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Management of people with intermediate-stage hepatocellular carcinoma: an attempted network meta-analysis (Review)

Roccarina D, Majumdar A, Thorburn D, Davidson BR, Tsochatzis E, Gurusamy KS

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[Intervention Review]

Management of people with intermediate-stage hepatocellular carcinoma: an attempted network meta-analysis

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ABSTRACT

Background

There is significant uncertainty in the treatment of intermediate-stage hepatocellular carcinoma which is defined by the Barcelona Clinic Liver Cancer (BCLC) as hepatocellular carcinoma stage B with large, multi-nodular, Child-Pugh status A to B, performance status 0 to 2, and without vascular occlusion or extrahepatic disease.

Objectives

To assess the comparative benefits and harms of different interventions used in the treatment of intermediate-stage hepatocellular carcinoma (BCLC stage B) through a network meta-analysis and to generate rankings of the available interventions according to their safety and efficacy. However, we found only one comparison. Therefore, we did not perform the network meta-analysis, and we assessed the comparative benefits and harms of different interventions versus each other, or versus placebo, sham, or no intervention (supportive treatment only) using standard Cochrane methodology.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, Science Citation Index Expanded, World Health Organization International Clinical Trials Registry Platform, and randomised clinical trials registers to September 2016 to identify randomised clinical trials on hepatocellular carcinoma.

Selection criteria

We included only randomised clinical trials, irrespective of language, blinding, or publication status, in participants with intermediate-stage hepatocellular carcinoma, irrespective of the presence of cirrhosis, size, or number of the tumours (provided they met the criteria of intermediate-stage hepatocellular carcinoma), of presence or absence of portal hypertension, of aetiology of hepatocellular carcinoma, and of the future remnant liver volume. We excluded trials which included participants who had previously undergone liver transplantation. We considered any of the various interventions compared with each other or with no active intervention (supportive treatment only). We excluded trials which compared variations of the same intervention: for example, different methods of performing transarterial chemoembolisation.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. We calculated the hazard ratio (HR) with 95% confidence intervals (CI) using both fixed-effect and random-effects models based on available-participant analysis with Review Manager. We assessed risk of bias according to Cochrane, controlled risk of random errors with Trial Sequential Analysis using Stata, and assessed the quality of the evidence using GRADE.

Main results

Three randomised clinical trials, including 430 participants, met the inclusion criteria for this review; however, data from two trials with 412 participants could be included in only one primary outcome (i.e. mortality). All three trials were at high risk of bias. All three trials included supportive care as cointervention. The comparisons included in the two trials reporting on mortality were: systemic chemotherapy with sorafenib versus no active intervention; and transarterial chemoembolisation plus systemic chemotherapy with sorafenib versus transarterial chemoembolisation alone. The trials did not report the duration of follow-up; however, it appeared that the participants were followed up for a period of about 18 to 30 months. The majority of the participants in the trials had cirrhotic livers. The trials included participants with intermediate-stage hepatocellular carcinoma arising from viral and non-viral aetiologies. The trials did not report the portal hypertension status of the participants. The mortality was 50% to 70% over a median follow-up period of 18 to 30 months. There was no evidence of difference in mortality at maximal follow-up between systemic chemotherapy versus no chemotherapy (hazard ratio 0.85, 95% CI 0.60 to 1.18; participants = 412; studies = 2; $I^2 = 0\%$; very low quality evidence). A subgroup analysis performed by stratifying the analysis by the presence or absence of transarterial chemoembolisation as cointervention did not alter the results. None of the trials reported on serious adverse events other than mortality, health-related quality of life, recurrence of hepatocellular carcinoma, or length of hospital stay. One of the trials providing data was funded by the pharmaceutical industry, the other did not report the source of funding, and the trial with no data for the review was also funded by the pharmaceutical industry. We found two ongoing trials.

Authors' conclusions

Currently, there is no evidence from randomised clinical trials that people with intermediate-stage hepatocellular carcinoma would benefit from systemic chemotherapy with sorafenib either alone or when transarterial chemoembolisation was used as a cointervention (very low quality evidence). We need high-quality randomised clinical trials designed to measure differences in clinically important outcomes (e.g. all-cause mortality or health-related quality of life).

PLAIN LANGUAGE SUMMARY

Treatment of intermediate-stage primary liver cancer (hepatocellular carcinoma)

Background

Hepatocellular carcinoma (primary liver cancer) arises from the liver cells and is distinct from secondary liver cancer, arising from other parts of the body and spreading to the liver. Hepatocellular carcinoma can be classified in many ways. One classification is by Barcelona Clinic Liver Cancer (BCLC) group stage which classifies the cancer based on how long the person is expected to live (life expectancy). This classification is broadly based on the size of the cancer, number of cancers in the liver, how well the liver works, and whether one's activities are affected by the cancer. People with intermediate-stage hepatocellular carcinoma have large, multiple cancers, but they do not have full-blown liver failure. Cancer is confined to the liver, and there is no restriction of daily activities. There is significant uncertainty in the treatment of people with intermediate-stage hepatocellular carcinoma. We sought to resolve this uncertainty by searching for existing studies on the topic. We included all randomised clinical trials (well-designed clinical trials where people are randomly put into one of two or more treatment groups) whose results were reported to September 2016. We included only trials in which participants with intermediate-stage hepatocellular carcinoma had not undergone liver transplantation previously. Apart from using standard Cochrane methods which allow comparison of only two treatments at a time (direct comparison), we planned to use an advanced method which allows comparison of the many different treatments that are individually compared in the trials (network meta-analysis). However, because there was only one comparison, we could only use standard Cochrane methodology.

Study characteristics

Only three trials with 430 participants met our inclusion criteria; however, two of the trials (412 participants) only reported death and no other measures of how well the treatments worked. All three trials included supportive care (treatment to prevent, control, or

relieve complications and side effects and improve comfort and quality of life) as a co-intervention. The trials assessed transarterial chemoembolisation (where anti-cancer drugs block the blood supply and treat the cancer through the vessels supplying the cancer), chemotherapy using sorafenib (a drug which blocks cancer growth), or a combination of transarterial chemoembolisation and sorafenib. It appeared that the trials followed participants for about 18 to 30 months from the initiation of treatment.

Two trials were funded by the pharmaceutical industry; one trial did not report the source of funding.

Key results

Over 18 to 30 months, 50% to 75% of participants died. There was no evidence of any difference between the people who received chemotherapy and those who did not receive chemotherapy. None of the trials reported complications, health-related quality of life (a measure of a person's satisfaction with their life and health), cancer recurrence, or length of hospital stay. Overall, there is currently no evidence for benefit of any active treatment in addition to supportive treatment for intermediate-stage hepatocellular carcinoma. There is significant uncertainty on this and further high-quality randomised clinical trials are required.

Quality of evidence

The overall quality of evidence was low or very low and all the trials were at high risk of bias, which means that there is possibility of making the wrong conclusions, overestimating benefits, or underestimating harms of one treatment or the other because of the way that the trials were conducted.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Chemotherapy versus no chemotherapy for intermediate-stage hepatocellular carcinoma					
Patient or population: people with intermediate-stage hepatocellular carcinoma Settings: secondary or tertiary care Intervention: systemic chemotherapy Control: no systemic chemotherapy ^a Cointervention: transarterial chemoembolisation in both groups in 1 trial					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	No systemic chemotherapy	Systemic chemotherapy ^a			
Mortality (at maximal follow-up) - chemotherapy versus no chemotherapy Median follow-up in trials: 12 to 24 months	500 per 1000	445 per 1000 (340 to 559)	HR 0.85 (0.60 to 1.18)	412 (2 trials)	⊕⊕○○ Very low ^{1,2,3}
Short-term and medium-term mortality	None of the trials reported short-term or medium-term mortality				
Adverse events	None of the trials reported adverse events.				
Quality of life	None of the trials reported quality of life at any time point				
Disease recurrence	None of the trials reported disease recurrence.				
Length of hospital stay	None of the trials reported length of hospital stay.				

* The basis for the **assumed risk** was the control group proportion in the studies. 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; HR: hazard 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.

¹ Downgraded one level because of within-study risk of bias: the trials were at high risk of bias.

² Downgraded one level because of imprecision: the sample size was small.

³ Downgraded one level because of imprecision: the confidence intervals overlapped no effect and clinically significant effect.

BACKGROUND

Description of the condition

Hepatocellular carcinoma is the major form of primary liver cancer (Bosetti 2014; NCBI 2014). An estimated 782,000 people develop hepatocellular carcinoma and 746,000 people die because of primary liver cancer each year worldwide (IARC 2014a). It is the sixth most common cancer overall with an age standardised incidence rate of 10.1 per 100,000 population per year (IARC 2014b). It is the second most common cause of death from cancer worldwide (IARC 2014a). It is more common in men than women (IARC 2014a). There is global variation in the incidence and mortality related to primary liver cancer. Approximately half of all primary liver cancers occur in China (395,000 people per year). Northern Europe has the lowest incidence of primary liver cancer (IARC 2014a). There is an increase in the incidence of hepatocellular carcinoma in many countries (Davila 2004; Jepsen 2007; Pocobelli 2008; Taura 2009; Von Hahn 2011; Witjes 2012; Bosetti 2014; Ladep 2014). This increase is attributed to hepatitis C virus infection (Davila 2004; Taura 2009). Alcohol-related liver disease, hepatitis B virus infection, and hepatitis C virus infection are major risk factors for hepatocellular carcinoma (Davila 2004; Bosetti 2014). Other risk factors include aflatoxin in foods (toxins produced by *Aspergillus* fungus), smoking, being overweight, diabetes, and non-alcohol related steatohepatitis (Lee 2009; Polesel 2009; Starley 2010; Chen 2012; Liu 2012; Bosetti 2014; Turati 2014). The incidence of hepatocellular carcinoma is higher in people with a family history of hepatocellular carcinoma, and lower in people with high intake of vegetables and coffee (Turati 2012; Sang 2013; Bosetti 2014; Yang 2014). The association between oral contraceptives and hepatocellular carcinoma is unclear and there is currently no evidence of an increased risk between women using oral contraceptives and women who do not use oral contraceptive based on one meta-analysis of observational studies (Maheshwari 2007). Hepatocellular carcinoma usually develops in cirrhotic livers although it may also develop in non-cirrhotic livers (Arnaoutakis 2014; Gaddikeri 2014). Hepatocellular carcinomas that develop in non-cirrhotic livers are usually solitary but larger compared to hepatocellular carcinomas that develop in cirrhotic livers (Gaddikeri 2014). The role of routine screening for hepatocellular carcinomas in people with chronic liver disease is controversial with one systematic review concluding that there was no evidence of benefit of routine screening for people with hepatocellular carcinoma (Kansagara 2014).

