Uitgangsvraag 2 a: Wat is de optimale beeldvorming voor diagnosestelling HCC?

primary Studies

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary and other outcomes	VII Critical appraisal of study quality
Bernatik 2010[1], Strobel 2008 [2] [2]	• Prospective cohort study • Support and conflicts of interest: not reported • Setting: multi-centre (14 ultrasound centers), Germany • Sample size: N=1349 • Duration: May 2004 – December 2006	• Inclusion: patients with a newly detected focal liver lesion with an unclear diagnosis on routine ultrasound • Exclusion: typical findings of simple cysts, hyper echoic haemangioma in a nonsteatotic liver, fatty spearing lesions without clinical signs or symptoms, malignant tumours infiltrating hepatic vessels. Also: critically ill patients; severe pulmonary hypertension; unstable angina; pregnant or nursing women • Patient characteristics: 50% male; mean age 59.8 y, range: 12-91 y. In 62% of patients the liver lesion was an incidental finding. In 17% of patients liver cirrhosis and in 27% of patients extra-hepatic malignancy was known • Disease prevalence: 56.9% malignant lesions	• Index test: CEUS • Reference standards: all available imaging and clinical data, including follow-up. Histology (N=1006), cytology (n=19), MRI (N=269), CT (N=269) (multiple examinations possible)	For malignant liver lesion, all lesions: - Se: 95.8% - Sp: 83.1% - PPV: 95.4% - NPV: 95.9% - Accuracy: 90.3% Lesions ≤2 cm: - Se: 93.3% - Sp: 75.9% - PPV: 91.5% - NPV: 94.7% - Accuracy: 84.5% Lesions >2 cm: - Se: 96.5% - Sp: 86% - PPV: 96.5% - NPV: 96.4% - Accuracy: 92.2%	19/86 (22.1%) of indeterminate CEUS classifications were malignant 10/86 (11.6%) of indeterminate CEUS classifications were HCC 31 lesions (2.3%) were incorrectly classified as malignant (of which 6 were incorrectly classified as HCC) 8 lesions (0.6%) were incorrectly classified as benign (of which 5 were HCC)	Level of evidence: B • Consecutive patients • 0.2% (N=21) of patients had an unclear final diagnosis and were excluded from analyses (risk of bias through handling of indeterminate results) • Indeterminate CEUS classifications (6.8%, N=86) were rated as false classifications in Se & Sp calculations • Blinded assessment of index test or reference standard not reported (risk of reviewer bias) • In patients with a clear diagnosis of hemangioma or focal nodular hyperplasia on CEUS, CT &/ MRI was used as the reference standard (risk of differential verification bias)

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary and other outcomes	VII Critical appraisal of study quality
Catala 2007 [3]	• Prospective cohort study • Support and conflicts of interest: in part supported by the Carolina Foundation • Setting: single centre, Spain • Sample size: N=77 • Duration: December 2001 – August 2003	• Inclusion: patients with a focal liver lesion on routine ultrasound, malignant lesions had to be confirmed by pathology • Exclusion: age <18 y; pregnant or nursing; more than 1 month between CEUS and sCT • Patient characteristics: 48% male; mean age 62 y. 69% of patients had a history of chronic liver disease • Disease prevalence: 74.0% malignant lesions; 58.4% HCC	• Index tests: CEUS and sCT • Reference standards: pathology, MRI and follow-up of at least 12 months	For malignant liver lesion CEUS - Se: 91% - Sp: 90% - PPV: 96% - NPV: 78% - Accuracy: 91% sCT - Se: 88% - Sp: 89% - PPV: 96% - NPV: 75% - Accuracy: 88%	CEUS correctly diagnosed 41/45 (91.1%) HCCs sCT correctly diagnosed 39/45 (86.7%) HCCs No statistically significant difference was found between CEUS and sCT in the characterization of focal liver lesions	Level of evidence: B • Consecutive patients (46/123 patients met exclusion criteria) • Blinded assessment of reference standard not reported (risk of reviewer bias) • In 2/20 patients with a diagnosis of a benign lesion pathology was the reference standard, vs. in all patients with a malignant lesion (risk of verification bias)
Clevert 2009[4]	• Prospective cohort study • Support and conflicts of interest: not reported • Setting: 2 centers, Germany • Sample size: N=100 • Duration: two years, dates not reported	• Inclusion: patients with histologically confirmed hepatic tumours ≤5 cm • Exclusion: more than 5 hepatic lesions; strong allergic reactions; liver or kidney disease with elevated laboratory parameters; acute heart failure or myocardial infarction; subcutaneous emphysema; meteorism; tachypnea; or aerobilia. No complete visualisation of the liver on echo • Patient characteristics: 57% male; mean age 57 y (range: 25-83 y) • Disease prevalence: 59.0% malignant lesions; 7.0% HCC	• Index tests: CEHIUS or msCT • Reference standard: histology	For malignant liver lesion CEHIUS - Se: 98.6% - Sp: 96.6% - PPV: 98.6% - NPV: 96.6% - Accuracy: 98.0% msCT: - Se: 96.6% - Sp: 71.4% - PPV: 90.3% - NPV: 88.2% - Accuracy: 77.2%	The accuracy of CEHIUS was significantly better than the accuracy of msCT (p=0.04)	Level of evidence: B • **Consecutive patients** • 32/132 patients were excluded because the liver could not be visualised completely • Patients without histology or without complete visualisation of the liver on echo were excluded (risk of selection bias) • Indeterminate msCT classifications (14.1%) were not included in Se, Sp, PPV or NPV but were rated as false classifications in the accuracy assessment (risk of bias through the handling of indeterminate results) • Blinded assessment of reference standard not reported (risk of reviewer bias)
Gheorghe 2009 [5]	• Prospective cohort	• Inclusion: cirrhotic patients with	• Index test:	For HCC	-	Level of evidence: B

