Uitgangsvraag 1 b: Hoe vaak moet gescreend worden op HCC, elke 6 maanden of elke 12 maanden?

Primary studies

1 Treatment

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
Santagostino 2003 {Santagostino, 2003 #16}	• Design: controlled trial • Source of funding: not stated • Setting: 11 Italian hospitals • Sample size: n=559 • Duration: 6 years	• Eligibility criteria: haemophiliacs with HCV infection • *A priori* patient characteristics: 99% males, 54% severe haemophilia A, 28% moderate/mild haemophilia A, 37% severe haemophilia B, 22% moderate/mild haemophilia B, 12% cirrhosis • Group comparability: not reported	Intervention(s): Screening with 6 months interval with US+AFP vs. Comparator(s): screening with 12 months interval with US+AFP	• Effect size Primary outcome Detection of multinodular HCC: 2.4% in 6-month screening 0.6% in 12-month screening (not significant)	• Effect size secondary outcome(s) 8 patients with HCC older at time of HCV infection, more often had cirrhosis, alcohol abuse, hgher AFP levels, higher ALT levels. • Effect size all other outcomes multivariate analysis of 8 HCC cases and 104 age-matched controls: AFP at entry >11 ng/ml Alcohol intake >80 g/d	Level of evidence: B • Dropouts • Results critical appraisal: Controlled but not randomised trial, probably more differences between groups than just intervention
Zhang 2004{Zhang, 2004 #26}	• Design: cluster RCT • Source of funding: none reported • Setting: Shanghai, China • Sample size: n=18816 • Duration: 1993-1995	• Eligibility criteria: chronic hepatitis B patients • *A priori* patient characteristics: 63% males, mean age 42 and 41y respectively • Group comparability: well balanced on individual level for sex, age, no. HBsAg+, no information on balance between clusters	Intervention(s): AFP+US every 6 months Vs. Comparator(s) usual care	• Effect size Primary outcome - Overall mortality: not reported - HCC mortality: 0.62 (0.40-0.94)	• Effect size secondary outcome(s) • Effect size all other outcomes - Number of HCC detected: Peto OR 1.32 (0.96-1.82) - Stage I HCC: Peto OR 7.65 (4.44-13.18)	Level of evidence: B • Dropouts: not reported • Results critical appraisal Duplicate of study by Yang et al. which is included in the Cochrane review, cluster RCT with unclear allocation concealment, unclear balance between clusters, unblinded outcome assessment

1.1 Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Gebo 2002{Gebo, 2002 #9}	• Design: systematic review • Sources of funding: AHRQ • Search date: March 2002 • Searched databases: Medline, BIOSIS, Science Citation Index, MANTIS, AMED, PsycINFO and Sociological abstracts, reference lists, hand searching • Included study designs: studies on surveillance (design not specificed) + diagnostic accuracy studies • Number of included studies: 1 study on the efficacy of screening tests and 7 diagnostic accuracy studies for US	• Eligibility criteria: studies on patients with chronic hepatitis C • *A priori* patient characteristics: 5 studies on hepatitis C patients only, 19 on hepatitis B or C or both	Intervention(s): Surveillance of screening for HCC vs Comparator(s): not specified	• Effect size primary outcome(s) 1 prospective cohort, n=360, US+AFP 6 months interval, n=2170 usual care *incidence HCC* 6.7% screened 5.5% usual care *lesions unifocal and <3cm* 75% in screened 16% in usual care	• Effect size secondary outcome(s) sens 11-99% spec 95-100% • Effect size all other outcomes	Level of evidence: A2 • Results critical appraisal Good search strategy but poorly reported results
Thompson Coon 2007{Thompson Coon, 2007 #21}	• Design: systematic review • Sources of funding: HTA UK • Search date: 2005 • Searched: databases: MEDLINE, Embase, Cochrane Controlled Trials Register, BIOSIS, DARE, ISTP (Index to Scientific and Technical Proceedings), ISI Science Citation Index, National Research Register. • Included study designs: RCTs • Number of included	• Eligibility criteria: RCTs in English on cirrhotic patients undergoing surveillance with AFP and/or US • *A priori* patient characteristics: no studies included	Intervention(s): AFP or US (alone or in combination) vs. Comparator(s): no intervention or either AFP or US alone	• Effect size primary outcome(s) No studies included	• Effect size secondary outcome(s) • Effect size all other outcomes • No studies included	Level of evidence: A2 • Results critical appraisal: Good search strategy

	studies: none					
Wun 2009{Wun, 2003 #23}	• Design: systematic review • Sources of funding: Copenhagen Hospital Corporation's Medical Research Council's Grant on Getting Research into Practice (GRIP), Denmark • Search date: August 2002 • Searched databases: Cochrane Hepato-Biliary Group Controlled Trials • Register, The Cochrane Controlled Trials Register, MEDLINE, EMBASE, Health- • Star, and Chinese Medical Literature Electronic • Databases, reference lists, author contacts • Included study designs: RCTs • Number of included studies: n=2	• Eligibility criteria: hepatitis B patients with or without cirrhosis • *A priori* patient characteristics: • 1 study in Shanghai hep B patients 35-55 years, • 1 study in Canada hep B patients >18 years	Intervention(s): AFP, US or a combination of both vs. Comparator(s): no screening, AFP, or US	• Effect size primary outcome(s) US vs no screening: no studies AFP + US vs no screening (Yang 1999) • All-cause mortality: not reported • HCC mortality: Peto OR 0.81 (0.54-1.22) AFP vs AFP+US: (Sherman 1995) • Overall mortality: not reported • HCC mortality: not reported	• Effect size secondary outcome(s) • Effect size all other outcomes AFP + US vs no screening • number of HCC detected: Peto OR 1.69 (1.20-2.36), updated in 2002 Peto OR 1.29 (0.94-1.78) • HCC resectability: Peto OR 7.14 (3.53-14.43) • 5-year survival of resected patients: 84.9% vs 0% AFP vs AFP+US • Number of HCC detected: Peto OR 0.74 (0.26-2.12)	Level of evidence: A2 • Results critical appraisal Good search, adequate quality assessment

1. Diagnosis

2.1 Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Colli 2006{Colli, 2006 #6}	• Design: systematic review • Source of funding: Cariplo foundation • Search date: December 2004 • Searched databases: Medline, Embase, Cochrane Library,	• Eligibility criteria: studies on patients with chronic liver disease and outcome HCC • Patient characteristics: 10 studies included patients with cirrhosis only (remaining 2 studies 93% and 29%	Index test(s): US Reference standard: histology and/or follow-up	• Sensitivity, specificity, PPV, NPV, LR+, LR-: Across 10 studies with cirrhotic patients: Sens 30-92% Spec 73-100%	• Effect size secondary outcome(s) • Effect size all other outcomes	Level of evidence: A2 • Results critical appraisal (definition of positive and negative cases, completeness of verification) Valid systematic review but included studies of unclear

	CancerLit, reference lists, proceedings major meetings • Included study designs: diagnostic accuracy studies • Number of included studies: 14 on US	cirrhotics respectively; 2 studies did not report proportion of cirrhotics), 11 studies in asymptomatic patients		Subgroup 8 studies with explanted liver histology as reference standard, pooled results Sens 48% (34-62) Spec 97% (95-98) LR+ 8.2 (5.3-12.7) LR- 0.6 (0.5-0.7) (clinical heterogeneity!)		and probably low quality (case-control studies, studies >25 years old)
De Masi 2005{De Masi, 2005 #8}	• Design: systematic review • Source of funding: not reported • Search date: 2003 • Searched databases: Medline and Embase • Included study designs: not stated • Number of included studies: not stated	• Eligibility criteria: studies on screening for HCC • Patient characteristics: not stated	Index test(s): US Reference standard: not stated	• Sensitivity, specificity, PPV, NPV, LR+, LR- In cirrhotic patients: Sens 58-87% Spec 93-94% In non-cirrhotic patients Sens 71-90% Spec 93-94%	• Effect size secondary outcome(s) Median survival 20-30 months among cirrhotic patients 6 month screening: 36 months median survival 12 month screening: 34 months survival no screening 14 months 1 RCT in HBV patients (Yang et al): 1-year survival 88.1% in screened group, 0% control group 2-year survival: 77.5% in screened group, 0% in control group. All studies used US+AFP • Effect size all other outcomes	Level of evidence: A2 • Results critical appraisal (definition of positive and negative cases, completeness of verification) Study quality not assessed, characteristics studies insufficiently described
Singal 2009{Singal, 2009 #17}	• Design: systematic review • Sources of funding: grant numbers but no institution given • Search date: July 2007 • Searched databases: Medline, Scopus and reference lists • Included study designs: diagnostic accuracy studies • Number of included studies: n=13	• Eligibility criteria: prospective studies on US with or without AFP for HCC surveillance in cirrhotic patients • Patient characteristics: not given	Index test(s): US with or without AFP Reference standard: variable: histology, angiography, CT, MRI, AFP	• Sensitivity, specificity, PPV, NPV, LR+, LR- **All HCC** (5 studies) sens 94% (83–98) spec 94% (89–97) OR 232.7 (105.9–511.2) **Early HCC** (13 studies) sens 63% (49–76) sens of studies with concurrent tests	• Effect size secondary outcome(s) • Effect size all other outcomes	Level of evidence: A1 • Results critical appraisal (definition of positive and negative cases, completeness of verification) Good search strategy, little information on patients included in the studies, suboptimal pooling method

				such as CT 33% (7.7-58.9) studies with <6 month surveillance sens 70.1% (55.6-84.6) studies with 6-12 months surveillance sens 50.1% (40.0-59.2) spec not reported because false positives only reported in 6/13 studies		

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

Uitgangsvraag 3: Welke prognostische factoren moeten er beschreven worden in het pa-verslag van het resectiepreparaat van HCC patiënten?

Primaire studies

I Study ID	II Method	III Patient characteristics	IV Prognostic factors included in analysis	V Results multivariate analysis	VI Results other analyses	VII Critical appraisal of study quality
Minagawa 2007	• Retrospective single cohort study • Funding/CoI: not reported • Setting: nationwide registry, Japan • Sample size: N=13566 • Duration: 1995-2001	• Eligibility criteria: ○ Patients with HCC undergoing curative hepatic resection ○ N0M0 ○ Patients without pathologic data, incomplete survival data and without data on operative curability, distant metastasis, or hepatic lymph node metastasis were excluded • *A priori* patient characteristics: ○ Male: 79.5% ○ 60+: 67% ○ HBV: 19.8%; HCV: 66.5% ○ Child-Pugh A: 62.4%	• Number of HCC lesions (including intrahepatic metastasis) • Tumour diameter (largest dimension of tumour specimen) • Portal invasion (none, 3rd branch, 2nd branch, 1st branch or trunk) • Hepatic venous invasion (none, branch of HV, trunk of HV or IVC) • Bile duct invasion (none, intrahepatic bile duct, extrahepatic bile duct) • Grade of differentiation (well, moderately, poorly, undifferentiated) • Background liver (normal, hepatitis, cirrhosis) • Gross classification (type 1, 2 or 3, multinodular type, massive type of Eggel, diffuse type of Eggel) • Hepatic involvement (1 segment, 1 sector, 2 sectors, at least 3 sectors) • Fibrous capsule • Macroscopic intrahepatic metastasis (none, within 1 sector, within 2 sectors, 3 sectors or more)	Significant pathologic factors for OS (RR [95%CI]): • Vascular or bile duct invasion: RR 1.36 (1.29-1.43) • Liver cirrhosis: RR 1.26 (1.20-1.32) • Tumour diameter > 2cm: RR 1.21 (1.14-1.28) • Multiple HCC lesions: RR 1.18 (1.12-1.23) • Hepatic involvement > 1 segment: RR 1.14 (1.09-1.19) • Differentiation: RR 1.14 (1.08-1.20) • Gross classification: RR 1.13 (1.08-1.18)	• Based on the results of the MVA, 3 factors were selected for the LCSGJ-T staging system: vascular or bile duct invasion, diameter, and single/multiple. Patients with 0 factors were T1, with 1 factor T2, 2 factors T3 and 3 factors T4 • 5-year overall survival, LCSGJ-T vs. AJCC-T: ○ T1: 70% vs. 61% ○ T2: 58% vs. 46% ○ T3: 41% vs. 30% ○ T4: 24% vs. -	Level of evidence: C • Population-based study • 5382 patients excluded based on exclusion criteria • Median follow-up: not reported
Ikai 2004	• Retrospective single	• Eligibility criteria:	• Number of HCC lesions	Significant pathologic		Level of evidence: C

