Details of the methods and interpretation of the index test (assessed technology), comparator test(s) and reference standard (for test accuracy studies only) used in included studies

Study	SonoVue CEUS details	Comparator test(s) details	Reference standard details
Blondin 2011[48]	Aplio 80 scanner (Toshiba Medical Systems, Neuss, Germany) Real time B-mode sonography; low mechanical index (0.2–0.4) CEUS was carried out after administration of a 2.4-ml bolus of SonoVue (Nycomed, Germany) into the antecubital vein Images were interpreted by a internist and a radiologist; both were blinded	1.5T MRI (MAGNETOM Avanto, Siemens Medical Solutions, Erlangen, Germany) The contrast agent used was Gd-EOB-DTBA (Primovist®, Bayer Schering Pharma, Berlin, Germany), injected at 2 ml/second via the antecubital vein Axial T1- and T2-weighted imaging with contrast enhancement in the arterial (after 20 seconds), venous (after 60 seconds) and equilibrium (after 180 seconds) phases as well as the late phase (after 15 minutes, consisting of a coronal and axial T1) were used for analysis Images were interpreted by two independent blinded radiologists	Histology after biopsy or surgery in all lesions
Catala 2007[52]	Sequoia 512 scanner (Acuson, Mountain View, CA). CEUS used specific software Coherent Contrast Imaging with the same convex array probe as baseline US Baseline US of the liver (to identify FLLs) in the fundamental mode, using a greyscale and a multifrequency 4 × C1 convex array probe CEUS was carried out after administration of a 2.4-ml bolus of SonoVue (Bracco, Milan, Italy) followed by a 5-ml saline flush. Enhancement patterns were studied for up to 3.5 minutes, including the arterial (0–49 seconds), portal (50–120 seconds) and late (>120 seconds) phases. The following settings were used: insonating frequency: 3 MHz; acoustic power: −75 dB to −90 dB; frame rate: 17–20; double focus; low mechanical index (<0.2) Images were interpreted by two independent radiologists with more than 5 years' experience of liver CEUS; disagreements were resolved by a third radiologist. Images were interpreted without knowledge of the final diagnosis or other imaging results, but with knowledge of the presence or absence of signs of chronic liver disease on US/SCT	SCT scanner (Somatom Plus 4, Siemens) Scans in a cranial–caudal direction with a 5-mm collimation in the arterial phase and an 8-mm collimation in the other phases (pitch 1.5) for a single held breath at a spiral acquisition of up to 15 seconds. Acquisition of the arterial phase started 6 seconds after the automatic detection of peak aortic enhancement; portal and late venous phases were scanned 70 and 180 seconds after the start of the injection of the contrast agent The contrast agent used was 100 ml iopromide, 300 mg iodine/ml (Ultravist®, Schering AG, Berlin, Germany) via the antecubital vein at 4 ml/second Images were interpreted by two independent radiologists with more than 5 years' experience of liver CT; disagreements were resolved by a third radiologist. Images were interpreted without knowledge of the final diagnosis or other imaging results, but with knowledge of the presence or absence of signs of chronic liver disease on US/SCT	All malignant lesions were histologically confirmed: biopsy ($n = 52$); partial hepatic resection ($n = 3$); explanation ($n = 2$). For benign FLLs the final diagnosis was obtained by biopsy ($n = 2$); MRI and follow-up ≥ 12 months ($n = 18$)

Study	SonoVue CEUS details	Comparator test(s) details	Reference standard details
Chen 2007[59] (related publication Chen 2007[60])	Esaote Technos DU8 (Esaote SpA, Genoa, Italy) or Philips iU22 (Philips Medical Systems, Bothell, WA), using 2.5- to 5-MHz probes CEUS was carried out after administration of a 2.4-ml intravenous bolus of SonoVue (Bracco) injected over 2–3 seconds; low mechanical index (0.04–0.1) Images were assessed by three experienced radiologists	US without contrast CT or MRI was performed within 1 week before RFA in both groups. CT examinations were performed with a GE LightSpeed 64-slice spiral CT scanner. MRI was performed with a GE EchoSpeed 1.5T scanner Images were assessed by three experienced radiologists	Reference standard not applicable (not a test accuracy study) Outcomes of treatment were determined by imaging follow-up 1 month after RFA and every following 2–3 months in the first year and every 4–6 months in the second year. RFA was considered successful if there was no contrast enhancement in or around the tumour, the margins of the ablation zone were clear and smooth and the ablation zone extended beyond the tumour borders
Clevert 2009[51]	Multifrequency curved array transducer, 2.5–4 MHz (Logic 9, GE Healthcare, Milwaukee, WI). Transmitted energy reduced to < 30%, with a low mechanical index (0.15) After B-scan analysis of vascularisation with power Doppler US, CEUS used intravenous administration of a 2.4-ml bolus of SonoVue (Bracco) followed by a 10-ml bolus of saline Scanning was carried out during the arterial phase (<30 seconds), the portal venous phase (40–120 seconds) and the late phase (>120 seconds) CEUS was performed by two blinded radiologists with >7 years of clinical US experience. Interpretation was by consensus	Biphasic contrast-enhanced CT using a 16- or 64-slice scanner (Somatom Sensation 16 or 64, Siemens). Image volume included the whole liver. Unenhanced axial sections were not performed Contrast agent was 120 ml of Solutrast® (Bracco, Milan, Italy), iodine concentration 300 mg/ml, administered as an intravenous bolus (flow rate 5 ml/second), followed by 50 ml of saline The appropriate delay for the arterial and venous phases was determined by semiautomatic bolus tracking on the thoracic aorta Acquisition direction was craniocaudal. Images were reconstructed as thin-slice (3 mm) maximum-intensity projections in the axial and coronal planes CT examinations were performed by two blinded, experienced radiologists	Malignant liver lesions were confirmed by biopsy For haemangioma, US follow-up for 2 years and MRI or multiphase CT follow-up for 1 year was used to confirm the diagnosis No details of who interpreted the reference standard examinations were reported

