonography in a tertiary clinical practice. *J Ultrasound Med* 2007;**26**:1703–14. (**Study design**)
- 67. Larsen LPS, Rosenkilde M, Christensen H, Bang N, Bolvig L, Christiansen T, et al. The value of contrast enhanced ultrasonography in detection of liver metastases from colorectal cancer: a prospective double-blinded study. Eur J Radiol 2007;62:302–7. (Reference standard)
- 68. Larsen LPS, Rosenkilde M, Christensen H, Bang N, Bolvig L, Christiansen T, *et al.* Can contrast-enhanced ultrasonography replace multidetector-computed tomography in the detection of liver metastases from colorectal cancer? *Eur J Radiol* 2009;**69**:308–13. (**Reference standard**)
- 69. Lassau N, Lacroix J, Taieb S, Aziza R, Vilgrain V, Cuinet M, et al. French, multicentric, prospective study of dynamic contrast-enhanced ultrasound (DCE-US) for the evaluation of antiangiogenic treatments in 400 patients. *Paper presented at the* 2010 Annual Meeting of the American Society of Clinical Oncology (ASCO), Chicago, IL, 4–9 June 2010. *J Clin Oncol* 2010;**28**. (**Outcomes**)
- 70. Leen E. The role of contrast-enhanced ultrasound in the characterisation of focal liver lesions. *Eur Radiol* 2001;**11**:E27–34. (**Study design**)
- 71. Leen E, Ceccotti P, Kalogeropoulou C, Angerson WJ, Moug SJ, Horgan PG. Prospective multicenter trial evaluating a novel method of characterizing focal liver lesions using contrast-enhanced sonography. *AJR Am J Roentgenol* 2006;**186**:1551–9. (**Reference standard, M**)
- 72. Lemke AJ, Chopra SS, Hengst SA, Brinkmann MJ, Steinmuller T, Felix R. [Characterization of hepatic tumors with contrast-enhanced ultrasound and digital grey-scale analysis.] *Tumor Diagn Ther* 2004;**25**:276–85. (**Reference standard**)
- 73. Lemke AJ, Chopra SS, Hengst SA, Brinkmann MJ, Steinmuller T, Felix R. [Characterization of hepatic tumors with contrast-enhanced ultrasound and digital grey-scale analysis.] *Rofo* 2004;**176**:1607–16. (**Duplicate**)
- 74. Lencioni R, Cioni D, Crocetti L, Donati F, Franchini C, Giusti S, *et al.* Ultrasound imaging of focal liver lesions with a second-generation contrast agent. *Acad Radiol* 2002;**9**:S371–4. (**Reference standard**)

- 75. Leoni S, Piscaglia F, Granito A, Salvatore V, Cappelli A, Lucidi V, *et al.* Diagnostic accuracy of different patterns of contrast enhanced ultrasound in characterization of new nodules in liver cirrhosis with and without history of previous hepatocellular carcinoma. Paper presented at the Italian Association for the Study of the Liver (AISF) Annual Meeting, Rome, Italy, 24–25 February 2011. *Dig Liver Dis* 2011;**43**:S73–4. (**Reference standard**)
- 76. Li R, Guo YL, He Y, Zhang XH, Ding J, Chen ZH. [Real-time pulse-inversion sonography using contrast agent: differentiation between benign and malignant focal liver lesions.] *Chin J Med Imaging Technol* 2006;**22**:186–8. (**Comparator**)
- 77. Lin L, Gui YZ, Liang Z, Chen J, Lu Q, Min M. [Contrast-enhanced ultrasound in assessment of the therapeutic efficacy of high intensity focused ultrasound in treating hepatocellular carcinoma.] *World Chin J Dig* 2009;**17**:1879–82. (**Comparator**)
- 78. Liu GJ, Xu HX, Xie XY, Xu ZF, Zheng YL, Liang JY, et al. Does the echogenicity of focal liver lesions on baseline gray-scale ultrasound interfere with the diagnostic performance of contrast-enhanced ultrasound? Eur Radiol 2009;**19**:1214–22. (**Reference standard**)
- 79. Liu GJ, Wang W, Xie XY, Xu HX, Xu ZF, Zheng YL, et al. Real-time contrast-enhanced ultrasound imaging of focal liver lesions in fatty liver. Clin Imaging 2010;34:211–21. (Comparator)