I Study ID	II Method	III Patient characteristics	IV Prognostic factors included in analysis	V Results multivariate analysis	VI Results other analyses	VII Critical appraisal of study quality
	cohort study • Funding/CoI: not reported • Setting: nationwide registry, Japan • Sample size: N=12118 • Duration: 1/1990-12/1999	○ Patients with HCC undergoing hepatic resection • *A priori* patient characteristics: ○ Male: 78.9% ○ Mean age: 62.5 years	• Tumour diameter (maximal tumour dimension) • Intrahepatic extent of tumour (H1: 1 segment; H2: 2 segments; H3: 3 segments; H4: >3 segments) • Extrahepatic metastasis • Growth type (expansive or invasive growth) • Septum formation • Portal invasion • Hepatic venous invasion • Bile duct invasion • Surgical curability • Surgical free margin • Background liver • Fibrous capsule	factors for OS (HR [95%CI]): • Tumour diameter > 10cm vs. ≤ 2cm: HR 2.53 (2.07-3.09) • Multiple HCC lesions: HR 1.19 (1.05-1.35) • Intrahepatic extent of tumour (H3/H4 vs. H1 or less): HR 1.03 (??) (1.07-1.57) • Extrahepatic metastasis: HR 2.19 (1.55-3.09) • Portal vein invasion: HR 1.46 (1.31-1.62) • Hepatic vein invasion: HR 1.17 (1.01-1.36) • Surgical curability: HR 1.40 (1.18-1.65) • Surgical free margin: HR 1.10 (1.01-1.20)		• Population-based study • Dropouts not discussed • Median follow-up: 21.5 months (range 0.03-119.7 months)
Zhang 2000	• Retrospective single cohort study • Funding/CoI: not reported • Setting: single university centre, China • Sample size: N=1457 • Duration: 1/1990-12/1995	• Eligibility criteria: ○ Patients with HCC undergoing curative or relatively curative hepatic resection • *A priori* patient characteristics: ○ Male: 87.5% ○ Mean age: 49.0 years ○ Preoperative TACE: 8.2%	• Intraoperative lesion number • Extent of resection • Surgical margin • Intraoperative tumor thrombus • Tumour size • Tumour gross type • Pathologic type • Edmondson16 classification • Tumour growth style • Capsular invasion • Daughter nodules • Vascular invasion • Cirrhosis • pTNM stage	Significant pathologic factors for DFS: • Daughter nodules: HR 9.259, p<0.001 • Vascular invasion: HR 2.662, p=0.007 • Intraoperative thrombus: HR 0.247, p=0.005 • Tumour size: HR 1.374, p=0.010 • Tumour gross type: HR 0.202, p=0.003		Level of evidence: C • Follow-up results not obtained for 268/1725 cases: excluded from analysis • Median follow-up: not reported • No clear definitions of prognostic factors provided
Qiang 2006	• Retrospective single cohort study • Funding/CoI: supported by the Department of Hepatobiliary Surgery, Cancer Hospital of	• Eligibility criteria: ○ Patients with HCC undergoing curative hepatic resection • *A priori* patient characteristics:	• Number of nodules • Tumour capsule • Tumour size of main nodule • Vascular invasion (portal or hepatic vein	Significant pathologic factors for DFS (RR [95%CI]): • Vascular invasion: RR 2.72 (2.31-3.20) • Liver cirrhosis: RR 1.46		Level of evidence: C • Lost-to-follow-up: 3.46% • Median follow-up: not reported

I Study ID	II Method	III Patient characteristics	IV Prognostic factors included in analysis	V Results multivariate analysis	VI Results other analyses	VII Critical appraisal of study quality
	Tianjin Medical University, and Division of Community Health, Memorial University of Newfoundland, St. John's, Newfoundland, Canada; CoI not reported • Setting: single university centre, China • Sample size: N=1157 • Duration: 1/1998-12/2003	○ Male: 87.6% ○ Age: 16-85 years ○ HBV: 89% ○ Child-Pugh A: 29.1%	invasion) • Cirrhosis	(1.13-1.87) • Tumour diameter > 5cm: RR 2.21 (1.85-2.63) • Multiple nodules: RR 2.69 (2.22-3.24) • Tumour capsule: RR 1.67 (1.40-1.99)		
Fan 2009	• Retrospective single cohort study • Funding/CoI: supported by combined grants from National Natural Science Foundation of China (No.30873039, 30571801), Shanghai Science and Technology Development Funds (No.06QA14012, No.054119530), Foundation of Shanghai Science Technology Commission (No. 07JC14010, 06xD14004, 044119608 and 07SP07003), the National Key Sci-Tech Special Project of China (No.2008ZX10002-022), and the Program for Excellent Disciplinary Leaders of Shanghai Health Bureau (No.LJ06004) • Setting: 7 centres, China • Sample size: N=1078 • Duration: 4/2001-5/2007	• Eligibility criteria: ○ Patients with HCC undergoing liver transplantation • *A priori* patient characteristics: ○ Male: 90.0% ○ Median age: 49.0 years ○ HBV: 85.3%; HCV: 3.2% ○ Cirrhosis: 90.4% ○ Child-Pugh A: 47.0%	• Cirrhosis • Tumour differentiation (modified Edmondson) • Total tumour size (sum of maximal diameter of each lesion) • Number of nodules • Tumour satellite • Tumour site (left lobe, right lobe, bilobe) • Tumour capsule • Lymph node invasion • Macrovascular invasion • Microvascular invasion • pTNM (UICC)	Significant pathologic factors for OS (HR [95%CI]): • Tumour differentiation: HR 1.46 (1.16-1.84) • Total tumour size (≤9 vs. >9 cm): HR 1.74 (1.31–2.32) • Tumour number > 3: HR 1.50 (1.09–2.08) • Macrovascular invasion: HR 1.38 (1.05-1.83)	Significant pathologic factors for DFS (HR [95%CI]): • Tumour differentiation: HR 1.62 (1.33–1.98) • Total tumour size (≤9 vs. >9 cm): HR 1.71 (1.33–2.18) • Tumour number > 3: HR 1.41 (1.07–1.86) • Tumour capsule: HR 0.74 (0.56–0.98) • Macrovascular invasion: HR 1.56 (1.23-1.96)	Level of evidence: C • Lost-to-follow-up: N=81 • Mean follow-up: 35.3 months • Consecutive patient inclusion
Wu 2011	• Retrospective single cohort study	• Eligibility criteria: ○ Patients with HCC	• Cirrhosis • Tumour grade	**HCC size > 5 cm**	**HCC size < 5 cm**	Level of evidence: C

I Study ID	II Method	III Patient characteristics	IV Prognostic factors included in analysis	V Results multivariate analysis	VI Results other analyses	VII Critical appraisal of study quality
	• Funding/CoI: no CoI to declare • Setting: single university centre, Taiwan • Sample size: N=1048 • Duration: 1/1999-6/2005	undergoing liver resection • *A priori* patient characteristics: ○ Male: 79.8% ○ Mean age: 56.3 years ○ HBV: 62.3%; HCV: 29.9%	(Edmondson) • Tumour size • Resection weight • Tumour satellite • Tumour rupture • Tumour capsule • Vascular invasion • Steatosis	Significant pathologic factors for OS (OR [95%CI]): • Vascular invasion: OR 2.30 (1.69-3.12) • Steatosis: OR 0.67 (0.47-0.95) Significant pathologic factors for DFS (OR [95%CI]): • Vascular invasion: OR 1.79 (1.37-2.33) • Cirrhosis: OR 1.36 (1.05-1.77)	Significant pathologic factors for OS (OR [95%CI]): • Vascular invasion: OR 1.64 (1.21-2.21) • Cirrhosis: OR 1.70 (1.21-2.38) Significant pathologic factors for DFS (OR [95%CI]): • Vascular invasion: OR 1.29 (1.01-1.64) • Cirrhosis: OR 1.79 (1.39-2.29)	• Dropouts: not reported • Median follow-up: 53.1 months • No clear definition of most pathologic factors
Nathan 2009	• Retrospective single cohort study • Funding/CoI: Support by grant 1KL2RR025006-01 from the National Center for Research Resources (NCRR) • Setting: SEER database, US • Sample size: N=788 • Duration: 1988-2005	• Eligibility criteria: ○ Patients with HCC undergoing hepatic resection (not ablation or transplantation) ○ Patients with tumors >5 cm in size or missing size data, extrahepatic tumor extension, or major vascular invasion were excluded ○ Patients with nodal disease (N1) or unknown N classification and patients with metastatic disease (M1) or unknown M classification were excluded • *A priori* patient characteristics: ○ Male: 70% ○ Median age: 63 years	• Tumour grade (well, moderately, poorly, undifferentiated, unknown) • Tumour size • Microvascular invasion • Number of nodules • Cirrhosis	Significant pathologic factors for OS (HR [95%CI]): • Microvascular invasion: HR 1.44 (1.11-1.86) • Tumour size >2 cm: HR 1.51 (1.12–2.03) • Multifocality: HR 1.44 (1.11–1.86) • Cirrhosis: HR 1.67, p=0.003 (subset of 253 patients)		Level of evidence: C • Consecutive patients • Dropouts not reported • Median follow-up not reported
Shimada 2005	• Retrospective single cohort study • Funding/CoI: Supported by a Grant-in-Aid for cancer research from the Ministry of Health,	• Eligibility criteria: ○ Patients with HCC undergoing curative hepatic resection ○ Surviving at least 1 month after surgery	• Tumour size • Resection margin • Number of nodules • Portal vein invasion • Intrahepatic metastases • Background liver	Significant pathologic factors for 10-year OS (OR [95%CI]): • Intrahepatic metastases: OR 2.48 (1.31-4.68)		Level of evidence: C • Dropouts: 8 patients who were lost to follow-up, and 14 patients who died of

I Study ID	II Method	III Patient characteristics	IV Prognostic factors included in analysis	V Results multivariate analysis	VI Results other analyses	VII Critical appraisal of study quality
	Labor, and Welfare of Japan • Setting: single centre, Japan • Sample size: N=481 • Duration: 1/1987-12/1993	and discharge from hospital after surgery • *A priori* patient characteristics: ○ Male: 79.6% ○ Mean age: 60 years ○ Preoperative TACE: 68.4%	parenchyma	• Portal vein invasion: OR 1.98 (1.05-3.74) • Noncancerous liver parenchyma: OR 3.09 (1.69-5.64) • Solitary nodule: OR 3.12 (1.62-6.02)		non-cancer causes within 10 years of the surgery were excluded from the study • Median follow-up: 6 years
Vauthey 2002	• Retrospective single cohort study • Funding/CoI: not reported • Setting: 4 centres, multinational • Sample size: N=557 • Duration: 1980-1998	• Eligibility criteria: ○ Patients with HCC undergoing curative hepatic resection ○ Surviving at least 1 month after surgery ○ Patients with incomplete survival data were excluded • *A priori* patient characteristics: ○ Male: 69% ○ Mean age: 59 years ○ HBV: 36% ○ Child-Pugh A: 83%	• Fibrosis stage • Tumour size (largest dimension of tumour specimen) • Number of nodules • Tumour location (unilobular, bilobular) • Microvascular invasion • Macrovascular invasion • Edmondson Steiner	Significant pathologic factors for OS (HR [95%CI]): • Major vascular invasion: HR 2.1 (1.4-3.3) • Microvascular invasion: HR 1.6 (1.2-2.1) • Tumour size >5 cm: HR 1.4 (1.1–1.9) • Multifocality: HR 1.5 (1.1–1.9) • Severe fibrosis/cirrhosis: HR 1.6 (1.2-2.2)		Level of evidence: C • Dropouts not reported • Median follow-up: 35 months
Regimbeau 2004	• Retrospective single cohort study • Funding/CoI: not reported • Setting: 4 centres, multinational • Sample size: N=547 • Duration: 1980-1999	• Eligibility criteria: ○ Patients with HCC undergoing curative partial hepatic resection ○ Exclusion of patients who died of unknown causes (N=28) or with follow-up < 1 year (N=16) • *A priori* patient characteristics: not presented for entire cohort	• Fibrosis grade • Hepatitis grade • Tumour size (largest dimension of tumour specimen) • Number of nodules • Tumour location (unilobar, bilobar) • Histopathologic type (microtrabecular, macrotrabecular, acinar, diffuse) • Tumour grade (Edmondson) • Degree of necrosis • Fibrous capsule • Minor vascular invasion • Major vascular invasion • Nuclear polymorphism (mild, moderately, marked) • Resection margin	Significant pathologic factors for early death due to recurrence (OR [SE]): • Nuclear polymorphism: OR 3.0 (0.52) • Tumour size >5 cm: OR 3.0 (0.51) • Multifocality: OR 3.3 (0.50)		Level of evidence: C • Median follow-up: 33 months • Dropouts not reported • Very probably same patients as Vauthey 2002

