H.4 Surveillance for the early detection of hepatocellular carcinoma (HCC)

Study	Giannini 2000[53]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=61)
Countries and setting	Conducted in Italy; setting: Department of Internal Medicine
Line of therapy	Not applicable
Duration of study	Recruited at time of HCC diagnosis (duration of surveillance unclear)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Presence of cirrhosis assessed on the basis of clinical signs of portal hypertension, Doppler ultrasonography measurements, and/or endoscopic presence of oesophageal or gastric varices.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Anti-HCV positive cirrhosis associated HCC
Exclusion criteria	HBV, HIV or autoimmunity. Metabolic causes of liver disease or alcohol abuse.
Recruitment/selection of patients	Consecutive patients meeting inclusion criteria from August 1993 to September 1998
Age, gender and ethnicity	Age – mean (SD): 68 (9) years. Gender (M:F): 42/19. Ethnicity: not reported.
Further population details	1. Aetiology of liver injury: Hepatitis C. 2. Severity of the underlying liver disease/degree of liver decompensation at the time of HRS: Child-Pugh A or B (CP A 35 [57.4%], CP B 18 [29.5%], CP C 8 [13.1%]). 3. Treatment/prior treatment for underlying condition versus not on treatment (for example if the hepatitis C virus has been treated or not): not treated for underlying condition/not abstaining from alcohol (11 patients had previously undergone a course of interferon therapy, and none of them had responded to anti-viral therapy).
Indirectness of population	No indirectness
Interventions	(n=34) Intervention 1: Surveillance – ultrasound+AFP 6-monthly. Biannual biochemical (AFP) and ultrasound follow-up. Diagnosis of HCC made by cytological examination of the smear obtained from an ultrasound-guided fine needle biopsy of hepatic nodules revealed by ultrasound or CT scan. Duration: unclear. Concurrent medication/care: therapeutic intervention was chosen following clinical and functional staging, according to recommended criteria. (n=27). Intervention 2: No surveillance (HCC detected incidentally). Found during examinations performed at non-scheduled intervals or referred to the centre for evaluation of liver masses found during examinations performed due

Study	Giannini 2000[53]
	to extrahepatic diseases. Duration: unclear. Concurrent medication/care: therapeutic intervention was chosen following clinical and functional staging, according to recommended criteria.
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRASOUND+AFP 6-MONTHLY versus NO SURVEILLANCE (HCC DETECTED INCIDENTALLY) Protocol outcome 1: Survival - Actual outcome: Survival at end of study; HR 2.61 (95% CI 1.15 to 5.93) (B: estimated coefficient of regression [SE] 0.96 [0.0419]); risk of bias: high (not adjusted for lead time bias; not adjusted for all key confounders); indirectness of outcome: no indirectness. Adjusted relative hazard RH (RH=e^B). Variables: gender, Child-Pugh score, number of tumoural nodules (1/>1), AFP value, AFP (normal/increased), type of treatment (treated/not treated) and modality of diagnosis (follow-up/incidental).	
Protocol outcomes not reported by the study	Quality of life; HCC occurrence; lesion of HCC less than or equal to 3cm, greater than 3cm; number of lesions; liver cancer staging (according to BCLC system); liver transplant

Study	Miquel 2012[88]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=110)
Countries and setting	Conducted in Spain; setting: hepatology unit
Line of therapy	Not applicable
Duration of study	Recruited people diagnosed with HCC between January 2004 and December 2006. Prospectively followed up until February 2011.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: The diagnosis of cirrhosis was established from clinical, laboratory test, ultrasound and/or endoscopic data, or according to histological criteria.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosed with HCC. All patients had cirrhosis.
Exclusion criteria	Not reported
Recruitment/selection of patients	All patients diagnosed with HCC between January 2004 and December 2006 in the Hepatology Unit (Corporació

Study	Miquel 2012[88]
	Sanitària Parc Taulí, Sabadell, Catalonia, Spain).
Age, gender and ethnicity	Age – mean (SD): 65.8 (11.2) years. Gender (M:F): 77/33. Ethnicity: not reported.
Further population details	1. Aetiology of liver injury: Mixed aetiologies (HCV: 56.1%, alcohol: 25.1%, HBV: 2%, HCV+alcohol: 11.2%, cryptogenic: 5.2%). 2. Severity of the underlying liver disease/degree of liver decompensation at the time of HRS: Child-Pugh A or B (only 3.6% Child-Pugh C). 3. Treatment/prior treatment for underlying condition versus not on treatment (for example if the hepatitis C virus has been treated or not): not applicable/not stated/unclear.
Indirectness of population	No indirectness
Interventions	(n=56) Intervention 1: Surveillance – ultrasound+AFP 6-monthly. Patients mainly derived from the outpatient clinic, diagnosed with cirrhosis and enrolled in a screening program. EASL diagnostic criteria for HCC: compatible biopsy findings, two imaging methods with consistent findings in lesions <2 cm in size, one imaging method with consistent findings in lesions ≥2 cm in size, and AFP >200 ng/ml. Duration: Follow-up: end of the study (5–7 years from recruitment). Concurrent medication/care: treatment for HCC in each patient was decided by the tumour committee according to the criteria proposed by the BCLC staging system. Two management groups: potentially curative (resective surgery, liver transplant or percutaneous treatment) and palliative (embolisation or symptomatic treatment). (n=54) Intervention 2: No surveillance. Patients not enrolled in the screening program and who were referred to the unit from primary care for the study of liver lesions detected as a result of imaging explorations, following confirmation of the diagnosis of HCC. EASL diagnostic criteria for HCC: compatible biopsy findings, two imaging methods with consistent findings in lesions <2 cm in size, one imaging method with consistent findings in lesions ≥2 cm in size, and AFP >200 ng/ml. Duration: Follow-up: end of the study (5–7 years from recruitment). Concurrent medication/care: treatment for HCC in each patient was decided by the tumour committee according to the criteria proposed by the BCLC staging system. Two management groups: potentially curative (resective surgery, liver transplant or percutaneous treatment) and palliative (embolisation or symptomatic treatment).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRASOUND+AFP 6-MONTHLY versus NO SURVEILLANCE