- 80. Liu LP, Dong BW, Yu XL, Liang P, Zhang DK, An LC. Focal hypoechoic tumors of fatty liver: characterization of conventional and contrast-enhanced ultrasonography. *J Ultrasound Med* 2009;**28**:1133–42. (**Outcomes**)
- 81. Loria F, Loria G, Crea G, Basile S, Frosina L, Cantoni S. Comparison of unenhanced and contrast-enhanced ultrasonography in the diagnosis of focal liver lesions. Abstract MO-114. Paper presented at the 9th World Congress of the International Hepato-Pancreato-Biliary Association, Buenos Aires, Argentina, 18–22 April 2010. *HPB* 2010;**12**:100–1. (**Outcomes**)
- 82. Loria F, Loria G, Frosina L, Crea G, Basile S, Cantoni S. Metastatic disease of the liver: comparison of CEUS vs. US and CT in the evaluation of diagnostic performance and confidence. Paper presented at the 9th World Congress of the International Hepato-Pancreato-Biliary Association, Buenos Aires, Argentina, 18–22 April 2010. *HPB* 2010;**12**:269. (**Authors contacted**)
- 83. Lu MD, Yu XI, Li AH, Jiang TA, Chen MH, Zhao BZ, *et al.* Comparison of contrast enhanced ultrasound and contrast enhanced CT or MRI in monitoring percutaneous thermal ablation procedure in patients with hepatocellular carcinoma: a multi-center study in China. *Ultrasound Med Biol* 2007;**33**:1736–49. (**Reference standard**)
- 84. Marcus CD, Brixi-Benmansour H, Job L, Ladam-Marcus V, Lagarde S, Cadiot G. Detection and characterization of hepatic metastases from gastrointestinal endocrine tumor with contrast-specific US modes and a sulfur hexafluoride-filled microbubble contrast agent. *Gastroenterology* 2006;**130**:A193–4. (**Outcomes**)
- 85. Martin-Algibez A, Fernandez-Vazquez I, Lopez-Martinez C, Gallego-Gallego MS, San Roman R, Mnoz-Codocero C, et al. Evaluation of local recurrence after treatment for hepatocellular carcinoma by contrast-enhanced ultrasonography: comparison with dynamic computed tomography and/ or magnetic resonance imaging. Paper presented at the 46th Annual Meeting of the European Association for the Study of the Liver (EASL) International Liver Congress, Berlin, Germany, 30 March–3 April 2011. J Hepatol 2011;54:S393–4. (Reference standard)
- 86. Mork H, Ignee A, Schuessler G, Ott M, Dietrich CF. Analysis of neuroendocrine tumour metastases in the liver using contrast enhanced ultrasonography. *Scand J Gastroenterol* 2007;**42**:652–62. (**Outcomes**)
- 87. Mucciarini C, Bellentani S, Razzini G, Bernardini I, Artioli F, Iop A, et al. The role of contrastenhanced ultrasound in detection of liver metastases from colorectal cancer: a prospective monocentric study. Paper presented at the 2009 Annual Meeting of the American Society of Clinical

- Oncology (ASCO), Orlando, FL, 29 May–2 June 2009. *J Clin Oncol* 2009;**27**:e15105. (**Reference standard**)
- 88. Muhi A, Ichikawa T, Motosugi U, Sou H, Nakajima H, Sano K, *et al.* Diagnosis of colorectal hepatic metastases: comparison of contrast-enhanced CT, contrast-enhanced US, superparamagnetic iron oxide-enhanced MRI, and gadoxetic acid-enhanced MRI. *J Magn Reson Imaging* 2011;**34**:326–35. (**Reference standard**)
- 89. Nicolau C, Vilana R, Catala V, Bianchi L, Gilabert R, Garcia A, et al. Importance of evaluating all vascular phases on contrast-enhanced sonography in the differentation of benign from malignant focal liver lesions. *AJR Am J Roentgenol* 2006;**186**:158–67. (**Comparator**)
- 90. Oldenburg A, Hohmann J, Foert E, Skrok J, Hoffmann CW, Frericks B, *et al.* Detection of hepatic metastases with low MI real time contrast enhanced sonography and SonoVue. *Ultraschall Med* 2005;**26**:277–84. (**Reference standard**)