I Study ID	II Method	III Patient characteristics	IV Prognostic factors included in analysis	V Results multivariate analysis	VI Results other analyses	VII Critical appraisal of study quality
Zhou 2010	• Retrospective single cohort study • Funding/CoI: not reported • Setting: single university centre, China • Sample size: N=528 • Duration: 1/2000-4/2005	• Eligibility criteria: ○ Patients with HCC undergoing curative hepatic resection • *A priori* patient characteristics: ○ Male: 86.9% ○ Median age: 65.8 years ○ HBV: 36.3%; HCV: 46.4%	• Tumour differentiation (Edmondson) • Vascular invasion • TNM stage • pAkt expression • PTEN expression • p27 expression • pS6 expression	Significant pathologic factors for OS (OR [95%CI]): • Tumour differentiation: OR 2.15 (1.32-1.51) • Vascular invasion: OR 4.98 (1.46-12.01) • TNM stage: OR 2.32 (1.11-3.09) • pAkt expression: 2.96 (1.18-10.79) • PTEN expression: 2.61 (1.69-3.98) • p27 expression: OR 1.69 (1.12-2.55) • pS6 expression: OR 3.86 (1.71-8.76)		Level of evidence: C • Consecutive patient inclusion • Median follow-up: 42 months • Vascular invasion not clearly defined
Yang 2009	• Retrospective single cohort study • Funding/CoI: Supported by National Key Technologies R and D Program of China, (2001BA703B04, 2004BA703B02), National Keystone Basic Research Program of China (2004CB720303), National Science Fund for Distinguished Young Scholars of China (30328028), National Natural Science Foundation of China (30571826), and National High Technology Research and Development Program of China (2006AA02Z4B2); CoI not reported • Setting: single centre, China • Sample size: N=481 • Duration: 1/1992-12/2002	• Eligibility criteria: ○ Patients with HCC undergoing hepatic resection • *A priori* patient characteristics: ○ Male: 89.4% ○ Age ≥ 50: 42.8% ○ HBV: 92.5% ○ Child-Pugh A: 81.1%	• Cirrhosis • Tumour size • Degree of necrosis • Fibrous capsule • Vein invasion • Edmondson-Steiner Grade • Tumour nodule number	Significant pathologic factors for OS (HR [95%CI]): • Vein invasion: HR 48.74 (4.76-498.37)		Level of evidence: C • Consecutive patient inclusion • Median follow-up: 38 months • Dropouts not reported • No clear definition of prognostic factors

I Study ID	II Method	III Patient characteristics	IV Prognostic factors included in analysis	V Results multivariate analysis	VI Results other analyses	VII Critical appraisal of study quality
Wang 2009	• Retrospective single cohort study • Funding/CoI: not reported • Setting: single university centre, Taiwan • Sample size: N=473 • Duration: 1/1993-12/2002	• Eligibility criteria: ○ Patients with HCC undergoing hepatic resection with curative intent • *A priori* patient characteristics: ○ Male: 80.1% ○ Mean age: 53.1 years ○ HBV: 68.5%; HCV: 28.9% ○ Child-Pugh A: 83.3%	• Histopathology of non-tumour tissue • Adjacent tissue invasion • Tumour size (largest diameter of tumour) • Number of nodules (single vs. multiple) • Tumour location (unilateral, bilateral) • Microvascular invasion • Daughter nodule • Resection margin	Significant pathologic factors for DFS (RR [95%CI]): • Microvascular invasion: RR 1.85 (1.41-2.42) • Liver cirrhosis: RR 1.83 (1.40-2.40) • Tumour diameter > 10cm: RR 2.07 (1.34-2.90) • Bilateral disease: RR 2.22 (1.16-4.26) • Daughter nodule: RR 2.18 (1.58-3.01)		Level of evidence: C • Consecutive patient inclusion • Mean follow-up: 3.6 years • Dropouts not reported
Duffy 2007	• Retrospective single cohort study • Funding/CoI: grant support from The George T. Pfleger Foundation, The DuMont Foundation, The JoAnn Barr Foundation, Dr. Soliman Fakeeh, The W.K. Day Foundation, and Mr. Gilbert I. Garfield; CoI not reported • Setting: single centre, US • Sample size: N=467 • Duration: 1984-2006	• Eligibility criteria: ○ Patients with HCC undergoing orthotopic liver transplantation • *A priori* patient characteristics: ○ Male: 60% ○ Mean age: 57 years ○ HBV: 17%; HCV: 55%	• Multifocal tumour • Lymphovascular invasion • Tumour differentiation (well, moderately, poorly) • Tumour size	Significant pathologic factors for OS: • Multifocal tumour: HR 0.22, p<0.001 • Lymphovascular invasion: HR 2.44, p<0.001 • Tumour differentiation: HR 4.53, p=0.002		Level of evidence: C • Mean follow-up: 6.6 years • Dropouts not reported
Lim 2011	• Retrospective single cohort study • Funding/CoI: Supported by the Khoo Clinical Discovery Project Award of the Duke-NUS Graduate Medical School; CoI not reported • Setting: two centres, Singapore • Sample size: N=454 • Duration: 1/2000-3/2009	• Eligibility criteria: ○ Patients with HCC undergoing curative hepatic resection ○ No concomitant non-HCC cancers • *A priori* patient characteristics: ○ Male: 81% ○ Mean age: 61.3 years ○ HBV: 66% ○ Child-Pugh A: 93%	• Cirrhosis • Adjacent tissue invasion • Tumour size (size of largest tumour) • Number of nodules • Tumour grade (Edmondson) • Microvascular invasion • Resection margin	Significant pathologic factors for OS (HR [95%CI]): • Microvascular invasion: HR 2.12 (1.52-2.97) • Invasion of contiguous organs: HR 2.74 (1.08-6.94) • Cirrhosis: HR 1.49 (1.07-2.07)		Level of evidence: C • Median follow-up: 27.7 months • Dropouts not reported
Pawlik 2004	• Retrospective single cohort study	• Eligibility criteria: ○ Patients with HCC undergoing hepatic	• Cirrhosis • Tumour size (largest	Significant pathologic factors for OS (HR [95%CI]):		Level of evidence: C • Median follow-up: 33

I Study ID	II Method	III Patient characteristics	IV Prognostic factors included in analysis	V Results multivariate analysis	VI Results other analyses	VII Critical appraisal of study quality
	• Funding/CoI: not reported • Setting: 5 centres, multinational • Sample size: N=446 • Duration: 1990-2000	resection ○ Complete HBV and HCV serology • *A priori* patient characteristics: not reported for entire group ○ HBV: 54%; HCV: 35%	diameter of tumour specimen) • Number of nodules • Tumour location • Microvascular invasion • Macrovascular invasion	• Microvascular invasion: HR 1.88 (1.44-2.46) • Macrovascular invasion: HR 2.36 (1.50-3.72) • Firbosis/cirrhosis: HR 2.16 (1.48-3.15)		months • Dropouts not reported • Potential overlap with Vauthey 2002 and Regimbeau 2004
Lei 2006	• Retrospective single cohort study • Funding/CoI: no CoI to declare • Setting: single centre. Taiwan • Sample size: N=440 • Duration: 7/1991-1/1999	• Eligibility criteria: ○ Patients with HCC undergoing hepatic resection ○ Patients dying in the hospital before discharge were excluded • *A priori* patient characteristics: not reported for entire group ○ Male: 86.8% ○ Mean age: 59.6 years ○ HBV: 65.7%; HCV: 22%	• Fibrosis score • Adjacent tissue invasion • Tumour size • Number of nodules • Tumour location (unilobar, bilobar) • Microvascular invasion • Resection margin • Macrovascular invasion • Major vascular invasion • Tumour rupture • Edmondson-Steiner grading • Tumour DNA ploidy	Significant pathologic factors for OS (HR [95%CI]): • Microvascular invasion: HR 1.48 (1.12-1.95) • Major vascular invasion: HR 2.3676 (1.88-3.78) • Surgical margin < 1cm: HR 1.65 (1.29-2.12) • Multiple tumours: HR 1.59 (1.23-2.05) • Tumour rupture: HR 1.76 (1.22-2.53)		Level of evidence: C • Median follow-up: 66 months • Dropouts not reported
Wang 2010	• Retrospective single cohort study • Funding/CoI: supported by the Special Research Foundation of the National Nature Science Foundation of China (30872487); no CoI to declare • Setting: single university centre, China • Sample size: N=438 • Duration: 1/1991-12/2004	• Eligibility criteria: ○ Patients with HCC undergoing partial hepatic resection ○ Patients dying in the hospital before discharge were excluded • *A priori* patient characteristics: not reported for entire group ○ Male: 86.8% ○ Mean age: 50 years	• Tumour size (sum of largest dimension of each nodule) • Number of nodules • Tumour location (unilobar, bilobar) • Capsular invasion • Satellite nodules • Resection margin • Macrovascular invasion • Lymph node metastasis • Extrahepatic metastasis • Histological grade (G1, G2, G3) • Tumour stage (AJCC)	Significant pathologic factors for OS (95%CI, p value): • Tumour size: 1.17-1.6, p<0.001 • Capsular invasion: 0.48-0.99, p=0.047 • Resection margin: 0.5-0.91, p=0.011 • Macrovascular invasion: 1.18-1.56, p=0.003 • Tumour stage: 1.14-1.43, p<0.001		Level of evidence: C • Median follow-up: 21 months • 46 (10.5%) patients lost to follow-up
Lauwers 2002	• Retrospective single cohort study • Funding/CoI: not reported • Setting: multicentre, multinational • Sample size: N=425 • Duration: 1980-1998	• Eligibility criteria: ○ Patients with HCC undergoing complete resection and with complete histopathologic information ○ Patients who died within 30 days after	• Microvascular invasion • Nuclear grade (mild, moderate, severe atypia) • Mitosis activity • Tumour architecture (microtrabecular, macrotrabecular,	Significant pathologic factors for OS: • Microvascular invasion: p<0.001 • Nuclear grade 3: p=0.008		Level of evidence: C • Median follow-up: 62 months for survivors, 27 months for patients who died • Dropouts not reported • Same patients as

I Study ID	II Method	III Patient characteristics	IV Prognostic factors included in analysis	V Results multivariate analysis	VI Results other analyses	VII Critical appraisal of study quality
		resection or lost to follow-up were excluded from the analysis ○ Pure fibrolamellar HCCs and hepatocholangio-carcinomas were not included • *A priori* patient characteristics: not reported for entire group ○ Male: 70% ○ Median age: 62 years	compact, acinar) • Tumour necrosis • Growth interface (sinusoidal, replacing, pseudocapsular, capsular)			Vauthey 2002
Wu 2005	• Retrospective single cohort study • Funding/CoI: not reported • Setting: single centre, Taiwan • Sample size: N=426 • Duration: 1991-2002	• Eligibility criteria: ○ Patients with cirrhosis and HCC undergoing elective curative hepatectomy ○ Patients with recurrent HCC whose first liver resection was carried out elsewhere and those who underwent emergency surgery for ruptured HCC were excluded • *A priori* patient characteristics: not reported for entire group ○ Male: 77.6% in period 1, 81.1% in period 2 ○ Median age: 56.5 and 61.1 years	• Tumour size • Number of nodules • Tumour capsule • Satellite nodules • Resection margin • Vascular invasion • Tumour grade (Edmondson) • Tumour stage (UICC)	Significant pathologic factors for OS (RR [95%CI]): • TNM stage II: RR 0.26 (0.15-0.46) • TNM stage III: RR 0.48 (0.29-0.63)	Significant pathologic factors for DFS (RR [95%CI]): • TNM stage II: RR 0.73 (0.57-0.93) • TNM stage III: RR 0.88 (0.73-1.07)	Level of evidence: C • Median follow-up: 49.6 and 40.1 months • Dropouts not reported • No clear definition of vascular invasion
Zhang 2009	• Retrospective single cohort study • Funding/CoI: no CoI to report • Setting: single university centre, China • Sample size: N=412 • Duration: 10/1996-10-2006	• Eligibility criteria: ○ Patients with liver cirrhosis and newly diagnosed HCC undergoing liver resection • *A priori* patient characteristics: not reported for entire group ○ Male: 79.6% ○ Median age: 52 years ○ Child-Pugh A: 82%	• Tumour size • Number of nodules • Tumour location (unilobar, bilobar) • Tumour capsule • Resection margin • Vascular invasion (portal or hepatic vein invasion) • TNM stage (UICC)	Significant pathologic factors for OS: • Tumour location (1 lobe/2 lobes): HR 4.93 • Vascular invasion: HR 2.82 • Tumour capsule: HR 2.51	Significant pathologic factors for DFS: • Tumour location (1 lobe/2 lobes): HR 48.81 • Vascular invasion: HR 3.97 • Tumour capsule: HR 2.39	Level of evidence: C • Median follow-up: 21 months • 10% (46/458) were lost in follow-up

