Online Supplementary Document

Appendix 1

Protocol: Screening for Hepatocellular Carcinoma in Chronic Liver Disease: a Systematic Review and Meta-Analysis of Randomised Controlled Trials Comparing Screening Methodologies

Date created 18/4/18

Introduction

Hepatocellular carcinoma (HCC) is the 5th most prevalent cancer and the second most common cause of cancer related mortality worldwide [1]. In 2012 there are estimated to have been 782,000 new cases of hepatocellular carcinoma worldwide. 83% of these cases occurred in less developed regions with 50% occurring in China alone [1]. It is 2-4 times more common in men than women [2]. Chronic liver diseases such as hepatitis B, hepatitis C, alcoholic liver disease and non-alcoholic fatty liver disease are major risk factors for HCC [3,4]. It usually occurs in patients where liver disease has progressed to liver cirrhosis [5, 6]. The incidence of hepatocellular carcinoma is increasing in certain regions such as the United States (incidence men: 8.11/100,000, women: 2.47/100,000). This may be related to an increase in the prevalence of hepatitis C in the United States of America [7] and increased immigration from high prevalence regions. In regions such as China the incidence is decreasing (incidence men: 22.5/100,000, women: 6.5/100,000). This may be related to increased immunisation against hepatitis B [8]. The median age at diagnosis varies worldwide. In the United States according to data from the Surveillance Epidemiology and End Results (SEER) program the median age of HCC diagnosis by region of birth was 70-74 years for people from Europe, 65-69 years for people from Asia and 40-45 years for people from West Africa [9]. Hepatocellular carcinoma is often asymptomatic until an advanced stage. Early stage tumours are more likely to be amenable to treatment and have better overall survival [10]. Patients with symptomatic hepatocellular carcinoma have a 3-year survival of 8% [11]. Patients with well-compensated liver disease may be considered for surgical resection. The survival rates are 58% at 3 years and 42% at 5 years in non-cirrhotic patients with surgical resection [12]. Liver transplantation is the main course of therapy in patients with cirrhosis of the liver. 5-year survival rates after liver transplantation are 69%, with a tumour recurrence rate of 7% [13]. Patients with intermediate-stage hepatoma treated with transcatheter arterial chemo-embolisation (TACE) have median overall survival of 19-20 months [10].

Screening is the periodic application of a test in people at risk of developing a given disease to identify an early or latent stage. Hepatocellular carcinoma fits many of the requirements of a screening program because it follows a known clinical course, has an early treatable stage and is an important health problem. The purpose of this review is to determine if there is evidence from randomised controlled trials evaluating the efficacy of screening for HCC in patients with chronic liver disease.

Objectives

The primary objectives are:

1) To determine if screening for hepatocellular carcinoma is beneficial or harmful in patients with chronic liver disease when compared to no screening.

2) To determine which screening methodology for hepatocellular carcinoma is most beneficial in patients with chronic liver disease.

The secondary objectives are:

1) To determine if screening more frequently versus less frequently for hepatocellular carcinoma is beneficial or harmful in patients with chronic liver disease.

Methods

Included studies will be randomised controlled trials. Other types of studies will be excluded. This is to minimise confounding due to the potential for selection bias, performance bias and detection bias in non-randomised studies. Studies which evaluate the diagnostic accuracy of a test in the confirmation of suspected hepatocellular carcinoma will be excluded. There are no restrictions based on language, publication status or year of study. Only studies of Individuals with chronic liver disease will be included for review. Studies including individuals with a history of hepatocellular carcinoma will be excluded. To be included studies must compare screening with no screening, compare different screening methodologies or compare different screening intervals. Screening methodologies to be included for review are alpha-feto protein, ultrasound, computed tomography (CT) and Magnetic Resonance Imaging (MRI).

Primary outcomes are:

1. All-cause mortality

2. Quality of Life (any reported measure of quality of life was accepted)

Secondary outcomes are:

1. Mortality due to hepatocellular carcinoma

2. Number of cases of hepatocellular carcinoma detected

3. Adverse Events (According to the International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice (ICH 1997) adverse event is defined as any untoward medical occurrence in the participant in the clinical trial which does not necessarily have a causal relationship with this treatment. A serious adverse event is any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect).

Search methods for identification of studies

Electronic searches will be performed using MEDLINE (1946- May 2018), EMBASE (1974- May 2018), Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (1974- May 2018) and the Web of Science Citation Index Expanded (1900- May 2018) will all be searched according to the search strategy. Clinical trials registries will also be searched (clinicaltrials.gov, WHO International Clinical Trials Registry Platform (ICTRP) search portal). The references of identified relevant randomised controlled trials will be searched.

Data Extraction and Analysis

The first systematic reviewer will screen titles and abstracts for inclusion. The full articles of studies deemed eligible will then assessed by both first and second systematic reviewers for inclusion. All studies to be excluded will be recorded with the relevant explanation. Any disagreements between the first and second systematic reviewer will be resolved by discussion. Data extraction will be performed independently by two reviewers. A standardised data extraction spreadsheet will be used. Any disagreement between systematic reviewers about data extracted will be resolved by discussion. The assessment of the risk of bias in included studies will be performed using the

Cochrane Collaboration's recommended domain-based evaluation [14]. The odds ratio will be used as the measure of treatment effect for all-cause mortality, mortality secondary to hepatocellular carcinoma and number of cases of hepatocellular carcinoma. Using a random effect model the Manthel-Haensel method will be used to calculate an odds ratio as the measure of treatment effect.