Protocol outcome 1: Survival
- Actual outcome: Survival at end of study; OR 1.13 (95% CI 0.64 to 2.01) (p value 0.68); risk of bias: high (not adjusted for lead time bias; not adjusted for all key confounders); indirectness of outcome: no indirectness. Multivariate analysis considered those factors found to be statistically significant in the univariate analysis: degree of liver function, screening, tumour size, and curative versus palliative. In this analysis, screening was not statistically significant (not an independent predictor

Study	Miquel 2012[88]
of survival).	
Protocol outcomes not reported by the study	Quality of life; HCC occurrence; lesion of HCC less than or equal to 3cm, greater than 3cm; number of lesions; liver cancer staging (according to BCLC system); liver transplant

Study	Pascual 2008[100]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=290)
Countries and setting	Conducted in Spain; setting: university hospital
Line of therapy	Not applicable
Duration of study	Minimum follow-up 6 months from recruitment. Recruited at time of HCC diagnosis (duration of surveillance unclear). Recruitment started January 1996 and data collected until December 2004.
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: Method of diagnosis of cirrhosis not reported
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with cirrhosis and HCC (unclear if all patients had cirrhosis – reported in paper that the liver unit records data for all patients with HCC and cirrhosis – presume all HCCs in study had cirrhosis)
Exclusion criteria	Not reported
Recruitment/selection of patients	All patients with cirrhosis and HCC attending the University Hospital since January 1996
Age, gender and ethnicity	Age – mean (SD): surveillance: 68.8 years; no surveillance: 68.2 years. Gender (M:F): 218/72. Ethnicity: not reported.
Further population details	1. Aetiology of liver injury: Mixed aetiologies (alcohol: 29.3%, HCV: 45.9%, HBV: 4.8%, alcohol+virus: 8.3%, other: 11.7%). 2. Severity of the underlying liver disease/degree of liver decompensation at the time of HRS: Child-Pugh A or B (14.5% Child-Pugh C). 3. Treatment/prior treatment for underlying condition versus not on treatment (for example if the hepatitis C virus has been treated or not): not applicable/not stated/unclear.
Indirectness of population	No indirectness
Interventions	(n=117) Intervention 1: Surveillance – ultrasound+AFP 6-monthly. Patients being diagnosed with HCC during the course of surveillance. Diagnosis of HCC based on criteria of EASL Barcelona conference: combining an increased AFP with typical features and one imaging technique (CT or MRI) or two HCC-compatible imaging techniques. In the rest of

Study	Pascual 2008[100]
	the cases, HCC diagnosis was confirmed by histology. Duration: minimum 6 months after HCC diagnosis. Concurrent medication/care: treatment according to tumour characteristics and protocol of care: i) liver transplantation for patients younger than 65 years, with a solitary tumour ≤5 cm or 3 nodules in diameter without vascular invasion or extrahepatic dissemination; ii) percutaneous ethanol injection or radiofrequency thermal ablation in patients not suitable for liver transplantation with small tumours (<3.5–4 cm); iii) transarterial chemoembolisation considered for patients with large/multinodular tumours without portal thrombosis and preserved liver function; iv) symptomatic treatment was applied for end-stage patients. (n=173) Intervention 2: No surveillance (HCC detected by symptoms or incidentally). Patients diagnosed with HCC outside surveillance (because of symptoms or at the same time as cirrhosis diagnosis). Diagnosis of HCC based on criteria of EASL Barcelona conference: combining an increased AFP with typical features and one imaging technique (CT or MRI) or two HCC-compatible imaging techniques. In the rest of the cases, HCC diagnosis was confirmed by histology. Duration: minimum 6 months after HCC diagnosis. Concurrent medication/care: treatment according to tumour characteristics and protocol of care: i) liver transplantation for patients younger than 65 years, with a solitary tumour ≤5 cm or 3 nodules in diameter without vascular invasion or extrahepatic dissemination; ii) percutaneous ethanol injection or radiofrequency thermal ablation in patients not suitable for liver transplantation with small tumours (<3.5–4 cm); iii) transarterial chemoembolisation considered for patients with large/multinodular tumours without portal thrombosis and preserved liver function; iv) symptomatic treatment was applied for end-stage patients.
Funding	Academic or government funding (supported in part by a grant from Instituto de Salud Carlos III, Madrid, Spain and from Diputacion Provincial de Alicante)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRASOUND+AFP 6-MONTHLY versus NO SURVEILLANCE (HCC DETECTED BY SYMPTOMS OR INCIDENTALLY) Protocol outcome 1: Survival - Actual outcome: Survival (following HCC diagnosis) at end of study (median 13 months, 0.5–100 months); other: beta coefficient from multivariate analysis: 0.4 (95% CI 0.3 to 0.6) (p value 0.0003); risk of bias: high (not adjusted for lead time bias; not adjusted for all key confounders); indirectness of outcome: no indirectness. Multivariate analysis included the following variables: Child-Pugh status, tumour characteristics, treatment applied for HCC.	
Protocol outcomes not reported by the study	Quality of life; HCC occurrence; lesion of HCC less than or equal to 3 cm, greater than 3 cm; number of lesions; liver cancer staging (according to BCLC system); liver transplant