I Study ID	II Method	III Patient characteristics	IV Prognostic factors included in analysis	V Results multivariate analysis	VI Results other analyses	VII Critical appraisal of study quality
Vauthey 2007	• Retrospective single cohort study • Funding/CoI: no CoI to declare • Setting: multicentre, multinational • Sample size: N=489 • Duration: 1985-2005	• Eligibility criteria: ○ Patients who underwent liver transplantation for HCC ○ Patients with fibrolamellar variant of HCC and those who died postoperatively were excluded • *A priori* patient characteristics: not reported for entire group ○ Male: 81.8% ○ Median age: 56 years ○ Child-Pugh A: 23.5% ○ HCV: 48.6%; HBV: 18.1%	The following staging systems were evaluated: • AJCC/UICC • Japanese TNM • Pittsburgh • UNOS • CLIP • Japan Integrated Staging • Barcelona Clinic Liver Cancer	• In only three systems - AJCC/UICC, Japanese TNM and Pittsburgh - were OS and RFS longer for patients with low stage vs. more advanced stage	For OS and RFS, sequential stages were different only for AJCC/UICC: • OS: ○ II vs. I: HR 1.58 (1.08-2.30) ○ IIIA vs. II: HR 1.995 (1.25-3.19) • RFS: ○ II vs. I: HR 1.74 (1.21-2.49) ○ IIIA vs. II: HR 2.01 (1.29-3.14)	Level of evidence: C • Consecutive patient inclusion • Median follow-up: 40 months • Dropouts not reported
Eguchi 2011	• Retrospective single cohort study • Funding/CoI: no CoI to declare • Setting: nationwide, Japan • Sample size: N=1199 • Duration: 1988-2003	• Eligibility criteria: ○ Patients with HCC who had undergone liver resection with curative intent ○ Patients who survived more than 10 years without recurrence of HCC (N=281) and those who died from recurrent HCC within 5 years of liver resection were identified (N=918) • *A priori* patient characteristics: 10y RFS vs. died within 5 years ○ Male: 77.9% vs. 82.2% ○ Median age: 57.5 vs. 60.8 years ○ Child-Pugh A: 79.1% vs. 65.1% ○ HCV: 52.0% vs. 75.1%; HBV: 32.2% vs. 22.0%	• Tumour size • Number of nodules • Intrahepatic metastases • Non-cancerous liver (normal, chronic hepatitis, fibrosis, cirrhosis) • Vascular invasion (microscopic portal vein invasion?) • Tumour differentiation (well, moderate, poor, unknown) • Macroscopic type: type 1 (simple nodular type), type 2 (simple nodular type with extranodular growth), type 3 (confluent multinodular type), type 4 (multinodular type), type 5 (others, including infiltrative, mass and diffuse types) or unknown	Significant pathologic factors for death from recurrence within 5 years (OR [95%CI]): • Tumour size >5 cm: OR 2.56 (1.16-5.65) • Poor tumour differentiation: OR 3.33 (1.46-7.60) • Intrahepatic metastasis: OR 2.34 (1.02-5.37)		Level of evidence: C • Median follow-up: 11.2 and 0.9 years respectively • Dropouts not reported
Liu 2009	• Retrospective single cohort study	• Eligibility criteria: ○ Patients with HCC	• Tumour size • Liver cirrhosis	Significant pathologic factors for RFS (HR		Level of evidence: C

I Study ID	II Method	III Patient characteristics	IV Prognostic factors included in analysis	V Results multivariate analysis	VI Results other analyses	VII Critical appraisal of study quality
	• Funding/CoI: supported by the Research Foundation from Shanghai Municipal Education Commission, PR China, No 06CZ016; no CoI to declare • Setting: single university centre, China • Sample size: N=458 • Duration: 1/2002-6/2005	who had undergone liver resection • *A priori* patient characteristics: ○ Male: 71.4% ○ Median age: not reported ○ HBV: 76.2%	• Intrahepatic metastases • Tumour capsule • Histological grade (well, moderately, poor) • P53 • Ki67 • BUBR1 overexpression	[95%CI]): • Intrahepatic metastasis: HR 2.32 (1.24-4.72) • P53: HR 2.67 (1.25-6.84) • BUBR1: HR 3.25 (1.42-7.9)		• Median follow-up: not reported • Lost to follow-up: 19.5%

Uitgangsvraag 5: Welke methode van biopteren verkleint het risico op het ontstaan van metastasen door needle tract seedling bij HCC patiënten?

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
Silva MA 2008	• SR + MA • Funding/CoI: no conflicts of interest to declare • Search date: March 2007 • Databases: NCBI, PubMed, EMBASE, internet, referencing • Study designs: cross-sectional case studies, case series, case-control studies • N included studies: N=8	• Eligibility criteria: ○ Patients with a liver lesion suspected of being HCC ○ Excluded: seeding following PEI and RFA, reports on intrahepatic seeding	Liver biopsy	• 1340 patients undergoing biopsy, 26 patients with seeding • Pooled estimates: ○ 0.027 patients with seeding per 100 patients (95%CI 0.018-0.040) ○ 0.009 patients with seeding per 100 patients per year (95%CI 0.006-0.013) ○ No observed heterogeneity	• Median time to seeding: 17 months • Incidence of seeding: range 0-5.8%	Level of evidence: C • Good-quality SR • 7 retrospective and 1 prospective study • Median follow-up: range 14-44 months

Abbreviations: HCC: hepatocellular carcinoma; MA: meta-analysis; PEI: percutaneous ethanol injection; RFA: radio-frequency ablation; SR: systematic review

Uitgangsvraag 6: Wat is de plaats van stereotactische radiotherapiebehandeling (SBRT) bij HCC patiënten?

Primaire studies

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VII Results secondary and other outcomes	VII Critical appraisal of study quality
Lin C-S 2006 [1]	• Prospective controlled trial • Funding/CoI: partly supported by CY Foundation for Advancement of Education, Sciences, and Medicine; conflicts of interest not reported • Setting: single centre, Taiwan • Sample size: N=43 • Duration: inclusion from 3/2002-11/2004	• Eligibility criteria: ○ Patients with unresectable HCC accompanied by tumour thrombosis in the portal trunk and/or bilateral main portal vein branches • *A priori* patient characteristics: ○ 7 patients received surgery before diagnosis of PVTT ○ 18 patients received TACE before diagnosis of PVTT ○ 6 patients had distant metastases ○ Median age: 57y ○ HBV: N=31; HCV: N=14 • Group comparability: no significant differences (SBRT vs. 3DCRT) ○ Male: 77% vs. 81% ○ Mean age: 59.5 vs. 54.0y ○ Child-Pugh A: 32% vs. 24%	SBRT (Elekta), 45 Gy in fractions of 3 Gy 3x/week for 5 weeks (N=22) vs. 3D-conformal radiotherapy , 45 Gy in fractions of 1.8 Gy 5x/week for 5 weeks (N=21)	• Response (ITT, N=43): ○ CR: 0% vs. 5% ○ PR: 27% vs. 19% ○ SD: 9% vs. 5% • Survival and mortality: ○ Median survival (evaluable patients only, N= 14): 6.0 vs. 6.7 months (p=0.911) ○ Death before response evaluation: 64% vs. 71%	• No separate safety results for SBRT	Level of evidence: B • No randomization • No blinding • Completion of RT: 41% vs. 33%. Treatment interruptions by cancer death or poor performance status • Response evaluated within 3 months after completion of RT • Median follow-up: 2.5 maanden

Case series

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VII Results secondary and other outcomes	VII Critical appraisal of study quality
Andolino 2011 [2]	• Retrospective • Funding/CoI: no conflicts declared • Setting: single centre, US • Sample size: N=60 • Duration: 2005-2009	• Patients with HCC confined to the liver at the time of treatment • Age: 59y • Male: 82% • HCV: 50%; HBV: 13% • Child-Pugh A: 60% • Median diameter: 3.1 cm • 6 patients received prior	SBRT (Elekta): • Child-Pugh A: 48 Gy in 3 fractions • Child-Pugh B: 40 Gy in 5 fractions	• Response: ○ CR: 30% ○ PR: 40% ○ SD: 25% • Survival: ○ Median OS: 44.4 months ○ Median PFS: 20.4 months ○ 2-year OS: 67% ○ 2-year PFS: 48%	• Grade 3/4 toxicity: ○ Liver enzymes/ hyperbilirubinemia: N=10 (17%) ○ Thrombocytopenia: N=10 (17%) ○ Elevated INR: N=2 (7%) ○ Hypoalbuminemia:	Level of evidence: C • Unclear if consecutive patients • Median follow-up: 27 months

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VII Results secondary and other outcomes	VII Critical appraisal of study quality
		TACE • 23 patients proceeded to OLT (time to transplant 7 months)			N=7 (12%)	
Cardenes 2010 [3]	• Prospective, phase I • Funding/CoI: no conflicts declared • Setting: single university centre, US • Sample size: N=17 • Duration: 3/2005-8/2007	• Patients with HCC, Child-Pugh A or B, ECOG performance status 0-2, >18y, and minimum life expectancy 3 months; no candidate for resection; solitary tumour ≤ 6 cm, or up to 3 lesions with the sum of the diameters ≤ 6 cm; no evidence of progressive or untreated gross extrahepatic disease • Median age: 61y • Male: 94% • HCV: 53%; HBV: 12% • Child-Pugh A: 35% • Median diameter: 4 cm • Prior therapy: 23.5% • 6 patients proceeded to OLT	SBRT (Elekta): escalation in dose; maximum dose: • Child-Pugh A: 48 Gy in 3 fractions • Child-Pugh B: 40 Gy in 5 fractions	• Response (16 evaluable patients): ○ CR: 25% ○ PR: 56% ○ SD: 19% • Survival: ○ 1-year OS: 75% ○ 2-year OS: 60%	• Grade 3/4 toxicity: ○ AST: N=3 (18%) ○ Hyperbilirubinemia: N=4 (18%) ○ Thrombocytopenia: N=4 (24%) ○ Elevated INR: N=1 (6%) ○ Hypoalbuminemia: N=1 (6%) ○ Leukopenia: N=1 (6%)	Level of evidence: C • Unclear if consecutive patients • Median follow-up: 24 months • All patients potentially included in Price TR 2011
Yang 2010 [4]	• RCT • Funding/CoI: support from National Natural Science Foundation of China (no. 30872975) • Setting: single university centre, China • Sample size: N=40, of which 20 received SBRT • Duration: 8/2004-5/2007	• Patients with HCC without extrahepatic metastasis, Child-Pugh A or B, ECOG-score 0-2, no previous RT, single lesion • Median age: 53y • Male: 75% • Child-Pugh A: 60% • Median diameter: 3.2 cm	SBRT (OUR company): 5x5 Gy for 2 weeks	• Response: ○ CR: 20% ○ PR: 50% ○ SD: 30% • Survival: ○ Median OS: 20 months ○ 1-year OS: 70% ○ 1-year DFS: 65%	• Grade 3/4 toxicity: N=0	Level of evidence: C • RCT comparing SBRT with SBRT and rAd-p53; results of SBRT arm are included here • Consecutive patients • Median follow-up: 35 months
Kwon 2010 [5]	• Retrospective • Funding/CoI: no conflicts declared • Setting: single university centre, South-Korea • Sample size: N=42 • Duration: 3/2004-5/2007	• Patients with HCC without extrahepatic metastasis, tumour volume ≤ 100 cc, inoperable or inaccessible for local treatment • Mean age: 60.1y • Male: 76% • HCV: 17%; HBV: 69% • Child-Pugh A: 90% • Median tumour volume: 15.4 cc • Previous TACE: 26%	SBRT (CyberKnife): median total dose 33 Gy (range 30-39), in 3 fractions on consecutive days	• Response: ○ CR: 60% ○ PR: 26% ○ SD: 14% • Survival: ○ 1-year OS: 92.9% ○ 3-year OS: 58.6% ○ 1-year PFS: 72% ○ 3-year PFS: 68% ○ Median PFS: 15.4 months	• Grade 3/4 toxicity: ○ Liver failure: N=1 (2%)	Level of evidence: C • Includes 31 patients from Choi BO, BMC Cancer 2008 • Unclear if consecutive patients • Median follow-up: 28.7 months
Seo 2010 [6]	• Retrospective analysis	• Patients with a single HCC ±	SBRT (CyberKnife):	• Response:	• Grade 3/4 toxicity:	Level of evidence: C