Description of the intervention

Several classifications of hepatocellular carcinoma have been proposed. This includes clinical staging classifications, histopathological classifications, and molecular classifications (Wu 1996;

Henderson 2003; Van Deusen 2005; Cillo 2006; Nanashima 2006; Van Malenstein 2011). Of these, the Barcelona Clinic Liver Cancer (BCLC) staging system (Llovet 1999; Llovet 2003), and the Milan criteria (Mazzaferro 1996), are important classification systems that determine the management of hepatocellular carcinoma. Appendix 1 and Appendix 2 show these classification systems in detail. Stage 0 (very early hepatocellular carcinoma) and stage A (early hepatocellular carcinoma) of BCLC staging correspond approximately to tumours falling within Milan criteria although Stage A of the BCLC staging system includes a single tumour of any size while a single tumour should be less than 5 cm to fall within Milan criteria. This review examines the treatment options for people with intermediate-stage hepatocellular carcinoma (large multi-nodular tumours with no evidence of vascular invasion or extrahepatic spread and performance status 0). A separate review covers the treatment options for people with very-early hepatocellular carcinoma (single nodule less than 2 cm in diameter, Child-Pugh A cirrhosis, and performance status 0) and early hepatocellular carcinoma (single tumour or two or three lesions less than 3 cm in maximum diameter with no evidence of vascular invasion or extrahepatic spread, Child-Pugh A or B cirrhosis, and performance status 0) (Majumdar 2017).

Various treatments are aimed at intermediate-stage hepatocellular carcinoma. These can be broadly classified as surgical, ablative techniques, radiotherapy, transcatheter arterial embolisation (TAE), and transcatheter arterial chemoembolisation (TACE).

The surgical management of hepatocellular carcinoma is in the form of liver resection and liver transplantation (Bruix 2011; EASL 2012; Asham 2013). Liver resection is performed to ensure that all the tumours are removed with adequate remnant liver to carry out the normal functions of the liver (Asham 2013). Liver resection is usually performed by open technique although laparoscopic (key hole) liver resection can be performed in a selection of people (Nguyen 2009). Complications related to liver resection include mortality, liver failure, bile leak, bleeding, liver abscess, abdominal abscess, wound infection, and general complications such as heart failure and renal failure (Nguyen 2009; Xiong 2012). Liver transplantation involves removal of the diseased liver and transplanting a liver graft from another donor (usually a cadaveric donor) (SRTR 2012; NHSBT 2014). Living donor liver transplantation is associated with increased complications and increased incidence of retransplantation and constitutes only a small proportion of the global liver transplantation (Wan 2014). The complications of liver transplantation include mortality, graft failure, graft rejection, biliary stricture, hepatic artery thrombosis, and wound infections (Gurusamy 2014; Wan 2014).

Ablation is usually in the form of radiofrequency ablation (Bruix 2011; EASL 2012; Asham 2013), but other modalities exist, such as chemical ablation using percutaneous alcohol or acetic acid injections, ablations such as microwave ablation, laser (light amplification by stimulated emission of radiation) ablation, cryoablation, high-intensity focused ultrasound (HIFU), and irreversible elec-

troporation (Head 2004; Germani 2010; Sindram 2010; Chan 2013a). Complications related to ablation include mortality, liver failure, bleeding, liver abscess, bile duct injuries, and tumour dissemination through the needle tract ('seeding') or into the peritoneum (Chan 2013a; McDermott 2013).

Radiotherapy is usually in the form of stereotactic body radiotherapy and radioembolisation. Stereotactic body radiotherapy involves delivering external radiotherapy in large divided doses (usually five or fewer doses) with the radiation focused on the lesions (Kollar 2014). Radioembolisation involves intra-arterial injection of small microspheres (25 mm to 35 mm) containing the radionuclide Yttrium (Forner 2014). Major complications of radiotherapy include worsening of cirrhosis and liver toxicity, which may manifest as liver failure (Forner 2014; Kollar 2014).

TAE involves embolisation of the hepatic artery without using any chemotherapeutic agents, while TACE involves injection of a chemotherapeutic agent prior to embolisation of the hepatic artery (Pleguezuelo 2008). TACE can also be performed using drug-eluting beads (Forner 2014; Hoffmann 2014). Both TAE and TACE are unstandardised procedures, with varying chemotherapeutic and embolising agents used and different protocols of retreatment following the index embolisation (Tsochatzis 2014). Major complications of TAE and TACE include mortality, liver failure, liver and splenic abscesses, acute cholecystitis, damage to the bile ducts, renal failure, and severe upper gastrointestinal bleeding (Pleguezuelo 2008).

How the intervention might work

Liver resection and liver transplantation work by removing the cancer. Chemical ablations using alcohol injections and acetic acid injections destroy the cancer tissue (Sindram 2010). Thermal ablations cause destruction of cancer tissue by heat or cold (Sindram 2010). TAE and TACE cause ischaemia to the tumour thereby causing tumour necrosis (Pleguezuelo 2008). TACE combines the effect of chemotherapy agents, which inhibit the tumour in addition to the effect of ischaemia on the tumour, although the main effect of TACE may be due to the ischaemia rather than the chemotherapy delivered via the artery (Pleguezuelo 2008).

Why it is important to do this review

The current guidelines on the management of hepatocellular carcinoma by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases recommend TACE for people with intermediate-stage hepatocellular carcinoma (Bruix 2011; EASL 2012). In this situation, TACE is considered palliative (Bruix 2011; EASL 2012) and there is no evidence that TACE increases survival or health-related quality of life (Oliveri 2011). Some researchers advocate liver transplantation for selected people with intermediate-stage hepatocellular

carcinoma, while other researchers do not (Germani 2011; Prasad 2011). However, it must be noted that people with hepatocellular carcinoma have to compete with other people waiting for liver transplantation. In 2012, pretransplant deaths occurred at the rate of 5.8 deaths per 100 waiting-list years in the US (SRTR 2012), and in the year to the end of March 2014, 12% of people on the liver transplantation waiting list in the UK died or became too unwell to have a transplant (NHSBT 2014). This indicates an organ shortage necessitating an organ allocation policy. The Milan criteria are now used for organ transplant allocation in many countries. In the US, eligible people with hepatocellular carcinoma are given exceptional status so that they do not remain on the waiting list too long, as delay in transplantation will increase the chance of tumour progression or dissemination (OPTN 2014). People with hepatocellular carcinoma must meet the Milan criteria but, in addition, need to have a minimum tumour size of 2 cm if they have a single tumour and a minimum tumour size of 1 cm each if they have two or three lesions to be considered eligible for exceptional status (OPTN 2014). However, expanding the existing criteria for liver transplantation for people with intermediate-stage hepatocellular carcinoma should be carefully assessed and should be evidence-based because of the impact that this might have on other people requiring liver transplantation. There have also been calls to recommend liver resection for people with intermediate-stage hepatocellular carcinoma (Guglielmi 2014). Thus, the optimal management of people with intermediate-stage hepatocellular carcinoma is not known. Network meta-analysis allows combination of the direct evidence and indirect evidence and allows ranking of different interventions in terms of the different outcomes (Salanti 2011; Salanti 2012). There has been no network meta-analysis on the different interventions for intermediate-stage hepatocellular carcinoma. This systematic review and attempted network meta-analysis attempts to provide the best level of evidence for the role of different treatment options for people with intermediate-stage hepatocellular carcinoma.

OBJECTIVES

To assess the comparative benefits and harms of different interventions used in the treatment of intermediate-stage hepatocellular carcinoma (BCLC stage B) through a network meta-analysis and to generate rankings of the available interventions according to their safety and efficacy. However, there was only one comparison included for this review. Therefore, we did not perform the network meta-analysis, and we assessed the comparative benefits and harms of different interventions using standard Cochrane methodology. When more trials become available, we will attempt to conduct network meta-analysis in order to generate rankings of the available interventions according to their safety and efficacy. This is why we retain the planned methodology for network meta-analysis in our Appendix 3. Once data appear allowing for the

conduct of network meta-analysis, this [Appendix 3](#) will be moved back into the Methods section.

METHODS

Criteria for considering studies for this review

Types of studies

We considered only randomised clinical trials, irrespective of language, publication status, or date of publication. We excluded studies of other design because of the risk of bias in such studies. We are all aware that such exclusions make us focus much more on potential benefits and not fully assess the risks of serious adverse events as well as risks of adverse events.

Types of participants

We included participants with intermediate-stage hepatocellular carcinoma (BCLC stage B) irrespective of the presence of cirrhosis, size and number of the tumours (provided they met the criteria of intermediate-stage hepatocellular carcinoma), presence or absence of portal hypertension, aetiology of hepatocellular carcinoma, and the future remnant liver volume. We excluded randomised clinical trials in which participants had undergone liver transplantation previously.

Types of interventions

We planned to include any of the following interventions that are possible treatments for intermediate-stage hepatocellular carcinoma either alone or in combination tested versus each other, or versus placebo or sham, or no intervention (supportive care):

- liver resection;
- liver transplantation;
- radiofrequency ablation;
- microwave ablation;
- other ablations (laser ablation, cryoablation, HIFU, irreversible electroporation);
- alcohol injection;
- acetic acid injection;
- radiotherapy (stereotactic body radiotherapy or radioembolisation);
- systemic chemotherapy;
- TAE;
- TACE;
- supportive care.

The above list is not exhaustive. If we identified interventions that we were not aware of, we would have considered them as eligible and would have included them in the review, if they were used

primarily for the treatment of hepatocellular carcinoma. If liver resection or liver transplantation were combined with ablation, TAE, or TACE, we planned to categorise the intervention as liver resection or liver transplantation. This is because liver resection and liver transplantation are the major components in such interventions, with ablation, TAE, or TACE playing exclusively a supportive role to liver resection or liver transplantation. However, we planned to exclude such interventions from a sensitivity analysis (see [Sensitivity analysis](#)). If we found a sufficient number of trials on one or more of the other methods of ablation (laser ablation, cryoablation, HIFU, irreversible electroporation), we planned to consider the specific method of ablation with sufficient trials as a separate intervention.

Types of outcome measures

We planned to assess the comparative benefits and harms of available interventions aimed at treating people with intermediate-stage hepatocellular carcinoma for the following outcomes.

Primary outcomes

- Mortality at maximal follow-up (time to death).
- Mortality:
 - short-term mortality (up to one year);
 - medium-term mortality (one to five years).
- Adverse events (within three months of cessation of treatment). Depending on the availability of data, we planned to attempt to classify adverse events as serious and non-serious. We defined a non-serious adverse event as any untoward medical occurrence not necessarily having a causal relationship with the treatment but resulting in a dose reduction or discontinuation of treatment (any time after commencement of treatment) ([ICH-GCP 1997](#)). We defined a serious adverse event as any event that would increase mortality; was life threatening; required hospitalisation; resulted in persistent or significant disability; was a congenital anomaly/birth defect; or any important medical event that might jeopardise the person or require intervention to prevent it. We used the definition used by study authors for non-serious and serious adverse events:
 - proportion of participants with serious adverse events;
 - number of serious adverse events;
 - proportion of participants with any type of adverse event;
 - number of any type of adverse event.
- Quality of life as defined in the included trials using a validated scale such as EQ-5D or 36-item Short Form (SF-36) ([EuroQol 2014](#); [Ware 2014](#)):
 - short-term (up to one year);
 - medium-term (one to five years);
 - long-term (beyond five years).