Study	SonoVue CEUS details	Comparator test(s) details	Reference standard details
Dai 2008[43]	Technos MPX scanner (Esaote Biomedica, Genoa, Italy) Baseline US of the liver (to identify FLLs) using 3.5-MHz convex probe CEUS was carried out after intravenous administration of SonoVue (Bracco) as a 2.4-ml bolus within 2–3 seconds with continuous observation for 6 minutes from injection time using the same convex probe as baseline US; low mechanical index (0.05–0.06) Images were interpreted in consensus by two blinded sinologists with at least 10 years' experience who were unaware of the results of other imaging techniques and pathology	SCT scanner (Somatom Plus 4, Siemens) 5 mm collimation and 7.5 mm/second table speed. CT images were obtained before and 25 seconds (arterial phase), 60 seconds (portal venous phase) and 2–4 minutes (late phase) after the start of contrast injection The contrast agent used was 100 ml Omnipaque® (Amersham Health, Princeton, NJ), 300 mg/ml iodine, at a rate of 3.5 ml/second Images were interpreted in consensus by two radiologists with at least 10 years' experience of CT who were unaware of the results of other imaging techniques and pathology	Histopathology in all patients. US-guided biopsy with two- to threefold aspiration of each nodule using an 18-gauge needle Histopathological diagnoses were made in consensus by two pathologists with more than 20 years' experience Negative biopsies were confirmed by further follow-up for a minimum of 6 months
Feng 2007[57] (Chinese language)	US and CEUS using Sequoia 512 scanner. CEUS was carried out following injection of 2 ml of SonoVue (Bracco); low mechanical index (0.19) Imaging was conducted between 1 week and 3 months after cryosurgery, and all imaging tests were conducted within 2 weeks of each other No details of who interpreted CEUS were reported	CECT or CEMRI, no details reported Imaging was conducted between 1 week and 3 months after cryosurgery, and all imaging tests were conducted within 2 weeks of each other No details of who interpreted CECT and CEMRI were reported	Histopathological diagnosis; no further details reported
Flor 2009[39] (abstract only)	US and CEUS using Logic 9 CEUS performed after bolus injection of 4.8 ml of SonoVue (Bracco); low mechanical index (<0.2) No details of interpretation were reported	None	Biopsy or follow-up at 3–6 months No further details were reported
Forner 2008[44]	US used Sequoia 512 scanner Baseline US of the liver (to identify FLLs) using a multifrequency 4C1 convex and 4V1 storial array probe CEUS was carried out after administration of a 2.4-ml bolus of SonoVue (Bracco); observation for up to 3.5 minutes from injection time CEUS used contrast coherent imaging (CCI, Siemens-Acuson, Mountain View, CA, USA) and the 4C1 convex array probe; low mechanical index (<0.2). Enhancement patterns were studied during the vascular phase up to 3.5 minutes, including the arterial (0–49 seconds), portal (50–179 seconds) and late (>180 seconds) phases Images were recorded blindly and reviewed by at least two radiologists. Doubtful images were interpreted by consensus	Symphony 1.5T system (Siemens), using a phased-array torso coil Transverse T1-weighted and T2-weighted MRI and multiphasic contrast-enhanced dynamic breath-hold three-dimensional MRI of the whole liver with fat suppression The contrast agent used was gadolinium (gadodiamide 0.5 mmol/l, Omniscan-Amersham), injected at 0.2 ml/kg and 2 ml/second. Bolus tracking was used to obtain arterial phase (20 seconds after injection), portal venous phase (60–65 seconds after injection) and late phase (100–110 seconds after injection) images Images were interpreted by two radiologists experienced in liver MRI who were unaware of the biopsy results	All imaging-positive nodules were confirmed with FNB using a 20-guage or 18-guage needle and multiple passages. Specimens were routinely processed and stained with haematoxylin–eosin Imaging-negative patients were followed up with CEUS every 3 months and MRI every 6 months. Median follow-up 23 months (range 4 to 41 months)