Study	Santi 2010[118]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=649)
Countries and setting	Conducted in Italy; setting: 10 medical institutions
Line of therapy	Not applicable
Duration of study	Recruited at time of HCC diagnosis (duration of surveillance unclear)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Cirrhosis was histologically confirmed in 271 patients and by laparotomy or laparoscopy in 11. In the remaining patients, the diagnosis was made unequivocal by clinical evaluation, presence of nodular liver margins at ultrasound examination, endoscopic and/or ultrasound findings suggesting the presence of portal hypertension, and laboratory features.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) Child-Pugh class A or B; (2) HCC diagnosis made during a regular surveillance based on liver ultrasound, with or without AFP performed every 6 (±1 month) or 12 months (±1 month); (3) description of presenting cancer stage available.
Exclusion criteria	Child-Pugh class C or unspecified; diagnosis of HCC made outside any surveillance; unspecified modality of HCC diagnosis; unspecified interval of surveillance; interval outside the above mentioned ranges.
Recruitment/selection of patients	Analysed patients matching inclusion criteria from the ITA.LI.CA database (HCC patients seen consecutively from January 1987 to December 2006)
Age, gender and ethnicity	Age: median (range): 67 (30–89). Gender (M:F): 457/192. Ethnicity: Italian.
Further population details	1. Aetiology of liver injury: Mixed aetiologies (HCV 63.3 %; HBV 9.1%; alcohol 7.9 %; multiple 15.9%; others 3.9%). 2. Severity of the underlying liver disease/degree of liver decompensation at the time of HRS: Child-Pugh A or B. 3. treatment/prior treatment for underlying condition versus not on treatment (for example if the hepatitis C virus has been treated or not): not applicable/not stated/unclear .
Extra comments	HBV 9.1% (unclear how many people with multiple aetiologies had HBV)
Indirectness of population	No indirectness
Interventions	(n=139) Intervention 1: Surveillance – ultrasound+AFP yearly. HCC detected during annual (+/-1 month) ultrasound surveillance (with or without AFP). The diagnosis was based on histology or cytology in 96 patients. Otherwise, diagnosis was confirmed by combining an increase (>200 ng/ml) of AFP with typical features of the lesion in one imaging technique CT scan or MRI or contrast-enhanced ultrasound [CEUS]) or, in the absence of diagnostic AFP

Study	Santi 2010[118]
	elevation, in at least two techniques. Cancer was staged by CT scan or MRI. For the purpose of this study, HCC was staged as: solitary nodule ≤2 cm without macrovascular invasion (V0), lymph-node invasion (L0) or distant metastases (M0); solitary nodule of 2.1–3 cm, V0, L0, M0; solitary nodule of 3.1–5 cm, V0, L0, M0; 2–3 nodules, each ≤3 cm (paucifocal), V0, L0, M0; advanced tumour (outside the Milano criteria). Duration: median duration of surveillance: 9 years, range: 1–40. Concurrent medication/care: cancer stage was scored according to the latest versions of both the United Network for Organ Sharing (UNOS) tumour nodes metastases (TNM) system and Cancer of the Liver Italian Program (CLIP) system. The potential orthotopic liver transplant feasibility was evaluated according to the "Milano criteria" proposed by Mazzaferro et al. Patients were considered suitable for resection according to the following criteria: 1) unifocal HCC located in the peripheral portions of the liver; 2) Child-Pugh score ≤7; 3) no evidence of portal vein infiltration/thrombosis; 4) no evidence of extrahepatic metastases; and 5) no extrahepatic contraindications to surgery. Patients were considered suitable for PEI when: 1) OLT was not offered or was refused by the patient, and surgical resection was not possible or was refused; 2) the tumour was unifocal and ≤4 cm, or was paucifocal with each node ≤3 cm; 3) the tumour was not subcapsular; 4) the Child-Pugh score was ≤10; and 5) there was no evidence of either main portal vein infiltration/thrombosis or extrahepatic metastases. Finally, transarterial chemoembolization (TACE) was offered to the patients with: 1) a paucifocal tumour not treatable with PEI or a multifocal tumour involving less than 40% of the liver volume; 2) Child-Pugh score ≤10; 3) no main portal vein infiltration/thrombosis and extrahepatic metastases; and 4) no severe associated diseases. (n=510) Intervention 2: Surveillance – ultrasound+AFP 6 monthly. HCC detected during semiannual (+/-1 month) ultrasound surveillance (with or without AFP). The diagnosis was based on histology or cytology in 96 patients. Otherwise, diagnosis was confirmed by combining an increase (>200 ng/ml) of AFP with typical features of the lesion in one imaging technique CT scan or MRI or contrast-enhanced ultrasound [CEUS]) or, in the absence of diagnostic AFP elevation, in at least two techniques. Cancer was staged by CT scan or MRI. For the purpose of this study, HCC was staged as: solitary nodule ≤2 cm without macrovascular invasion (V0), lymph-node invasion (L0) or distant metastases (M0); solitary nodule of 2.1–3 cm, V0, L0, M0; solitary nodule of 3.1–5 cm, V0, L0, M0; 2–3 nodules, each ≤3 cm (paucifocal), V0, L0, M0; advanced tumour (outside the Milano criteria). Duration: median duration of surveillance: 10 years, range: 0.5–42. Concurrent medication/care: cancer stage was scored according to the latest versions of both the United Network for Organ Sharing (UNOS) tumour nodes metastases (TNM) system and Cancer of the Liver Italian Program (CLIP) system. The potential orthotopic liver transplant feasibility was evaluated according to the "Milano criteria" proposed by Mazzaferro et al. Patients were considered suitable for resection according to the following criteria: 1) unifocal HCC located in the peripheral portions of the liver; 2) Child-Pugh score ≤7; 3) no evidence of portal vein infiltration/thrombosis; 4) no evidence of extrahepatic metastases; and 5) no extrahepatic contraindications to surgery. Patients were considered suitable for PEI when: 1) OLT was not offered or was refused by the patient, and surgical resection was not possible or was refused; 2) the tumour was unifocal and ≤4 cm, or was paucifocal with each node ≤3 cm; 3) the tumour was not subcapsular; 4) the Child-Pugh score was ≤10; and 5) there