We considered long-term quality of life more important than short-term or medium-term quality of life, although short-term or medium-term quality of life are also important primary outcomes.

Secondary outcomes

- Disease recurrence (maximum follow-up):
 - proportion of participants with hepatocellular carcinoma recurrence (includes recurrence in the liver and metastatic disease);
 - proportion of participants with local recurrence (recurrence in the liver);
 - time to hepatocellular carcinoma recurrence;
 - time to local recurrence.
- Length of hospital stay for the intervention and intervention-related complications. If intervention was performed in two or more sessions, we planned to calculate the total length of hospital stay for all the sessions. Similarly, we planned to include length of hospital stay for readmissions within 30 days of intervention because of intervention-related complications in the length of hospital stay.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 8), MEDLINE (OvidSP), Embase (OvidSP), and Science Citation Index Expanded (Web of Knowledge) (Royle 2003) from inception to 30 September 2016 for randomised clinical trials comparing two or more of the above interventions. We searched for all possible comparisons formed by the interventions of interest. To identify further ongoing or completed trials, we also searched the World Health Organization International Clinical Trials Registry Platform search portal (apps.who.int/trialsearch/), which searches various trial registers, including ISRCTN and ClinicalTrials.gov. Appendix 4 shows the search strategies that we used and the time spans of the searches.

Searching other resources

We searched the references of the identified trials and the existing Cochrane Reviews on hepatocellular carcinoma to identify additional trials for inclusion.

Data collection and analysis

Selection of studies

Review authors (KG, AM, or DR between them) independently identified the trials for inclusion by screening the titles and abstracts. We sought full-text articles for any references that at least one of the review authors identified for potential inclusion. We selected trials for inclusion based on the full-text articles. We have listed the excluded full-text references with reasons for their exclusion in the [Characteristics of excluded studies](#) table. We listed any ongoing trials identified primarily through the search of the clinical trial registers for further follow-up ([Characteristics of ongoing studies](#) table). We resolve discrepancies through discussion.

Data extraction and management

Two review authors (KG and AM or DR) independently extract the following data.

- Outcome data (for each outcome and for each intervention arm whenever applicable):
 - number of participants randomised;
 - number of participants included for the analysis;
 - number of participants with events for binary outcomes, mean and standard deviation for continuous outcomes, number of events for count outcomes, and the number of participants with events and the mean follow-up period for time-to-event outcomes;
 - definition of outcomes or scale used if appropriate.
- Data on potential effect modifiers:
 - participant characteristics such as age, sex, comorbidities, proportion of people with or without cirrhosis, tumour size, number of tumours, presence of portal hypertension, aetiology of hepatocellular carcinoma, and adjuvant treatments such as immunotherapy;
 - details of the intervention and control (including dose, frequency, and duration);
 - risk of bias (assessment of risk of bias in included studies).
- Other data:
 - year and language of publication;
 - country in which the participants were recruited;
 - year(s) in which the trial was conducted;
 - inclusion and exclusion criteria;
 - follow-up time points of the outcome.

If available, we planned to obtain the data separately for people with and without cirrhosis, presence compared to absence of portal hypertension, and viral compared to non-viral aetiology. We sought unclear or missing information by attempting to contacting the trial authors, but we did not obtain any additional information. If there was any doubt whether trials shared the same participants, completely or partially (by identifying common authors and centres), we planned to contact the trial authors to clarify whether the trial report was duplicated. We resolved any differences in opinion through discussion.

Assessment of risk of bias in included studies

We followed the guidance given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and described in the Cochrane Hepato-Biliary Group Module (Gluud 2016) to assess the risk of bias in included studies. Specifically, we assessed the risk of bias in included trials for the following domains using the methods below (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Savović 2012a; Savović 2012b; Lundh 2017).

Allocation sequence generation

- Low risk of bias: the study authors performed sequence generation using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were adequate if an independent person not otherwise involved in the study performed them.
- Unclear risk of bias: the study authors did not specify the method of sequence generation.
- High risk of bias: the sequence generation method was not random. We only included such studies for assessment of harms.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. A central and independent randomisation unit controlled allocation. The investigators were unaware of the allocation sequence (e.g. if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Unclear risk of bias: the study authors did not describe the method used to conceal the allocation so the intervention allocations may have been foreseen before, or during, enrolment.
- High risk of bias: it is likely that the investigators who assigned the participants knew the allocation sequence. We only included such studies for assessment of harms.

Blinding of participants and personnel

- Low risk of bias: any of the following: no blinding or incomplete blinding, but the review authors judged that the outcome was not likely to be influenced by lack of blinding; or blinding of participants and key study personnel ensured, and it was unlikely that the blinding could have been broken.
- Unclear risk of bias: any of the following: insufficient information to permit judgement of 'low risk' or 'high risk'; or the trial did not address this outcome.
- High risk of bias: any of the following: no blinding or incomplete blinding, and the outcome was likely to be influenced by lack of blinding; or blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome was likely to be influenced by lack of blinding.

Blinding of outcome assessors

- Low risk of bias: any of the following: no blinding of outcome assessment, but the review authors judged that the outcome measurement was not likely to be influenced by lack of blinding; or blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
- Unclear risk of bias: any of the following: insufficient information to permit judgement of 'low risk' or 'high risk'; or the trial did not address this outcome.
- High risk of bias: any of the following: no blinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding; or blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. The study used sufficient methods, such as multiple imputation, to handle missing data.
- Unclear risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias on the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk of bias: the trial reported the following predefined outcomes: at least medium-term or long-term mortality and treatment-related adverse events. If the original trial protocol was available, the outcomes should have been those called for in that protocol. If the trial protocol was obtained from a trial registry (e.g. www.clinicaltrials.gov), the outcomes sought should have been those enumerated in the original protocol if the trial protocol was registered before or at the time that the trial was begun. If the trial protocol was registered after the trial was begun, those outcomes were not considered to be reliable.
- Unclear risk of bias: not all predefined, or clinically relevant and reasonably expected, outcomes were reported fully, or it was unclear whether data on these outcomes were recorded or not.
- High risk of bias: one or more predefined or clinically relevant and reasonably expected outcomes were not reported, despite the fact that data on these outcomes should have been available and even recorded.

For-profit bias

- Low risk of bias: the trial appeared to be free of industry sponsorship or other type of for-profit support that could manipulate the trial design, conductance, or results of the trial.
- Unclear risk of bias: the trial may or may not be free of for-profit bias as no information on clinical trial support or sponsorship was provided.
- High risk of bias: the trial was sponsored by industry or received other type of for-profit support.

Other bias

- Low risk of bias: the trial appeared to be free of other components (e.g. inappropriate control or dose or administration of control) that could put it at risk of bias.
- Unclear risk of bias: the trial may or may not be free of other components that could put it at risk of bias.
- High risk of bias: there were other factors in the trial that could put it at risk of bias (e.g. inappropriate control or dose or administration of control).

We considered a trial to be at low risk of bias if we assessed the trial as at low risk of bias across all domains. Otherwise, we considered trials at unclear risk of bias or at high risk of bias regarding one or more domains as at high risk of bias. Since blinding of healthcare providers is impossible for all the comparisons and blinding of the participants is unlikely for comparisons involving surgery, we planned to assess the potential influence of lack of blinding on the outcomes carefully. We planned to classify the trials to be at high risk of bias for all the outcomes other than mortality because of the potential influence of lack of blinding on the other outcomes.

Measures of treatment effect

For dichotomous variables (e.g. short-term mortality, medium-term mortality, and proportion of participants with adverse events), we planned to calculate the odds ratio with 95% confidence intervals (CI). For continuous variables (e.g. hospital stay and quality of life reported on the same scale), we planned to calculate the mean difference with 95% CI. We planned to use standardised mean difference values with 95% CI for quality of life if included trials used different scales. For count outcomes (e.g. number of adverse events), we planned to calculate the rate ratio with 95% CI. For time-to-event data (e.g. mortality at maximal follow-up), we calculated hazard ratio (HR) with 95% CI.

Unit of analysis issues

The unit of analysis was the person with intermediate-stage hepatocellular carcinoma according to the intervention group to which they were randomly assigned.

Cluster randomised clinical trials

We found no cluster randomised clinical trials. However, if we found them, we planned to include them provided that the effect estimate adjusted for cluster correlation was available.

Cross-over randomised clinical trials

We found no cross-over randomised clinical trials. If we identified any, we planned to only include the outcome results after the period of first intervention since the first intervention may have a permanent impact on the outcome (i.e. have a residual effect).

Trials with multiple treatment groups

We planned to collect data for all trial treatment groups that met the inclusion criteria.

Dealing with missing data

We performed an intention-to-treat analysis whenever possible (Newell 1992). Otherwise, we used the data available to us (e.g. a trial may have reported only per-protocol analysis results). As such 'per-protocol' analyses may be biased, we planned to conduct best-worst case scenario analyses (good outcome in intervention group and bad outcome in control group) and worst-best case scenario analyses (bad outcome in intervention group and good outcome in control group) as sensitivity analyses whenever possible.

For continuous outcomes, we planned to impute the standard deviation from P values according to guidance given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If the data were likely to be normally distributed, we planned to use the median for meta-analysis when the mean was not available. If it was not possible to calculate the standard deviation from the P value or the confidence intervals, we planned to impute the standard deviation using the largest standard deviation in other trials for that outcome. This form of imputation may decrease the weight of the study for calculation of mean differences and may bias the effect estimate to no effect for calculation of standardised mean differences (Higgins 2011).

Assessment of heterogeneity

We planned to assess clinical and methodological heterogeneity by carefully examining the characteristics and design of included trials. We planned to assess the presence of clinical heterogeneity by comparing effect estimates in people with and without cirrhosis, presence or absence of portal hypertension, aetiology of hepatocellular carcinoma, and adjuvant treatment with immunotherapy. Different study designs and risk of bias may contribute to methodological heterogeneity.

We used the I^2 test and Chi^2 test for heterogeneity, and overlapping of CIs to assess heterogeneity. If we identified substantial heterogeneity, clinical, methodological, or statistical, we explored

and address heterogeneity in a subgroup analysis (see [Subgroup analysis and investigation of heterogeneity](#)).

Assessment of reporting biases

We planned to use visual asymmetry on a funnel plot to explore reporting bias in the presence of at least 10 trials that could be included for a direct comparison ([Egger 1997](#); [Macaskill 2001](#)). In the presence of heterogeneity that could be explained by subgroup analysis, we planned to produce a funnel plot for each subgroup in the presence of the adequate number of trials. We planned to use the linear regression approach described by [Egger 1997](#) to determine funnel plot asymmetry.

We also considered selective reporting as evidence of reporting bias.