References

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Appendix 2

Search Strategy

Medline

1. exp Mass Screening/

2. (screen* or assess* or detect*).ab,ti.

3. 1 or 2

4. exp Liver Diseases/

5. ((liver or hepat*) and (disease* or cirrhosis*)).ab,ti.

6. 4 or 5

7. exp Carcinoma, Hepatocellular/

8. (((hepat* or liver) and carcinoma*) or hepatocellular carcinoma or hepatocarcinoma or hepatoma or HCC or "primary liver cancer").ab,ti.

9. 7 or 8

10. 3 and 6 and 9

11. randomized controlled trial.pt.

12. controlled clinical trial.pt.

13. randomized.ab,ti.

14. randomly.ab,ti.

15. trial.ab,ti.

16. groups.ab,ti.

17. 11 or 12 or 13 or 14 or 15 or 16

18. 10 and 17

Embase

1 exp mass screening/

2 (screen* or exam* or assess* or detect*).ab,ti.

3 1 or 2

4 (((hepat* or liver) and carcinoma*) or hepatocellular carcinoma or hepatocarcinoma or hepatoma or HCC or "primary liver cancer").ab,ti.

5 exp liver cell carcinoma/

6 4 or 5

7 exp liver cirrhosis/

8 exp liver fibrosis/

9 ((hepatic or liver) and (fibrosis or cirrhosis)).ab,ti.

10 7 or 8 or 9

11 exp crossover-procedure/ or exp double-blind procedure/ or exp randomized controlled trial/ or single-blind procedure/ (565710)

12 (((((random* or factorial* or crossover* or cross over* or cross-over* or placebo* or double*) adj blind*) or single*) adj blind*) or assign* or allocat* or volunteer*).af.

13 11 or 12

14 3 and 6 and 10 and 13

Cochrane Central Register of Controlled Trials (CENTRAL)

1 MeSH descriptor: [Carcinoma, Hepatocellular] explode all trees
2 (((hepat* or liver) and carcinoma*) or hepatocellular carcinoma or hepatocarcinoma or hepatoma or HCC or "primary liver cancer"):ti,ab,kw (Word variations have been searched)
3 #1 or #2
4 ((hepat* or liver) and disease*):ti,ab,kw (Word variations have been searched)
5 MeSH descriptor: [Liver Diseases] explode all trees
6 #4 or #5
7 MeSH descriptor: [Mass Screening] explode all trees
8 screen* or exam* or detect*:ti,ab,kw (Word variations have been searched)
9 #7 or #8
10 #9 and #6 and #3

Web of Science Citation Index Expanded (1900- May 2018)

1 TI=(((hepat* or liver) and carcinoma*) or hepatocellular carcinoma or hepatocarcinoma or hepatoma or HCC or "primary liver cancer")
DocType=All document types; Language=All languages;

2 TS=((Liver OR hepa*) AND (disease OR Cirrhosis))
DocType=All document types; Language=All languages

3 TS=(screen* or assess* or detect*)
DocType=All document types; Language=All languages;

4 #3 AND #2 AND #1
DocType=All document types; Language=All languages;

5 TS= (random* OR control* OR trial*)
DocType=All document types; Language=All languages;

6 #5 AND #4
DocType=All document types; Language=All languages;

7 TS= (animal*)
DocType=All document types; Language=All languages;

8 #6 NOT #7
DocType=All document types; Language=All languages;

Appendix 3

Table 1: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

Appendix 4

Table 2: Included Studies

Zhang 2004[18]	
Methods	This was a cluster randomised controlled trial. There were over 300 clusters consisting of enterprises, factories and schools.
Participants	Country: China Number randomised: 19200 Post-randomisation drop-outs: 384 Revised sample size: 18816 Average age: 42 years Females: 6968 Inclusion criteria: Serum evidence of hepatitis B or a history of chronic hepatitis. Aged 35-59. Exclusion criteria: Known history of hepatocellular carcinoma or other malignant disease or serious illness Statistical analysis: Intention-to-treat
Interventions	The screening group had an alpha-feto protein checked 6 months. The control group had no intervention. There were 9757 in the screening group and 9443 in the control group. The screening group participants were invited by their GP to have a serum alpha- feto protein checked.
Outcomes	The outcomes reported were mortality due to hepatocellular carcinoma, the number of cases of hepatocellular carcinoma detected and 5- year survival. All-cause mortality was not reported.
Chen 2003[19]	

Methods	This was a cluster randomised controlled trial. Participants were stratified at township level. There were 23 clusters.
Participants	Country: China Number randomised: 5581 Post-randomisation drop-outs: 0 Revised sample size: 5581 Average age: 41 years Females: 0 Inclusion criteria: male, aged 30-69, hepatitis B surface antigen positive Exclusion criteria: nil Statistical analysis: Intention-to-treat
Interventions	Clusters were randomised to either a screening group (3712) or a control group (1869). Screening involved serial alpha-feto protein check every 6 months. If the alpha-feto protein level detected was raised then it was repeated at a shorter interval. For subjects with an alpha-feto protein greater than 200 micrograms/litre or greater than 100 micrograms/litre on two occasions then an ultrasound examination was performed. Clusters randomised to the control group had an alpha-feto protein checked at enrolment but no further follow up.
Outcomes	The outcomes reported were all-cause mortality, mortality due to hepatocellular carcinoma and the number of cases of hepatocellular carcinoma detected.
Notes	The assay used for alpha-feto protein was the R-PHA which may have limited sensitivity. Radioimmunoassay was used if the R-PHA was positive.