	study • Support and conflicts of interest: no conflicts of interest to declare • Setting: single centre, Romania • Sample size: N=42 • Duration: February 2007 - August 2008	liver nodules 1-3 cm • Exclusion: perihepatic ascites; obesity; thick thoracic wall (>3cm); negative histopathology results despite the presence of 2 imaging methods indicating presence of HCC; refusing liver biopsy; nodules localized close to large vessels; dysplastic nodules according to histology • Patient characteristics: 60% male; mean age 56 y • Disease prevalence: 71.4% malignant lesions (all HCC)	sonoelastography • Reference standards: histology (92.9%) or follow-up in case of contraindication to biopsy	Elastography color blue at a cut-off value of >128.9 - Se: 78.9% - Sp: 92.2% - PPV: 95.4% - NPV: 68% - Accuracy: 83.2% - Area under ROC: 0.94 Elastography color green at a cut-off value of <108.7 - Se: 50% - Sp: 91.1% - PPV: 92.1% - NPV: 47.1% - Accuracy: 63.6% - Area under ROC: 0.81 Elastography color red at a cut-off value of <71.2 - Se: 15.1% - Sp: 91.1% - PPV: 77.7% - NPV: 34.3% - Accuracy: 40%		• Consecutive patients • Discriminant cut-off values were determined post-hoc • Blinded assessment of reference standard not reported (risk of reviewer bias)
Chou 2010 [6]	• Design: cross-sectional • Source of funding: not stated • Setting: University hospital, Taiwan • Sample size: 49 patients (55 lesions) • Duration : 18 months	• Eligibility criteria: chronic liver disease and suspicion of tumour after US • Patient characteristics (e.g. age, tumour characteristics, stage, etc.): 34 men and 15 women, 28-85 years old, mean age 57.4 years, 40 liver cirrhosis (21 hep B, 15 hep C, 1 both hep B+C, 3 alcoholic), other 9 chronic hepatitis (7 hep B, 2 hep C), • Prevalence of disease: 35 HCC/55 lesions	• Index test(s): percentage significant intentisity loss (PSIL) MRI • Reference standard: histology and/or follow-up imaging	For HCC AUC: • PSIL T2WI 0.854 (±0.051), • PSIL FS-T2WI 0.978 (±0.016) PSIL FS-T2WI threshold at 40%: • Se 88.6% • Sp 95% • PPV 96.9% • NPV 82.6%	•	• Level of evidence: B • Dropouts: 3 • Results critical appraisal (definition of positive and negative cases, completeness of verification): complete verification, lesion-based analysis
Di Martino 2010 [7]	• Design: cross-sectional • Source of funding: Gadoxetate provided by Bayer Schering • Setting:	• Eligibility criteria: patients with cirrhosis and suspicion of HCC after US, α-foetoprotein >400 µg/L. • Patient characteristics (e.g. age, tumour characteristics, stage, etc.): mean age, 63 year (range 35–84), 39 men	• Index test(s): gadexetic acid-enhanced MRI and multiphasic 64-section CT • Reference standard: histology, imaging or follow-	For HCC: Sens: CT Se 69% (59-79) PPV 92% (82-97) MRI Se 82% (69-94)	Accuracy (defined as prevalence thereby showing the extent of incorporation bias): • CT 74% (65-82) • MRI 87% (77-96) lesions <2 cm	• Level of evidence: B • Dropouts: interval between CT and MR >30 days (n=140), lost to follow-up (n=26), radiofrequency thermoablation of the tumour between CT