Study	SonoVue CEUS details	Comparator test(s) details	Reference standard details
Gierbliński 2008[53]	Baseline US/CT not specified CEUS was carried out after administration of a 2.4-ml bolus (86 patients) or a 4.8-ml bolus (14 patients) of SonoVue (Bracco) followed by 10 ml of 0.9% saline; low mechanical index (<0.09). Philips HDI 5000 SonoCT (Philips Medical Systems, Bothell, WA) using a 2- to 5-MHz curved linear-array transducer Imaging duration was 4 minutes: arterial phase 15–30 seconds after injection, portal phase 35–90 seconds after injection and late venous phase 90–240 seconds after injection Images were interpreted by gastroenterologists with 2 years' experience of CEUS, who were blind to the initial US and CT results	None	FNB in all patients with a 20-guage Chiba aspirating needle or 19-guage trucut biopsy; this diagnosis was considered final if the lesion was positive Negative biopsies were confirmed by clinical and imaging follow-up (median 10 months) Biopsies were assessed by a pathologist blinded to the CEUS results and follow-up imaging was evaluated by blinded examiners
Giorgio 2007[45]	All abdominal US scans were performed with Prosound SSD-5500 PHD Extended (Aloka, Tokyo, Japan) using a 3- to 6-MHz convex array broadband probe CEUS was carried out after administration of a 2.4-ml bolus of SonoVue (Bracco) followed by a 5-ml saline flush; low mechanical index (0.11) The scan lasted up to 5 minutes and the whole vascular phase was observed: arterial (15–30 seconds after injection), portal (30–60 seconds after injection), sinusoidal (60–240 seconds after injection) One operator with over 20 years' experience of CEUS performed all studies the day before the MRI studies	1.5T Symphony system Three contiguous sets of T1-weighted, in-phase, breath-hold, spoiled gradient-echo images The contrast agent used was a 20-ml bolus of gadobenate dimeglumine (MultiHance®, Bracco, Milan, Italy), injection rate 3.0 ml/second, followed by 40 ml of saline. Evaluation of arterial, portal and delayed phases was obtained through the whole liver at 22, 48 and 90 seconds after injection start Images were interpreted by one experienced radiologist who was unaware of the CEUS results	US-guided FNB in all patients using a 19-guage modified Menghini cutting needle Biopsy was performed the day after both imaging investigations were complete
Jonas 2011[50] (abstract only)	SonoVue CEUS; no further details reported	MRI with hepatocyte-specific contrast (Primovist); no further details reported Triple-phase contrast-enhanced abdominal CECT; no further details reported	All patients underwent intraoperative US and imaging (CEUS, CECT or CEMRI) follow-up at 3, 6, 12, 24 and 36 months Histology was used to confirm all resected metastases detected on preoperative imaging No further details reported

Study	SonoVue CEUS details	Comparator test(s) details	Reference standard details
Leoni 2010[42]	Technos MPX scanner for unenhanced US CEUS (Esatune, CnTI or Technos MPX, Esaote Biomedica, Genoa, Italy) was conducted after administration of SonoVue (Bracco), dose not reported; low mechanical index (0.04–0.07) The examination was assessed in both the arterial and late phases (up to 3 minutes recorded) Images were interpreted by an operator with at least 3 years' experience of CEUS, immediately after the examination by the same operator	Helical MDCT with Emotion 6 system (Siemens) Unenhanced and contrast-enhanced images for arterial, portal venous and delayed phases The contrast agent used was an intravenous bolus injection of 2 ml/kg of non-ionic contrast (Iomeron® 350, Bracco, Milan, Italy) at 4 ml/second. Scans started 5 seconds (arterial phase) after reaching the threshold, 70 seconds (portal venous phase) and 170 seconds (delayed phase) MRI performed with 1.5T system (Signa, GE Medical Systems, WI, USA) using a body-phased array multicoil. Unenhanced sequences were breath-hold T1 weighted Contrast-enhanced images acquired after injection of ferucarbotran (Resovist®, Schering, Berlin, Germany) 10 µmol/kg bolus, followed by a 10-ml saline flush. Two sets of SPIO-enhanced images (10 and 20 minutes after contrast injection) using breath-hold T2-weighted sequences with fat saturation. Dynamic three-dimensional MRI performed after administration of gadolinium (gadopentetate dimeglumine, Magnevist®, Schering, Berlin, Germany) 0.2 ml/kg, injection at 2 ml/second, followed by a 20-ml saline flush. The time delay for the arterial, portal venous and delayed phases was 18, 80 and 180 seconds respectively CT and MRI examinations were interpreted in consensus by two operators experienced in liver imaging who were blind to the results of other contrast imaging	Two or more contrast imaging techniques positive was treated as a correct positive diagnosis that did not require further confirmation (EASL and AASLD guidelines for non-invasive diagnosis) Patients with no or one positive contrast-enhanced imaging test were confirmed using US-guided FNB (19-guage modified Menghini needle, haematoxylin and eosin stain) or follow-up (US or CT) at 3-month intervals Diagnosis of HCC was made according to the International Working Party criteria[110]
Li 2007[54]	HDI 5000 scanner used for baseline US and CEUS. In patients with more than one FLL detected at baseline US, only the largest lesion was subjected to CEUS CEUS was carried out after administration of a 2.4-ml bolus injection of SonoVue (Bracco) to the cubital vein, followed by a 5-ml saline flush; low mechanical index (0.09–0.15) pulse-inversion harmonic imaging, with a convex-array broadband transducer Scans covered the entire vascular phase (up to 5 minutes): arterial phase (0–40 seconds), portal venous phase (41–100 seconds), late phase (101–300 seconds) Images were interpreted in consensus by two sonologists who were unaware of the CECT results	A three-phase contrast-enhanced protocol was used: unenhanced CT scan followed by intravenous infusion of 100–120 ml (4 ml/second) of non-ionic, iodine-containing contrast media (Ultravist 370). Scans were obtained in the arterial, portal venous and late phases, with bolus test trigger Data obtained through the whole liver in a craniocaudal direction during a single breath-hold helical acquisition (6–8 seconds) Images were interpreted by two radiologists who were blinded to the results of CEUS	Histopathology following surgical resection or FNB with an 18-guage needle within 2 weeks after CEUS and CECT