Study	Santi 2010[118]
	was no evidence of either main portal vein infiltration/thrombosis or extrahepatic metastases. Finally, transarterial chemoembolization (TACE) was offered to the patients with: 1) a paucifocal tumour not treatable with PEI or a multifocal tumour involving less than 40% of the liver volume; 2) Child-Pugh score ≤10; 3) no main portal vein infiltration/thrombosis and extrahepatic metastases; and 4) no severe associated diseases.
Funding	Academic or government funding (supported by a grant from the Ministero del l'Istruzione, dell'Università e della Ricerca)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRASOUND+AFP YEARLY versus ULTRASOUND+AFP 6-MONTHLY Protocol outcome 1: Survival - Actual outcome: mortality (in group 1 patients, the survival was corrected for the lead time bias) at mean follow up after HCC diagnosis 38.6 ± 32.8 months; HR 1.39 (95% CI 1.05 to 1.82); risk of bias: low; indirectness of outcome: no indirectness. Adjusted HR from multivariate analysis (variables: age, platelet count, AFP, Child-Pugh class and oesophageal varices). Protective effect of semiannual surveillance disappeared when cancer stage was added to the model (HR for surveillance not provided as an independent variable). Protocol outcome 2: Liver cancer staging (according to BCLC system) - Actual outcome: detection of a HCC beyond the very early stage (that is, solitary nodule >2 cm or multinodular tumour with/without vascular invasion and/or metastases) at unclear; OR 5.99 (95% CI 2.57 to 13.98); risk of bias: low; indirectness of outcome: no indirectness. Adjusted OR from multivariate analysis (variables included those associated with a tumour beyond the very early stage: surveillance interval, sex, aetiology, ALT, AFP, and Child-Pugh class).	
Protocol outcomes not reported by the study	Quality of life; HCC occurrence; number of lesions; lesion of HCC less than or equal to 3 cm, greater than 3 cm; liver transplant

Study	Stroffolini 2011[142]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=418)
Countries and setting	Conducted in Italy; setting: hospital
Line of therapy	Not applicable
Duration of study	Recruited at time of HCC diagnosis (duration of surveillance unclear)

Study	Stroffolini 2011[142]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Liver cirrhosis was diagnosed by liver biopsy or in the presence of unequivocal clinical, biochemical and ultrasound signs. Presence of cirrhosis 94.7%.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	HCC cases
Exclusion criteria	Not reported
Recruitment/selection of patients	All HCC cases consecutively observed over a six-month period (October 2008–March 2009) in 23 hospitals throughout the country. All the areas of our country were adequately represented due to the large geographical distribution of the participating centres.
Age, gender and ethnicity	Age – mean (SD): 67.5 (10.6). Gender (M:F): 310/108. Ethnicity: not reported.
Further population details	1. Aetiology of liver injury: Mixed aetiologies (HBsAg−/HCV+ 56.1% [15% HBsAg positive or HBsAg positive and anti-HCV positive]). 2. Severity of the underlying liver disease/degree of liver decompensation at the time of HRS: Child-Pugh A or B (Child-Pugh A 70.8%, B 20.6%, C 8.6%). 3. Treatment/prior treatment for underlying condition versus not on treatment (for example if the hepatitis C virus has been treated or not): not applicable/not stated/unclear.
Indirectness of population	No indirectness
Interventions	(n=247) Intervention 1: Surveillance – ultrasound 6–12 monthly. Reports that people had ultrasound surveillance (unclear if also used AFP). Surveillance had been performed twice a year in 80.3% of cases and annually in 19.7%. The diagnostic criteria for HCC were: (1) histological, based on internationally accepted criteria and (2) clinical, based on an alpha-fetoprotein (AFP) value greater than 200 ng/ml and evidence of focal liver lesions at imaging techniques, according to the guidelines of EASL or, for tumours diagnosed after 2005, of the AASLD. Duration: unclear. Concurrent medication/care: treatment not reported but staging according to the following criteria: best stage for curative treatment (“very early stage”: single nodule ≤2 cm) or at a stage when curative options are still applicable, that is, within the Milan criteria (“non-advanced stage”: single nodule ≤5 cm or no more than 3 nodules, each ≤3 cm, without vascular invasion and metastases). (n=154) Intervention 2: No surveillance. The diagnostic criteria for HCC were: (1) histological, based on internationally accepted criteria and (2) clinical, based on an alpha-fetoprotein (AFP) value greater than 200 ng/ml and evidence of focal liver lesions at imaging techniques, according to the guidelines of EASL or, for tumours diagnosed after 2005, of the AASLD. Duration: unclear. Concurrent medication/care: treatment not reported but staging according to the following criteria: best stage for curative treatment (“very early stage”: single nodule ≤2 cm) or at a stage when curative options are still applicable, that is, within the Milan criteria (“non-advanced stage”: single nodule ≤5 cm or no more than 3 nodules, each ≤3 cm, without vascular invasion and metastases).

Study	Stroffolini 2011[142]
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRASOUND 6–12 MONTLY versus NO SURVEILLANCE Protocol outcome 1: Liver cancer staging (according to BCLC system) - Actual outcome: Detection of HCC at a very early stage (single nodule ≤2 cm) at unclear; OR 5.4 (95%CI 2.4 to 12.4); risk of bias: low; indirectness of outcome: no indirectness. OR adjusted for the confounding factors of age, gender, surveillance, aetiologies, AFP levels, cirrhosis. - Actual outcome: Detection of HCC at a non-advanced stage (single nodule ≤5 cm or 3 nodules each ≤3 cm without vascular and lymphonodal invasion and metastases) at unclear; OR 3.1 (95% CI 1.9 to 5.2); risk of bias: low; indirectness of outcome: no indirectness. OR adjusted for the confounding factors of age, gender, surveillance, aetiologies, AFP levels, cirrhosis.	
Protocol outcomes not reported by the study	Survival; quality of life; HCC occurrence; number of lesions; lesion of HCC less than or equal to 3cm, greater than 3cm; liver transplant

Study	Trevisani 2004[149]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=363)
Countries and setting	Conducted in Italy; setting: 7 medical institutions
Line of therapy	Not applicable
Duration of study	Recruited at time of HCC diagnosis (duration of surveillance unclear)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: the diagnosis of chronic liver disease was based on histology, laparoscopy, or laparotomy in 130 patients (all but 9 had cirrhosis). In the remaining 233 the diagnosis of cirrhosis was made unequivocal by clinical (endoscopic and/or ultrasound signs of portal hypertension, and/or an irregular margin of the liver at ultrasound examination) and laboratory features.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with HCC. Presence of underlying chronic liver disease; indication of the modality of HCC diagnosis; description of the cancer stage; aged 70 years or over.