Pocha 2013[20]	
Methods	This was a randomised controlled trial conducted by the Minneapolis Veterans Affairs Healthcare System.
Participants	Country: United States of America Number randomised: 165 Post-randomisation drop-outs: 2 Revised sample size: 163 Average age: 59 Females: 1 Inclusion criteria: Aged 18-70 with Child's A cirrhosis. Participants had to be potential candidates for treatment of hepatocellular carcinoma. Exclusion criteria: Active malignancy, history of a hepatic mass identified on imaging study, advanced renal insufficiency Statistical analysis: Intention-to-treat
Interventions	Patients were randomised to screening with either biannual ultrasonography (83) or annual computed tomography (80). All participants were received alpha-feto protein testing twice a year. Ultrasonography was performed by designated technicians using a standardised protocol, as was CT. Hepatic lesions identified were evaluated as follows; biopsy was not required for the diagnosis of hepatocellular carcinoma in the setting of a diagnostic alpha-feto protein or rising alpha-feto protein. In the absence of typical features on CT or a diagnostic alpha-feto protein a liver biopsy was obtained.
Outcomes	The outcomes reported were all-cause mortality, mortality due to hepatocellular carcinoma and the number of cases of hepatocellular carcinoma detected.

Sherman 1995[21]	
Methods	A randomised controlled trial conducted in Canada, this study was designed as a feasibility study predicated on the design of a planned larger randomised controlled study. Follow up of 5 years. Median follow up 26 months.
Participants	Country: Canada Number randomised: 1069 Post-randomisation drop-outs: 0 Revised sample size: 1069 Average age: 39 years Females: 374 Inclusion criteria: Hepatitis B surface antigen positive for at least 6 months. Age over 18 years. Exclusion criteria: Nil reported Statistical analysis: Intention-to-treat
Interventions	Patients were randomised to either serial alpha-feto protein check every 6 months (n=531) or serial alpha-feto protein plus ultrasound check every 6 months (n=538). All subjects with a raised alpha-feto protein had a repeat test performed one month later. All subjects with an alpha-feto protein greater than 20 micrograms per litre had an ultrasound examination performed.
Outcomes	This study was not designed to compare serial alpha-feto protein vs. serial alpha-feto protein plus ultrasound. The incidence of HCC is reported. All-cause mortality, mortality due to hepatocellular carcinoma and the number of

	hepatocellular carcinomas detected were not reported separately for each arm.
Trinchet 2011[22]	
Methods	A multi-centre randomised clinical trial conducted over 43 sites. Patients was stratified according to site and according to cirrhosis aetiology.
Participants	Country: France and Belgium Number randomised: 1340 Post-randomisation drop-outs: 62 Revised sample size: 1278 Average age: 55 years Females: 395 Inclusion criteria: Aged over 18 years. Histologically proven cirrhosis. Cirrhosis related to excessive alcohol consumption or chronic infection with hepatitis B or C or hereditary haemochromatosis. Participant must belong to Child Pugh class A or B. Exclusion criteria: Focal liver lesion present or complications of cirrhosis present (ascites, gastrointestinal haemorrhage, hepatocellular carcinoma). Statistical analysis: Modified intention-to-treat
Interventions	Patients were randomised to either ultrasound examination every 3 months (GR3M, n=640) or ultrasound examination every 6 months (GR6M, n=638). Initially patients were randomised on a two-by-two factorial design with balanced randomisation to assess the value of ultrasound and simultaneously alpha-feto protein.

Outcomes	The outcomes reported were all-cause mortality, mortality due to hepatocellular carcinoma,the number of cases of hepatocellular carcinoma detected and 5-year survival.
Notes	Due to the high number of participants with alpha-feto protein assays performed in all groups the authors restricted the final analysis to a comparison of 3-monthly ultrasound versus 6-monthly ultrasound.
Wang 2011[23]	
Methods	This was a cluster randomised controlled trial conducted in 10 townships
Participants	Country: Taiwan Number randomised: 1581 Post-randomisation drop-outs: 837 Revised sample size: 744 Average age: 65 years Females: 374 Inclusion criteria: Positive for hepatitis B Surface Antigen or antibody of hepatitis C virus (anti-HCV). Platelet count less than or equal to 15 x 10^4 mm3. Age greater than or equal to 40 years. Exclusion criteria: Previous history of hepatic malignancy. Statistical analysis: Modified intention-to-treat
Interventions	Patients were randomised to either US surveillance every 4 months (Group A, N= 387) or US surveillance every 12 months (Group B, N= 357). Randomisation was stratified according to township and before all participants had been invited to take part in the study.

Outcomes	This study reported on the number of cases of hepatocellular carcinoma detected, tumour size and overall survival in each arm. It did not report on all-cause mortality and mortality due to hepatocellular carcinoma.