Study	SonoVue CEUS details	Comparator test(s) details	Reference standard details
Lüttich 2006[40] (abstract only)	CEUS using sulphur hexafluoride, 4 weeks after treatment (RFA) No further details reported	Gadolinium-enhanced CEMRI, 4 weeks after treatment (RFA) No further details reported	All patients were biopsied after CEUS No further details reported
Mainenti 2010[49]	HDI 5000 scanner with a large band frequency convex transducer (3.5–7.5 MHz) used for baseline US and CEUS CEUS was carried out after administration of a 5-ml injection of SonoVue (Bracco) to the cubital vein, followed by a 10-ml saline flush; pulse inversion harmonic imaging and low mechanical index (<0.09) Scans covered the arterial phase (25 seconds), portal venous phase (70 seconds) and delayed phase (300 seconds) Images were interpreted by two observers with >10 years' experience each who were blinded to the results of other tests. When there was disagreement, the final decision was made by a consensus panel of the original two plus one additional observer	Four-slice MDCT (Aquilion 4, Toshiba Medical Systems, Tochigi-ken, Japan) Scans acquired from the diaphragm to the pubic symphysis. Parameters: 4x3 mm beam collimation, pitch 5.5, 120 kV, 300 mA, rotation time 0.5 seconds, effective slice thickness 3 mm Contrast-enhanced imaging was performed 75 seconds after an intravenous bolus (3 ml/second) of 150 ml iodinated, non-ionic iopromide (Ultravist, 370 mg iodine/ml) 1.5T MRI system (Gyroscan Intera 1.5T, Philips Medical Systems, Best, the Netherlands), with a phased-array body coil. Transverse breath-hold T1-weighted and T2-weighted images with and without fat saturation Extracellular enhanced CEMRI performed after bolus injection of 0.1 mmol/kg gadopentetate dimeglumine (Magnevist) at a rate of 3 ml/second, followed by a 20-ml saline flush. Images were acquired during the arterial (25 seconds), portal (60 seconds) and equilibrium (180 seconds) phases Intracellular enhanced CEMRI performed after intravenous injection of 0.12–0.7 mmol/kg of ferucarbotran. Images were obtained 15 minutes from the end of the injection, repeating the transverse breath-hold T2-weighted image with and without fat saturation All images (both CT and MRI) were interpreted by two observers with >10 years' experience each, who were blinded to the results of other tests. When there was disagreement, the final decision was made by a consensus panel of the original two plus one additional observer. Imaging tests (including CEUS) were performed randomly over a 4- to 8-day period	All patients underwent surgery within 10 days of the last imaging examination. In all patients who were imaging test positive for metastases, biopsy or resection of at least one lesion was performed All patients were followed up by MDCT (same technique as described) at 6 and 12 months, either to assess the size of a benign classified FLL or to assess the development of new metastases Comparisons of imaging with the reference standard were made by a different radiologist (with at least 10 years' experience) from those undertaking the initial blinded assessments

Study	SonoVue CEUS details	Comparator test(s) details	Reference standard details
Quaia 2009[46]	Sequoia system using a convex array 2- to 4-MHz 4C1 transducer used for baseline greyscale and colour or power Doppler unenhanced US, followed by CEUS, in both participating centres CEUS was carried out after administration of a 2.4-ml bolus injection of SonoVue (Bracco), followed by a 10-ml saline flush; low mechanical index (0.09–0.14), dynamic range 65 dB, temporal resolution between frames 75–100 ms (10–13 frames per second). Each nodule was examined Scans covered the arterial phase (10–40 seconds), portal venous phase (45–90 seconds) and delayed sinusoidal phase (100 seconds to microbubble disappearance) Images were reviewed independently by two radiologists with 2–8 years' experience in liver imaging, who were blinded to clinical history, biopsy results and other imaging results	64-row MDCT system (Aquilion, Toshiba, or Brilliance, Philips, Cleveland, OH, USA). CT performed 2–30 days after CEUS Breath-hold scan; technical parameters: rotation time 400 ms; beam collimation 64 x 0.5 mm (Aquilion), 64 x 0.625 mm (Brilliance); normalise pitch 1; z-axis coverage 32 mm; reconstruction interval 0.3 mm; 120 kV; 180–250 mA; field of view 40 cm Unenhanced CT, followed by CECT. Contrast-enhanced imaging performed 8 seconds after 2 ml/kg intravenous bolus of iodinated contrast (Iomeron 400, 400 mg iodine/ml, Bracco), 5 ml/s, followed by a 50-ml saline flush. The arterial phase started 18 seconds after the threshold was reached, the portal venous phase 70–80 seconds after the start of contrast injection and the delayed equilibrium phase 180–210 seconds after the start of contrast injection Images were reviewed in the same way as for CEUS	US-guided biopsy using an 18- to 20-gauge modified Menghini needle. Samples stained with haematoxylin–eosin and Masson's trichrome method. Biopsy performed within 15 days of CT A senior pathologist from each centre made the diagnosis
Sangiovanni 2010[47,61]	iU22 system using a multifrequency 2- to 5-MHz convex transducer, for both baseline greyscale US of the upper abdomen and CEUS CEUS was carried out after administration of a 2.4-ml bolus injection of SonoVue (Bracco), followed by a 10-ml saline flush; low mechanical index (<0.1) Scans covered the entire vascular phase (3 minutes): arterial phase (0–35 seconds), portal phase (35–120 seconds) and late phase (120–180 seconds) Examinations were interpreted by two expert echographists who were unaware of the biopsy results	64-MDCT Definition system (Siemens) Technical parameters: 2.5-mm slice thickness; rotation time 0.5 s The contrast agent used was 1.5 mg/kg of iodinated contrast, Iomeron 400, injected at a rate of 4 ml/s Acquisition time, from the start of contrast injection, was 40 seconds for the arterial phase, 80 seconds for the portal venous phase and 180 seconds for the delayed phase Images were interpreted by one experienced radiologist who was unaware of the biopsy results MRI performed with a 1.5T system (Avanto, Siemens). All patients underwent transverse T1-weighted and T2-weighted MRI and multi-phasic 3D CEMRI of the whole liver, with fat suppression Dynamic MRI was performed with a three-dimensional volumetric interpolated breath-hold examination sequence in the axial plane by using the following parameters: 4.7/2.3, 10-degree flip angle, 320 x 157 matrix, slice thickness of 3 mm The contrast agent used was gadolinium (gadobenate dimeglumine 0.5 mmol/l, MultiHance), injected at 0.2 ml/kg and 2 ml/second. Arterial, portal venous and delayed venous phases acquired at 30 seconds, 80 seconds and 180 seconds from the start of contrast injection Images were interpreted by one experienced radiologist who was unaware of the biopsy results	Histology following FNB using a 21-gauge trenchant needle, carried out within 2 months of detection of nodule Formalin-fixed paraffin-embedded liver sections were examined by an experienced liver pathologist who was unaware of the results of clinical and imaging examinations Benign FLLs were followed up by imaging: by US every 3 months and by CT/MRI every 6 months