Data synthesis

We performed the meta-analyses according to the recommendations of The Cochrane Collaboration ([Higgins 2011](#)), using the software package Review Manager 5 ([RevMan 2014](#)). We used a random-effects model ([DerSimonian 1986](#)) and a fixed-effect model ([DeMets 1987](#)). In the case of a discrepancy between the two models, we planned to report both results. However, since there was no discrepancy, we have reported only the results from the fixed-effect model.

Calculation of required information size and Trial Sequential Analysis

For calculation of the required information size, see [Appendix 5](#). We performed Trial Sequential Analysis to control the risks of random errors ([Wetterslev 2008](#); [Thorlund 2011](#); [TSA 2011](#)) when there were at least two trials included in the outcome. We used an alpha error as per guidance of [Jakobsen 2014](#), power of 90% (beta error of 10%), a relative risk reduction of 20%, a control group proportion observed in the trials, and the heterogeneity observed in the meta-analysis. Since the only outcome was mortality at maximal follow-up, a time-to-event outcome, we performed the Trial Sequential Analysis using [Stata/SE 14.2](#) using methods suggested by [Miladinovic 2013](#).

Subgroup analysis and investigation of heterogeneity

We planned to assess the differences in the effect estimates between the following subgroups.

- Trials at low risk of bias compared to trials at high risk of bias.
- People with and without cirrhosis.
- Presence compared to absence of portal hypertension.

- Viral compared to non-viral aetiology.
- Use of immunotherapy or antiviral therapy or other treatments as adjuvant therapy compared to no use.

We planned to use the χ^2 test for subgroup differences to identify subgroup differences.

Sensitivity analysis

If a trial reported only per-protocol analysis results, we planned to reanalyse the results using the best-worst case scenario and worst-best case scenario analyses as sensitivity analyses whenever possible. In addition, we planned to exclude trials in which liver resection or liver transplantation were combined with ablation, TAE, or TACE.

Presentation of results and GRADE assessments

If trials reported on all our predefined outcomes, we planned to report all of them in a 'Summary of findings' table format, downgrading the quality of evidence for risk of bias, inconsistency, indirectness, imprecision, and publication bias using GRADE ([Guyatt 2011](#)).

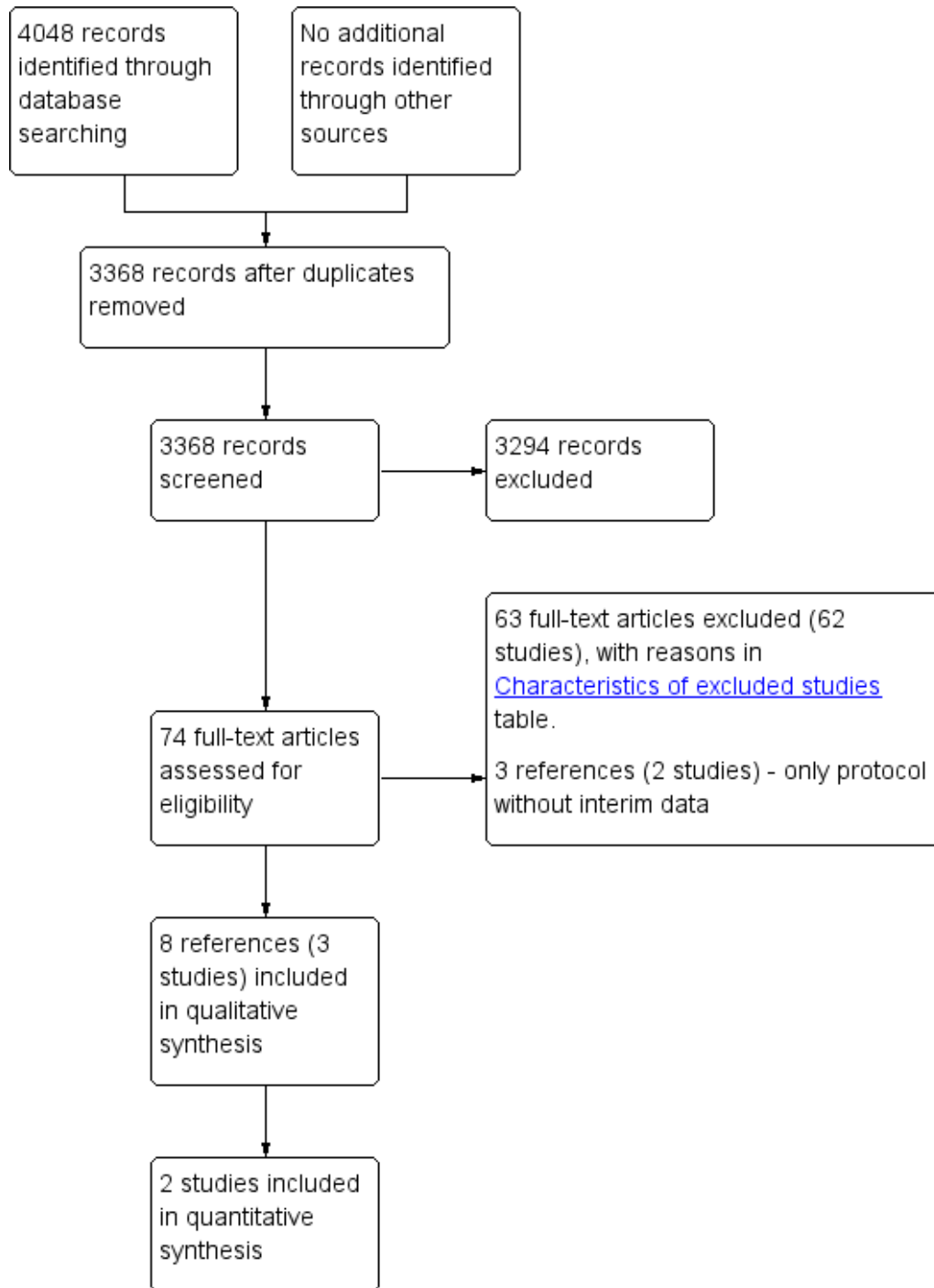
RESULTS

Description of studies

Results of the search

We identified 4048 references through electronic searches of CENTRAL (N = 264), MEDLINE (N = 1723), Embase (N = 451), Science Citation Index Expanded (N = 1443), World Health Organization International Clinical Trials Registry Platform (N = 137), and ClinicalTrials.gov (N = 30). After the removal of 680 duplicates, we obtained 3368 references. We then excluded 3294 clearly irrelevant references through screening titles and reading abstracts. We retrieved 74 references for further assessment. No references were identified through scanning reference lists of the identified randomised trials. We excluded 63 references (62 studies) for the reasons listed in the [Characteristics of excluded studies](#) table; three references (two trials) were ongoing trials with no interim data ([Seinstra 2012](#); [NCT02854839](#); [Characteristics of ongoing studies](#) table). In total, eight references (three trials) met the inclusion criteria ([Bruix 2012](#); [de Stefano 2015](#); [Lencioni 2016](#)). The study flow diagram summarises the reference flow ([Figure 1](#)).

Figure 1. Study flow diagram.



Included studies

We included three trials with 430 participants in this review (Bruix 2012; de Stefano 2015; Lencioni 2016). Two of the trials (412 participants) provided data for only one outcome of this review, that is, mortality (Bruix 2012; Lencioni 2016). All trials included supportive care as a cointervention. The comparisons included in the trials were:

- systemic chemotherapy with sorafenib versus no active intervention (one trial with 105 participants; Bruix 2012);
- radiofrequency ablation plus systemic chemotherapy with sorafenib versus radiofrequency ablation (one trial with 18 participants; de Stefano 2015 - an ongoing trial and the interim report did not contain any outcomes of interest);
- transarterial chemoembolisation plus systemic chemotherapy with sorafenib versus transarterial chemoembolisation (one trial with 307 participants; Lencioni 2016).

The mean age in the trials that reported this information was 64 years (Lencioni 2016) and 69 years (Bruix 2012). The proportion of females in the trials that reported this information was 15% (46/307 participants) (Lencioni 2016) and 15.2% (16/105 participants) (Bruix 2012). The proportion of participants with cirrhosis in the trial that reported this information was 87.9% (270/307 participants) (Lencioni 2016). None of the trials reported

whether participants had portal hypertension. The proportion of participants with viral aetiology in the trials that reported this information was 37.1% (39/105 participants) (Bruix 2012) and 64.2% (197/307 participants) (Lencioni 2016). None of the trials reported use of immunotherapy or antiviral therapies as adjuvant therapy.

Follow-up period: the three trials did not report the duration of follow-up. However, the Kaplan-Meier curves from the two trials that provided data for this review suggested that participants were followed up for a period of about 18 to 30 months (Bruix 2012; Lencioni 2016).

Source of funding: two trials were funded by the pharmaceutical industry (Bruix 2012; de Stefano 2015); one trial did not report the source of funding (Lencioni 2016).

Excluded studies

We excluded 63 references for the reasons given in the [Characteristics of excluded studies](#) table.

Risk of bias in included studies

The risk of bias is summarised in [Figure 2](#) and [Figure 3](#). None of the trials were at low risk of bias for all domains; hence, all trials were at high risk of bias.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

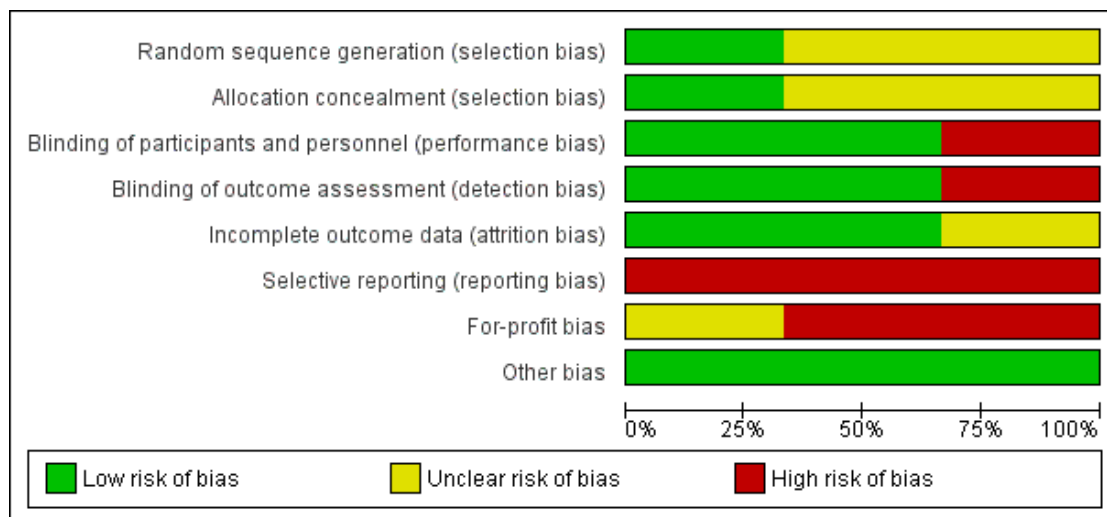


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	For-profit bias	Other bias
Bruix 2012	+	+	+	+	+	-	-	+
de Stefano 2015	?	?	-	-	?	-	-	+
Lencioni 2016	?	?	+	+	+	-	?	+

Allocation

One trial reported the sequence generation adequately and was at low risk of bias in this domain (Bruix 2012). The remaining trials were at unclear risk of bias in this domain (de Stefano 2015; Lencioni 2016). One trial reported allocation concealment adequately, and was at low risk of bias in this domain (Bruix 2012). The remaining trials were at unclear risk of bias in this domain (de Stefano 2015; Lencioni 2016). Overall, one trial was at low risk of selection bias (Bruix 2012); the remaining trials were at unclear risk of bias (de Stefano 2015; Lencioni 2016).