	University hospital, Italy • Sample size: 58 patients, 109 lesions • Duration: Feb 2007-Oct 2008	and 19 women • Prevalence of disease: 87/109 lesions	up imaging	PPV 100% (95-100) Lesions <2cm CT Se 56% (42-71) PPV 88% (72-96) MRI Se 73% (55-91) PPV 100% (91-99) Differences between sensitivity statistically significant	• CT 67% (56-79) • MRI 83% (53-78) Differences statistically significant	and MRI (n=9), insufficient proof of tumour burden (n=8), subdiagnostic MR images, patient withdrew consent due to unexpected claustrophobia (n=3) • Results critical appraisal (definition of positive and negative cases, completeness of verification) spectrum bias, incorporation bias
Forner 2008[8]	• Design: cross-sectional • Source of funding: grants from Instituto de Salud Carlos III and NIH-NIDDK • Setting: University hospital Spain • Sample size: 89 patients • Duration: Nov 2003-August 2006	• Eligibility criteria: asymptomatic patients with Child-Pugh A-B cirrhosis with no history of HCC, with new solitary, well-defined, solid nodule between 5 and 20 mm detected by screening US Excluded: patients who would have undergone transplantation even without HCC diagnosis, significant comorbidities, severe clotting alterations or contraindications to perform MRI, CEUS, or fine-needle biopsy. • Patient characteristics (e.g. age, tumour characteristics, stage, etc.): median • age 65 years; hepatitis C 76.4%, Child-Pugh class A: 80 • Prevalence of disease: 67.4%	• Index test(s): CEUS and MRI • Reference standard: fine needle biopsy except in 5 cases where imaging was diagnostic in itself	For HCC: CEUS suspicious • se 78.3%, • sp 86.2%, • PPV 92.2% • NPV 71.4% • LR+ 5.682 CEUS conclusive • se 51.7% • sp 93.1% • PPV 93.9% • NPV 50.9% • LR+ 7.519 MRI suspicious • se 85% • sp 89.7% • PPV 94.4% • NPV 74.3% • LR+ 8.264 MRI conclusive • se 61.7% • sc96.6% • PPV 97.4% • NPV 54.9% • LR+ 18.182	CEUS susp + MRI susp • Se 66.7% • Sp 100% • PPV 100% • NPV 59.2% CEUS susp + MRI concl • Se 48.3% • Sp 100% • PPV 100% • NPV 48.3% CEUS concl + MRI susp • Se 46.7% • Sp 100% • PPV 100% • NPV 47.5% CEUS concl + MRI concl (=AASLD criteria) • Se 33.3% • Sp 100% • PPV 100% • NPV 42%	• Level of evidence: A2 • Dropouts: not stated • Results critical appraisal (definition of positive and negative cases, completeness of verification): complete verification, consecutive inclusion
Giorgio 2007 [9]	• Prospective cohort	• Inclusion: cirrhotic patients with	• Index tests: CEUS and	For HCC	No side-effects after injection	Level of evidence: B

	study • Support and conflicts of interest: not reported • Setting: single centre, Italy • Sample size: N=73 • Duration: September 2003 - June 2004	a single liver nodule ≤30 mm detected on previous ultrasound • Exclusion: presence of any heart disease • Patient characteristics: 100% cirrhosis; 21 (28.8%) of patients had a lesion ≤10 mm • Disease prevalence: 68.5% malignant lesions; 65.7% HCC	MRI • Reference standard: histology	CEUS, ≤10 mm: - Se: 27.3% - Sp: 100% - PPV: 100% - NPV: 55.6% MRI, ≤10 mm: - Se: 72.7% - Sp: 90.0% - PPV: 88.9% - NPV: 75.0% CEUS, >10 mm: - Se: 91.9% - Sp: 93.3% - PPV: 97.1% - NPV: 82.4% MRI, >10 mm: - Se: 94.6% - Sp: 86.7% - PPV: 94.6% NPV: 86.7%	of the contrast agent for CEUS were observed in any of the patients	• Consecutive patients • Blinded assessment of reference standard not reported (risk of reviewer bias)
Golfieri Eur Radiol 2009 [10]	• Design: cross-sectional • Source of funding: not stated • Setting: University hospital Italy • Sample size: 62 atypical nodules in 42 patients • Duration: May 2008-Oct 2009	• Eligibility criteria: atypical nodules ≤2 cm at dynamic MRI after CEUS and MDCT • Patient characteristics (e.g. age, tumour characteristics, stage, etc.): 127 male patients (91 [71.5%], mean age 54 years [range 31–77] with alcoholic [n = 18] or HBV/HCV-related cirrhosis [n = 44/65]), (not all patients included in analyses) • Prevalence of disease: 20/62 nodules, 23% of patients	• Index test(s): Gd-EOB-DTPA MRI • Reference standard: histology	For high grade dysplastic nodules or early HCC Unenhanced and dynamic MRI • Se 88.4% • Sp 88% • PPV 97% • NPV 65% Unenhanced, dynamic and hepatobiliary phase • Se 99.4% • Sp 95% • PPV 99% • NPV 97.5%	• Effect size • secondary outcome(s) • Effect size • all other outcomes	• Level of evidence: B • Dropouts: not stated • Results critical appraisal (definition of positive and negative cases, completeness of verification): unclear selection criteria, possible spectrum bias, differential verification
Golfieri Radiol Med 2009 [11]	• Design: cross-sectional • Source of funding: not stated • Setting: University hospital, Italy • Sample size:	• Eligibility criteria: cirrhotic patients with 1-3 cm nodule on US examination • Patient characteristics (e.g. age, tumour characteristics, stage, etc.): 53 men, mean age 62.8 (range 38–85) years; 10 women, mean age 65.9 (range 44–88)	• Index test(s): MDCT, SPIO-MRI and dynamic MRI • Reference standard: transplant (n=10), resection (n=6), biopsy (n=38) or follow-up (n=9)	Per-patient analyses Dynamic MRI: • Se 81.5 (68.6–90.6) • Sp 36.1 (7.5–70.1) • PPV 88.0 (75.7–95.5) • NPV 23.1 (5.0–53.8) MDCT • Se 61.1 (51.0–72.3)	Significance testing (per-patient only) • Dynamic MRI more sensitive than MDCT (i*p*=0.0034) and more accurate than MDCT (*p*=0.0490) • DC-MRI more sensitive than dynamic MRI	• Level of evidence: B • Dropouts: not stated • Results critical appraisal (definition of positive and negative cases, completeness of verification): differential verification, spectrum bias,