Study	SonoVue CEUS details	Comparator test(s) details	Reference standard details
Seitz 2009[55]	The US device used was not specified (different 'high-end' US devices and different contrast software) CEUS was conducted after administration of a 1.2- to 4.8-ml intravenous bolus of SonoVue (Bracco), followed by a 10-ml saline flush. The dose could be doubled or a second dose could be given. Low mechanical index (<0.4) Imaging lasted up to 5 minutes: arterial phase (5–25 seconds), portal venous phase (25–60 seconds) and late phase (>120 seconds) For patients with multiple lesions, the dominant lesion was analysed; when lesions had different sonomorphology in the late phase each lesion was analysed separately with additional contrast media injection US was performed by physicians with >5 years' experience; at least 2 years' experience with CEUS in liver tumours. CEUS was performed up to 4 weeks before the CT examination. The definitive CEUS diagnosis was made at the time of the US examination by the physician performing it. The US investigator was not blinded to the results of the preceding CT in eight cases	The SCT device used was not specified Single- or multislice CT collimation and reconstructed slice thickness at least 5 mm; the liver SCT examination performed as three-phasic-SCT: native scan application of 140 ml of iodinated contrast media (non-ionic, various vendors, iodine concentration >300 mg/ml; flow >3 ml/second). Two additional scans: early phase (25–30 seconds) and late phase (60–90 seconds) All reporting radiologists had access to the patients' clinical information	Subgroup A: final diagnosis was achieved by SCT or proven clinical data including follow-up Subgroup B: diagnosis was based on US-guided FNB
Seitz 2010[56]	The US device used was not specified (different 'high end' US devices and different contrast software) CEUS was conducted after administration of a 1.2 to 4.8 ml intravenous bolus of SonoVue (Bracco), followed by a 10-ml saline flush. The dose could be doubled or a second dose could be given. Low mechanical index (<0.4) Imaging lasted up to 5 minutes: Arterial phase (5–25 seconds), portal venous phase (25–60 seconds) and late phase (>120 seconds) If multiple lesions, those suspicious for malignancy or if benign the largest lesion were analysed. Where lesions had different sonomorphology in the late phase each lesion was analysed separately with additional contrast media injection US was performed by physicians with more than 5 years' experience, at least 2 years' experience with CEUS in liver tumours: CEUS was performed up to 4 weeks prior to MRI examination. The definitive CEUS diagnosis was made at the time of the US examination by the physician performing it	The MRI device used was not specified; MRI device with minimum of 1.5 Tesla T1-weighted localiser; T2 TSE axial. Three-dimensional TFE dynamics breath-hold native, arterial, portal venous using gadolinium DTPA [15 ml ProHance® (gadoteridol), 78.61 mg/ml], 5–8 mm slice thickness. Resovist contrast used in 88/269 MRI studies	Subgroup A: final diagnosis was made by MRI, proven clinical data and follow-up for >6 months Subgroup B: diagnosis was based on US-guided FNB

Study	SonoVue CEUS details	Comparator test(s) details	Reference standard details
Solbiati 2006[41] (abstract only)	CEUS was performed with contrast-specific software (CPS, Acuson-Siemens, and CnTI, Esaote) after bolus injection of 2.4 ml of SonoVue (Bracco); low mechanical index No details of interpretation were reported	Triphasic, helical CECT No further details were reported	When CEUS and CECT results were concordant, this was treated as a correct diagnosis that did not require further confirmation (EASL and AASLD guidelines for non-invasive diagnosis) When there was a discordant result FNB was used as the reference standard No details of who made the diagnosis
Zhou 2007[58] (Chinese language)	Sequoia 512 system with a 2.5- to 6.0-MHz probe CEUS was carried out after administration of a 2.4-ml bolus injection of SonoVue (Bracco) followed by a 5-ml saline flush; low mechanical index (0.15–0.21) Arterial phase 30 seconds, portal venous phase 60 seconds, late phase 180 seconds Imaging carried out within 1 week of treatment. No details of who interpreted images	Somatom Balance system (Siemens) Iodinated contrast medium, iohexol (350 mg/ml iodine, Omnipaque) was used Arterial phase 30 seconds, portal venous phase 60 seconds, late phase 180 seconds Imaging carried out within 1 week of treatment. No details of who interpreted images	Imaging-positive results were confirmed by US-guided FNB Imaging-negative results were confirmed by follow-up imaging at 3 months No details of who made the diagnosis

DTPA, diethylenetriamine penta-acetic acid; SCT, spiral computed tomography; TFE, turbo field echo; TSE, turbo spin echo.