Blinding

Two trials achieved blinding of participants, healthcare providers, and outcome assessors (Bruix 2012; Lencioni 2016); these two trials were at low risk of performance and detection biases. In one trial, there was no blinding of participants, healthcare providers, or outcome assessors (de Stefano 2015); this trial was at high risk of performance and detection biases.

Incomplete outcome data

There were no post-randomisation dropouts in two trials (Bruix 2012; Lencioni 2016); these two trials were at low risk of attrition bias. The remaining trial did not report whether there were any post-randomisation dropouts (de Stefano 2015); this trial was at unclear risk of attrition bias.

Selective reporting

Published protocols of the trials were not available for any of the trials. The trials did not report either mortality or adverse events, or both; therefore, all three trials were at high risk of reporting bias (Bruix 2012; de Stefano 2015; Lencioni 2016).

Other potential sources of bias

Two trials were funded by the pharmaceutical industry and were at high risk of 'for-profit bias' (Bruix 2012; de Stefano 2015). One trial did not report the source of funding and was at unclear risk of 'for-profit bias' (Lencioni 2016). There was no other bias in any of the trials.

Effects of interventions

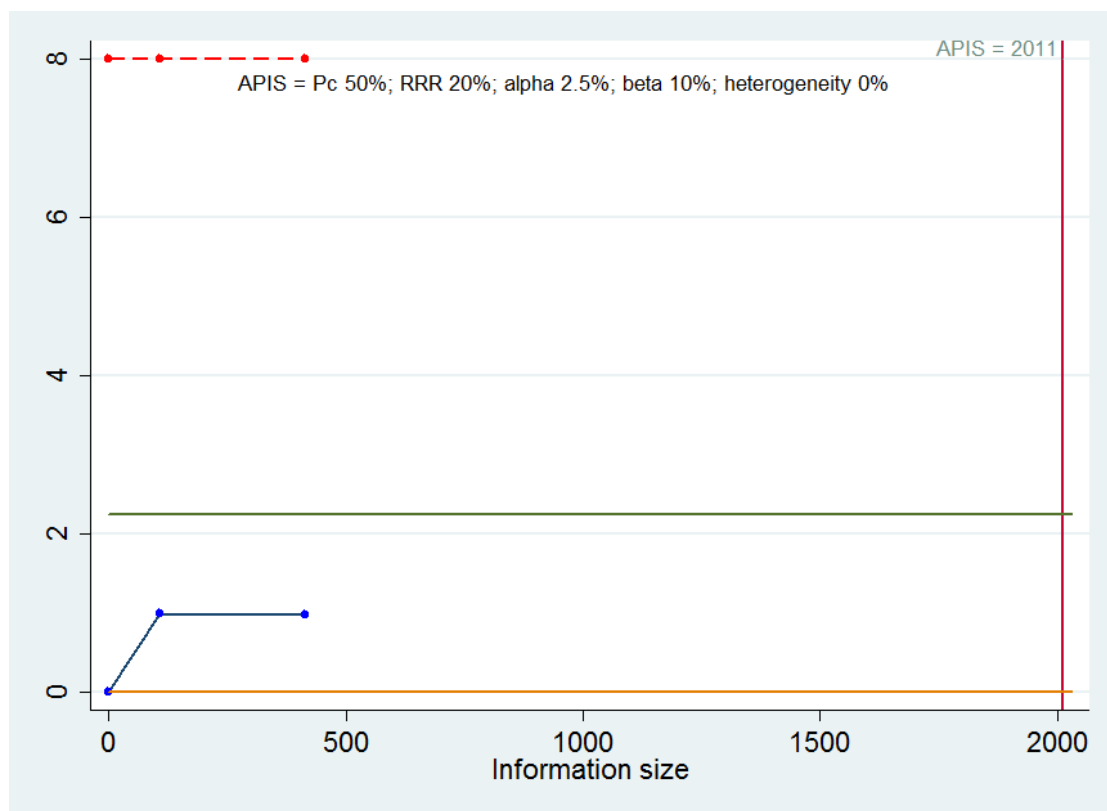
See: [Summary of findings for the main comparison](#)
[Chemotherapy versus no chemotherapy for intermediate-stage hepatocellular carcinoma](#)

Mortality (at maximal follow-up)

Two trials (412 participants) reported mortality at maximal follow-up (Bruix 2012; Lencioni 2016). Mortality was 50% to 75% over a median follow-up period of 12 to 24 months in the two trials (Bruix 2012; Lencioni 2016). We performed a meta-analysis assuming that the presence or absence of transarterial embolisation did not influence the effect of systemic chemotherapy. There was no evidence of difference in mortality at maximal follow-up between systemic chemotherapy versus no chemotherapy (hazard ratio 0.85, 95% CI 0.60 to 1.18; participants = 412; studies = 2; $I^2 = 0$; very low quality evidence; [Analysis 1.1](#)). The interpretation of results did not change by using a random-effects model. A subgroup analysis stratified by the presence or absence of transarterial chemoembolisation as cointervention did not alter the results.

Trial Sequential Analysis: based on an alpha error of 5%, power of 90% (beta error of 10%), a relative risk reduction of 20%, the control group proportion of 50%, and observed heterogeneity of 0%, the required information size was 2011. As shown in [Figure 4](#), the z-curve (blue line) did not cross any of the boundaries indicating a high risk of random error.

Figure 4. Trial Sequential Analysis of mortality at maximal follow-up: based on an alpha error of 2.5%, power of 90% (beta error of 10%), a relative risk reduction (RRR) of 20%, the control group proportion (Pc) of 50%, and observed heterogeneity (0%), the a priori information size (APIS) was 2011. As shown in the figure, the cumulative Z-curve (blue line) do not cross any of trial sequential monitoring boundaries (red lines). They do not cross the conventional alpha boundary of 2.5% (green line) either.



Short-term mortality (up to one year)

None of the trials reported proportion of people dead in the short-term (up to one year).

Medium-term mortality (one to five years)

None of the trials reported proportion of people dead in the medium-term (one to five years).

Serious adverse events

None of the trials reported serious adverse events.

Adverse events

None of the trials reported the proportion or number of adverse events.

Quality of life

None of the trials reported quality of life at any time point.

Disease recurrence

None of the trials reported recurrence of hepatocellular carcinoma.

Length of hospital stay

None of the trials reported length of hospital stay.

Reporting bias

We did not explore reporting bias because of the sparse data.

Subgroup analysis

We did not perform any subgroup analyses other than stratification by presence or absence of transarterial chemoembolisation as a cointervention because of the sparse data.

Sensitivity analysis

Since none of the trials reported any binary outcomes, we did not perform any sensitivity analyses. Since none of the trials reported length of hospital stay, the issue of imputing standard deviation did not arise.

Quality of evidence

The overall quality of the evidence was very low for the reported outcome of mortality. All the trials were at high risk of bias (resulting in downgrading it one level). There was no evidence of inconsistency in the only outcome. There was no issue of indirectness, since the outcome reported was a clinical outcome and only direct comparisons were used. The sample size was small (downgraded by one level) and the confidence intervals overlapped no effect and clinically significant effect (downgraded one level). We did not explore publication bias because of the too few trials included in this review ([Summary of findings for the main comparison](#)).

DISCUSSION

Summary of main results

We included two trials (412 participants) in one outcome for this review ([Bruix 2012](#); [Lencioni 2016](#)). Because of the sparse data, we did not perform a network meta-analysis (as there were no comparisons in which it was possible to obtain direct and indirect estimates, which would have allowed the assessment of inconsistency) and we used Frequentist methods for performing the direct comparisons. Of the two trials which provided data for this review, one trial compared active interventions (systemic chemotherapy; [Bruix 2012](#)) in addition to supportive treatments versus supportive treatments only. One trial compared two active interventions (transarterial chemoembolisation with and without systemic chemotherapy; [Lencioni 2016](#)). The only outcome reported in the trials was mortality at maximal follow-up. The trials did not report the mean or median follow-up, but it appeared that the participants were followed up for 18 to 30 months ([Bruix 2012](#); [Lencioni 2016](#)). Thus, even the mortality at maximal follow-up appeared to refer to medium-term mortality only. There was no evidence of differences in mortality between the groups in any of the comparisons. None of the trials reported the proportion of people with serious adverse events or number of serious adverse events, adverse events (proportion), adverse events (number), quality of life, disease recurrence, or length of hospital stay. In one trial, more than

70% of people died during the follow-up period ([Bruix 2012](#)); in another trial, approximately 50% of people died during the follow-up period ([Lencioni 2016](#)). Therefore, the follow-up period appears to be sufficiently long to detect any survival benefits of the active intervention. However, the sample size was small in all the comparisons and significant benefits or harms of intervention could not be ruled out.

Overall completeness and applicability of evidence

This review included only trial participants with intermediate-stage hepatocellular carcinoma (i.e. BCLC B stage; i.e. large, multinodular, Child-Pugh status A to B, and performance status 0). Therefore, this review is applicable only to people with intermediate-stage hepatocellular carcinoma. It included a mixture of viral and non-viral aetiologies and people with cirrhotic and non-cirrhotic livers. Hence, the review is applicable to viral or non-viral aetiologies and people with cirrhotic and non-cirrhotic livers. None of the trials reported the proportion of people with portal hypertension. Therefore, it is not clear whether the findings of the review are applicable in people with portal hypertension.

Quality of the evidence

The overall quality of the evidence was very low. All the trials were at high risk of bias resulting in downgrading by one level. Since there was only one trial included under each comparison, it was not possible to assess inconsistency. There was no issue of indirectness, since mortality at maximal follow-up is a clinical outcome and only direct comparisons were used. The sample size was small (all comparisons downgraded by one level) and the confidence intervals overlapped no effect and clinically significant effect for all comparisons (downgraded by one level). Within-study risk of bias and imprecision were the major reasons for downgrading the quality of evidence. We did not explore publication bias because of the too few trials included in this review.

Potential biases in the review process

The strengths of our review process are that we selected a range of databases without any language restrictions. Three review authors independently selected the trials and extracted the data, minimising the errors. We conducted the systematic review according to the guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We included only randomised clinical trials as they provide the best estimates of intervention effect.

The quality of evidence was very low. This is mainly because of the sparse data. This is the major limitation of this review. The BCLC classification is widely used in the Western hemisphere.