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VII Results secondary and other outcomes	VII Critical appraisal of study quality
	of prospective database • Funding/CoI: supported by Nuclear Research Development Program of Korea Science and Engineering Foundation (KOSEF) grant funded by the Korean government • Setting: single university centre, South-Korea • Sample size: N=38 • Duration: 3/2003-4/2008	daughter nodule, < 10 cm, ECOG 0-1, no extrahepatic metastases, unresectable • Median age: 61y • Male: 63% • Child-Pugh A: 89% • Median tumour volume: 40.5 cc • Previous TACE: 100%	dose depending on tumour volume • <50 ml: 39-57 Gy • 50-100: 36-51 Gy • 100-300: 33-51 Gy • 300-500: 40-44 Gy	○ CR: 3% ○ PR: 61% ○ SD: 29% ○ PD: 8% • Survival: ○ Median OS: 32 months ○ 1-year OS: 68.4% ○ 2-year OS: 61.4% ○ 3-year OS: 42.1% ○ 1-year local PFS: 78.5% ○ 2-year local PFS: 66.4% ○ 1-year disease PFS: 46.4% ○ 2-year disease PFS: 37.5%	○ Soft tissue toxicity: N=1 (3%)	• Unclear if consecutive patients • Median follow-up: 15 months
Tse 2008 [7]	• Prospective, phase I • Funding/CoI: 1 author received research funding from Elekta Oncology Systems • Setting: single university centre, Canada • Sample size: N=41, of wich 31 with HCC • Duration: 8/2003-3/2006	• Patients with unresectable HCC, >18y,Child-Pugh A, KI at least 60% • Median age: 66y • Male: 77% • HCV: 39%; HBV: 42% • Child-Pugh A: 100% • Median tumour volume: 173 cm^3 • Previous treatment: 61%	SBRT (Elekta): dose escalation, 6 fractions in 2 weeks	• Response: not separated for HCC • Survival: ○ Median OS: 11.7 months ○ 1-year OS: 48%	• Grade 3/4 toxicity: ○ Liver enzymes: N=8 (26%) ○ Hyperbilirubinemia: N=2 (6%) ○ Thrombocytopenia: N=1 (3%) ○ Lethargy: N=1 (3%) ○ Nausea: N=3 (10%)	Level of evidence: C • Unclear if consecutive patients • 1 patient excluded after start of treatment, 1 patients had no 3-month follow-up data because of death • Median follow-up: 17.6 months
Price 2011 [8]	• Prospective, phase 2 • Funding/CoI: no conflicts or support declared • Setting: single university centre, US • Sample size: N=26 • Duration: 3/2005-6/2008	• Patients with unresectable HCC, solitary tumour ≤ 6 cm or up to 3 lesions with sum of diameter ≤ 6 cm, Child-Pugh A/B, no ascites • Median age: 60y • Male: 88% • HCV: 58%; HBV: 12% • Child-Pugh A: 54% • Previous treatment: 27%	SBRT (Elekta): • Child-Pugh A: 48 Gy in 3 fractions • Child-Pugh B: 40 Gy in 5 fractions	• Response: ○ CR: 15% ○ PR: 58% ○ SD: 27% • Survival: ○ 1-year OS: 77% ○ 2-year OS: 60%		Level of evidence: C • Unclear if consecutive patients • Median follow-up: 13 months • Overlap with Cardenes 2010?
Louis 2010 [9]	• Retrospective • Funding/CoI: not reported • Setting: single university centre, Belgium • Sample size: N=25 • Duration: not reported	• Patients with a single HCC lesion, ECOG 0-2, Child-Pugh A/B • Mean age: 70y • Male: 76% • Alcoholic cirrhosis: 80% • Child-Pugh A: 88% • Median diameter: 4.5 cm	SBRT (CyberKnife): 45 Gy in 3 fractions of 15 Gy	• Response (14 evaluable patients): ○ CR: 57% ○ PR: 29% ○ PD: 7% • Survival: ○ 1-year OS: 79% ○ 2-year OS: 52% ○ Median DFS: 15.8 months	• Grade 3/4 toxicity: ○ Hepatic toxicity: N=1 (5%) ○ Hepatic pain: N=1 (5%) ○ Gastroduodenal ulcer: N=1 (5%) ○ Late toxicity (after 9 months): N=2	Level of evidence: C • Unclear if consecutive patients • Median follow-up: 12.7 months

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VII Results secondary and other outcomes	VII Critical appraisal of study quality
		• Previous treatment: 36%			(10%)	
Choi 2006 [10]	• Retrospective • Funding/CoI: not reported • Setting: single university centre, South-Korea • Sample size: N=20 • Duration: 7/1999-6/2002	• Patients with a solitary HCC nodule, no extrahepatic metastasis, Child Pugh A/B, ECOG 0-2, no previous RT • Median age: 59y • Male: 80% • Child-Pugh A: 75% • Median tumour volume: 25.2 cc • Previous TACE: 60%	SBRT, total dose of 50 Gy (3-5x 5-10 Gy/week for 2 weeks)	• Response: ○ CR: 20% ○ PR: 60% • Survival: ○ Median OS: 22 months ○ 1-year OS: 70.0% ○ 2-year OS: 43.1% ○ Median DFS: 19 months ○ 1-year DFS: 65.0% ○ 2-year DFS: 32.5%	• Grade 3/4 toxicity: N=0	Level of evidence: C • Consecutive patients • Median follow-up: 23 months
Chan 2011 [11]	• Retrospective • Funding/CoI: not reported • Setting: single centre, Hong Kong • Sample size: N=16 • Duration: 5/2000-11/2004	• Patients with a intrahepatic HCC, irresectable or not suitable for local treatment • Median age: 58y • Male: 94% • HBV: 81% • Child-Pugh A: 75% • Median diameter: 3 cm	SBRT (ExacTRA): 10x4.5 Gy	• Response: ○ CR: 13% ○ PR: 19% ○ SD: 31% ○ PD: 6% • Survival: ○ Median OS: 23 months ○ 1-year OS: 62% ○ 3-year OS: 28%	• Grade 3/4 toxicity: ○ 1 death due to radiation-induced liver disease ○ ALT: N=1 (6%) ○ Liver pain: N=1 (6%)	Level of evidence: C • Unclear if consecutive patients • Median follow-up: 24 months
Takeda 2008 [12]	• Retrospective • Funding/CoI: not reported • Setting: single centre, Japan • Sample size: N=16 • Duration: 12/2002-9/2004	• Patients with a HCC not previously treated with ablation therapy • Median age: 69y • Male: 88% • HCV: 75%; HBV: 13% • Child-Pugh A: 88% • Median tumour volume: 13.6 cm^3 • Previous TACE: 88%	SBRT, total dose of 35-50 Gy in 5-7 fractions over 5-9 days	• Response: ○ CR: 50% ○ SD: 44% • Survival: ○ All patients alive at the end of 612 days follow-up ○ 1-year RFS: 100% ○ 2-year RFS: 90%	• Grade 3/4 toxicity: not explicitly mentioned	Level of evidence: C • Unclear if consecutive patients • Mean follow-up: 612 days
Mendez Romero 2006 [13]	• Retrospective • Funding/CoI: no conflicts declared • Setting: single centre, The Netherlands • Sample size: N=25, of which 8 with HCC • Duration: 10/2002-6/2006	• Patients with a HCC confined to the liver, not eligible for surgery or other local treatment, Child Pugh A/B, maximum size 7 cm, maximum of 3 lesions • Child-Pugh A: 63% • Other characteristics not provided separately for HCC	SBRT (Elekta), 3x10-12.5 Gy or 5x5 Gy	• Local control rate: ○ 1-year: 75% • Survival: ○ 1-year OS: 75% ○ 2-year OS: 40%	• Grade 3/4 toxicity: not provided separately for HCC	Level of evidence: C • Unclear if consecutive patients • Maximum follow-up: 22 months
Goyal 2010 [14]	• Retrospective • Funding/CoI: not reported • Setting: single university centre, US • Sample size: N=17, of	• Patients with an unresectable HCC, life expectancy of at least 12 weeks • Mean age: 62.7y • Male: 67 % • Mean tumour diameter:	SBRT (CyberKnife)	• No local failure • Distant recurrence: 33% • Response: ○ CR: 0% ○ PR: 83% ○ SD: 17%	• 1 patient with gastric ulcer	Level of evidence: C • Consecutive patients • Mean follow-up: 10 months

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VII Results secondary and other outcomes	VII Critical appraisal of study quality
	which 6 with HCC • Duration: 10/2007-5/2009	9.3 cm				
Iwata 2010 [15]	• Prospective • Funding/CoI: no conflicts declared • Setting: single centre, Japan • Sample size: N=18, of which 6 with HCC • Duration: 2/2008-10/2009	• Patients with an inoperable HCC, WHO performance status 0-2, tumour diameter maximum 5 cm, Child-Pugh A/B • Characteristics not provided separately for HCC	SBRT: • Child-Pugh A: 55 Gy in 10 fractions • Child-Pugh B: 50 Gy in 10 fractions	• Local control: ○ 1-year: 100% • Survival: ○ 1-year DFS: 78%	• Grade 3/4 toxicity: not provided separately for HCC	Level of evidence: C • Unclear if consecutive patients • Median follow-up:
Shin 2010 [16]	• Unclear design • Funding/CoI: not reported • Setting: single university centre, South-Korea • Sample size: N=6 • Duration: 3/2003-3/2008	• Patients with a single HCC with/without daughter nodule, longest diameter > 12 cm or target volume > 1000 mL, inoperable, failure to respond to TACE, ECOG 0-1, Child-Pugh A, no extrahepatic metastases • Median age: 48.5y • HBV: 50% • Child-Pugh A: 100% • Previous TACE: 100%	SBRT (CyberKnife): 32-40 Gy in 4 fractions	• Response: ○ PR: 67% ○ SD: 17% ○ PD: 17% • Survival: ○ Median OS: 10 months ○ Median PFS: 6 months	• Grade 3/4 toxicity: ○ Liver enzymes: N=1 (17%)	Level of evidence: C • Unclear if consecutive patients • Median follow-up: 25.9 months
Sanuki-Fujimoto 2010 [17]	• Retrospective • Funding/CoI: not reported • Setting: single centre, Japan • Sample size: N=47 • Duration: 3/2005-7/2008	• Patients with a solitary HCC ≤ 4 cm, inoperable, percutaneous ablative therapy not feasible, Child-Pugh A/B • Median age: 71y • HBV: 4%; HCV 74% • Child-Pugh A: 87% • Previous TACE: 100%	SBRT, 30-40 Gy in 5 fractions over 5-9 days	• Response: ○ CR: 72% ○ PR: 14%	•	Level of evidence: C • Unclear if consecutive patients • Median follow-up: 18.1 months

Abbreviations: 3DCRT: 3D-conformal radiotherapy; ALT: alanine transaminase; AST: aspartate aminotransferase; CoI: conflicts of interest; CR: complete resonse; DFS: disease-free survival; ECOG: Eastern Cooperative Oncology Group; Gy: Gray; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; INR: international normalized ratio; KI: Karnofsky index; OLT: orthotopic liver transplantation; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PR: partial response; PVTT: portal vein tumour thrombosis; RFS: recurrence-free survival; RT: radiotherapy; SBRT: stereotactic body radiotherapy; SD: stable disease; TACE: transarterial chemo-embolisation.

Vraag 7: Welke lokale behandeling wordt aanbevolen bij HCC patiënten die niet in aanmerking komen voor chirurgische resectie?