	63 patients • Duration: July 2003-Oct 2004	• Prevalence of disease: 87 HCCs of 123 nodules		• Sp 72.2 (54.8–85.8) • PPV 84.4 (73.1–92.2) • NPV 44.1 (31.2–57.6) SPIO-MRI • Se 79.6 (66.5–89.4) • Sp 77.8 (40.0–97.2) • PPV 95.6 (84.9–99.5) • NPV 38.9 (17.3–64.3) Dynamic MRI+MDCT • Se 83.3 (70.7–92.1) • Sp 22.2 (2.8–60.0) • PPV 86.5 (74.2–94.4) • NPV 18.2 (2.3–51.8) Dynamic MRI + SPIO-MRI • Se 100.0 (93.4–100) • Sp 22.2 (2.8–60.0) • PPV 88.5 (77.8–95.3) • NPV 100.0 (15.8–100.0)	alone (p=0.0020) MDCT alone (p<.0001), SPIO-MRI alone (p=0.0010) and the dynamic MRI/MDCT combination (p=0.0039) • DC-MRI more accurate than dynamic MRI (p=0.0117), MDCT (p=0.0005) and than the dynamic MRI/MDCT combination (p=0.0117), • Dynamic MRI/MDCT higher accuracy than MDCT alone (p=0.0352). • Dynamic MRI/MDCT more sensitive than MDCT alone (p=0.0005) and than SPIO-MRI (p=0.0009).	unclear selection criteria
Jang 2009[12]	• Prospective study • Support and conflicts of interest: not reported • Setting: single centre, Canada • Sample size: N=59 • Duration: 10 months, dates not reported	• Inclusion: patients at risk for HCC with hepatic nodules measuring 1–2 cm in their largest dimension • Exclusion: not reported • Patient characteristics: 73% male; mean age 56 y (range: 33 – 82 y). All patients had a history of chronic liver disease • Disease prevalence: 50.8% malignant lesions (all HCC)	• Index test: CEUS • Reference standards: histology (47%) or follow-up imaging for >12 months (53%)	FOR HCC CEUS - Se: 86.7% - Sp: 100% - PPV: 100% - NPV: 87.9% - Accuracy: 93.2%	-	Level of evidence: B • Not reported whether patients were consecutive (risk of selection bias) • Blinded assessment of index test and reference standards not reported (risk of reviewer bias) • Likely that benign lesions were less often verified by histology (risk of differential verification bias)
Khalili 2011 [13]	• Prospective cohort study • Support and conflicts of interest: no conflicts of interest to declare	• Inclusion: cirrhotic patients with 1–2 cm nodules found on sonographic surveillance for HCC • Exclusion: follow-up < 18 months; unconfirmed final	• Index tests: CEUS, CT and MRI • Reference standards: for lesions considered HCC: histology, growth on CT or MRI during	FOR HCC CEUS - Se: 53% (95%CI: 37-69%) - Sp: 91% (95%CI: 82-96%)	There was no statistically significant difference in the sensitivities of individual imaging modalities (p=0.6). MRI was significantly more specific than CEUS (p=0.04), but not	Level of evidence: B • Consecutive patients • Exclusion of patients with liver metastasis (risk of selection bias)

	• Setting: single centre, Canada • Sample size: N=84 patients (101 nodules) • Duration: 2 y, dates not reported	diagnosis of malignancy (i.e. treated immediately by radiofrequency ablation with no biopsy or recurrence); having hepatic metastases from colon primary • Patient characteristics: 63% male; mean age 58 y (range: 22-79) • Disease prevalence: 33.7% malignant (all HCC)	follow-up, recurrence after treatment; for lesions considered benign: long-term stability (mean follow-up 27.2 months, median 25 months, range 18–41)	- PPV: 75% (95%CI: 58-87%) - NPV: 79% (95%CI: 74-83%) - Accuracy: 78% CT - Se: 53% (95%CI: 37-69%) - Sp: 99% (95%CI: 92-100%) - PPV: 95% (95%CI: 78-99%) - NPV: 80% (95%CI: 77-82%) - Accuracy: 83% MRI - Se: 62% (95%CI: 45-76%) - Sp: 100% (95%CI: 95-100%) - PPV: 100% (95%CI: 96-100%) - NPV: 84% (95%CI: 80-84%) - Accuracy: 87%	CT Value of both CEUS and MRI positivity for the diagnosis of HCC: - Se: 35% (95%CI: 21-52%) - Sp: 100% (95%CI: 95-100%) - PPV: 100% (95%CI: 77-100%) - NPV: 75% (95%CI: 72-75%) - Accuracy: 78% Value of both CEUS and CT positivity for the diagnosis of HCC: - Se: 29% (95%CI: 17-46%) - Sp: 99% (95%CI: 92-100%) - PPV: 91% (95%CI: 64-98%) - NPV: 73% (95%CI: 70-74%) - Accuracy: 75% Value of both CT and MRI positivity for the diagnosis of HCC: - Se: 41% (95%CI: 26-58%) - Sp: 100% (95%CI: 95-100%) - PPV: 100% (95%CI: 81-100%) - NPV: 77% (95%CI: 74-77%) - Accuracy: 80% There was no significant difference in the sensitivity ($p \geq 0.61$) or specificity ($p \geq 0.07$) between the modality combinations Value of MRI negative than CEUS for the diagnosis of HCC: - Se: 79% (95%CI: 63-90%)	• The reference standard differed for lesions considered malignant, compared to lesions considered benign (risk of differential verification bias) • CT and MRI form part of the reference standard (risk of incorporation bias) • Blinded assessment of reference standards not reported (risk of reviewer bias) • Lesion-based analysis