Appendix 5 Quality of Evidence (GRADE) and Summary of Findings

Table 3 Six-monthly alpha-feto protein compared to no screening for patients with chronic liver disease at risk of hepatocellular carcinoma

Six-monthly alpha-feto protein compared to no screening for patients with chronic liver disease at risk of hepatocellular carcinoma					
Patient or population: patients with patients with chronic liver disease **Intervention:** six-monthly alpha-feto protein **Comparison:** no screening					
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**
	Assumed risk	**Corresponding risk**			
	No screening	**Six-monthly alpha-feto protein**			
Mortality due to hepatocellular carcinoma Total number of deaths due to hepatocellular carcinoma Follow-up: 60 months	**Study population**		**OR 0.6** (0.31 to 1.15)	18816 (1 study)	⊕⊕⊕⊖ **moderate**[1,2]
	6 per 1000	**3 per 1000** (2 to 7)			
	Low				
	3 per 1000	**2 per 1000** (1 to 4)			
	High				
	88 per 1000	**59 per 1000** (29 to 100)			
Number of cases of hepatocellular carcinoma detected Total Number of Cases of Hepatocellular Carcinoma Detected Follow-up: 60 months	**Study population**		**OR 1.30** (0.81 to 2.08)	18816 (1 study)	⊕⊕⊕⊖ **moderate**[1,2]
	7 per 1000	**9 per 1000** (6 to 15)			
	Moderate				
	50 per 1000	**64 per 1000** (41 to 99)			
	High				
	90 per 1000	**114 per 1000** (74 to 171)			
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **OR:** Odds ratio;					
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of					

effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Footnotes

[1] The number of events in each group was small.
[2] The confidence intervals were wide and would likely include a minimal clinically important difference for a trial evaluating the effectiveness of screening.

* The assumed risk for mortality due to hepatocellular carcinoma was based on the range of control group rates from the included studies (low risk= 0.33%, high risk 8.8%). The assumed risk for the number of cases of hepatocellular carcinoma detected was based on the range of control group rates from the included studies (moderate risk= 5%, high risk= 9%).

Table 4 Six-monthly alpha-feto protein compared to single alpha-feto protein check for hepatocellular carcinoma screening those with chronic liver disease

Six-monthly alpha-feto protein compared to single alpha-feto protein check for hepatocellular carcinoma screening in those with hepatocellular carcinoma					
Patient or population: patients with chronic liver disease **Intervention:** six-monthly alpha-feto protein **Comparison:** single alpha-feto protein check					
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**
	Assumed risk	**Corresponding risk**			
	Single alpha-feto protein check	**Six-monthly alpha-feto protein**			
All-cause mortality Total number of deaths Follow-up: mean 62 months	**Study population**		**OR 1.02** (0.65 to 1.6)	5581 (1 study)	⨁⨁⊖⊖ **low**[1,2,3]
	94 per 1000	**96 per 1000** (63 to 142)			
	Low				
	20 per 1000	**20 per 1000** (13 to 32)			
	High				
	176 per 1000	**179 per 1000** (122 to 255)			
	Study population				

Mortality due to hepatocellular carcinoma Total number of deaths due to hepatocellular carcinoma Follow-up: mean 62 months	**58 per 1000**	**59 per 1000** (34 to 99)	**OR 1.01** (0.57 to 1.78)	5581 (1 study)	⊕⊕⊖⊖ **low**[1,2,3]
	Low				
	3 per 1000	**3 per 1000** (2 to 6)			
	High				
	80 per 1000	**81 per 1000** (47 to 134)			
Number of cases of hepatocellular carcinoma detected Total number of cases of hepatocellular carcinoma detected Follow-up: mean 62 months	**Study population**		**OR 1.11** (0.64 to 1.93)	5581 (1 study)	⊕⊕⊖⊖ **low**[1,2,3]
	63 per 1000	**67 per 1000** (20 to 202)			
	Low				
	7 per 1000	**8 per 1000** (2 to 26)			
	High				
	90 per 1000	**96 per 1000** (30 to 271)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Footnotes

[1] In the screening group 400 subjects (10.8%) were tested at enrollment only and did not attend for further screening. It is unclear how these were followed up.
[2] The total sample size was small
[3] The confidence intervals were wide and would likely include a minimal clinically important difference for a trial evaluating the effectiveness of screening methodologies.

*The assumed risk for all-cause mortality was based on the range of control group rates from the included studies (low risk= 2%, high risk= 17.6%). The assumed risk for mortality due to hepatocellular carcinoma was based on the range of control group rates from the included studies (low risk= 0.33%, high risk 8.8%). The assumed risk for the number of cases of hepatocellular carcinoma detected was based on the range of control group rates from the included studies (low risk= 0.71%, high risk= 9%).

Table 5 Ultrasound plus alpha-feto protein compared to CT for hepatocellular carcinoma screening in patients with chronic liver disease