- 91. Ooi C-C, Low S-CA, Schneider-Kolsky M, Lombardo P, Lim S-Y, Abu Bakar R, et al. Diagnostic accuracy of contrast-enhanced ultrasound in differentiating benign and malignant focal liver lesions: a retrospective study. *J Med Imaging Radiat Oncol* 2010;**54**:421–30. (**Reference standard**)
- 92. Peschl R, Werle A, Mathis G. Differential diagnosis of focal liver lesions in signal-enhanced ultrasound using BR 1, a second-generation ultrasound signal enhancer. *Dig Dis* 2004;**22**:73–80. (**Comparator**)
- 93. Piscaglia F, Bolondi L. The safety of Sonovue in abdominal applications: retrospective analysis of 23188 investigations. *Ultrasound Med Biol* 2006;**32**:1369–75. (**Study design, M**)
- 94. Piscaglia F, Corradi F, Mancini M, Giangregorio F, Tamberi S, Ugolini G, *et al.* Real time contrast enhanced ultrasonography in detection of liver metastases from gastrointestinal cancer. *BMC Cancer* 2007;**7**. (**Reference standard**)
- 95. Pompili M, Riccardi L, Covino M, Barbaro B, Di Stasi C, Orefice R, *et al.* Contrast-enhanced gray-scale harmonic ultrasound in the efficacy assessment of ablation treatments for hepatocellular carcinoma. *Liver Int* 2005;**25**:954–61. (**Reference standard**)
- 96. Quaia E, Stacul F, Bertolotto M, Locatelli M, Mucelli RP. Characterization of focal liver lesions with pulse inversion harmonic imaging (PIHI) using a second generation US contrast agent. *Acad Radiol* 2002;**9**(Suppl. 2):S376–9. (**Reference standard**)
- 97. Quaia E, Bertolotto M, Calderan L, Mosconi E, Mucelli RP. US characterization of focal hepatic lesions with intermittent high-acoustic-power mode and contrast material. *Acad Radiol* 2003;**10**:739–50. (**Outcomes**)
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- 103. Rafaelsen SR, Jakobsen AJ. Contrast enhanced ultrasonography versus multidetector-computed tomography in detection of liver metastases from colorectal cancer. A prospective, blinded, patient by patient analysis. Paper presented at the 5th European Multidisciplinary Colorectal Cancer Congress (EMCC), Nice, France, 23–30 March 2010. Ann Oncol 2010;21:i27. (Reference standard)
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- 108. Salvaggio G, Campisi A, Lo Greco V, Cannella I, Meloni MF, Caruso G. Evaluation of posttreatment response of hepatocellular carcinoma: comparison of ultrasonography with second-generation ultrasound contrast agent and multidetector CT. *Abdom Imaging* 2010;**35**:447–53. (**Reference standard**)
- 109. Şirli R, Sporea I, Martie A, Popescu A, Danila M. Contrast enhanced ultrasound in focal liver lesions: a cost efficiency study. *Med Ultrason* 2010;**12**:280–5. (**Study design**)
- 110. Societatea Romana de Ultrasonografie in Medicina si Biologie, Centrul de Cercetare in Gastroenterologie si Hepatologie C, Clinica de Gastroenterologie si Hepatologie UT, Institutul Regional de Gastroenterologie-Hepatologie C-N, Institutul Clinic Fundeni B, Clinica de Gastroenterologie C. Contrast enhanced ultrasound for the evaluation of focal liver lesions. NCT01329458. Bethesda, MD: National Library of Medicine; 2011. URL: http://ClinicalTrials.gov/show/NCT01329458 (accessed 12 December 2011) (Reference standard)
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- 115. Soye JA, Mullan CP, Porter S, Beattie H, Barltrop AH, Nelson WM. The use of contrast-enhanced ultrasound in the characterisation of focal liver lesions. *Ulster Med J* 2007;**76**:22–5. (**Reference standard, M**)
- 116. Sporea I, Şirli R, Martie A, Popescu A, Danila M. How useful is contrast enhanced ultrasonography for the characterization of focal liver lesions? *J Gastrointestin Liver Dis* 2010;**19**:393–8. (**Outcomes**)