Study	Trevisani 2004[149]
Exclusion criteria	Not reported
Recruitment/selection of patients	Consecutive from January 1988 to December 2001
Age, gender and ethnicity	Age – mean (SD): surveillance: 73.9 (3.6), incidental HCC 74.9 (3.7); symptomatic HCC 74.6 (4.5). Gender (M:F): 242/121. Ethnicity: Italian.
Further population details	1. Aetiology of liver injury: Hepatitis C (79.6% HCV or HCV co-infection (not including people with mixed alcohol and viral aetiology, proportion of people with HCV in this group not reported). 2. Severity of the underlying liver disease/ degree of liver decompensation at the time of HRS: Child-Pugh A or B (Child-Pugh A 67.2%, Child-Pugh B 27.6%, Child-Pugh C 5.2%). 3. Treatment/prior treatment for underlying condition versus not on treatment (for example if the hepatitis C virus has been treated or not): not applicable/not stated/unclear.
Extra comments	All but 9 patients had cirrhosis. 12.7% HBV or HBV co-infection (not including people with mixed alcohol and viral aetiology, proportion of people with HBV in this group not reported).
Indirectness of population	No indirectness
Interventions	(n=158) Intervention 1: Surveillance – ultrasound+AFP 6–12 monthly. Diagnosis made during regular surveillance performed every 6 (96 patients) or 12 months (62 patients). Diagnosis of HCC corroborated by histology or cytology. In the remaining cases it was made according to the Italian guidelines for the diagnosis of HCC, by combining an AFP increase (>200 ng/mL) with typical features on one imaging technique, or coincident findings were found on at least 2 techniques. Cancer was staged with both ultrasound and CT scan features and, when appropriate, by angiography and MRI. Macroscopic HCC was classified as: solitary nodular; paucifocal ≤3 nodules, multifocal >3 nodules, diffuse and massive type. The cancer stage was considered advanced or non-advanced according to the Milano criteria. Duration: unclear. Concurrent medication/care: cancer stage was scored according to the latest versions of both the United Network for Organ Sharing (UNOS) tumour nodes metastases (TNM) system and Cancer of the Liver Italian Program (CLIP) system. The potential orthotopic liver transplant feasibility was evaluated according to the "Milano criteria" proposed by Mazzaferro et al. Patients were considered suitable for resection according to the following criteria: 1) unifocal HCC located in the peripheral portions of the liver; 2) Child-Pugh score ≤7; 3) no evidence of portal vein infiltration/thrombosis; 4) no evidence of extrahepatic metastases; and 5) no extrahepatic contraindications to surgery. Patients were considered suitable for PEI when: 1) OLT was not offered or was refused by the patient, and surgical resection was not possible or was refused; 2) the tumour was unifocal and ≤4 cm, or was paucifocal with each node ≤3 cm; 3) the tumour was not subcapsular; 4) the Child-Pugh score was ≤10; and 5) there was no evidence of either main portal vein infiltration/thrombosis or extrahepatic metastases. Finally, transarterial chemoembolization (TACE) was offered to the patients with: 1) a paucifocal tumour not treatable with PEI or a multifocal tumour involving less than 40% of the liver volume; 2) Child-Pugh score ≤10; 3) no main portal vein infiltration/thrombosis and extrahepatic metastases; and 4) no severe associated diseases.

Study	Trevisani 2004[149]
	(n=138) Intervention 2: No surveillance (HCC detected incidentally). HCC detected incidentally outside surveillance or during diagnostic procedures for other diseases. Diagnosis of HCC corroborated by histology or cytology. In the remaining cases it was made according to the Italian guidelines for the diagnosis of HCC, by combining an AFP increase (>200 ng/ml) with typical features on one imaging technique, or coincident findings were found on at least 2 techniques. Cancer was staged with both ultrasound and CT scan features and, when appropriate, by angiography and MRI. Macroscopic HCC was classified as: solitary nodular; paucifocal ≤3 nodules, multifocal >3 nodules, diffuse and massive type. The cancer stage was considered advanced or non-advanced according to the Milano criteria. Duration: unclear. Concurrent medication/care: cancer stage was scored according to the latest versions of both the United Network for Organ Sharing (UNOS) tumour nodes metastases (TNM) system and Cancer of the Liver Italian Program (CLIP) system. The potential orthotopic liver transplant feasibility was evaluated according to the "Milano criteria" proposed by Mazzaferro et al. Patients were considered suitable for resection according to the following criteria: 1) unifocal HCC located in the peripheral portions of the liver; 2) Child-Pugh score ≤7; 3) no evidence of portal vein infiltration/thrombosis; 4) no evidence of extrahepatic metastases; and 5) no extrahepatic contraindications to surgery. Patients were considered suitable for PEI when: 1) OLT was not offered or was refused by the patient, and surgical resection was not possible or was refused; 2) the tumour was unifocal and ≤4 cm, or was paucifocal with each node ≤3 cm; 3) the tumour was not subcapsular; 4) the Child-Pugh score was ≤10; and 5) there was no evidence of either main portal vein infiltration/thrombosis or extrahepatic metastases. Finally, transarterial chemoembolization (TACE) was offered to the patients with: 1) a paucifocal tumour not treatable with PEI or a multifocal tumour involving less than 40% of the liver volume; 2) Child-Pugh score ≤10; 3) no main portal vein infiltration/thrombosis and extrahepatic metastases; and 4) no severe associated diseases. (n=67) Intervention 3: No surveillance (HCC detected by symptoms). HCC discovered because of symptom appearance. Diagnosis of HCC corroborated by histology or cytology. In the remaining cases it was made according to the Italian guidelines for the diagnosis of HCC, by combining an AFP increase (>200 ng/ml) with typical features on one imaging technique, or coincident findings were found on at least two techniques. Cancer was staged with both ultrasound and CT scan features and, when appropriate, by angiography and MRI. Macroscopic HCC was classified as: solitary nodular; paucifocal ≤3 nodules, multifocal >3 nodules, diffuse and massive type. The cancer stage was considered advanced or non-advanced according to the Milano criteria. Duration: unclear. Concurrent medication/care: cancer stage was scored according to the latest versions of both the United Network for Organ Sharing (UNOS) tumour nodes metastases (TNM) system and Cancer of the Liver Italian Program (CLIP) system. The potential orthotopic liver transplant feasibility was evaluated according to the "Milano criteria" proposed by Mazzaferro et al. Patients were considered suitable for resection according to the following criteria: 1) unifocal HCC located in the peripheral portions of the liver; 2) Child-Pugh score ≤7; 3) no evidence of portal vein infiltration/thrombosis; 4) no evidence of extrahepatic metastases; and 5) no extrahepatic contraindications to surgery. Patients were considered suitable for PEI when: 1) OLT was not offered or was refused by the patient, and