Inclusion/exclusion criteria and participant characteristics of included studies

Study	Participant number	Inclusion criteria	Exclusion criteria	Participant characteristics
Blondin 2011[48]	33 patients, 47 lesions (per-lesion data)	Patients with liver cirrhosis, identified from a radiology database, who had received MRI of the liver with Primovist and CEUS with SonoVue with no more than 4 weeks in between each examination. Histology of the FLL had to be performed	Known malignancy	Mean age: 63 ± 11 years 25 men/8 women Chronic liver disease: 33 (due to viral hepatitis 15; alcohol abuse 13; haemochromatosis 1; unknown reason 4, therefore classified as cryptogen) Mean nodule size: not specified Final diagnosis: HCC 41; RN 6
Catala 2007[52]	213 patients assessed for inclusion, 77 patients with 77 FLLs enrolled. For patients with multiple FLLs, the histologically confirmed or largest lesion was selected	Adult patients (≥18 years) with FLLs detected on US Only FLLs evaluated with an interval of no more than 1 month between CEUS and SCT were included Malignant FLLs were included only if confirmed by pathology	Patients who were pregnant or nursing	Mean age: 62 ± 11 years 45 men/32 women Chronic liver disease: 53 Mean nodule size: 3.5 ± 2.2 cm Final diagnosis: HCC 45; metastases 12; haemangioma 10; FNH 8
Chen 2007[59] (related publication Chen 2007[60])	179 patients originally recruited (intervention CEUS 92, comparator US 87); 165 patients who were suitable for RFA (intervention CEUS 83, comparator US 82) were included in the analyses	Patients with HCC who were being assessed for RFA. Patients were allocated alternately to intervention and comparator groups	14 patients who were not suitable for RFA were excluded from the analyses	

	Intervention (CEUS)	Comparator (US)
	n = 92	*n* = 87
Mean age (years)	67.5	66.9
Male/female (*n*)	59/33	52/35
TNM stage II/III (*n*)	55	51
Child–Pugh A (*n*)	67	65
Mean tumour size (cm)	3.6 ± 1.1	3.5 ± 1.1
Mean no. of tumours	1.6 ± 0.7	1.7 ± 0.7
CECT (*n*)	81	74
CEMRI (*n*)	11	13

Study	Participant number	Inclusion criteria	Exclusion criteria	Participant characteristics
Clevert 2009[51]	100 consecutive patients with suspected malignant liver lesions (maximum five lesions per patient); 21 patients were excluded from the CT analysis, eight because they did not undergo CT and 13 because CT imaging was inconclusive	Patients with suspected liver malignancy whose liver could be visualised completely by US examination	Exclusion criteria: tumour lesion >5 cm, more than five lesions, strong allergic reactions, liver or kidney disease with confirmed elevation of laboratory parameters, acute heart failure, acute myocardial infarction, subcutaneous emphysema, meteorism, tachypnea, aerobilia	Mean age: 57 years (range 25–83 years) 57 men/43 women Final diagnosis (by patient): liver metastases 52 (primary tumour site: colon 43, breast 5, neuroendocrine 2, renal 2); HCC 7; haemangioma 15; FNH 7; complicated cyst 5; abscess 2; focal fatty degeneration 12
Dai 2008[43]	498 patients with cirrhosis assessed for inclusion; 72 patients with indeterminate hepatic nodules included; 103 FLLs enrolled	Patients with confirmed cirrhosis and indeterminate hepatic nodules on US	NR	Mean age: 59 years (range 35–80 years) 59 men/13 women Cirrhosis, without extrahepatic malignancies: 72 Previous treatment for HCC: 9 Elevated AFP: 9 Mean nodule size: 1.5 ± 0.3 cm Final diagnosis (by nodule): HCC 56; RN 47
Feng 2007[57] (Chinese language)	23 patients with 26 malignant lesions undergoing cryosurgery	NR	NR	Mean age: 57 years (range 45–68 years) 20 men/3 women Initial diagnosis: HCC 21 (23 lesions); metastases 2 (3 lesions) Mean tumour size: 31.5 mm (range 16.7–42.6 mm) Final diagnosis (by lesion): complete treatment response 21; recurrence 5
Flor 2009[39] (abstract only)	18 patients with known primary cancer and indeterminate liver lesions ($n = 26$) detected at MDCT. All lesions were <1.5 cm	NR	NR	Mean age: 65 years 6 men/12 women Primary cancer: colon 8; breast 3; lung 2; pancreas 2; kidney 1; pleura 1; tongue 1 Final diagnosis: metastases 5; cysts 11; focal steatosis 2; haemangioma 2; intrahepatic biliary tract 1; CT artifacts 5