- 117. Sporea I, Badea R, Martie A, Şirli R, Socaciu M, Popescu A, et al. Contrast enhanced ultrasound for the characterization of focal liver lesions. *Med Ultrason* 2011;**13**:38–44. (**Outcomes**)
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- 123. Tarantino L, De Rosa A, Sorrentino P, Tambaro O, Celiento M, Del Prete M, et al. Impact of contrast-enhanced ultrasonography on diagnostic work-up of focal liver anomalies: experience in a single hepatology unit. Paper presented at the 45th Annual Meeting of the European Association for the Study of the Liver (EASL) International Liver Congress, Vienna, Austria, 14–18 April 2010. *J Hepatol* 2010;**52**:s235–6. (**Outcomes**)
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- 127. Tranquart F, Le Gouge A, Correas JM, Ladam Marcus V, Manzoni P, Vilgrain V, et al. Role of contrast-enhanced ultrasound in the blinded assessment of focal liver lesions in comparison with MDCT and CEMRI: results from a multicentre clinical trial. Eur J Cancer Suppl 2008;6:9–15. (Reference standard, M)

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- 135. von Herbay A, Vogt C, Willers R, Haussinger D. Real-time imaging with the sonographic contrast agent SonoVue: differentiation between benign and malignant hepatic lesions. *J Ultrasound Med* 2004;**23**:1557–68. (**Comparator**)
- 136. von Herbay A, Westendorff J, Gregor M. Contrast-enhanced ultrasound with SonoVue: differentiation between benign and malignant focal liver lesions in 317 patients. *J Clin Ultrasound* 2010;**38**:1–9. (**Comparator**)
- 137. Wang HB, Hou XJ, Wang XL, Wang H, Liu AW. [Diagnostic value of real-time grey-scale contrast-enhanced ultrasonography for hepatic tumors.] *World Chin J Dig* 2007;**15**:2726–9. (**Comparator**)
- 138. Wang J-H, Lu S-N, Hung C-H, Chen T-Y, Chen C-H, Changchien C-S, et al. Small hepatic nodules (<or = 2 cm) in cirrhosis patients: characterization with contrast-enhanced ultrasonography. *Liver Int* 2006;**26**:928–34. (**Index test**)
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- 142. Wu W, Chen MH, Yin SS, Yan K, Fan ZH, Yang W, *et al.* The role of contrast-enhanced sonography of focal liver lesions before percutaneous biopsy. *AJR Am J Roentgenol* 2006;**187**:752–61. (**Population**)

- 143. Xia Y, Jiang YX, Dai Q, Lv K, Gao P. [Diagnostic value of arterial enhancement pattern on contrast-enhanced ultrasound in focal liver lesions.] *Chin J Med Imaging Technol* 2008;**24**:692–5. (**Comparator**)
- 144. Xie L, Guang Y, Ding H, Cai A, Huang Y. Diagnostic value of contrast-enhanced ultrasound, computed tomography and magnetic resonance imaging for focal liver lesions: a meta-analysis. *Ultrasound Med Biol* 2011;**37**:854–61. (**Study design**)
- 145. Xu H-X, Liu G-J, Lu M-D, Xie X-Y, Xu Z-F, Zheng Y-L, et al. [Characterization of focal liver lesions using an innovative contrast-enhanced ultrasound technique.] Zhonghua Wai Ke Za Zhi 2005;43:1375–8. (Comparator)
- 146. Xu HX, Liu GJ, Lu MD, Xie XY, Xu ZF, Zheng YL, *et al.* Characterization of small focal liver lesions using real-time contrast-enhanced sonography: diagnostic performance analysis in 200 patients. *J Ultrasound Med* 2006;**25**:349–61. (**Reference standard**)
- 147. Xu HX, Liu GJ, Lu MD, Xie XY, Xu ZF, Zheng YL, *et al.* Characterization of focal liver lesions using contrast-enhanced sonography with a low mechanical index mode and a sulfur hexafluoride-filled microbubble contrast agent. *J Clin Ultrasound* 2006;**34**:261–72. (**Comparator**)
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- 149. Yan K, Chen M-H, Dai Y, Shen L, Jiang X-L. [Results of enhanced ultrasonography in assessing hepatoma treated with radiofrequency ablation.] *Zhonghua Zhong Liu Za Zhi* 2005;**27**:41–4. (**Comparator**)