					- Sp: 91% (95%CI: 82-96%) - PPV: 82% (95%CI: 70-90%) - NPV: 90% (95%CI: 84-94%) - Accuracy: 87% Value of MRI negative than CT for the diagnosis of HCC: - Se: 74% (95%CI: 57-85%) - Sp: 99% (95%CI: 92-100%) - PPV: 96% (95%CI: 84-99%) - NPV: 88% (95%CI: 84-89%) - Accuracy: 90% Value of CT negative than CEUS for the diagnosis of HCC: - Se: 76% (95%CI: 60-88%) - Sp: 91% (95%CI: 82-96%) - PPV: 81% (95%CI: 69-90%) - NPV: 88% (95%CI: 83-92%) - Accuracy: 86%	
Li 2007 [14]	• Prospective study • Support and conflicts of interest: financially supported by the Clinical New Technology Foundation of Southwest Hospital • Setting: single centre, China • Sample size: N=109 • Duration: not reported	• Inclusion: patients with focal liver lesions on conventional sonography and unenhanced CT • Exclusion: not reported • Patient characteristics: 66% male; mean age 46 y (range: 18-79) • Disease prevalence: 74.3% malignant lesions; 56.0% HCC	• Index tests: CEUS and ceCT • Reference standard: histology	CEUS correctly diagnosed 54/61 (88.5%) HCCs CEUS correctly diagnosed 74/81 (91.4%) malignant lesions as malignant ceCT correctly diagnosed 51/61 (83.6%) HCCs ceCT correctly diagnosed 72/81 (88.9%) malignant lesions as malignant	CEUS correctly diagnosed 26/28 (92.9%) benign lesions as benign ceCT correctly diagnosed 22/28 (78.6%) benign lesions as benign	Level of evidence: B • Unclear whether patients were consecutive (risk of selection bias) • Blinded assessment of reference standard not reported (risk of reviewer bias) • CEUS did not visualise lesions in 3/109 (2.8%) of patients, compared to 7/109 patients (6.4%) in ceCT • Incomplete outcome reporting (risk of reporting bias)
Luo 2010 [15]	• Prospective cohort study • Support and	• Inclusion: patients with suspicious focal liver lesions detected by prior conventional	• Index tests: 3D and 2D CEUS • Reference standards:	FOR HCC 3D CEUS - Se: 93%	Value of 3D CEUS for the diagnosis of liver metastasis: - Se: 84%	Level of evidence: B • Consecutive patients

	conflicts of interest: not reported • Setting: not reported • Sample size: N=119 • Duration: November 2007-May 2008	ultrasound or CT • Exclusion: patients unable to hold breath; lesions with inappropriate locations for 3D CEUS images; patients with lesions requiring histopathological diagnosis according to a reference standard but in whom surgery or biopsy was not possible due to poor liver function or lack of consent • Patient characteristics: 56% male; • Disease prevalence: 82.4% malignant lesions; 58.8% HCC	histology (45.4%) or radiological imaging (54.6%): dynamic multi-detector CT or ceMRI with at least 6 months follow-up	- Sp: 91% - Area under the ROC: 0.95 2D CEUS - Se: 92% - Sp: 87% - Area under the ROC: 0.95	- Sp: 97% - Area under the ROC: 0.95 Value of 3D CEUS for the diagnosis of hemangioma: - Se: 91% - Sp: 98% - Area under the ROC: 0.98 Value of 3D CEUS for the diagnosis of focal nodular hyperplasia: - Se: 80% - Sp: 99% - Area under the ROC: 0.99 Value of 2D CEUS for the diagnosis of liver metastasis: - Se: 84% - Sp: 97% - Area under the ROC: 0.94 Value of 2D CEUS for the diagnosis of hemangioma: - Se: 84.5% - Sp: 98% - Area under the ROC: 0.95 Value of 2D CEUS for the diagnosis of focal nodular hyperplasia: - Se: 70% - Sp: 98% - Area under the ROC: 0.98 There were no significant differences in diagnostic accuracy between 2D and 3D CEUS	• The study included a retrospective part which is not reported here as it had no data on Se, Sp, PPV or NPV • Benign lesions were less often evaluated by histology (risk of differential verification bias) • Blinded assessment of reference standard not reported (risk of reviewer bias)
Luo 2009 [16]	• Retrospective cohort study • Support and conflicts of interest: not reported • Setting: not reported	• Inclusion: focal liver tumour detected at conventional greyscale sonography; 3D CEUS clearly depicted the tumour without artefact interference; final diagnosis confirmed with histopathology	• Index test: 3D CEUS • Reference standards: histopathology (47.6%); ceCT (44.0%); ceMRI (8.3%)	For HCC CEUS - Se: 98.0% - Sp: 94.1% - PPV: 96.1% - NPV: 97.0%	Value of CEUS for the diagnosis of liver metastases: - Se: 90.0% - Sp: 95.3% - PPV: 85.7% - NPV: 96.8%	Level of evidence: B • Consecutive patients • Inconclusive index tests excluded in retrospect (risk of bias through handling of indeterminate