Study	Trevisani 2004[149]
	surgical resection was not possible or was refused; 2) the tumour was unifocal and ≤4 cm, or was paucifocal with each node ≤3 cm; 3) the tumour was not subcapsular; 4) the Child-Pugh score was ≤10; and 5) there was no evidence of either main portal vein infiltration/thrombosis or extrahepatic metastases. Finally, transarterial chemoembolization (TACE) was offered to the patients with: 1) a paucifocal tumour not treatable with PEI or a multifocal tumour involving less than 40% of the liver volume; 2) Child-Pugh score ≤10; 3) no main portal vein infiltration/thrombosis and extrahepatic metastases; and 4) no severe associated diseases.
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRASOUND+AFP 6–12 MONTHLY versus NO SURVEILLANCE (HCC DETECTED INCIDENTALLY) Protocol outcome 1: Survival - Actual outcome: survival; other: adjusted HR for surveillance not reported as it was not found to be an independent prognostic factor Protocol outcome 2: Liver cancer staging (according to BCLC system) at end of study - Actual outcome: HCC advanced stage according to Milano criteria at unclear; OR 0.29 (95% CI 0.17 to 0.49) (p value <0.001); risk of bias: low; indirectness of outcome: no indirectness. Surveillance shown to be an independent protective factor against advanced HCC. Adjusted OR (multivariate analysis adjusted for centre of enrolment, age, sex, aetiology of cirrhosis, Child-Pugh class, AFP level and type of diagnosis). RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRASOUND+AFP 6–12 MONTHLY versus NO SURVEILLANCE (HCC DETECTED BY SYMPTOMS) Protocol outcome 1: Survival - Actual outcome: survival; other: adjusted HR for surveillance not reported as it was not found to be an independent prognostic factor Protocol outcome 2: Liver cancer staging (according to BCLC system) at end of study - Actual outcome: HCC advanced stage according to Milano criteria at unclear; OR 0.18 (95% CI 0.09 to 0.37) (p value <0.001); risk of bias: low; indirectness of outcome: no indirectness. Surveillance shown to be an independent protective factor against advanced HCC. Adjusted OR (multivariate analysis adjusted for centre of enrolment, age, sex, aetiology of cirrhosis, Child-Pugh class, AFP level and type of diagnosis).	
Protocol outcomes not reported by the study	Quality of life; HCC occurrence; lesion of HCC less than or equal to 3cm, greater than 3cm; number of lesions; liver transplant

Study	Trevisani 2007[150]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=608)
Countries and setting	Conducted in Italy; setting: 10 medical institutions
Line of therapy	Adjunctive to current care
Duration of study	Recruited at time of HCC diagnosis (duration of surveillance unclear)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: cirrhosis was confirmed by histology in 168 patients and by laparotomy/laparoscopy in 10. In the remaining cases, the diagnosis was made unequivocally by clinical (endoscopic and/or ultrasound signs of portal hypertension and a nodular margin of the liver at ultrasound examination) and laboratory features.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	HCC and cirrhosis
Exclusion criteria	Class A Child-Pugh; surveillance interval not reported
Recruitment/selection of patients	ITA.LI.CA database: data of HCC patients seen consecutively from January 1987 to December 2004
Age, gender and ethnicity	Age – mean (SD): Child Pugh B: surveillance 63.8 ± 9.2, no surveillance 65.7 ± 10.0; Child-Pugh C: surveillance 61.6 ± 10.6, no surveillance: 60.4 ± 10.8. Gender (M:F): 455/153. Ethnicity: not reported.
Further population details	1. Aetiology of liver injury: mixed aetiologies (predominantly HCV). 2. Severity of the underlying liver disease/degree of liver decompensation at the time of HRS: not applicable/not stated/unclear (Child-Pugh A excluded. Results stratified by Child-Pugh B and C). 3. Treatment/prior treatment for underlying condition versus not on treatment (for example if the hepatitis C virus has been treated or not): not applicable/not stated/unclear.
Extra comments	10.4% HBV included (unclear how many of the people with multiple aetiologies had HBV)
Indirectness of population	No indirectness
Interventions	(n=252) Intervention 1: Surveillance – ultrasound+AFP 6-12 monthly. HCC was detected during regular surveillance based on liver ultrasound and AFP performed every 6 (172 cases [68.3%]) or 12 (80 [31.7%]) months. These patients were grouped since their prognosis was unaffected by the interval (data not shown, p=0.531). Allocated to group 1 even if the surveillance was brought forward due to the occurrence of symptoms. Diagnosis of HCC was based on histology or cytology in 42 patients. Otherwise, diagnosis was made by combining a diagnostic AFP increase (>200 ng/ml) with a typical feature of the lesion (arterial hypervascularity) in one imaging technique or, in the absence of diagnostic AFP, in at least two techniques. Duration: unclear. Concurrent medication/care: cancer stage was scored