Ultrasound plus alpha-feto protein compared to CT for hepatocellular carcinoma screening in patients with chronic liver disease					
Patient or population: patients with chronic liver disease **Intervention:** Ultrasound plus alpha-feto protein **Comparison:** CT					
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**
	Assumed risk	**Corresponding risk**			
	CT	**Ultrasound plus alpha-feto protein**			
All-cause mortality Total number of deaths Follow-up: mean 30 months	**Study population**		**OR 0.81** (0.26 to 2.53)	163 (1 study)	⊕⊕⊖⊖ **low**[1,2,3]
	88 per 1000	**72 per 1000** (24 to 195)			
	Low				
	20 per 1000	**16 per 1000** (5 to 49)			
	High				
	176 per 1000	**147 per 1000** (53 to 351)			
Mortality due to hepatocellular carcinoma Total number of deaths due to hepatocellular carcinoma Follow-up: mean 30 months	**Study population**		**OR 0.67** (0.2 to 2.2)	163 (1 study)	⊕⊕⊖⊖ **low**[1,2,3]
	88 per 1000	**60 per 1000** (19 to 174)			
	Low				
	3 per 1000	**2 per 1000** (1 to 7)			
	Moderate				
	58 per 1000	**40 per 1000** (12-119)			
Number of cases of hepatocellular carcinoma detected Total number of cases of hepatocellular carcinoma detected	**Study population**		**OR 1.09** (0.4 to 2.99)	163 (1 study)	⊕⊕⊖⊖ **low**[1,2,3]
	100 per 1000	**108 per 1000** (43 to 249)			
	Low				
	7 per 1000	**8 per 1000** (3 to 21)			
	Moderate				

Follow-up: mean 30 months	**50 per 1000**	**54 per 1000** (21 to 136)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Footnotes

[1] There was a high risk of bias due to incomplete outcome data because of post randomisation drop outs.
[2] The total sample size was small
[3] The confidence intervals were wide and would likely include a minimal clinically important difference for a trial comparing the efficacy of screening methodologies.

*The assumed risk for all-cause mortality was based on the range of control group rates from the included studies (low risk= 2%, high risk= 17.6%). The assumed risk for mortality due to hepatocellular carcinoma was based on the range of control group rates from the included studies (low risk= 0.33%, moderate risk 5.8%). The assumed risk for the number of cases of hepatocellular carcinoma detected was based on the range of control group rates from the included studies (low risk= 0.71%, moderate risk= 5%).

Table 6 More frequent screening compared to less frequent screening for hepatocellular carcinoma in those with chronic liver disease

More frequent screening compared to less frequent screening for in those with chronic liver disease at risk of hepatocellular carcinoma					
Patient or population: patients with chronic liver disease **Intervention:** more frequent screening (3-monthly or 4-monthly) **Comparison:** less frequent screening (6-monthly or 12 monthly)					
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**
	Assumed risk	**Corresponding risk**			
	Less frequent screening	**More frequent screening**			

All-cause mortality Total Number of Deaths Follow-up: mean 47 months	**Study population**		**OR 0.86** (0.56 to 1.32)	1278 (1 study)	⊕⊕⊖⊖ **low**[1,2,3]
	129 per 1000	**113 per 1000** (77 to 164)			
	Low				
	20 per 1000	**17 per 1000** (11 to 26)			
	Moderate				
	129 per 1000	**113 per 1000** (77 to 164)			
Mortality due to hepatocellular carcinoma Total number of deaths due to hepatoceullar carcinoma Follow-up: mean 47 months	**Study population**		**OR 1.42** (0.55 to 3.64)	1278 (1 study)	⊕⊕⊖⊖ **low**[1,2,3]
	20 per 1000	**28 per 1000** (11 to 68)			
	Low				
	3 per 1000	**5 per 1000** (2 to 12)			
	High				
	88 per 1000	**121per 1000** (50 to 260)			
Number of cases of hepatocellular carcinoma detected Total number of cases of hepatocellular carcinoma detected Follow-up: 66 months	**Study population**		**OR 0.90** (0.47 to 1.71)	2022 (2 studies)	⊕⊕⊖⊖ **low**[1,2,3]
	90 per 1000	**81 per 1000** (44 to 144)			
	Low				
	7 per 1000	**6 per 1000** (3 to 12)			
	Moderate				
	50 per 1000	**45 per 1000** (24 to 83)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Footnotes

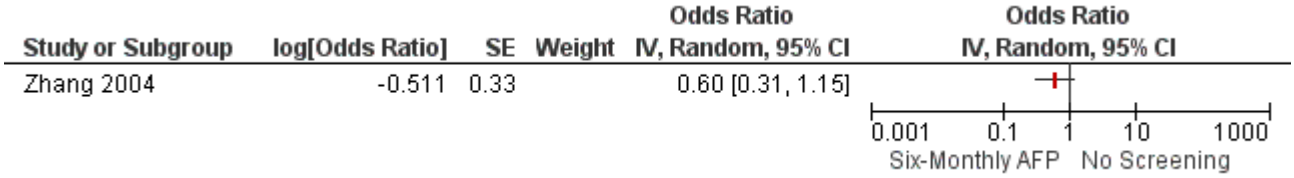
[1] There was a high risk of attrition bias because of poor compliance with follow up screening tests.
[2] The total small sample size was small
[3] The confidence intervals were wide and would likely include a minimal clinically important difference for a trial comparing screening frequencies for hepatocellular carcinoma

*The assumed risk for all-cause mortality was based on the range of control group rates from the included studies (low risk= 2%, moderate risk= 12.9%). The assumed risk for mortality due to hepatocellular carcinoma was based on the range of control group rates from the included studies (low risk= 0.33%, high risk 8.8%). The assumed risk for the number of cases of hepatocellular carcinoma detected was based on the range of control group rates from the included studies (low risk= 0.71%, moderate risk= 5%).