Study	Participant number	Inclusion criteria	Exclusion criteria	Participant characteristics
Forner 2008[44]	89 patients with cirrhosis and a single new FLL detected at screening	Patients with cirrhosis (Child–Pugh class A or B) and no history of HCC in whom a new solid nodule (5–20 mm) was detected on US	Patients with poor liver function who would undergo transplantation regardless of HCC diagnosis; patients with significant comorbidities; patients with severe clotting alterations or contraindications for CEUS, CEMRI or FNB	Median age: 65 years (range 37–83 years) 53 men/36 women Cirrhosis: 89 Median AST: 81 UI/l (range 25–322 UI/l) Median ALT: 70 UI/l (range 16–537 UI/l) Median prothrombin ratio: 78.5% (range 35–100%) Median bilirubin: 1 mg/dl (range 0.3–4.1 mg/dl) Median baseline AFP: 8 ng/ml (range 1–1154 ng/ml) Median nodule size: 14 mm (7–20 mm) Final diagnosis: HCC 60; CCC 1; RN 24; haemangioma 3; FNH 1
Gierbliński 2008[53]	100 patients with 100 incidentally detected FLLs who were referred for liver biopsy	Patients with incidentally detected FLLs referred for biopsy following inconclusive US and/or CT, which had suggested the possibility of malignancy	Patients with current or previous neoplastic disease; patients with lesions with features characteristic of haemangioma; patients in whom biopsy was not possible	No details of age and sex of patients reported Final diagnosis: HCC 9; metastases 14; haemangioma 34; FNH 19; skip area in fatty liver 11; focal steatosis 10; adenoma 1; dysplatic nodule 1; hyperregenerative nodule 1
Giorgio 2007[45]	73 patients with cirrhosis and a single FLL detected at surveillance US	Patients with cirrhosis and a single liver nodule ≤30 mm detected on US	Patients with heart disease (because of rare adverse event reported for SonoVue)	Mean age: 63 years (range 40–84 years) 49 men/24 women Cirrhosis: 73 (HCV associated 65, alcoholic 2, alcoholic and HCV associated 2, HBV associated 3, cryptogenic 1) Child–Pugh class A: 46, Child–Pugh class B: 27 AFP < 20 ng/ml: 73 Final diagnosis: HCC 48; RN 8; dysplastic nodule 4; focal steatosis 6; haemangioma 4; metastases 1; non-Hodgkin's lymphoma 1; FNH 1
Jonas 2011[50] (abstract only)	20 patients with CRC and 48 liver lesions	Patients with CRC liver metastases who underwent complete preoperative workup and could be rendered tumour free by a single-stage surgical intervention	Patients with concomitant resectable extrahepatic disease and previous hepatobiliary surgery, other than cholecystectomy	No details on primary disease, age and sex of patients reported Mean size of metastases: 24 mm (range 8–80 mm) All patients had CRC and metastasis was the only diagnosis reported

Study	Participant number	Inclusion criteria	Exclusion criteria	Participant characteristics
Leoni 2010[42]	60 patients with cirrhosis and 75 FLLs (28 newly detected and 32 recurrent)	Adult patients (>18 years) with cirrhosis and one to three liver nodules between 1 and 3 cm, which were visible on US	Previously treated nodules; contraindications to imaging, allergy to contrast agent, claustrophobia or magnetic or metallic devices in the body; neoplastic portal thrombosis or extrahepatic metastases	Mean age: 65 years (range 40–83 years) 52 men/8 women HCV 33; HBV 18; HCV and HBV 1; history of heavy alcohol intake 6; cryptogenetic 2 Child–Pugh class A/B/C: 40/18/2 Bilirubin: 1.9 ± 2.2 mg/dl Median AFP: 11 ng/ml (range 2–2849 ng/ml) AST: 96 ± 78 U/l ALT: 82 ± 57 U/l gamma-GT: 97 ± 72 U/l Alkaline phosphatase: 305 ± 119 U/l Final diagnosis (by lesion): HCC 55; not HCC 20
Li 2007[54]	109 patients with incidentally detected FLLs; one FLL assessed per patient. For patients with multiple FLLs, the largest and most conspicuous lesion on US was selected	Patients with FLLs, examined by US and unenhanced CT	Not specified	Mean age: 49 ± 12 years (range 18–79 years) 72 men/37 women Mean nodule size: 2.9 ± 1.3 cm (range 0.9–12.8 cm) Final diagnosis: HCC 61; metastases 15; CCC 5; haemangioma 12; RN 5; FNH 3; adenoma 3; focal necrosis 4; angiomyolipoma 1
Lüttich 2006[40] (abstract only)	15 patients with HCC who were being treated by RFA	NR	NR	No details reported
Mainenti 2010[49]	34 patients with CRC and 57 liver lesions	Patients with histologically proven CRC who were scheduled for surgery	Patients who refused to participate in the study; patients with known contraindications to one of the examinations	No patient had cirrhosis or had received previous radio- or chemotherapy Mean age: 63 years (range 29–81 years) 20 men/14 women Metastatic lesion size: 3–80 mm Final diagnosis (by lesion): metastases 16; haemangioma 11; cysts 29; focal fatty liver 1