	• Sample size: N=84 • Duration: January - July 2007	or typical radiologic findings • Exclusion: no previous treatment for the liver lesion • Patient characteristics: 63% male; age range: 36-86 y • Disease prevalence: 83.3% malignant lesions; 59.5% HCC			Value of CEUS for the diagnosis of hemangioma: - Se: 88.9% - Sp: 98.7% - PPV: 88.9% - NPV: 98.7% Value of CEUS for the diagnosis of focal nodular hyperplasia: - Se: 80.0% - Sp: 100% - PPV: 100% - NPV: 98.8%	results) • Benign lesions were less often evaluated by histology (risk of differential verification bias) • Blinded assessment of reference standard not reported (risk of reviewer bias)
Marin Radiol 2009 [17]	• Design: cross-sectional • Source of funding: not stated • Setting: university hospital Italy • Sample size: 52 patients • Duration : Dec 2005-Dec 2006	• Eligibility criteria: patients with chronic hepatitis and suspected of having HCC based on US, elevated □-fetoprotein levels (>400 ng/mL) or both. • Patient characteristics (e.g. age, tumour characteristics, stage, etc.): 39 men (mean age, 66 years; range 29 – 74y) and 13 women (mean age, 70 years; range, 51–82y), hep- atitis B: n=15, hepatitis C: n=23, alcohol-related hepatitis: n=6, autoimmune hepatitis: n=2, cryptogenic cirrhosis: n=6. • Prevalence of disease: 69%	• Index test(s): gadobenate dime-glumine–enhanced MRI, MDCT • Reference standard: histology, follow-up imaging.	For HCC Lesion based analyses All lesions MDCT • Se 61% (49-73) • Sp 96% • PPV 96% (91-99) Dynamic MRI • Se 63% (50-74) • Sp 95.5% • PPV 95% (90-99) Combined dynamic and hepatobiliary phase MRI • Se 72% (61-82) • Sp 98% • PPV 98% (94-99) Lesions ≤2.0 cm • MDCT • Se 51% (36-69) • Dynamic MRI • Se 50% (35-69) • Combined dynamic and hepatobiliary phase MRI • Se 63% (48-77)		• Level of evidence: B • Dropouts: none • Results critical appraisal (definition of positive and negative cases, completeness of verification): exclusion of patients for not having the reference standard
Marin AJR 2009[18]	• Design: cross-sectional	• Eligibility criteria: chronic liver damage and	• Index test(s): coronal	For HCC Lesion based analyses	•	• Level of evidence: B • Dropouts: not stated

	• Source of funding: leading author has research fellowship from Bracco imaging • Setting: university hospital Italy • Sample size: 71 patients • Duration : April 2006-June 2007	suspected of having HCC on the basis of prior sonographic findings, elevated α-fetoprotein levels (> 400 ng/mL), or both. • Patient characteristics (e.g. age, tumour characteristics, stage, etc.): Child-Pugh class A: 14 cirrhosis, Child-Pugh class B cirrhosis: 39, Child-Pugh class C cirrhosis: 18. hepatitis B: 18, hepatitis C: 31, alcohol-related hepatitis: 16, autoimmune hepatitis: 2, cryptogenic cirrhosis: 4. • Prevalence of disease: 68%	reformations from isotropic voxels using 64-MDCT • Reference standard: histology or follow-up imaging	All lesions, Transverse scans only • Se 84%, • PPV 91% • AUC 0.85 Coronal scans only • Se 83%, • PPV 93% • AUC 0.86 Transverse + coronal • Se 87%, • PPV 93% • AUC 0.87 Lesions ≤2 cm, Transverse scans only • Se 72%, • PPV 85% • AUC 0.74 Coronal scans only • Se 70%, • PPV 89% • AUC 0.79 Transverse + coronal • Se 77%, • PPV 89% • AUC 0.81 No significant differences		• Results critical appraisal (definition of positive and negative cases, completeness of verification): spectrum bias
Mita 2010 [19]	• Study design: not reported • Support and conflicts of interest: not reported • Setting: not reported • Sample size: N=29 (34 nodules) • Duration: April 2008 - December 2009	• Inclusion: nodules <2 cm revealed by ultrasonography in patients with liver cirrhosis • Exclusion: not reported • Patient characteristics: 44.8% male; mean age 71 y (range: 55-84 y) • Disease prevalence: 100% malignant lesions (all HCC)	• Index test: CEUS, ceCT, CT arterioportal angiography or Gd-EOBDTPA-MRI • Reference standard: histology	For HCC CEUS f - Se: 67.6% (49.5-82.6%) ceCT f - Se: 52.9% (35.1-70.2%) CT arterioportal angiography f - Se: 88.2% (72.5-96.7%) Gd-EOBDTPA-MRI f - Se: 76.5% (58.8-89.3%) Significant difference between ceCT and CT arterioportal angiography ($p<0.05$)	Value of CEUS and Gd-EOBDTPA-MRI combined for the diagnosis of HCC: - Se: 94.1%	Level of evidence: B • Unclear whether patients were consecutive (risk of selection bias) • 100% HCC (risk of selection bias) • 1 nodule that was not histologically diagnosed as HCC despite irrespective of compatibility by imaging studies (risk of bias through handling of indeterminate results) • 2 nodules were excluded because of inconsistency in assessment by imaging reviewers (risk of bias