Appendix 6

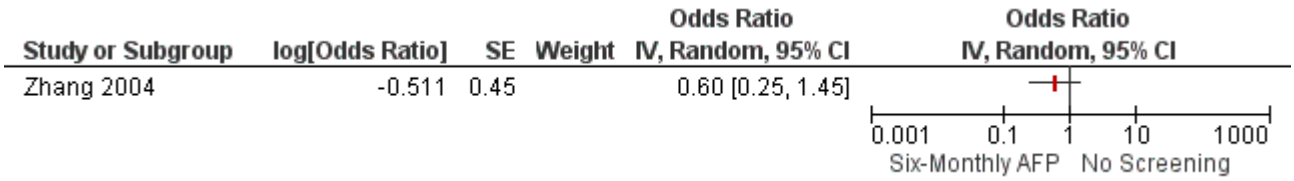
Forest Plots

Figure 1 (Analysis 1.1)



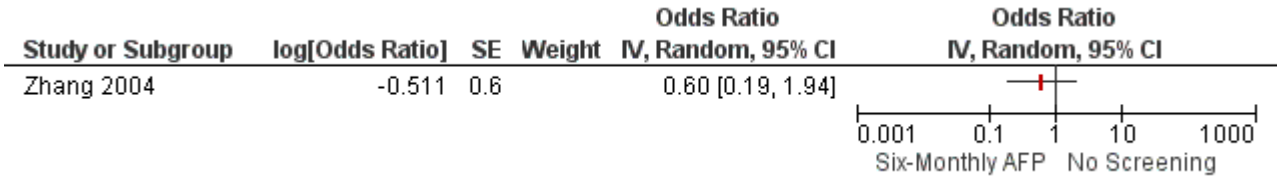
Forest plot of comparison: 1 Screening Methodology: Six-Monthly Alpha-Feto Protein Versus No Screening, outcome: 1.1 Mortality due to Hepatocellular Carcinoma(ICC=0.02).

Figure 2 (Analysis 1.2)



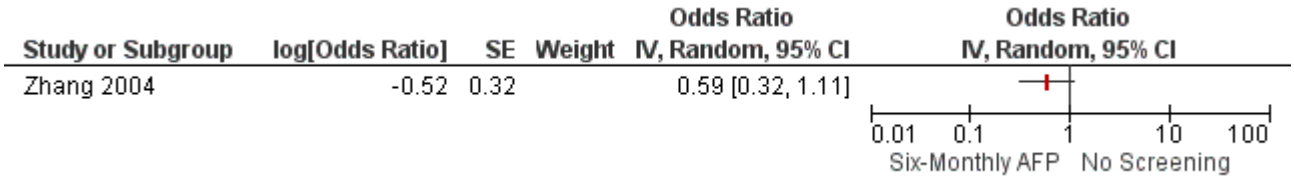
Forest plot of comparison: 1 Screening Methodology: Six-Monthly Alpha-Feto Protein Versus No Screening, outcome: 1.2 Mortality due to Hepatocellular Carcinoma (ICC=0.05).

Figure 3 (Analysis 1.3)



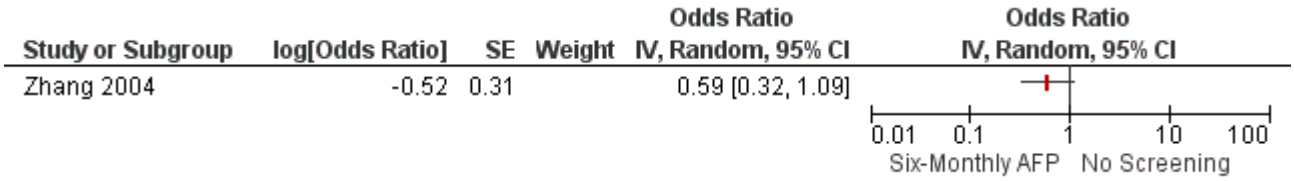
Forest plot of comparison: 1 Screening Methodology: Six-Monthly Alpha-Feto Protein Versus No Screening, outcome: 1.3 Mortality due to Hepatocellular Carcinoma (ICC=O.1).

Figure 4 (Analysis 1.4)



Forest plot of comparison: 1 Screening Methodology: Six-Monthly Alpha-Feto Protein Versus No Screening, outcome: 1.4 Mortality due to Hepatocellular Carcinoma (ICC=0.02, Clusters=350).

Figure 5 (Analysis 1.5)



Forest plot of comparison: 1 Screening Methodology: Six-Monthly Alpha-Feto Protein Versus No Screening, outcome: 1.5 Mortality due to Hepatocellular Carcinoma (ICC=0.02, Clusters=399).

Figure 6 (Analysis 1.6)

Forest plot of comparison: 1 Screening Methodology: Six-Monthly Alpha-Feto Protein Versus No Screening, outcome: 1.6 Number of Cases of Hepatocellular Carcinoma Detected (ICC=0.02).

Figure 7 (Analysis 1.7)

Forest plot of comparison: 1 Screening Methodology: Six-Monthly Alpha-Feto Protein Versus No Screening, outcome: 1.7 Number of Cases of Hepatocellular Carcinoma Detected (ICC=0.05).

Figure 8 (Analysis 1.8)

Forest plot of comparison: 1 Screening Methodology: Six-Monthly Alpha-Feto Protein Versus No Screening, outcome: 1.8 Number of Cases of Hepatocellular Carcinoma Detected (ICC=0.1).