However, a number of the excluded studies predated BCLC criteria. Furthermore, BCLC is not used in the Eastern hemisphere, where a number of the excluded trials originated from. As a result, the majority of studies were excluded on the basis of not meeting BCLC B criteria. Using an alternative classification for people with the hepatocellular carcinoma, such as the CLIP or Okuda classifications (Okuda 1985; CLIP 1998), might have resulted in the inclusion of more trials in the analysis. However, this would not have met our objectives.

We only included randomised clinical trials which are known to focus mostly on benefits and do not collect and report harms in a detailed manner. According to our choice of studies (i.e. only randomised clinical trials), we might have missed a large number of studies that address reporting of harms. Accordingly, this review is biased towards benefits ignoring harms. We did not search for interventions and trials registered at regulatory authorities (e.g., FDA (US Food and Drug Administration); EMA (European Medicines Agency), etc). This may have overlooked trials and as such trials usually are unpublished, the lack of inclusion of such trials may make our comparisons look more advantageous than they really are.

Agreements and disagreements with other studies or reviews

This is the first systematic review on this topic in people with intermediate-stage hepatocellular carcinoma. We agreed with Lencioni 2016 that systemic therapy with sorafenib in addition to transarterial chemoembolisation did not offer any clinical benefit. We disagreed with Bruix 2012 that systemic chemotherapy with sorafenib in addition to supportive treatment is beneficial in people with intermediate-stage hepatocellular carcinoma. While there has been no systematic review of the effect of sorafenib in people with intermediate-stage hepatocellular carcinoma, one network meta-analysis on advanced hepatocellular carcinoma showed that sorafenib may have survival benefit (Niu 2016).

We found no evidence from randomised clinical trials to support the American Association for the Study of Liver Diseases recommend TACE for people with intermediate-stage hepatocellular carcinoma (Bruix 2011; EASL 2012). The possible reason for disagreements is that we have used evidence from randomised clinical trials only, which are generally considered the best quality of evidence; non-randomised studies are likely to provide a biased estimate of the effects in this situation as TACE is generally performed only when there is sufficient remnant liver volume and when there is no vascular spread (Lencioni 2013), and palliative treatment alone is considered appropriate for people with insufficient remnant liver volume or when there is vascular spread. Any differences

in survival or quality of life could be due to the extent of disease rather than the intervention itself. Therefore, only evidence from randomised clinical trials can provide a reasonable estimate of the effects of TACE compared to symptomatic treatment only.

AUTHORS' CONCLUSIONS

Implications for practice

Currently, there is no evidence from randomised clinical trials that people with intermediate-stage hepatocellular carcinoma would benefit from systemic chemotherapy with sorafenib either alone or with transarterial chemoembolisation as a cointervention (very low quality evidence).

Implications for research

We need high-quality randomised clinical trials designed to measure clinically important differences (e.g. all-cause mortality or health-related quality of life) and following the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials; Chan 2013b) and CONSORT guidelines (Schulz 2010). Future trials on hepatocellular carcinoma should report the outcomes separately by stage of hepatocellular carcinoma, so that it is possible to determine whether interventions are beneficial in people with intermediate-stage hepatocellular carcinoma.

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Contact editor: Christian Gluud, Denmark.

Sign-off editor: Christian Gluud, Denmark.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bruix 2012

Methods	Randomised clinical trial.
Participants	Country: multi-centric, international. Number randomised: 105. Post-randomisation dropouts: 0 (0%). Revised sample size: 105. Mean age: 69 years. Females: 16 (15.2%). Cirrhosis: not stated. Portal hypertension: not stated. Viral aetiology: 39 (37.1%). Immunotherapy/antiviral adjuvant therapy: not stated. Mean follow-up period (for all groups): not stated. Criteria for intermediate-stage HCC and other inclusion criteria: <ul style="list-style-type: none"> • Authors clearly stated BCLC stage B but no further details available in the manuscript.
Interventions	Participants were randomly assigned to 2 groups. Group 1: sorafenib (n = 54). Further details: chemotherapy: sorafenib 400 mg twice daily until radiological or symptomatic progression Group 2: placebo (n = 51).
Outcomes	Mortality.
Notes	

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Study randomization was centralized, and assignment to study groups was conducted by computer to achieve a balance between the two groups"
Allocation concealment (selection bias)	Low risk	Quote: "Study randomization was centralized, and assignment to study groups was conducted by computer to achieve a balance between the two groups"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "phase 3, double-blind, placebo-controlled trial...All eligible patients were randomly assigned in a 1:1 ratio to receive continuous oral treatment with either 400 mg of sorafenib (consisting of two 200-mg tablets) twice daily or matching placebo"

Bruix 2012 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “phase 3, double-blind, placebo-controlled trial...All eligible patients were randomly assigned in a 1:1 ratio to receive continuous oral treatment with either 400 mg of sorafenib (consisting of two 200-mg tablets) twice daily or matching placebo”
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: morbidity was not reported.
For-profit bias	High risk	Quote: “The study was designed by Bayer HealthCare Pharmaceuticals in conjunction with the principal academic investigators”
Other bias	Low risk	Comment: no other bias noted.

de Stefano 2015

Methods	Randomised clinical trial.
Participants	Country: Italy. Number randomised: 18. Post-randomisation dropouts: not stated. Revised sample size: 18. Mean age: not stated. Females: not stated. Cirrhosis: not stated. Portal hypertension: not stated. Viral aetiology: not stated. Immunotherapy/antiviral adjuvant therapy: not stated. Mean follow-up period (for all groups): not stated. Criteria for intermediate-stage HCC and other inclusion criteria: <ul style="list-style-type: none"> • Not stated but the authors clearly state BCLC stage B; • People not eligible for TACE.
Interventions	Participants were randomly assigned to 2 groups. Group 1: sorafenib (n = not stated). Further details: chemotherapy: sorafenib 400 mg twice daily until radiological or symptomatic progression Group 2: sorafenib plus RFA (n = not stated). Further details: chemotherapy: sorafenib 400 mg twice daily until radiological or symptomatic progression. RFA: details not stated in abstract
Outcomes	None of the outcomes of interest to our review were reported
Notes	

<i>Risk of bias</i>		<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization will be performed with a list of a priori sample prepared in sealed envelopes opaque"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "randomized open study".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "randomized open study".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor morbidity was not reported.
For-profit bias	High risk	Quote: "Financial support Bayer HealthCare, Onyx Pharmaceuticals and Biocompatibles UK, Ltd"
Other bias	Low risk	Comment: no other bias noted.

Lencioni 2016

Methods	Randomised clinical trial.
Participants	<p>Country: multi-centric, international. Number randomised: 307. Post-randomisation dropouts: not stated. Revised sample size: 307. Mean age: 64 years. Females: 46 (15%). Cirrhosis: 270 (87.9%). Portal hypertension: not stated. Viral aetiology: 197 (64.2%). Immunotherapy/antiviral adjuvant therapy: not stated. Average follow-up period in months (for all groups): not stated Criteria for intermediate-stage HCC and other inclusion criteria:</p> <ul style="list-style-type: none"> • Unresectable, multi-nodular, without macrovascular involvement or extrahepatic metastasis. • Eastern Cooperative Oncology Group performance status 0.

	<ul style="list-style-type: none"> • Child-Pugh A liver function. • No previous local treatment.
Interventions	<p>Participants were randomly assigned to 2 groups.</p> <p>Group 1: TACE plus sorafenib (n = 154).</p> <p>Further details: TACE: drug-eluting beads containing doxorubicin 150 mg - multiple cycles - duration not stated</p> <p>Chemotherapy: sorafenib 400 mg twice daily in 4 week cycles - duration not stated</p> <p>Group 2: TACE plus placebo (n = 153).</p> <p>Further details: TACE: drug-eluting beads containing doxorubicin 150 mg - multiple cycles - duration not stated</p>
Outcomes	Mortality.
Notes	

<i>Risk of bias</i>		<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization will be performed with a list of a priori sample prepared in sealed envelopes opaque"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "phase II randomized, double-blind, placebo-controlled study... Patients were randomized 1:1 to DEB-TACE [doxorubicin-eluting bead transarterial chemoembolization] (300-500 µm beads; 150 mg doxorubicin) plus sorafenib (400 mg twice daily, continuously) or matching placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "phase II randomized, double-blind, placebo-controlled study... Patients were randomized 1:1 to DEB-TACE (300-500 µm beads; 150 mg doxorubicin) plus sorafenib (400 mg twice daily, continuously) or matching placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: morbidity was not reported.
For-profit bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other bias noted.

BCLC: Barcelona Clinic Liver Cancer; HCC: hepatocellular carcinoma; RFA: radiofrequency ablation; TACE: transarterial chemoembolisation.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abdelaziz 2015	Not intermediate-stage HCC (people with performance status 0 or 1)
Anonymous 1995	Not intermediate-stage HCC (people with single tumour with BCLC A)
Arai 2010	Not intermediate-stage HCC (insufficient information in abstract to confirm BCLC stage)
Bartolozzi 1995	Variations in transarterial chemoembolisation.
Becker 2005	Not intermediate-stage HCC (people with portal vein thrombosis and Okuda stage III)
Bruix 1998	Not intermediate-stage HCC (people with single tumour and performance status > 1)
Chen 2002	Variations in transarterial chemoembolisation.
Chen 2007	Not a randomised clinical trial.
Cheng 2004	Not intermediate-stage HCC (people with single tumour with BCLC A)
Cheng 2008	Not intermediate-stage HCC (people with single tumour with BCLC A. Retracted in DeAngelis 2009).
Choi 2014	Not intermediate-stage HCC (people with BCLC C).
Chow 2002	Not intermediate-stage HCC (people with performance status 0 to 3 and Child-Pugh C)
DeAngelis 2009	Retraction of an excluded trial (Cheng 2008).
Doffoel 2008	Not intermediate-stage HCC (people with portal vein thrombosis and performance status > 2)
El-Kady 2013	Not intermediate-stage HCC (people with BCLC A).
Ferrari 2004	Not intermediate-stage HCC (people with single tumour with BCLC A)
Fischman 2014	Not intermediate-stage HCC (people with BCLC C).
Gallo 2006	Not intermediate-stage HCC (people with Child-Pugh C).
Gish 2009	Not intermediate-stage HCC (people with performance status 1)
Golfieri 2014	Variations in transarterial chemoembolisation.