						through handling of indeterminate results) • Blinded assessment of index tests and reference standard not reported (risk of reviewer bias) • Sp, PPV and NPV not reported (risk of bias through incomplete reporting of results) • Lesion-based analysis
Soussan 2010 [20]	• Prospective cohort study • Support and conflicts of interest: not reported • Setting: two centers, France • Sample size: N=47 (50 lesions) • Duration: 2 y, dates not reported	• Inclusion: incidental solid focal liver lesions not characterised on ultrasound • Exclusion: history of cancer, chronic liver disease or chronic hepatitis B or C infection ; severe cardiac insufficiency, left to right cardiac shunts or acute coronaropathy; pregnant or lactating women • Patient characteristics: 26% male; mean age 45 y(range: 20-85 y) • Disease prevalence: 8.0% malignant lesions; 2% HCC	• Index tests: CEUS and ceMRI • Reference standards: histology (50%); imaging including CEUS and MRI and imaging follow-up of ≥1 y	A histotype diagnosis was obtained in 66–52% with ceMR imaging in 52–53% with CEUS (two independent reviewer data) All 4 malignant lesions were correctly classified	For hemangioma CEUS: - Se: 89% - Sp: 100% - LR: 70 ceMRI - Se: 100% - Sp: 100% - LR: 78 For focal nodular hyperplasia CEUS - Se: 74% - Sp: 88% - LR: 17 ceMRI - Se: 88% - Sp: 100% - LR: 34	Level of evidence: B • Consecutive patients • 2 CEUS tests were excluded because of uninterpretable readings (risk of bias through handling of indeterminate results) • Benign lesions were less often evaluated by histology (risk of differential verification bias) • CEUS and MRI could form part of the reference standard (risk of incorporation bias) • Clinical data were available when assessing index tests results (risk of clinical review bias) • Blinded assessment of reference standard not reported (risk of reviewer bias) • Lesion-based analysis • Se, Sp and LR were given for two independent reviewers. The best results are given here
Talbot 2010 [21]	• Design: cross-sectional • Source of funding: not stated • Setting: France	• Eligibility criteria: patients with cirrhosis or chronic liver disease including patients with a past history of HCC and newly discovered liver lesions, liver nodules	• Index test(s): F-fluorocholine and FDG-PET/CT • Reference standard: histology, physical examination,	For HCC or hepatocholangiocarcinoma F-fluorocholine Sens 88% (73-97) Spec 47% (23-72)	• Concordance between readers κ=0.76	• Level of evidence: B • Dropouts: 14 patients without ref standard • Results critical appraisal (definition of positive and negative cases,