Study	Trevisani 2007[150]
	according to the latest versions of both the United Network for Organ Sharing (UNOS) tumour nodes metastases (TNM) system and Cancer of the Liver Italian Program (CLIP) system. The potential orthotopic liver transplant feasibility was evaluated according to the "Milano criteria" proposed by Mazzaferro et al. Patients were considered suitable for resection according to the following criteria: 1) unifocal HCC located in the peripheral portions of the liver; 2) Child-Pugh score ≤7; 3) no evidence of portal vein infiltration/thrombosis; 4) no evidence of extrahepatic metastases; and 5) no extrahepatic contraindications to surgery. Patients were considered suitable for PEI when: 1) OLT was not offered or was refused by the patient, and surgical resection was not possible or was refused; 2) the tumour was unifocal and ≤4 cm, or was paucifocal with each node ≤3 cm; 3) the tumour was not subcapsular; 4) the Child-Pugh score was ≤10; and 5) there was no evidence of either main portal vein infiltration/thrombosis or extrahepatic metastases. Finally, transarterial chemoembolization (TACE) was offered to the patients with: 1) a paucifocal tumour not treatable with PEI or a multifocal tumour involving less than 40% of the liver volume; 2) Child-Pugh score ≤10; 3) no main portal vein infiltration/thrombosis and extrahepatic metastases; and 4) no severe associated diseases. (n=356) Intervention 2: No surveillance (HCC detected by symptoms or incidentally). HCC was detected “incidentally”, that is, outside any programmed surveillance or during examination for other diseases (181 patients [50.8%]), or because of symptom appearance (175 patients [49.2%]). These patients were grouped because both modalities of diagnosis reproduce an alternative to surveillance in detecting HCC in clinical practice. Most cases were referred to our centres by their GPs or other institutions to confirm diagnosis or start treatment of HCC (concomitant non-randomized controls). No conclusive information on surveillance (interval decided by referring physician). Diagnosis of HCC was based on histology or cytology in 42 patients. Otherwise, diagnosis was made by combining a diagnostic AFP increase (>200 ng/ml) with a typical feature of the lesion (arterial hypervascularity) in one imaging technique or, in the absence of diagnostic AFP, in at least two techniques. Duration: unclear. Concurrent medication/care: cancer stage was scored according to the latest versions of both the United Network for Organ Sharing (UNOS) tumour nodes metastases (TNM) system and Cancer of the Liver Italian Program (CLIP) system. The potential orthotopic liver transplant feasibility was evaluated according to the "Milano criteria" proposed by Mazzaferro et al. Patients were considered suitable for resection according to the following criteria: 1) unifocal HCC located in the peripheral portions of the liver; 2) Child-Pugh score ≤7; 3) no evidence of portal vein infiltration/thrombosis; 4) no evidence of extrahepatic metastases; and 5) no extrahepatic contraindications to surgery. Patients were considered suitable for PEI when: 1) OLT was not offered or was refused by the patient, and surgical resection was not possible or was refused; 2) the tumour was unifocal and ≤4 cm, or was paucifocal with each node ≤3 cm; 3) the tumour was not subcapsular; 4) the Child-Pugh score was ≤10; and 5) there was no evidence of either main portal vein infiltration/thrombosis or extrahepatic metastases. Finally, transarterial chemoembolization (TACE) was offered to the patients with: 1) a paucifocal tumour not treatable with PEI or a multifocal tumour involving less than 40% of the liver volume; 2) Child-Pugh score ≤10; 3) no main portal vein infiltration/thrombosis and extrahepatic metastases; and 4)

Study	Trevisani 2007[150]
	no severe associated diseases.
Funding	Academic or government funding (supported by a grant [Ricerca Fondamentale Orientata 2001–2003, Fondi ex 60%] from the Ministero della Istruzione, della Universita e della Ricerca [MIUR)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRASOUND+AFP 6–12 MONTHLY versus NO SURVEILLANCE (HCC DETECTED BY SYMPTOMS OR INCIDENTALLY) Protocol outcome 1: Survival - Actual outcome: survival at median follow up 17 months from the diagnosis of HCC; other: adjusted HR for surveillance not reported as it was not found to be an independent prognostic factor	
Protocol outcomes not reported by the study	Quality of life; HCC occurrence; lesion of HCC less than or equal to 3 cm, greater than 3 cm; number of lesions; liver cancer staging (according to BCLC system); liver transplant

Study	Trinchet 2011[152]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=1,340 randomized patients. Sixty-two were subsequently excluded from analysis after revision of individual data due to either immediate loss to follow-up [n=12] or to the presence of a focal liver lesion at inclusion [n=50]). Final number of subjects included=1,278
Countries and setting	Conducted in Belgium, France, multiple countries; setting: 43 specialist liver disease centres in France and Belgium
Line of therapy	Not applicable
Duration of study	Intervention + follow up: median 47 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: histologically proven compensated cirrhosis
Stratum	Overall
Subgroup analysis within study	Stratified then randomized
Inclusion criteria	(1) age older than 18 years; (2) histologically proven cirrhosis, whatever the time of biopsy; (3) cirrhosis related to either excessive alcohol consumption (80 g per day in males and 60 g per day in females for at least 10 years), chronic infection with hepatitis C virus (HCV) (serum anti-HCV antibodies-positive) or hepatitis B virus (HBV) (serum hepatitis B