Study	Participant number	Inclusion criteria	Exclusion criteria	Participant characteristics
Quaia 2009[46]	180 patients with cirrhosis and 195 nodules detected on surveillance US were initially recruited (up to two nodules per patient); 106 patients with 121 nodules finally included	Patients with a definite diagnosis of cirrhosis (Child–Pugh class A or B) and at least one hepatocellular nodule identified on surveillance US. Selection of nodules was based on the largest diameter and best visualisation Only those nodules ≤3 cm that underwent biopsy after CT corresponding to nodules not characterised by the Barcelona criteria (nodule ≤2 cm or nodule >2 cm with hypervascularity during the arterial phase without hypovascularity during the portal venous phase, or with isovascularity during the arterial phase and hypovascularity during the portal phase, or hypovascularity in all phases) were included in the study	Nodules with peripheral enhancement at CECT were excluded because of a high probability of haemangioma diagnosis Nodules were excluded because of a lack of histological diagnosis ($n = 60$), technical inadequacy of CT ($n = 10$) or inadequacy of CEUS examination ($n = 4$)	Cirrhosis: 180 (HBV 85, HCV 52, HBV and HCV 3, alcohol abuse 40) 106 included patients: Mean age: 70 ± 7 years 68 men/38 women Mean nodule size: 1.9 ± 1.1 cm (range 1–3 cm) Final diagnosis (by nodule): HCC 72; dysplastic nodule 10; RN 15; haemangioma 12; other benign 3; pseudotumour 9
Sangiovanni 2010[47,61]	64 patients with cirrhosis and abnormal US findings on surveillance were originally included (67 liver nodules); 55 small nodules (1–2 cm) were included in the analysis, 10 were >2 cm and 2 were <1 cm. All nodules >2 cm could be correctly diagnosed by at least one imaging modality	Patients with compensated cirrhosis (Child–Pugh A or B) who were under surveillance with US and had a new liver nodule detected	Patients with a pre-existing liver nodule; patients with poor liver function (Child–Pugh C) indicating liver transplantation regardless of HCC status; patients with an echo-coarse US pattern without a well-defined nodule	64 patients: Mean age 65 years (range 44–80 years) 47 men/17 women Child–Pugh A 63; Child–Pugh B 1 HBV 10; HCV 40; alcohol abuse 4 Median AFP: 11 ng/ml (range 1–2156 ng/ml) AFP >200 ng/ml: 3 Final diagnosis (by nodule for 1- to 2-cm nodules): HCC 34; CCC 1, low-grade dysplastic nodule 3; RN 17
Seitz 2009[55]	267 patients with incidentally detected FLLs: subgroup A (suspected benign lesions): 109 patients, 111 FLLs; subgroup B (suspected malignant lesions): 158 patients, 158 FLLs. For patients with multiple FLLs, the dominant lesion (most suspicious for malignancy or largest) was analysed	Patients with newly detected FLLs on US	Patients with specific liver lesions diagnosed by typical US echomorphology such as cysts or haemangiomas in a nonsteatotic liver without clinical signs and symptoms, as well as malignant tumours with infiltration into hepatic vessels; patients who were critically ill or who suffered from pulmonary hypertension or unstable angina, as well as pregnant and nursing women	Subgroup A + B (not specified by subgroup): Mean age: 60.3 years (range 21–89 years) 121 men/146 women Final diagnosis (subgroup A): HCC 7; metastases 7; haemangioma 48; FNH 31; fatty-sparing lesion 5; abscess 4; cyst 3; undefined 6 Final diagnosis (subgroup B): HCC 40; metastases 56; haemangioma 9; FNH 14; adenoma 2; lymphoma 3; fatty-sparing lesion 6; other benign lesion 14; other malignant lesion 10; undefined 4

Study	Participant number	Inclusion criteria	Exclusion criteria	Participant characteristics
Seitz 2010[56]	269 patients with incidentally detected FLLs (one lesion per patient). For patients with multiple FLLs, the dominant lesion (most suspicious for malignancy or largest) was analysed Subgroup A (suspected benign lesions): 185 Subgroup B (suspected malignant lesions): 84	Patients with newly detected FLLs on US	Patients with typical findings of simple cysts, hyperechoic haemangioma in a non-steatotic liver or fatty-sparing lesions without clinical signs and symptoms; patients with malignant tumours infiltrating hepatic vessels	Subgroup A: Mean age: 49.9 years (range 16–82 years) 58 men/127 women Final diagnosis: metastases 3; haemangioma 122; FNH 43; fatty-sparing lesion 2; abscess 1; cyst 4; cyst + haemorrhage 1; echinococcus 2; other benign lesion 2; undefined 5 Subgroup B: Mean age: 59.6 years (range 28–82 years) 53 men/31 women Final diagnosis: HCC 29; CCC 2; metastases 22; haemangioma 8; FNH 5; liver adenoma 1; fatty-sparing lesion 3; abscess 2; necrosis/scar 3; cyst 2; haemangioendothelioma 1; angiosarcoma 1; angiomyolipoma 1; RN 1; peliosis 1; undefined 2
Solbiati 2006[41] (abstract only)	686 patients with 694 incidentally detected FLLs	NR	NR	No details of age and sex of patients were reported Final diagnosis: HCC 275; metastases 214; CCC 6; haemangioma 167; FNH 11; adenoma 4; cyst 3; pseudolesion 13
Zhou 2007[58] (Chinese language)	56 patients with 64 HCC lesions who were undergoing non-surgical treatment	Patients with HCC who were undergoing non-surgical treatment	NR	Mean age 42 ± 13.8 years (range 21–68 years) 40 men/16 women Mean lesion diameter: 3.4 ± 1.6 cm (range 1.0–8.0 cm) Treatment: TACE 4; PEI 8; PMCT 11; RFA 5; TACE + PEI 4; TACE + PMCT 3; PEI + PMCT 11; PEI + PMAT + PMCT 10

ALT, alanine aminotransferase; AST, aspartate aminotransferase; FNH, focal nodular hyperplasia; gamma-GT, gamma-glutamyltransferase; NR, not reported; PMAT, percutaneous microwave ablation therapy; PMCT, percutaneous microwave coagulation therapy; RN, regenerative nodule; SCT, spiral computed tomography.