	• Sample size: 58 patients • Duration : Dec 2005-Sept 2008	detected by ultrasonography, spiral CT, MRI, or MR angiography • Patient characteristics (e.g. age, tumour characteristics, stage, etc.): not stated • Prevalence of disease: 59%	imaging, lab tests	FDG Se 68% (50-83) Spe94% (71-100) F-fluorocholine + FDG Se 94% (80-99) Sp 94% (71-100)		completeness of verification): unclear selection criteria
Wang 2008 [22]	• Prospective cohort study • Support and conflicts of interest: not reported • Setting: single centre, China • Sample size: N=52 (67 lesions) • Duration: 10 months, dates not reported	• Inclusion: patients with fatty liver and undetermined focal liver lesions on conventional ultrasound • Exclusion: not reported • Patient characteristics: 65% male; mean age 45 y (range: 17-86 y) • Disease prevalence: 17.9% malignant lesions; 6.0% HCC	• Index test: CEUS • Reference standard: histology	For malignant liver lesion CEUS - Se: 91.7% - Sp: 90.9% - PPV: 68.8% - NPV: 98.0% - Accuracy: 91%	All misdiagnosed lesions were >2cm 1 HCC was misdiagnosed as benign	Level of evidence: B • Consecutive patients • Blinded assessment of reference standard not reported (risk of reviewer bias) • Lesion-based analysis
Xu 2008[23]	• Prospective cohort study • Support and conflicts of interest: National Scientific Foundation and New Century Excellent Talent Supporting Program of Chinese Ministry of Education • Setting: single centre, China • Sample size: N=104 • Duration: March 2004 – March 2005	• Inclusion: patients with focal liver lesions ≤2 cm on conventional sonography • Exclusion: previous treatment of the lesion; simple cysts • Patient characteristics: 78% male; mean age 48 y (range: 20-79) • Disease prevalence: 53.8% malignant lesions; 47.1% HCC	• Index test: CEUS • Reference standards: histology, or imaging studies with a follow-up of ≥12 months; or for HCC based on international consensus of clinical diagnostic criteria for HCC sized 1–2 cm in cirrhotic patients, including coincidental typical vascular pattern on2 dynamic imaging studies such as contrast enhanced CT and MRI	For HCC CEUS f - Se: 79.6% - Sp: 92.7% - PPV: 90.7% - NPV: 83.6% - Accuracy: 86.5% Lesions ≤ 1.5 cm: - Se: 84.6% - Sp: 89.7% - PPV: 78.6% - NPV: 92.9% - Accuracy: 88.1% Lesions 1.6-2 cm: - Se: 77.8% - Sp: 96.2% - PPV: 96.6% - NPV: 75.8% - Accuracy: 85.8%	For HCC CEUS, lesions ≤ 6 cm depth: - Se: 77.4% - Sp: 97.5% - PPV: 92.3% - NPV: 86.7% - Accuracy: 88.7% CEUS, lesions >6 cm depth: - Se: 83.3% - Sp: 80.0% - PPV: 83.3% - NPV: 80.0% - Accuracy: 81.8%	Level of evidence: B • Consecutive patients • The study reports accuracy data for conventional ultrasound, which are not reported here • Not all CEUS findings underwent the same reference standard (risk of differential verification bias) • Blinded assessment of reference standard not reported (risk of reviewer bias)
Zuber-Jerger 2009[24]	• Prospective study • Support and	• Inclusion: patient with a liver lesion detected during	• Index test: CEUS • Reference standards:	For malignant liver lesion CEUS	For hemangioma CEUS	Level of evidence: B

	conflicts of interest: not reported • Setting: single centre, Germany • Sample size: N=86 (100 lesions) • Duration: April 2005 - January 2006	ultrasound • Exclusion: planned liver transplantation • Patient characteristics: 55% male; median age 65 y (range: 24-88 y) • Disease prevalence: 55.0% malignant lesions; 6.0%HCC	histology or ceCT or ceMRI in the case of suspected hemangioma	- Se: 98% - Sp: 93% - PPV: 95% - NPV: 98% - Accuracy: 93% For HCC: Accuracy 16.7%	- Se: 100% - Sp: 100% - PPV: 100% - NPV: 100% - Accuracy: 100%	• Unclear whether patients were consecutive (risk of selection bias) • The reviewer of the index test was aware of clinical data (risk of clinical review bias) • Blinded assessment of reference standard not reported (risk of reviewer bias) • Patients with a suspected hemangioma did not get histology verification (risk of differential verification bias) • Three patients with an unclear final diagnosis were excluded (risk of bias through handling of indeterminate results) • Lesion-based analysis

Abbreviations: 3D: 3-dimensional; ceCT: contrast enhanced CT; CEUS: contrast-enhanced ultrasound; CEHIUS: contrast enhanced harmonic imaging ultrasound; CI: confidence interval; CT: computer tomography; Gd-EOBDTPA: gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid; HCC: hepatocellular carcinoma; LR: likelihood ratio; MRI: magnetic resonance imaging; msCT: multi slice CT; NPV: negative predictive value; PPV: positive predictive value; ROC: receiver operating curve; sCT: spiral CT; Se: sensitivity; Sp: specificity; y: years, LR+: positive likelihood ratio, PSIL: percentage of signal intensity loss, T2WI: T2 weighted axial imaging, FS-T2WI: fat excitation suppression – T2 weighted axial imaging, MDCT: multidectector row CT, DC-MRI: double contrast MRI = dynamic MRI + SPIO-MRI, SPIO-MRI: superparamagnetic iron oxide MRI, Gd-EOB-DTPA gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid

SYSTEMATIC REVIEWS

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary and other outcomes	VII Critical appraisal of review quality
Xia 2010[25]	• Design: SR • Source of funding: none stated • Search date: Oct 2009 • Searched databases: Medline, Embase, Web of Science, Central • Included study designs: diagnostic accuracy studies • Number of included studies: 14	• Eligibility criteria: assessing the diagnostic accuracy of DW-MRI for malignant hepatic lesions; providing both sensitivity and specificity; • sufficient information to construct the 2x2 table for individual study subjects; stating • a test method for DW-MRI • Patient characteristics: 804 patients, 1665 hepatic lesions	• Index test(s): diffusion-weighted MRI • Reference standard: histology , follow-up, imaging including MRI	For malignant lesions: Pooled sensitivity 91% (86-94) Pooled specificity 93% (86-97) Significant heterogeneity	• metaregression for QUADAS score not significant • SENSE technique significantly affecting sensitivity • indications of publication bias, true accuracy may be lower	• Level of evidence • Results critical appraisal (definition of positive and negative cases, completeness of verification): incorporation bias in several studies, little information on individual design