(Continued)

Hebbar 2015	Not intermediate-stage HCC (insufficient information in abstract to confirm BCLC stage)
Hilgard 2008	Not intermediate-stage HCC (people with performance status > 1)
Hou 2009	Not intermediate-stage HCC (people with T4 N0 M0 stage, extrahepatic invasion)
Huo 2003	Quasi-randomised study.
Iezzi 2013	Not a randomised clinical trial.
Inaba 2013	Not intermediate-stage HCC (people with performance status 0 to 2 and Child Pugh C)
Kolligs 2015	Not intermediate-stage HCC (people with BCLC C).
Kudo 2002	Not intermediate-stage HCC (people with BCLC A).
Kudo 2014	Not intermediate-stage HCC (people with BCLC C/D and performance status 1)
Lammer 2010	Not intermediate-stage HCC (people with performance status 1)
Li 2009	Not intermediate-stage HCC (people with single tumour).
Li 2010	Not intermediate-stage HCC (people with portal vein tumour thrombus)
Liu 2010	Variations in microwave ablation.
Livraghi 2005	Not intermediate-stage HCC (people with BCLC C).
Llovet 2002	Not intermediate-stage HCC (people with BCLC C).
Llovet 2007	Not intermediate-stage HCC (people with performance status 1 or 2)
Lo 2002	Not intermediate-stage HCC (people with portal vein thrombosis and performance status > 2)
Malagari 2010	Not intermediate-stage HCC (people with BCLC A).
Meyer 2016	Not intermediate-stage HCC (people with performance status 1)
Mohnike 2013	Not intermediate-stage HCC (people with BCLC C).
Morimoto 2010	Not intermediate-stage HCC (people with single tumours and performance status > 1)
Morimoto 2011	Not intermediate-stage HCC (people with single tumours and performance status > 1)
Okusaka 2012	Not intermediate-stage HCC (people with single tumour and performance status 0 to 2)
Padia 2013	Not a randomised clinical trial.

(Continued)

Pelletier 1998	Not intermediate-stage HCC (people with Okuda III stage and therefore Child-Pugh C)
Sansonno 2012	Not intermediate-stage HCC (people with performance status 1)
Sarin 1994	Not intermediate-stage HCC (people with BCLC A).
Shi 2009	Variations in transarterial chemoembolisation.
Tanaka 2014	Not a randomised clinical trial.
Tang 2009	Not intermediate-stage HCC (people with portal vein tumour thrombus)
Ulbrich 2010a	Not intermediate-stage HCC (people with BCLC A).
Ulbrich 2010b	Not intermediate-stage HCC (people with BCLC A).
Wang 2007	Not intermediate-stage HCC (people with BCLC A).
Wang 2014	Not intermediate-stage HCC (people with BCLC C).
Wu 1995	Not intermediate-stage HCC (people with BCLC A).
Wu 1998	Not intermediate-stage HCC (people with Child-Pugh C).
Xie 2015	Not a randomised clinical trial.
Xu 2009	Not a randomised clinical trial.
Yang 2008	Not intermediate-stage HCC (people with Child-Pugh C).
Yin 2013	Not intermediate-stage HCC (people with BCLC A).
Zhang 2011	Not intermediate-stage HCC (people with recurrence after liver transplantation)
Zhou 2009	Not intermediate-stage HCC (people with portal vein thrombosis)

BCLC: Barcelona Clinic Liver Cancer; HCC: hepatocellular carcinoma.

Characteristics of ongoing studies *[ordered by study ID]*

NCT02854839

Trial name or title	NCT02854839.
Methods	Randomised clinical trial.
Participants	People with intermediate-stage hepatocellular carcinoma.
Interventions	Intervention: MG4101. Control: placebo.
Outcomes	Overall survival, adverse events.
Starting date	September 2016.
Contact information	Kyung Gue Lee (kglee@greencross.com).
Notes	

Scinstra 2012

Trial name or title	TRACE.
Methods	Randomised clinical trial.
Participants	Barcelona Clinic Liver Cancer staging system intermediate stage
Interventions	Transarterial radioembolisation versus transarterial chemoembolisation
Outcomes	Overall survival, adverse events, quality of life, costs, cost effectiveness
Starting date	Not stated, but the publication stated that they have already started including participants
Contact information	Maurice AAJ van den Bosch (mbosch@umcutrecht.nl).
Notes	

DATA AND ANALYSES

Comparison 1. Interventions for hepatocellular carcinoma

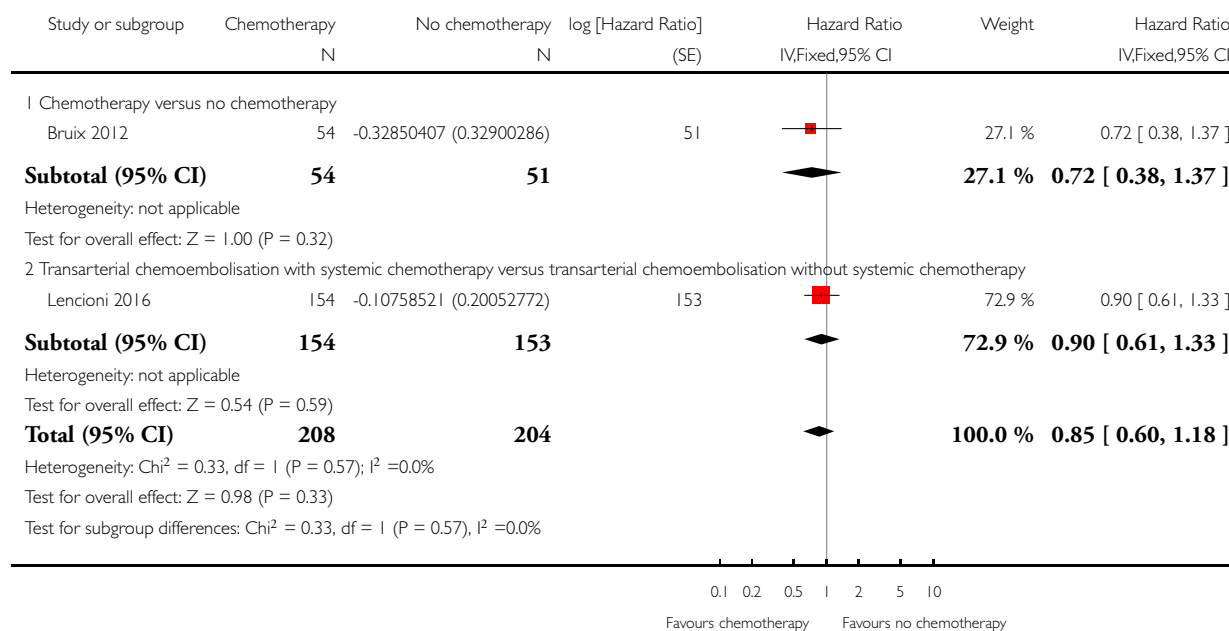
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality at maximal follow-up	2	412	Hazard Ratio (Fixed, 95% CI)	0.85 [0.60, 1.18]
1.1 Chemotherapy versus no chemotherapy	1	105	Hazard Ratio (Fixed, 95% CI)	0.72 [0.38, 1.37]
1.2 Transarterial chemoembolisation with systemic chemotherapy versus transarterial chemoembolisation without systemic chemotherapy	1	307	Hazard Ratio (Fixed, 95% CI)	0.90 [0.61, 1.33]

Analysis 1.1. Comparison 1 Interventions for hepatocellular carcinoma, Outcome 1 Mortality at maximal follow-up.

Review: Management of people with intermediate-stage hepatocellular carcinoma: an attempted network meta-analysis

Comparison: 1 Interventions for hepatocellular carcinoma

Outcome: 1 Mortality at maximal follow-up



APPENDICES

Appendix 1. Barcelona Clinic Liver Cancer (BCLC) staging classification

Stage 0: very early-stage hepatocellular carcinoma (single tumour less than 2 cm).

Stage A: early-stage hepatocellular carcinoma (single tumour or three tumours less than 3 cm in maximum diameter).

Stage B: intermediate-stage hepatocellular carcinoma (large multiple tumours).

Stage C: advanced-stage hepatocellular carcinoma (vascular invasion or extrahepatic spread or restriction in activities).

Stage D: end-stage hepatocellular carcinoma (poor performance status or Child-Pugh C liver functional status (based on bilirubin levels, albumin levels, prothrombin time or international normalised ratio (INR), presence of ascites, and presence hepatic encephalopathy).

Simplified from sources: [Llovet 1999](#); [Llovet 2003](#).

Appendix 2. Milan criteria

1. Single lesion less than 5 cm in diameter.

2. Two or three lesions less than 3 cm in maximum diameter.

3. No preoperative evidence or suspicion of invasion of blood vessels or lymph nodes by tumour.

4. No preoperative evidence of extrahepatic metastases.

People meet the Milan criteria if they meet either criteria numbers 1, 3, and 4 or criteria numbers 2, 3, and 4.

Simplified from source: [Mazzaferro 1996](#).

Appendix 3. Methods for network meta-analysis if we find this is possible in the future

Measures of treatment effect

Relative treatment effects

For dichotomous variables (e.g. proportion of participants with serious adverse events or any adverse events), we will calculate the odds ratio with 95% credible interval (or Bayesian confidence interval) ([Severini 1993](#)). For continuous variables (e.g. quality of life reported on the same scale), we will calculate the mean difference with 95% credible interval. We will use standardised mean difference values with 95% credible interval for quality of life if included trials use different scales. For count outcomes (e.g. number of adverse events and serious adverse events), we will calculate the rate ratio with 95% credible interval. For time-to-event data (e.g. mortality at maximal follow-up), we will calculate hazard ratio with 95% credible interval.

Relative ranking

We will estimate the ranking probabilities for all treatments of being at each possible rank for each intervention. Then, we will obtain the surface under the cumulative ranking curve (SUCRA) (cumulative probability) and rankogram ([Salanti 2011](#); [Chaimani 2013](#)).

Unit of analysis issues

We will collect data for all trial treatment groups that meet the inclusion criteria. The codes for analysis, that we will use, accounts for the correlation between the effect sizes from trials with more than two groups.

Assessment of heterogeneity

We will assess clinical and methodological heterogeneity by carefully examining the characteristics and design of included trials. We will assess the presence of clinical heterogeneity by comparing effect estimates under different categories of potential effect modifiers. Different study designs and risk of bias may contribute to methodological heterogeneity.

We will assess the statistical heterogeneity by comparing the results of the fixed-effect model meta-analysis and the random-effects model meta-analysis, between-study standard deviation (τ^2 and comparing this with values reported in the study of the distribution of between-study heterogeneity ([Turner 2012](#))), and by calculating I^2 (using [Stata/SE 14.2](#)). If we identify substantial heterogeneity,

clinical, methodological, or statistical, we will explore and address heterogeneity in a subgroup analysis (see 'Subgroup analysis and investigation of heterogeneity for network meta-analysis' section).

Assessment of transitivity across treatment comparisons

We will evaluate the plausibility of transitivity assumption (the assumption that the participants included in the different studies with different immunosuppressive regimens can be considered to be a part of a multi-arm randomised clinical trial and could potentially have been randomised to any of the treatments) (Salanti 2012). In other words, any participant that meets the inclusion criteria is, in principle, equally likely to be randomised to any of the above eligible interventions. If there is any concern that the clinical safety and effectiveness are dependent upon the effect modifiers, we will continue to do traditional Cochrane pair-wise comparisons and we will not perform a network meta-analysis on all participant subgroups.