Systematic reviews

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VII Results secondary and other outcomes	VII Critical appraisal of study quality
Cho 2009 [1]	• SR + MA • Funding not reported; no conflicts to report • Search date: July 2008 • Databases: Medline, Cochrane Library, Cancerlit • Study designs: RCTs • N included studies: N=4	• Eligibility criteria: ○ Patients with unresectable HCC ○ Primary treatment	RFA vs. PEI	• Overall 3-year survival (N=599): OR 0.48 (95%CI 0.34-0.67; p<0.001; Q=4.586, p=0.205) in favour of RFA		Level of evidence: A1 • Good-quality SR • Included RCTs: ○ Lin 2004 ○ Lin 2005 ○ Shiina 2005 ○ Brunello 2008 • Lencioni 2003 was excluded because no information regarding 3-year overall survival was provided • Quality appraisal with Jadad scale
Germani 2010 [2]	• SR + MA • No funding or conflicts to declare • Search date: Dec 2008 • Databases: Medline, CENTRAL, EMBASE • Study designs: RCTs, quasi-RCTs • N included studies: 6 RCTs, 2 quasi-RCTs	• Eligibility criteria: ○ Primary HCC ○ Studies dealing with liver metastases or HCC recurrence after hepatectomy were excluded	RFA vs. PEI	• HR of death: 0.53 (95%CI 0.44-0.64; p<0.00001) in favour of RFA • Proportion death (5 RCTs): OR 0.52 (95%CI 0.35-0.78; p=0.001; I^2 15%) in favour of RFA ○ HCC ≤ 2 cm: OR 0.63 (95%CI 0.27-1.49; p=0.29) ○ HCC > 2 cm: OR 0.41 (95%CI 0.20-0.86; p=0.02)	• Complete nodule necrosis: OR 0.29 (95%CI 0.16-0.53; p<0.0001) in favour of RFA • Local recurrence (4 RCTs): OR 0.27 (95%CI 0.16-0.45; p<0.00001; I^2 0%) in favour of RFA ○ HCC ≤ 2 cm: OR 0.43 (95%CI 0.12-1.51; p=0.19) ○ HCC > 2 cm: OR 0.35 (95%CI 0.15-0.71; p=0.005) • De novo tumours: OR 0.87 (95%CI 0.64-1.19; p=0.38) • Time to recurrence : HR 0.70 (95%CI 0.56-0.88 ; p=0.002) in favour of RFA • Number of sessions needed to achieve complete necrosis: MD -4.16 (95%CI -4.69 to -3.64; p<0.00001) in favour of RFA • Adverse events: OR 1.21 (95%CI 0.89-1.63; p=0.22) • Major complications: OR 2.00	Level of evidence: A1 • Good-quality SR of low-moderate quality primary studies • Meta-analysis using RevMan 5 • Quality of RCTs not addressed in meta-analysis • Results without Livraghi 1999 did not alter the results • Included studies for this comparison: ○ Livraghi 1999 (quasi-RCT) ○ Lencioni 2003 ○ Lin 2004 ○ Lin 2005 ○ Shiina 2005 ○ Brunello 2008

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VII Results secondary and other outcomes	VII Critical appraisal of study quality
					(95%CI 0.72-5.53; p=0.18)	
			RFA vs. PAAI	• Proportion death: ○ Direct: relative OR 0.62 (0.25-1.52) ○ Indirect: relative OR 1.32 (0.25-6.99) ○ Combined: relative OR 0.74 (0.33-1.62; I^2 0%) ○ Subgroup analysis by tumour size (1 RCT): ▪ HCC ≤ 2 cm: OR 0.69 (0.25-1.93; p=0.48) ▪ HCC > 2 cm: OR 0.34 (0.11-1.09 ; p=0.07) • Time to death: HR 0.65 (0.37-1.13 ; p=0.13)	• Local recurrence: ○ Direct: relative OR 0.36 (0.15-0.85) ○ Indirect: relative OR 0.21 (0.08-0.57) ○ Combined: relative OR 0.29 (0.15-0.55; p=0.0002; I^2 0%) in favour of RFA ○ Subgroup analysis by tumour size (1 RCT): ▪ HCC ≤ 2 cm: OR 0.47 (0.11-2.05; p=0.31) ▪ HCC > 2 cm: OR 0.30 (0.09-1.06 ; p=0.06) • De novo tumours: OR 0.94 (0.49-1.82; p=0.86) • Time to recurrence : HR 0.65 (0.30-1.38 ; p=0.26) • Number of sessions needed to achieve complete necrosis: MD -1.20 (-1.43 to -0.97; p<0.00001) in favour of RFA • Adverse events: OR 0.97 (0.46-2.02; p=0.93)	Level of evidence: B • Indirect comparison meta-analysis (RFA vs. PEI and PEI vs. PAAI) • Included study for direct comparison: ○ Lin 2005 (RCT): HCC ≤ 3 cm
Oliveri 2011 [3]	• SR + MA • Funding/CoI: The Copenhagen Trial Unit • Search date: Sept 2010 • Databases: Cochrane Library, CENTRAL, Medline, EMBASE, SCI Expanded, LILACS • Study designs: RCTs • N included studies: N=8 (9 comparisons)	• Eligibility criteria: patients diagnosed with HCC, unresectable	TACE or TAE vs. Placebo, sham or no treatment	• All-cause mortality (9 comparisons): HR 0.81 (95%CI 0.64-1.02; p=0.067; I² 30% ○ TACE (6 studies): HR 0.79 (0.58-1.06; p=0.11; I² 46%) ○ TAE (3 studies): HR 0.94 (0.62-1.42; p=0.76; I² 0%) ○ Similar results for subanalyses according to risk of bias, co-interventions, median survival in control group or trial truncation		Level of evidence: A1 • Good-quality SR • Included studies: ○ Pelletier 1990 ○ GETCH 1995 ○ Bruix 1998 ○ Pelletier 1998 ○ Llovet 2002 ○ Lo 2002 ○ Akamatsu 2004 ○ Doffoel 2008

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VII Results secondary and other outcomes	VII Critical appraisal of study quality
Orlando 2009 [4]	• SR + MA • Funding/CoI: no support; no conflicts of interest to declare • Search date: 1999 – 6/2008 • Databases: Medline, Cancerlit, CENTRAL, Cochrane Library, EMBASE • Study designs: RCTs • N included studies: N=5	• Eligibility criteria: ○ Patients with small HCC undergoing RFA vs. PEI: solitary HCC < 5 cm or with up to 3 nodules < 3 cm	RFA vs. PEI	• Overall survival (5 studies): OR 1.92 (95%CI 1.35-2.74) in favour of RFA • Survival rates: ○ 1 year: OR 2.30 (1.27-4.14) ○ 2 years: OR 2.39 (1.62-3.51) ○ 3 years: OR 2.32 (1.20-4.48) • Cancer-free survival (3 studies): ○ 1 year: OR 1.69 (1.02-2.76) ○ 2 years: OR 2.11 (1.36-3.26) ○ 3 years: OR 2.72 (1.54-4.79)	• Local recurrence (4 studies): OR 0.29 (0.18-0.47) in favour of RFA • Tumour response (4 studies): OR 2.28 (1.46-3.35) • Adverse events: narrative overview ○ Pain: 4 RCTs, no significant differences (5% after PEI vs. 7% after RFA) ○ Serious AE: no differences in 4 studies; in 1 study: 4.8% after RFA vs. 0% after PEI ○ Procedure-related death: N=1 after PEI across all 5 studies	Level of evidence: A1 • Good-quality SR • Included RCTs for this comparison: ○ Lencioni 2003: A2 ○ Lin 2004: A2 ○ Lin 2005: A2 ○ Shiina 2005: B ○ Brunello 2008: A2 • Quality appraisal with 4 criteria
Tiong 2011 [5]	• SR + MA • Funding/CoI: funding from University of Adelaide Discipline of Surgery; no conflict of interest to declare • Search date: Jan 2000 – Nov 2010 • Databases: Medline, EMBASE, CENTRAL, CDSR, Cochrane Methodology Register, DARE • Study designs: RCTs, quasi-RCTs and non-randomized comparative studies • N included studies: 12 RCTs, 31 non-randomized comparative studies	• Eligibility criteria: ○ Patients with unresectable HCC undergoing RFA with any of the commercially available radiofrequency generators or needle designs	RFA vs. PEI	• Overall 1-year survival (N=701): RR 0.62 (95%CI 0.41-0.94; p=0.02; I^2 0%) in favour of RFA • Overall 3-year survival (N=599): RR 0.79 (0.65-0.96; p=0.02; I^2 57%)	• Disease-free survival: ○ 1 year: range 74-86% vs. 61-77% in favour of RFA ○ 3 years: range 37-43% vs. 17-21% in favour of RFA	Level of evidence: A1 • Good-quality SR • Included RCTs for this comparison: ○ Lencioni 2003: A2 ○ Lin 2004: A2 ○ Lin 2005: A2 ○ Shiina 2005: B ○ Brunello 2008: A2 • Quality appraisal with Jadad scale and Cochrane Collaboration's tool
			RFA vs. Laser-induced thermal therapy	• No significant differences were found in ablation-site and intrahepatic recurrence rates, median disease-free survival, or median survival rate at 1, 3 and 5 years	• Patients with Child–Pugh grade A disease (HR 0.18; p=0.017) and those with tumours ≤ 2.5 cm (HR 0.18; p=0.018) had better survival rates when treated with RFA	Level of evidence: B • Included RCT for this comparison: ○ Ferrari 2007 (B): patients with single HCC ≤ 4 cm or up to 3 HCCs ≤ 3 cm

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VII Results secondary and other outcomes	VII Critical appraisal of study quality
			RFA vs. Microwave coagulation therapy	• No significant differences in disease-free survival or overall survival in 2 studies, but significantly better survival at 1, 3 and 4 years in favour of RFA in the 3rd study (100%, 70% and 70% vs. 89%, 49% and 39%, p=0.018)		Level of evidence: B • No RCTs available for this comparison; 3 comparative studies: ○ Lu 2005: B ○ Xu 2005: B ○ Ohmoto 2009: B
			RFA + TACE vs. TACE	• See Yang 2008 & Morimoto 2010	• See Yang 2008 & Morimoto 2010	Level of evidence: B • Included RCTs for this comparison: ○ Cheng 2008 (retracted RCT) ○ Yang 2008: B ○ Morimoto 2010: B • No pooling due to clinical heterogeneity
			RFA vs. surgery	• Resection within Milan criteria: ○ RFA: N=928, resection: N=708 ○ No significant differences in overall survival, but significant higher disease-free survival and lower local recurrence rates ○ Median disease-free survival: ▪ 1 year: range 78-83% vs. 80-83% ▪ 3 years: range 36-59% vs. 47-64% ▪ 5 years: range 17-25% vs. 22-38% ○ Median overall survival: ▪ 1 year: range 96-100% vs. 91-98% ▪ 3 years: range 53-92% vs. 57-92% ▪ 5 years: range 41-77% vs. 54-80%	• Resection outside Milan criteria: ○ RFA: N=797, resection: N=712 ○ Median disease-free survival: 16-25 vs. 36-53 months ○ Median overall survival: 28-51 vs. 37-57 months ▪ 1 year: range 78-98% vs. 75-97% ▪ 3 years: range 33-94% vs. 64-93% ▪ 5 years: range 20-75% vs. 31-81%	Level of evidence: B • No RCTs available for this comparison: ○ Resection within Milan criteria: 8 non-randomized studies ○ Resection outside Milan criteria: 8 non-randomized studies

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VII Results secondary and other outcomes	VII Critical appraisal of study quality
Wang 2010 [6]	• SR + MA • Funding/CoI: no conflicts of interest to declare • Search date: 1990 – July 2009 • Databases: PubMed, EMBASE, Web of Science, Cochrane Library • Study designs: RCTs • N included studies: N=10	• Eligibility criteria: ○ Patients with unresectable HCC	RFA + TACE vs. TACE	• See Yang 2008	• See Yang 2008	Level of evidence: B • Good-quality SR • Results of MA not useful, because combination therapy in general was compared to monotherapy in general • Included RCTs for this comparison: ○ Yang 2008: B ○ Wang 2007 (quasi-RCT): B • Quality appraisal with Jadad score
			RFA + TACE vs. RFA	• Survival: ○ 1 year: 3 studies, N=169, OR 1.11 (95%CI 0.39-4.08, p=0.88) ○ 2 year: 2 studies, N=133, OR 7.19 (1.24-41.90, p=0.03) in favour of RFA+TACE ○ 3-year: 2 studies, N=133, OR 1.38 (0.56-3.43, p=0.48)	• See Shibata 2009 & Yang 2008	Level of evidence: B • Results of MA partially useful, because combination therapy in general was compared to monotherapy in general • Included RCTs for this comparison: ○ Aikata 2006 (abstract): B ○ Shibata 2009: B ○ Yang 2008: B
			PEI + TACE vs. PEI	• Survival: ○ 1 year: 2 studies, N=91, OR 7.65 (95%CI 1.72-34.06, p=0.008) in favour of TACE+PEI ○ 2 year: 2 studies, N=84, OR 6.50 (1.08-39.25, p=0.04) in favour of TACE+PEI ○ 3-year: 2 studies, N=84, OR 2.50 (0.97-6.45, p=0.06)		Level of evidence: B • Results of MA partially useful, because combination therapy in general was compared to monotherapy in general • Included RCTs for this comparison: ○ Koda 2001: B (small sample size) ○ Francesco 2004: B