Study	Trinchet 2011[152]
	surface antigen (HBsAg)-positive), or hereditary haemochromatosis (liver-iron overload and C282Y homozygosity); (4) absence of previous complications of cirrhosis (particularly ascites, gastrointestinal haemorrhage or HCC); (5) patients belonging to Child-Pugh class A or B and without a focal liver lesion at inclusion; and (6) written informed consent.
Exclusion criteria	(1) patients belonging to Child-Pugh class C; (2) severe uncontrolled extrahepatic disease resulting in estimated life expectancy of less than 1 year; and (3) co-infection with human immunodeficiency virus (HIV), even if controlled by an antiviral treatment.
Recruitment/selection of patients	June 2000 to May 2005
Age, gender and ethnicity	Age – M=median (IQR): 3 month: 54 (47–61); 6 month: 55 (48–64). Gender (M:F): 883/395. Ethnicity: not reported.
Further population details	1. Aetiology of liver injury: mixed aetiologies (alcohol 39.2%; HCV 44.1%; HBV 13.2%; haemochromatosis 1.6%; other 2.5%). 2. Severity of the underlying liver disease/degree of liver decompensation at the time of HRS: Child-Pugh A or B (Child-Pugh C excluded [1% were Child-Pugh C]). 3. Treatment/prior treatment for underlying condition versus not on treatment (for example if the hepatitis C virus has been treated or not): not applicable/not stated/unclear.
Extra comments	HBV 13.2%
Indirectness of population	No indirectness
Interventions	(n=668) Intervention 1: Surveillance – ultrasound 3-monthly. Patients received either ultrasound every 3 months and a serum AFP assay every 6 months or ultrasound every 3 months and no serum AFP assay. For a given patient it was recommended to perform ultrasound in the same centre by the same experienced operator. Diagnosis of HCC: contrast enhanced imaging, a serum AFP assay, and/or a guided biopsy were performed according to EASL guidelines. HCC diagnosis was established in the following situations: (1) histological proof of HCC; and (2) when a focal lesion was >2 cm in diameter, assessed by early arterial hypervascularization, using two contrast-enhanced methods (CT scan, MRI, arteriography), or when there was an association between serum AFP level of >400 ng/mL plus early arterial hypervascularization, assessed by one contrast enhanced method. In case of an increase in serum AFP level without liver focal lesion at ultrasound, a CT scan was performed according to recommendations. Duration: mean follow-up 47.1 months. Concurrent medication/care: when a HCC diagnosis was established treatment was determined using a multidisciplinary approach at each medical centre, by the physicians in charge of the patient. It was recommended to perform curative treatment (percutaneous ablation, resection, or transplantation) whenever possible. Regular endoscopic surveillance was performed to detect oesophageal varices and other portal hypertension-related lesions. In cases of oesophageal varices, preventive therapy was recommended either by beta-blockers or endoscopic ligation, according to international recommendations. (n=672) Intervention 2: Surveillance – ultrasound 6-monthly. Patients received either ultrasound and a serum AFP assay every 6 months, or ultrasound every 6 months and no serum AFP assay. For a given patient it was recommended to perform ultrasound in the same centre by the same experienced operator. Diagnosis of HCC:

Study	Trinchet 2011[152]
	contrast enhanced imaging, a serum AFP assay, and/or a guided biopsy were performed according to EASL guidelines. HCC diagnosis was established in the following situations: (1) histological proof of HCC; and (2) when a focal lesion was >2 cm in diameter, assessed by early arterial hypervascularization, using two contrast-enhanced methods (CT scan, MRI, arteriography), or when there was an association between serum AFP level of >400 ng/ml plus early arterial hypervascularization, assessed by one contrast enhanced method. In case of an increase in serum AFP level without liver focal lesion at ultrasound, a CT scan was performed according to recommendations. Duration: mean follow-up 46.8 months. Concurrent medication/care: when a HCC diagnosis was established treatment was determined using a multidisciplinary approach at each medical centre, by the physicians in charge of the patient. It was recommended to perform curative treatment (percutaneous ablation, resection, or transplantation) whenever possible. Regular endoscopic surveillance was performed to detect oesophageal varices and other portal hypertension-related lesions. In cases of oesophageal varices, preventive therapy was recommended either by beta-blockers or endoscopic ligation, according to international recommendations.
Funding	Academic or government funding (funded by the French Ministry of Health [PHRC 1998 and 2003] and the French Ligue de Recherche contre le Cancer)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ULTRASOUND 3-MONTHLY versus ULTRASOUND 6-MONTHLY

Protocol outcome 1: Mortality at 5 years
- Actual outcome: Survival at median follow-up 47 months; HR 0.87 (95 %CI 0.63 to 1.19) calculated – from logrank P-value; risk of bias: low; indirectness of outcome: no indirectness

Protocol outcome 2: HCC occurrence at end of study
- Actual outcome: Final diagnosis of focal liver lesion=HCC at median follow-up 47 months; Group 1: 53/640, Group 2: 70/638; risk of bias: low; indirectness of outcome: no indirectness

Protocol outcome 3: Lesion of HCC less than or equal to 3cm, greater than 3cm at end of study
- Actual outcome: Diameter of the largest HCC nodule (≤30 mm) – results categorised in study by ≤10, 11–20, 21–30, 31–50, ≥50 at median follow-up 47 months; Group 1: 42/640, Group 2: 49/638; risk of bias: low; indirectness of outcome: no indirectness
- Actual outcome: Diameter of the largest HCC nodule (>30 mm) – results categorised in study by ≤10, 11–20, 21–30, 31–50, ≥50 at median follow-up 47 months; Group 1: 11/640, Group 2: 21/638; risk of bias: low; indirectness of outcome: no indirectness

Protocol outcome 4: Number of lesions at end of study
- Actual outcome: Uninodular tumour at median follow-up 47 months; Group 1: 31/640, Group 2: 41/638; risk of bias: high; indirectness of outcome: no indirectness

Study	Trinchet 2011[152]
- Actual outcome: 2 or 3 nodules at median follow-up 47 months; Group 1: 15/640, Group 2: 12/638; risk of bias: high; indirectness of outcome: no indirectness - Actual outcome: >3 nodules at median follow-up 47 months; Group 1: 4/640, Group 2: 7/638; risk of bias: high; indirectness of outcome: no indirectness - Actual outcome: Infiltrative at median follow-up 47 months; Group 1: 3/640, Group 2: 10/638; risk of bias: high; indirectness of outcome: no indirectness Protocol outcome 5: Liver cancer staging (according to BCLC system) at end of study - Actual outcome: Within Milan criteria (one nodule ≤50 mm or 2 or 3 nodules ≤30 mm) at median follow-up 47 months; Group 1: 42/640, Group 2: 50/638; risk of bias: low; indirectness of outcome: no indirectness - Actual outcome: Beyond Milan criteria (Milan criteria=one nodule ≤50 mm or 2 or 3 nodules ≤30 mm) at median follow-up 47 months; Group 1: 11/640, Group 2: 20/638; risk of bias: high; indirectness of outcome: no indirectness Protocol outcome 6: Liver transplant at end of study - Actual outcome: Transplantation at median follow-up 47 months; Group 1: 17/640, Group 2: 13/638; risk of bias: high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Quality of life