- 150. Yarmenitis SD, Karantanas A, Bakantaki A, Papantoniou Y, Gourtsoyiannis N. Detection of colorectal cancer hepatic metastases with contrast-enhanced ultrasound: comparison with conventional B-mode ultrasound. *Dig Dis* 2007;**25**:86–93. (**Reference standard**)
- 151. Zhang H, He Y, Du L, Wu Y. Shorter hepatic transit time can suggest coming metastases: through-monitoring by contrast-enhanced ultrasonography? *J Ultrasound Med* 2010;**29**:719–26. (**Reference standard**)
- 152. Zuber-Jerger I, Schacherer D, Woenckhaus M, Jung EM, Scholmerich J, Klebl F. Contrast-enhanced ultrasound in diagnosing liver malignancy. *Clin Hemorheol Microcirc* 2009;**43**:109–18. (**Comparator**)
- 153. Zviniene K, Zaboriene I, Basevicius A, Pundzius J. Comparative diagnostic value of computed tomography and contrast-enhanced ultrasonography in diagnosis of focal liver lesions. *Medicina-Lithuania* 2009;**45**:751–63. (**Outcomes**)

The following is a list of those studies provided in the submission from the manufacturer of SonoVue that had already been excluded at the title and abstract screening stage. Studies provided in submissions from manufacturers that related solely to clinical applications outside the scope of the current assessment (i.e. anatomy other than the liver) are not listed:

- 1. Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology 2005;42:1208–36.
- Claudon M, Cosgrove D, Albrecht T, Bolondi L, Bosio M, Calliada F, et al. Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS): update 2008. Ultraschall Med 2008;29:28–44.
- 3. Faccioli N, D'Onofrio M, Comai A, Cugini C. Contrast-enhanced ultrasonography in the characterization of benign focal liver lesions: activity-based cost analysis. *Radiol Med* 2007;**112**:810–20.

- 4. Forner A, Vilana R, Ayuso C, Bianchi L, Sole M, Ayuso JR, *et al.* Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. *Hepatology* 2008;**47**:97–104.
- 5. Leen E, Ceccotti P, Moug SJ, Glen P, MacQuarrie J, Angerson WJ, et al. Potential value of contrast-enhanced intraoperative ultrasonography during partial hepatectomy for metastases. An essential investigation before resection? *Ann Surg* 2006;**243**:236–40.
- 6. Liu GJ, Xu HX, Lu MD, Xie XY, Xu ZF, Zheng YL, et al. Enhancement pattern of hepatocellular carcinoma: comparison of real-time contrast-enhanced ultrasound and contrast-enhanced computed tomography. Clin Imaging 2006;**30**:315–21.
- 7. Rahbin N, Siosteen AK, Elvin A, Blomqvist L, Hagen K, Hultcrantz R, et al. Detection and characterization of focal liver lesions with contrast-enhanced ultrasonography in patients with hepatitis C-induced liver cirrhosis. Acta Radiol 2008;49:251–7.
- 8. Schuler A, Reuss J, Delorme S, Hagendorff A, Giesel F. Costs of clinical ultrasound examinations: an economical cost calculation and analysis. *Ultraschall Med* 2010;**31**:379–86.
- 9. Seitz K, Strobel D, Bernatik T, Blank W, Friedrich-Rust M, Herbay AV, et al. Contrast-enhanced ultrasound (CEUS) for the characterization of focal liver lesions prospective comparison in clinical practice: CEUS vs. CT (DEGUM multicenter trial). Parts of this manuscript were presented at the Ultrasound Dreilandertreffen 2008, Davos. Ultraschall Med 2009;30:383–9.
- Seitz K, Bernatik T, Strobel D, Blank W, Friedrich-Rust M, Strunk H, et al. Contrast-enhanced ultrasound (CEUS) for the characterization of focal liver lesions in clinical practice (DEGUM Multicenter Trial): CEUS vs. MRI – a prospective comparison in 269 patients. *Ultraschall Med* 2010;31:492–9.