Primaire studies

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VII Results secondary and other outcomes	VII Critical appraisal of study quality
Giorgio 2011 [7]	• RCT • Funding/CoI: not reported • Setting: single centre, Italy • Sample size: N=285 • Duration: inclusion from 1/2005-1/2010	• Eligibility criteria: ○ single HCC nodule 3 cm or less ○ cirrhotic patients ○ no previous HCC treatment ○ no ascites or portal vein thrombosis • *A priori* patient characteristics: ○ 67% males ○ Mean age: 70 years ○ Child-Pugh A: 51% ○ Cirrhosis due to HCV: 59% ○ Cirrhosis due to HBV: 41% • Group comparability: no significant differences (RFA vs. PEI) ○ Mean age: 70 vs. 72y ○ Male: 74% vs. 71% ○ Mean tumour diameter: 2.34 vs. 2.27 cm ○ Child-Pugh A: 49% vs. 52%	RFA (N=142) vs. PEI (N=143)	• Survival: ○ HCC ≤ 3 cm: HR 0.81 (95%CI 0.46-1.39, p=0.45) ▪ 1 year: 95% vs. 95% ▪ 2 year: 90% vs. 83% ▪ 3 year: 83% vs. 78% ▪ 4 year: 73% vs. 70% ▪ 5 year: 70% vs. 68% ○ HCC ≤ 2 cm: HR .81 (95%CI 0.46-1.39, p=0.45) ▪ 1 year: 96% vs. 94% ▪ 2 year: 88% vs. 86% ▪ 3 year: 79% vs. 79% ▪ 4 year: 72% vs. 70% ▪ 5 year: 70% vs. 68%	• Local recurrence rates: p=0.043 in favour of RFA ○ 1 year: 4.1% vs. 5.2% ○ 2 year: 5.7% vs. 6.7% ○ 3 year: 7.8% vs. 9.4% ○ 4 year: 8.9% vs. 11.5% ○ 5 year: 11.7% vs. 12.8% • Complications: ○ No procedure-related death ○ Major complications: 0.9% vs. 1.9% (NS)	Level of evidence: B • Randomisation with random number generator • Allocation was concealed, but is not mentioned how • No blinding reported • No ITT analysis: 14 patients randomised to RFA received PEI and were not included in the analysis • Mean follow-up: 37 months (range 8-68 months)
Kirchhoff 2006 [8]	• RCT, phase II trial • Funding/CoI: supported by Pharmacia, Germany • Setting: multicentre study, Germany • Sample size: N=74 • Duration: inclusion from 12/1995-6/2000	• Eligibility criteria: ○ Patients with histologically confirmed HCC and sufficient liver function ○ Detectable HCC nodules by CT or MRI ○ No evidence of metastasis to other organs or lymph nodes ○ Below 75 years ○ Technically feasible catheterization of the hepatic artery ○ Adequate haematologic, hepatic and renal function ○ Prothrombin activity >50% ○ Cardiac ejection fraction >50% ○ Patients with pregnancy, systemic chemotherapy within the last 4 weeks, occlusion of the hepatic artery or portal vein, Child C stage of liver cirrhosis, Okuda stage III, heart attack within the	TACE with doxorubicin 60 mg/m², cisplatin 100 mg/m², 600-1200 mg DSM; maximum of 6 cycles, 4-week treatment intervals (N=35) vs. Transarterial chemoperfusion (TACP) with doxorubicin 60 mg/m² and cisplatin 100 mg/m²; maximum of 6 cycles, 4-week treatment intervals (N=35)	• Overall survival: no significant difference ○ Median survival: 60 vs. 69 weeks ○ 6 months: 74% vs. 89% ○ 12 months: 57% vs. 71% ○ 24 months: 31% vs. 40% ○ 36 months: 29% vs. 29%	• Response: no significant differences ○ Partial response: 26% vs. 9% ○ Stable disease: 41% vs. 55% ○ Progressive disease: 33% vs. 36% • Complications: ○ No procedure-related death	Level of evidence: B • Randomisation method not clearly reported, no mention of allocation concealment • Blinding not reported • Unclear if ITT analysis was used: 84 patients were enrolled, but only 70 patients were eligible for data analysis. Were 84 or 70 patients randomised?

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VII Results secondary and other outcomes	VII Critical appraisal of study quality
		previous 12 months, or insufficient cardiac function (>NYHA stage II) were excluded from the study • *A priori* patient characteristics: ○ Child-Pugh A: 93% ○ Mean age: 61 years ○ Male: 81% • Group comparability: no significant differences (TACE vs. TACP) ○ Age: 60 vs. 61y ○ Male: 83% vs. 80% ○ Child-Pugh A: 94% vs. 91%				
Mabed 2009 [9]	• RCT • Funding/CoI: not reported • Setting: single university centre, Egypt • Sample size: N=100 • Duration: inclusion from 9/2003-6/2005	• Eligibility criteria: ○ Pathology-proven primary HCC, or AFP >400 ng/mL with a hepatic tumour highly suggestive of HCC by imaging studies ○ Unresectable tumour and patient was not a candidate for local ablative therapy with PEI or RFA ○ Bidimensional measurable disease ○ No previous systemic chemotherapy ○ Age between 16 and 65 years ○ Performance status 0-2 ECOG ○ Within normal renal, cardiac and haematological profile • Group comparability: no significant differences (TACE vs. doxorubicin) ○ Median age: 52 vs. 51y ○ Male: 64% vs. 66% ○ HCV: 74% vs. 79% ○ Child-Pugh A: 68% vs. 70%	TACE with 50 mg cisplatin, 40 mg doxorubicin and lipiodol 10 ml mixed with 10 mg doxorubicin (N=50) vs. Doxorubicin 45 mg/m² IV every 4 weeks (15 mg/m² on days 1, 8 and 15) with a maximum total dose of 500 mg/m² (N=50)	• Median overall survival: 38 vs. 32 weeks (log-rank test, p=0.08) • Median progression-free survival: 32 weeks vs. 26 weeks (p=0.03)	• Response: significantly better after TACE (p=0.007) ○ Partial response: 32% vs. 10% ○ Stable disease: 26% vs. 38% ○ Progressive disease: 36% vs. 44% • Complications: ○ Procedure-related death: 4% vs. 0% ○ Grade 4 toxicity: 4.3% vs. 4.5% • QoL: N=40, no significant difference after 3 treatment cycles	Level of evidence: B • Poor description of randomisation method • No blinding reported • ITT analysis • Follow-up time not reported
Malagari 2010 [10]	• RCT • Funding/CoI: not reported • Setting: university hospital, Greece • Sample size: N=84	• Eligibility criteria: ○ Patients with cirrhosis-related HCC that developed on an underlying controlled hepatitis infection ○ Compensated cirrhosis (Child-	DEB-TACE (DC beads loaded with doxorubicin at 37.5 mg/ml of bead suspension,	• Overall survival: no significant differences ○ 6 months: 100% both ○ 9 months: 97.5% vs. 95.3% ○ 1 year: 85.3% vs. 86%	• Local response (objective response: ○ 6 months: 73.2% vs. 55.8%, p=0.11 ○ 9 months: 55% vs. 31.7%, p=0.04	Level of evidence: B • Randomization after telephone registration • Blinding not mentioned

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VII Results secondary and other outcomes	VII Critical appraisal of study quality
	• Duration: inclusion from 2005 on (end date unclear)	Pugh A/B) ○ Unsuitable for curative treatment; potentially resectable but at high risk for surgery; or, suitable for RFA, but of high risk due to location ○ Bilirubin <3 mg/dl, AST <270 IU/L, ALT <270 IU/L, good performance status ○ No portal vein thrombosis ○ No extrahepatic metastases • Group comparability: no significant differences (DEB-TACE vs. BeadBlock) ○ Age: 70.7 vs. 70.0y ○ Male: 76% vs. 79% ○ Child A: 56% vs. 60%	dose per patient = 150 mg) (N=41) vs. Bland embolization with BeadBlock (non-loaded particles) (N=43)		○ 12 months: 25.7% vs. 18.9%, p=0.58 • Recurrence rate: 45.7% vs. 78.3% at 1 year, p=0.01 • Complications: no significant differences ○ No treatment-related death	• No ITT analysis: 105 patients originally randomized, 84 patients analyzed • Median follow-up: not reported
Mizuki 2010 [11]	• RCT • Funding/CoI: not reported • Setting: multicenter study, Japan • Sample size: N=30 • Duration: inclusion from 7/1997-4/1999	• Eligibility criteria: ○ Patients with small primary HCCs ○ Age <70 years ○ HCC nodules measuring 2-4 cm in maximum diameter ○ Number of HCC nodules ≤3 ○ No portal thrombosis or extrahepatic metastasis ○ Hypervascular nodules, as determined by dynamic CT and/or arteriography ○ No previous treatment for HCC prior to entry ○ No severe comorbidity (such as uncontrolled diabetes mellitus, heart failure, renal failure or other cancer) • *A priori* patient characteristics: ○ HCV 74.1%, HBV 18.5% • Group comparability: no significant differences (TACE+PEI vs. PEI) ○ Age: 65.8 vs. 63.6y ○ Male: 69% vs. 50%	TACE + PEI (N=16) vs. PEI (N=14)	• Mean overall survival: 42.4 vs. 57.2 months, NS • Mean cancer-free survival: 22.9 vs. 16.7 months, NS	• Complications: no treatment-related serious adverse events	Level of evidence: B • Randomisation with sealed envelope: no adequate allocation concealment • Blinding not reported • No ITT analysis: 3 patients in the TACE+PEI group withdrew from the study after randomisation • Median follow-up: 33.2 months
Morimoto 2010 [12]	• RCT • Funding/CoI: research grant from Yokohama	• Eligibility criteria: ○ Intermediate-sized unresectable solitary HCC	RFA + TACE (N=19)	• Overall survival: no significant difference (log-rank test, p=0.369)	• Local tumour progression rates: 6% vs. 39% at 3 years in favour of	Level of evidence: B • Central randomisation

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VII Results secondary and other outcomes	VII Critical appraisal of study quality
	City University • Setting: single university centre, Japan • Sample size: N=37 • Duration: inclusion from 8/2005-4/2009	(3.1-5.0 cm) detectable by US ○ ECOG performance status ≤2 ○ Child-Pugh A or B ○ Suitable divergence of hepatic artery ○ No portal and/or venous thrombosis, extrahepatic metastasis or uncontrollable ascites ○ Adequate haematologic, hepatic and renal function ○ No previous treatment for HCC • Group comparability: no significant differences (RFA+TACE vs. RFA) ○ Age: 70 vs. 73y ○ Male: 79% vs. 67% ○ HCV: 89% vs. 89% ○ Child-Pugh A: 95% vs. 89% ○ Mean tumour diameter: 3.6 vs. 3.7 cm	vs. RFA (N=18)	○ 1 year: 100% vs. 89% ○ 2 years: 93% vs. 89% ○ 3 years: 93% vs. 80%	RFA+TACE (p=0.12) • Overall recurrence rates: no significant difference (log-rank test, p=0.39) ○ 1 year: 33% vs. 44% ○ 2 year: 91% vs. 63% • Complications: ○ No major complications ○ Grade 1/2 pain: 1 in RFA+TACE group vs. 5 in RFA group ○ No procedure-related deaths	by computer • No blinding reported • ITT analysis • Small sample size
Okusaka 2009 [13]	• RCT • Funding/CoI: Grant from Ministry of Health, Labour and Welfare of Japan; no conflicts of interest to declare • Setting: multicentre study, Japan • Sample size: N=161 • Duration: inclusion from 10/1999-6/2003	• Eligibility criteria: ○ Patients with HCC, confirmed histologically and/or clinically using angiography and computed tomography ○ Intrahepatic lesions that showed tumour staining by angiography and those in which the total size was <50% of the entire liver ○ Adequate haematological, hepatic and renal function ○ ECOG performance status of 0-1 ○ Age 20-74 years ○ Technically eligible for intra-arterial therapy ○ Patients were excluded if they met any of the following criteria: history of allergy to iodine-containing agents and/or contrast material; concomitant malignancy; history of anti-cancer	TACE with SMANCS (zinostatin stimalamer) in lipiodol, followed by gelatine sponge particles (N=79) vs. Transarterial infusion chemotherapy (TAI) with SMANCS in lipiodol (N=82)	• Median overall survival: 646 vs. 679 days • 2-year survival: 48% vs. 50% (p=0.383)	• No significant differences in tumour response • Complications: ○ Grade 4 thrombocytopenia: 2.6% vs. 3.7% ○ No treatment-related death	Level of evidence: A2 • Central randomisation • Open-label study • ITT analysis • Follow-up until 2 years after enrollment of last patient