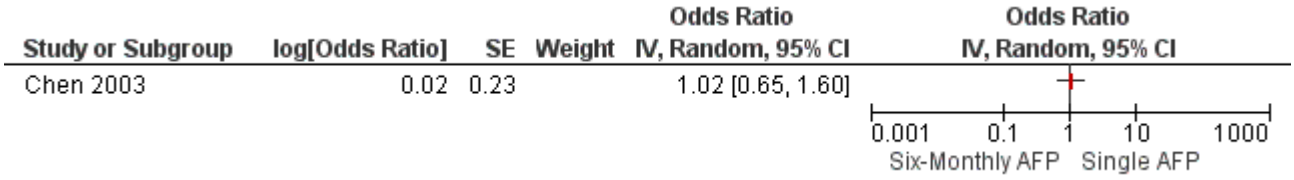
Figure 9 (Analysis 1.9)

Forest plot of comparison: 1 Screening Methodology: Six-Monthly Alpha-Feto Protein Versus No Screening, outcome: 1.9 Number of Cases of Hepatocellular Carcinoma Detected (ICC=0.02, Cluster=350).

Figure 10 (Analysis 1.10)

Forest plot of comparison: 1 Screening Methodology: Six-Monthly Alpha-Feto Protein Versus No Screening, outcome: 1.10 Number of Cases of Hepatocellular Carcinoma Detected (ICC=0.02, Clusters=399).

Figure 11 (Analysis 2.1)



Forest plot of comparison: 2 Screening Methodology: Six-Monthly Alpha-Feto Protein Versus Single Alpha-Feto Protein, outcome: 2.1 All-cause Mortality.

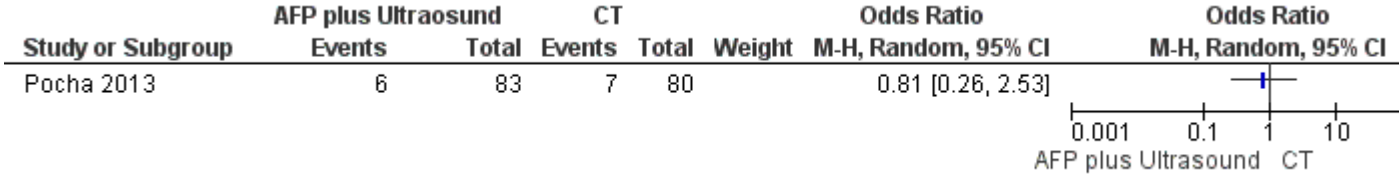
Figure 12 (Analysis 2.2)

Forest plot of comparison: 2 Screening Methodology: Six-Monthly Alpha-Feto Protein Versus Single Alpha-Feto Protein, outcome: 2.2 Mortality due to Hepatocellular Carcinoma.

Figure 13 (Analysis 2.3)

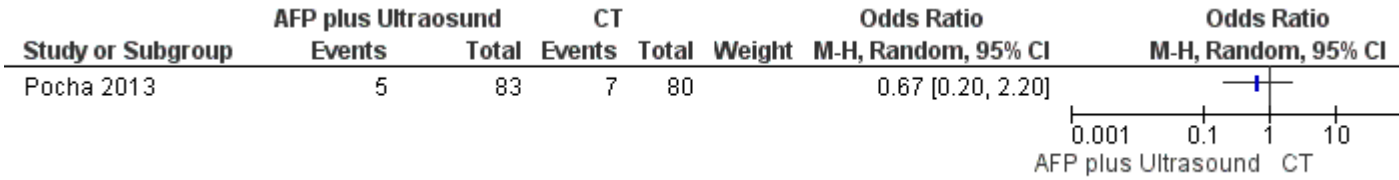
Forest plot of comparison: 2 Screening Methodology: Six-Monthly Alpha-Feto Protein Versus Single Alpha-Feto Protein, outcome: 2.3 Number of Cases of Hepatocellular Carcinoma Detected.

Figure 14 (Analysis 3.1)



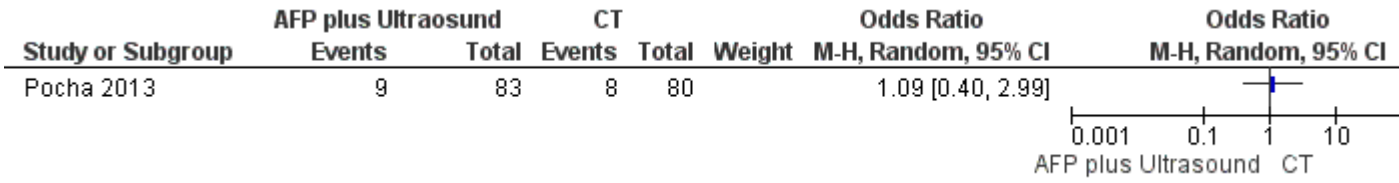
Forest plot of comparison: 3 Screening Methodology: Alpha-Feto Protein Plus Ultrasound Versus CT, outcome: 3.1 All-Cause Mortality.