Assessment of reporting biases

For the network meta-analysis, we will judge the reporting bias by the completeness of the search (i.e. searching various databases and including conference abstracts), as we do not currently find any meaningful order to perform a comparison-adjusted funnel plot as suggested by Chaimani 2012. However, if we find any meaningful order, for example, the control group used depended upon the year of conduct of the trial, we will use comparison-adjusted funnel plot as suggested by Chaimani 2012.

Data synthesis

Methods for indirect and mixed comparisons

We will conduct network meta-analyses to compare multiple interventions simultaneously for each of the primary and secondary outcomes. Network meta-analysis combines direct evidence within trials and indirect evidence across trials (Mills 2012). We will obtain a network plot to ensure that the trials were connected by treatments using *Stata/SE 14.2* (Chaimani 2013). We will exclude any trials that were not connected to the network. We will conduct a Bayesian network meta-analysis using the Markov chain Monte Carlo method in *OpenBUGS 3.2.3* as per the guidance from the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) documents (Dias 2014a). We will model the treatment contrast (i.e. log odds ratio for binary outcomes, mean difference or standardised mean difference for continuous outcomes, log rate ratio for count outcomes, and log hazard ratio for time-to-event outcomes) for any two interventions ('functional parameters') as a function of comparisons between each individual intervention and an arbitrarily selected reference group ('basic parameters') (Lu 2006) using appropriate likelihood functions and links. We will use binomial likelihood and logit link for binary outcomes, Poisson likelihood and log link for count outcomes, binomial likelihood and complementary log-log link for time-to-event outcomes, and normal likelihood and identity link for continuous outcomes. We will perform a fixed-effect model and random-effects model for the network meta-analysis. We will report both models for comparison with the reference group in a forest plot. For pairwise comparison, we will report the fixed-effect model if the two models reported similar results; otherwise, we will report the more conservative model.

We will use a hierarchical Bayesian model using three different initial values using codes provided by NICE DSU (Dias 2014a). We will use a normal distribution with large variance (10,000) for treatment effect priors (vague or flat priors). For the random-effects model, we will use a prior distributed uniformly (limits: 0 to 5) for between-trial standard deviation but assumed similar between-trial standard deviation across treatment comparisons (Dias 2014a). We will use a 'burn-in' of 5000 simulations, check for convergence visually, and run the models for another 10,000 simulations to obtain effect estimates. If we did not obtain convergence, we will increase the number of simulations for 'burn-in'. If we do not obtain convergence still, we will use alternate initial values and priors using methods suggested by van Valkenhoef 2012. We will also estimate the probability that each intervention ranks at one of the possible positions using the NICE DSU codes (Dias 2014a).

Assessment of inconsistency

We will assess inconsistency (statistical evidence of the violation of transitivity assumption) by fitting both an inconsistency model and a consistency model. We will use the inconsistency models used in the NICE DSU manual, as we plan to use a common between-study deviation for the comparisons (Dias 2014b). In addition, we will use the design-by-treatment full interaction model (Higgins 2012) and IF (inconsistency factor) plots (Chaimani 2013) to assess inconsistency. In the presence of inconsistency, we will assess whether the inconsistency is because of clinical or methodological heterogeneity by performing separate analyses for each of the different subgroups mentioned in the 'Subgroup analysis and investigation of heterogeneity for network meta-analysis' section below.

If there is evidence of inconsistency, we will identify areas in the network where substantial inconsistency might be present in terms of clinical and methodological diversities between trials and, when appropriate, limit network meta-analysis to a more compatible subset of trials.

Direct comparison

We will perform the direct comparisons using the same codes and the same technical details.

Sample size calculations

To control for the risk of random errors, we will interpret the information with caution when the accrued sample size in the network meta-analysis (i.e. across all treatment comparisons) was less than the required sample size (required information size). For calculation of the required information size, see [Appendix 5](#).

Subgroup analysis and investigation of heterogeneity for network meta-analysis

We will assess the differences in the effect estimates between the subgroups listed in Subgroup analysis and investigation of heterogeneity using meta-regression with the help of the OpenBUGS code ([Dias 2012a](#)) if we include a sufficient number of trials. We will use the potential modifiers as study level co-variables for meta-regression. We will calculate a single common interaction term ([Dias 2012a](#)). If the 95% credible intervals of the interaction term do not overlap zero, we will consider this as evidence of difference in subgroups.

Presentation of results

We will present the effect estimates with 95% CrI for each pairwise comparisons calculated from the direct comparisons and network meta-analysis. We will also present the cumulative probability of the treatment ranks (i.e. the probability that the treatment is within the top two, the probability that the treatment is within the top three, etc.) in graphs (surface under the cumulative ranking curve or SUCRA) ([Salanti 2011](#)). We will also plot the probability that each treatment is best, second best, third best etc for each of the different outcomes (rankograms), which are generally considered more informative ([Salanti 2011](#); [Dias 2012b](#)).

We will present the 'Summary of findings' tables for mortality. In the 'Summary of findings for the main comparison', we will follow the approach suggested by Puhan et al. ([Puhan 2014](#)). First, we will calculate the direct and indirect effect estimates and 95% credible intervals using the node-splitting approach ([Dias 2010](#)), i.e. calculate the direct estimate for each comparison by including only trials in which there was direct comparison of treatments and the indirect estimate for each comparison by excluding the trials in which there was direct comparison of treatments. Then we will rate the quality of direct and indirect effect estimates using GRADE which takes into account the risk of bias, inconsistency, directness of evidence, imprecision, and publication bias ([Guyatt 2011](#)). Then, we will present the estimates of the network meta-analysis and rate the quality of network meta-analysis effect estimates as the best quality of evidence between the direct and indirect estimates ([Puhan 2014](#)). In addition, in the same table, we will present illustrations and information on the number of trials and participants as per the standard 'Summary of Findings' Table.

Appendix 4. Search strategies

Database	Time span	Search strategy
The Central Register of Controlled Trials (CENTRAL)	Issue 8, 2016.	#1 MeSH descriptor: [Carcinoma, Hepatocellular] explode all trees #2 (((hepat* or liver) and carcinoma*) or hepatocellular caricoma or hepatocarcinoma or hepatoma or HCC or "primary liver cancer") #3 #1 or #2 #4 (intermediate or large or multinodular) #5 #3 and #4
MEDLINE (OvidSP)	January 1947 to September 2016.	1. exp Carcinoma, Hepatocellular/ 2. (((hepat* or liver) and carcinoma*) or hepatocellular caricoma or hepatocarcinoma or hepatoma or HCC or "primary liver cancer").ti,ab 3. 1 or 2 4. (intermediate or large or multinodular).ti,ab. 5. 3 and 4 6. randomized controlled trial.pt. 7. controlled clinical trial.pt. 8. randomized.ab. 9. placebo.ab. 10. drug therapy.fs.

(Continued)

		11. randomly.ab. 12. trial.ab. 13. groups.ab. 14. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 15. exp animals/ not humans.sh. 16. 14 not 15 17. 5 and 16
Embase (OvidSP)	January 1974 to September 2016.	1. exp liver cell carcinoma/ 2. (((hepat* or liver) and carcinoma*) or hepatocellular caricoma or hepatocarcinoma or hepatoma or HCC or “primary liver cancer”).ti,ab 3. 1 or 2 4. (intermediate or large or multinodular).ti,ab. 5. 3 and 4 6. exp crossover-procedure/ or exp double-blind procedure/ or exp randomized controlled trial/ or single-blind procedure/ 7. (((((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 8. 6 or 7 9. 5 and 8
Science Citation Index Expanded (Web of Knowledge)	January 1945 to September 2016.	#1 TS=(((hepat* or liver) and carcinoma*) or hepatocellular caricoma or hepatocarcinoma or hepatoma or HCC or “primary liver cancer”) #2 TS=(intermediate or large or multinodular) #3 TS=(random* OR rct* OR crossover OR masked OR blind* OR placebo* OR meta-analysis OR systematic review* OR meta-analys*) #4 #1 AND #2 AND #3
World Health Organization International Clinical Trials Registry Platform Search Portal (apps.who.int/trialsearch/Default.aspx)	September 2016.	Title: (intermediate or large or multinodular) Condition: “hepatocellular carcinoma” or “primary liver cancer” or “liver cell cancer” or hepatoma
ClinicalTrials.gov	September 2016.	intermediate OR large OR multinodular Inter-ventional Studies “hepatocellular carcinoma” OR “primary liver cancer” OR “liver cell cancer” OR hepatoma Phase 2, 3, 4

Appendix 5. Sample size calculation

On average, 75% of people with intermediate-stage hepatocellular carcinoma are alive at 24 months (Bruix 1998). The required information size based on a control group proportion of 75%, a relative risk reduction of 20% in the intervention group, type I error of 5%, and type II error of 50% is 304 participants. Network analyses are more prone to the risk of random errors than direct comparisons (Del Re 2013). Accordingly, a greater sample size is required in indirect comparisons than direct comparisons (Thorlund 2012). The power and precision in indirect comparisons depends upon various factors, such as the number of participants included under each comparison and the heterogeneity between the trials (Thorlund 2012). If there is no heterogeneity across the trials, the sample size in indirect comparisons would be equivalent to the sample size in direct comparisons. The effective indirect sample size can be calculated using the number of participants included in each direct comparison (Thorlund 2012). For example, a sample size of 2500 participants in the direct comparison A versus C (n_{AC}) and a sample size of 7500 participants in the direct comparison B versus C (n_{BC}) results in an effective indirect sample size of 1876 participants. However, in the presence of heterogeneity within the comparisons, the sample size required is higher. In the above scenario, for an I^2 statistic for each of the comparisons A versus C (I_{AC}^2) and B versus C (I_{BC}^2) of 25%, the effective indirect sample size is 1407 participants. For an I^2 statistic for each of the comparisons A versus C and B versus C of 50%, the effective indirect sample size is 938 participants (Thorlund 2012). If there were only three groups and the sample size in the trials is more than the required information size, we planned to calculate the effective indirect sample size using the following generic formula (Thorlund 2012):

$$((n_{AC} \times (1 - I_{AC}^2)) \times (n_{BC} \times (1 - I_{BC}^2))) / ((n_{AC} \times (1 - I_{AC}^2)) + (n_{BC} \times (1 - I_{BC}^2))).$$

There is currently no method to calculate the effective indirect sample size for a network analysis involving more than three intervention groups.

CONTRIBUTIONS OF AUTHORS

AM, DR, and KG selected the studies and extracted data.

AM completed the characteristics of included and excluded studies tables.

KG wrote the review.

AM, DR, ET, BD, and DT critically commented on the review.

All review authors approved this version before publication.

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BD has no financial disclosures.

ET has participated in advisory boards for AstraZeneca and ViiV Healthcare.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- There was only one comparison. So we did not perform the network meta-analysis, and assessed the comparative benefits and harms of different interventions using standard Cochrane methodology. The methodology that we plan to use if we conduct a network meta-analysis in future is available in [Appendix 3](#).
- We performed Trial Sequential Analysis in addition to conventional method of assessing the risk of random errors using P-value.

NOTES

Considerable overlap is evident in the 'Methods' sections of this review and those of several other reviews written by the same group of authors.