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VII Results secondary and other outcomes	VII Critical appraisal of study quality
		treatment for HCC; extrahepatic metastasis or tumour thrombus in the portal vein and/or the hepatic vein; intrahepatic arteriovenous shunting; ascites and/or pleural effusion not controlled by diuretics; pregnant or lactating woman and fertile patients not using effective contraception; myocardial infarction within the previous 6 months; or any serious physical and/or mental conditions • Group comparability: no significant differences (TACE vs. TAI) ○ Median age: 65 vs. 67y ○ Male: 77% vs. 85% ○ HCV: 72% vs. 73% ○ Max. tumour diameter: 35 mm				
Sacco 2011 [14]	• RCT • Funding/CoI: no conflicts to declare • Setting: university centre, Italy • Sample size: N=67 • Duration: inclusion from 1/2006-3/2009	• Eligibility criteria: ○ Patients with liver cirrhosis and no more than five previously untreated unresectable HCC nodules not suitable for ablative treatments ○ Bilirubin <3 mg/dl, AST <270 IU/L, ALT <270 IU/L ○ ECOG 0-1 ○ Child-Pugh A/B ○ No portal vein thrombosis ○ No extrahepatic metastases • Group comparability: no significant differences (TACE vs. DEB-TACE) ○ Mean age: 68.7 vs. 71.3y ○ Male: 64.7% vs. 69.7% ○ Child A: 73.5% vs. 87.9%	TACE (lipiodol + doxorubicin 50-75 mg) (N=34) vs. DEB-TACE (2-4 ml DC Bead loaded with doxorubicin 25-150 mg) (N=33)	• 2-year overall survival: 83.6% vs. 86.8%, p=0.96 • 2-year PFS: 80.1% vs. 82.5%, p=0.64 • 2-year RFS: 37.4% vs. 42.4% (p=0.99)	• Tumour response at 1 month: no significant difference ○ CR: 70.6% vs. 51.5% ○ PR: 29.4% vs. 48.5% • Complications: ○ Periprocedural major complications: 1 cholecystitis after TACE, 1 liver failure after DEB-TACE	Level of evidence: B • Unclear allocation concealment • Open label study • Mean follow-up: 816 days
Shibata 2009 [15]	• RCT • Funding/CoI: no conflicts of interest to declare • Setting: single	• Eligibility criteria: ○ Patients with 3 or less HCC nodules 3 cm or smaller ○ Child-Pugh A or B ○ No invasion in major portal or	RFA + TACE (N=46)	• Overall survival: no significant difference (log-rank test, p=0.515) ○ 1 year: 100% vs. 100% ○ 2 years: 100% vs. 89%	• Local tumour progression rates: no significant difference (log-rank test, p=0.797) ○ 1 year: 14% vs. 11%	Level of evidence: B • No clear description of randomisation procedure: risk of

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VII Results secondary and other outcomes	VII Critical appraisal of study quality
	university centre, Japan • Sample size: N=89 • Duration: inclusion from 7/2003-12/2007	hepatic vein branches ○ No extrahepatic metastasis ○ Platelet count > 40K/mm³ • *A priori* patient characteristics: ○ HCV N=62, HBV N=21 ○ Child-Pugh A: N=65 • Group comparability: no significant differences (RFA+TACE vs. RFA) ○ Age: 67.2 vs. 69.8y ○ Male: 67% vs. 77% ○ Child-Pugh A: 70% vs. 77% ○ Mean nodule size: 1.7 vs. 1.6 cm	vs. RFA (N=43)	○ 3 years: 85% vs. 85% ○ 4 years: 73% vs. 74% • Local progression-free survival: no significant difference (log-rank test, p=0.934) ○ 1 year: 85% vs. 88% ○ 2 years: 81% vs. 74% ○ 3 years: 70% vs. 74% ○ 4 years: 56% vs. 62% • Event-free survival: no significant difference (log-rank test, p=0.365) ○ 1 year: 71% vs. 74% ○ 2 years: 60% vs. 52% ○ 3 years: 49% vs. 30% ○ 4 years: 37% vs. 30%	○ 2 years: 18% vs. 14% ○ 3 years: 18% vs. 14% ○ 4 years: 18% vs. 14% • Major complications: ○ 1 patient in each group	pseudo-randomisation • No blinding reported • ITT analysis
Yang 2008 [16]	• RCT • Funding/CoI: not reported • Setting:single university centre, China • Sample size: N=78 • Duration: inclusion from 2/2004-7/2006	• Eligibility criteria: ○ Unresectable HCC • *A priori* patient characteristics: ○ Males: N=57 ○ Mean age: 60.3 years (range 33-75) ○ Tumour diameters: 5.2-10.1 cm • Group comparability: no obvious differences (RFA+TACE vs. TACE vs. RFA vs. combination) ○ Age: 59 vs. 58 vs. 61 vs. 60y ○ Male: 75% vs. 73% vs. 67% vs. 74% ○ Child-Pugh A: 46% vs. 91% vs. 67% vs. 32% ○ Mean tumour size: 6.6 vs. 6.4 vs. 5.2 vs. 6.5 cm	RFA + TACE (N=24) vs. TACE (N=11) vs. RFA (N=12) vs. RFA + TACE + Lentinan (N=31)	• Overall survival: mean survival time significantly higher in Lentinan group: 21.9 vs. 14.9 vs. 18.8 vs. 28.2 months ○ 6 months: 79% vs. 62% vs. 60% vs. 94% ○ 1 year: 68% vs. 53% vs. 58% vs. 81% ○ 18 months: 67% vs. 45% vs. 52% vs. 77%	• Tumour recurrence rate: 29% vs. 46% vs. 35% vs. 18% in favour of Lentinan group (p<0.05)	Level of evidence: B • No clear description of randomisation procedure • No blinding reported • ITT analysis • Median follow-up: not reported

Abbreviations: 95%CI: 95% confidence interval; AE: adverse events; AFP: alfa-fetoprotein; CoI: conflicts of interest; CR: complete response; CT: computed tomography; DEB: drug-eluting beads; ECOG: Eastern Cooperative Oncology Group; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HR: hazard ratio; ITT: intention to treat; MA: meta-analysis; MRI: magnetic resonance imaging; NS: not significant; NYHA: New York Heart Association; OR: odds ratio; PAAI: percutaneous acetic acid injection; PEI: percutaneous ethanol injection; PFS: progression-free survival; PR: partial response; QoL: quality of life; RCT: randomised controlled trial; RFA: radiofrequency ablation; RFS: recurrence-free survival; RR: relative risk; SR: systematic review; TACE: transarterial chemoembolisation; TACP: transarterial chemoperfusion; TAE: transarterial embolisation; TAI: transarterial infusion

Uitgangsvraag 8: Welke systemische therapie wordt aanbevolen bij HCC-patiënten?

Systematic reviews

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VII Results secondary and other outcomes	VII Critical appraisal of study quality
Zhang 2010 [1]	• SR + MA • Funding/CoI: no CoI to declare • Search date: 12/2008 • Databases: PubMed, ASCO and ESMO abstracts; reference lists & PDQR of clinical trials • Study designs: RCTs • N included studies: N=3	• Eligibility criteria: ○ Patients with advanced HCC	Sorafenib (N=496) vs. Placebo or other agent (N=428)	• Overall survival: HR 0.66 (95%CI 0.55-0.78, p<0.001) in favour of sorafenib	• Time-to-progression: HR 0.58 (95%CI 0.49-0.69, p<0.001) in favour of sorafenib • Toxicity: ○ Hand-foot syndrome: OR 13.43 (95%CI 3.53-71.47, p=0.002) in favour of placebo ○ Diarrhea: OR 2.41 (95%CI 0.99-5.88, p=0.05) in favour of placebo ○ No significant differences in other toxic events	Level of evidence: A1 • Simple search strategy • Study quality assessed, but not taken into account • Included studies: ○ Abou-Alfa 2009 (abstract) ○ Cheng 2009 (abstract) ○ Llovet 2008

Primaire studies

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VII Results secondary and other outcomes	VII Critical appraisal of study quality
Kudo 2011 [2]	• RCT • Funding/CoI: supported by Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals; several authors received fees from Bayer or are employees of Bayer • Setting: 69 Japanese and 7 South-Korean centres • Sample size: N=458 • Duration: inclusion from 4/2006-7/2009	• Eligibility criteria: ○ Patients with unresectable HCC ○ Child-Pugh A ○ At least 18y old ○ Sustained response 1-3 months after TACE ○ Maximum target lesion size of 70 mm ○ Maximum of 10 target lesions ○ Adequate bone marrow, liver, and renal function ○ No extrahepatic metastases ○ No prior use of systemic agents for HCC • Group comparability: no obvious differences (Sorafenib vs. placebo) ○ Male: 76% vs. 73%	Sorafenib 400 mg twice daily (N=229) vs. Placebo (N=229) All patients were treated with TACE (epirubicin, cisplatin, doxorubicin, mitomycin)	• 1-year overall survival: 94.6% vs. 94.1% • 2-year overall survival: 72.1% vs. 73.8% • HR of death: 1.06 (95%CI 0.69-1.64, p=0.79)	• Progression-free rates: ○ 3 mo: 65.0% vs. 58.7% ○ 6 mo: 45.7% vs. 33.5% • Safety: grade 3/4 ○ Hand-foot syndrome: 35% vs. 0% ○ Elevated lipase: 28% vs. 4% ○ Rash: 4% vs. 0%	Level of evidence: B • Unclear allocation concealment • Central evaluation of response • ITT analysis

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VII Results secondary and other outcomes	VII Critical appraisal of study quality
		○ Median age: 69 vs. 70y ○ HCV: 61% vs. 65% ○ CR to TACE: 62% both				
Abou-Alfa 2010 [3]	• RCT • Funding/CoI: supported by research grant from Bayer; several authors received fees from Bayer • Setting: multinational multicentre study • Sample size: N=96 • Duration: inclusion from 4/2005-10/2006	• Eligibility criteria: ○ Patients with inoperable HCC ○ Child-Pugh A ○ Adequate bone marrow, liver, renal and cardiac function ○ No prior systemic treatments for HCC • Group comparability: no obvious differences (Sorafenib vs. placebo) ○ Male: 66% vs. 86% ○ Median age: 66 vs. 65y ○ HCV: 21% vs. 14%	Doxorubicin 60 mg/m² every 21 days for maximum of 360 mg/m² + sorafenib twice orally (N=47) vs. Doxorubicin 60 mg/m² every 21 days for maximum of 360 mg/m² + placebo twice orally (N=49)	• Median OS: 13.7 (95%CI 8.9-) vs. 6.5 months (4.5-9.9); HR 0.49 (0.3-0.8; p=0.006) in favour of sorafenib	• Median PFS: 6 (4.6-8.6) vs. 2.7 months (1.4-2.8); HR 0.54 (0.3-0.8; p=0.006) in favour of sorafenib • Toxicity: grade 3/4 ○ Hand-foot syndrome: 6.4% vs. 0%	Level of evidence: A2 • Concealed allocation • Blinded outcome assessors • ITT analysis
Cheng 2009 [4]	• RCT • Funding/CoI: supported by Bayer; several authors received fees from Bayer or are employees of Bayer • Setting: multicentre study, Asia-Pacific region • Sample size: N=226 • Duration: inclusion from 9/2005-1/2007	• Eligibility criteria: ○ Patients with unresectable or metastatic HCC ○ At least 18y old ○ Child-Pugh A ○ Adequate bone marrow, liver, renal function ○ No prior systemic treatments for HCC • Group comparability: no obvious differences (Sorafenib vs. placebo) ○ Male: 85% vs. 87% ○ Median age: 51 vs. 52y ○ HCV: 16% vs. 3%	Sorafenib 400 mg orally twice daily (N=150) vs. Placebo (N=76)	• Median OS: 6.5 (95%CI 5.56-7.56) vs. 4.2 months (3.75-5.46); HR 0.68 (0.50-0.93; p=0.014) in favour of sorafenib • 6-month OS: 53.3% vs. 36.7%	• Toxicity: grade 3/4 ○ Hand-foot syndrome: 10.7% vs. 0% ○ Diarrhoea: 6% vs. 0%	Level of evidence: A2 • Concealed allocation • Double-blind study, although it is not clear who was blinded • ITT analysis
Llovet 2008 [5]	• RCT • Funding/CoI: supported by Bayer HealthCare Pharmaceuticals–Onyx Pharmaceuticals • Setting: multinational multicentre study • Sample size: N=602 • Duration: inclusion from 3/2005-4/2006	• Eligibility criteria: ○ Patients with advanced-stage HCC (not eligible for or disease progression after surgical or locoregional therapies) ○ Child-Pugh A ○ Adequate bone marrow, liver, renal function ○ No prior systemic treatments for HCC	Sorafenib 400 mg orally twice daily (N=299) vs. Placebo (N=303)	• Median OS: 10.7 vs. 7.9 months; HR 0.69 (95%CI 0.55-0.87; p<0.001) in favour of sorafenib • 1-year OS: 44% vs. 33%	• Toxicity: grade 3/4 ○ Hand-foot syndrome: 8% vs. <1% ○ Diarrhoea: 8% vs. 2%	Level of evidence: A2 • Concealed allocation • Double-blind study, although it is not clear who was blinded • ITT analysis • Early termination of study

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VII Results secondary and other outcomes	VII Critical appraisal of study quality
		• Group comparability: no obvious differences (Sorafenib vs. placebo) ○ Male: 87% vs. 87% ○ Median age: 65 vs. 66y ○ HCV: 29% vs. 27%				

Abbreviations: 95%CI: 95% confidence intervals; CR: complete remission; HCC: hepatocellular carcinoma; HR: hazard ratio; ITT: intention-to-treat; MA: meta-analysis; OR: odds ratio; OS: overall survival; PFS: progression-free survival; RCT: randomized controlled trial; SR: systematic review; TACE: transarterial chemo-embolisation.