Figure 15 (Analysis 3.2)



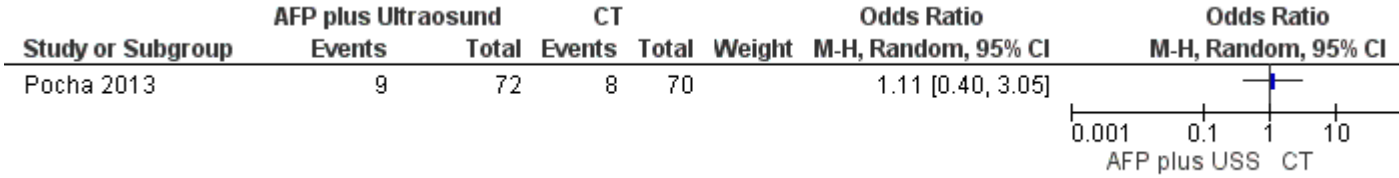
Forest plot of comparison: 3 Screening Methodology: Alpha-Feto Protein Plus Ultrasound Versus CT, outcome: 3.2 Mortality due to Hepatocellular Carcinoma.

Figure 16 (Analysis 3.3)



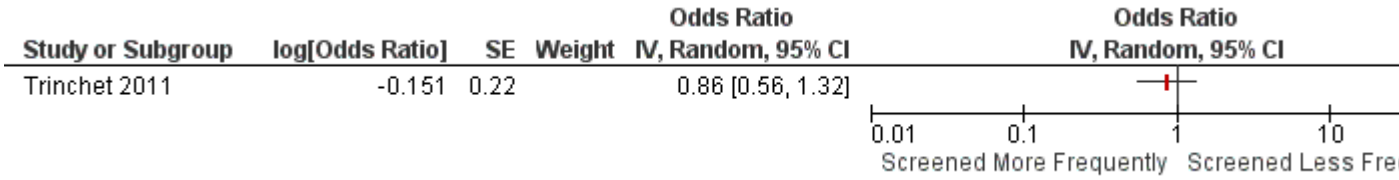
Forest plot of comparison: 3 Screening Methodology: Alpha-Feto Protein Plus Ultrasound Versus CT, outcome: 3.3 Number of Cases of Hepatocellular Carcinoma Detected.

Figure 17 (Analysis 3.4)



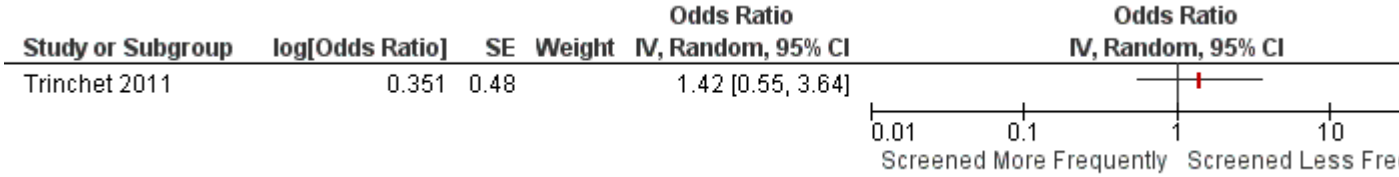
Forest plot of comparison: 3 Screening Methodology: Alpha-Feto Protein Plus Ultrasound Versus CT, outcome: 3.4 Number of Cases of Hepatocellular Carcinoma Detected in Participants with Hepatitis C.

Figure 18 (Analysis 4.1)



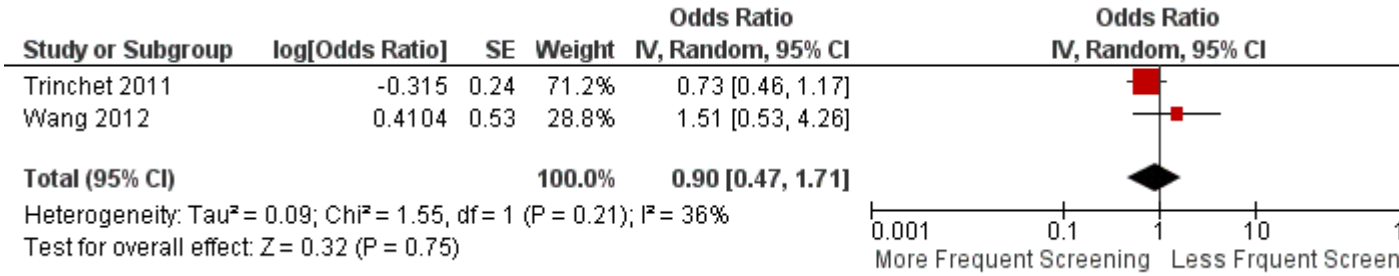
Forest plot of comparison: 4 Screening Frequency: More Frequent Versus Less Frequent, outcome: 4.1 All-Cause Mortality.

Figure 19 (Analysis 4.2)



Forest plot of comparison: 4 Screening Frequency: More Frequent Versus Less Frequent, outcome: 4.2 Mortality due to Hepatocellular Carcinoma.

Figure 20 (Analysis 4.3)



Forest plot of comparison: 4 Screening Frequency: More Frequent Versus Less Frequent, outcome: 4.3 Number of Cases of Hepatocellular Carcinoma Detected.

Figure 21 (Analysis 4.4)

Forest plot of comparison: 4 Screening Frequency: More Frequent Versus Less Frequent, outcome: 4.4 Number of Cases of Hepatocellular Carcinoma Detected in Participants with Hepatitis B.

Figure 22 (Analysis 4.5)

Forest plot of comparison: 4 Screening Frequency: More Frequent Versus Less Frequent, outcome: 4.5 Number of Cases of Hepatocellular Carcinoma Detected in Participants with Hepatitis C.