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Cryotherapy for liver metastases (Review)

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[Intervention Review]

Cryotherapy for liver metastases

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ABSTRACT

Background

The liver is affected by two of the most common groups of malignant tumours: primary liver tumours and liver metastases from colorectal carcinoma. Liver metastases are significantly more common than primary liver cancer and long-term survival rates reported for patients after radical surgical treatment is approximately 50%. However, R0 resection (resection for cure) is not feasible in the majority of patients. Cryotherapy is performed with the use of an image-guided cryoprobe which delivers liquid nitrogen or argon gas to the tumour tissue. The subsequent process of freezing is associated with formation of ice crystals, which directly damage exposed tissue, including cancer cells.

Objectives

To assess the beneficial and harmful effects of cryotherapy compared with no intervention, other ablation methods, or systemic treatments in people with liver metastases.

Search methods

We searched The Cochrane Hepato-Biliary Group Controlled Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE Ovid, Embase Ovid, and six other databases up to June 2018.

Selection criteria

Randomised clinical trials assessing beneficial and harmful effects of cryotherapy and its comparators for liver metastases, irrespective of the location of the primary tumour.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. We extracted information on participant characteristics, interventions, study outcomes, and data on the outcomes important for our review, as well as information on the design and methodology of the trials. Two review authors independently assessed risk of bias in each study. One review author performed data extraction and a second review author checked entries.

Main results

We found no randomised clinical trials comparing cryotherapy versus no intervention or versus systemic treatments; however, we identified one randomised clinical trial comparing cryotherapy with conventional surgery. The trial was conducted in Ukraine. The trial included 123 participants with solitary, or multiple unilobar or bilobar liver metastases; 63 participants received cryotherapy and 60 received conventional surgery. There were 36 women and 87 men. The primary sites for the metastases were colon and rectum (66.6%), stomach (7.3%), breast (6.5%), skin (4.9%), ovaries (4.1%), uterus (3.3%), kidney (3.3%), intestines (1.6%), pancreas (1.6%), and unknown (0.8%). The trial was not reported sufficiently enough to assess the risk of bias of the randomisation process, allocation concealment, or presence of blinding. It was also not possible to assess incomplete outcome data and selective outcome reporting bias. The certainty of evidence was low because of risk of bias and imprecision.

The participants were followed for up to 10 years (minimum five months). The trial reported that the mortality at 10 years was 81% (51/63) in the cryotherapy group and 92% (55/60) in the conventional surgery group. The calculated by us relative risk (RR) with 95% Confidence Interval (CI) was: RR 0.88, 95% CI 0.77 to 1.02. We judged the evidence as low-certainty evidence. Regarding adverse events and complications, separately and in total, our calculation showed no evidence of a difference in recurrence of the malignancy in the liver: 86% (54/63) of the participants in the cryotherapy group and 95% (57/60) of the participants in the conventional surgery group developed a new malignancy (RR 0.90, 95% CI 0.80 to 1.01; low-certainty evidence). The frequency of reported complications was similar between the cryotherapy group and the conventional surgery group, except for postoperative pain. Both insignificant and pronounced pain were reported to be more common in the cryotherapy group while intense pain was reported to be more common in the conventional surgery group. However, the authors did not report whether there was any evidence of a difference. There were no intervention-related mortality or bile leakages.

We identified no evidence for health-related quality of life, cancer mortality, or time to progression of liver metastases. The study reported tumour response in terms of the carcinoembryonic antigen level in 69% of participants, and reported results in the form of a graph for 30% of participants. The carcinoembryonic antigen level was lower in the cryotherapy group, and decreased to normal values faster in comparison with the control group ($P < 0.05$).

Funding: the trial did not provide information on funding.

Authors' conclusions

The evidence for the effectiveness of cryotherapy versus conventional surgery in people with liver metastases is of low certainty. We are uncertain about our estimate and cannot determine whether cryotherapy compared with conventional surgery is beneficial or harmful. We found no evidence for the benefits or harms of cryotherapy compared with no intervention, or versus systemic treatments.

PLAIN LANGUAGE SUMMARY

Cryotherapy for liver metastases

Review question

Is cryotherapy (cooling) beneficial or harmful for local destruction of cancer (tumours) spread to the liver?

Background

When cancer spreads in the body (metastasis), one of the most common sites is the liver. Besides cancers of the liver (primary liver cancer), liver metastases from colorectal cancer are the most common cancer affecting the liver. More than half of people who have cancer spread to the liver die from complications. Cryotherapy is one of methods, used to destroy metastases in the liver. This method requires placing a special probe near the cancer site. The probe is used to deliver extreme cold to the site, which is produced by liquid nitrogen or argon gas. Placement of the probe can be guided using ultrasound or computed tomography (a special x-ray). The rapid freezing process kills the cancer cells, and the size of the cancer is reduced. However, it is not clear if this treatment prolongs life or increases quality of life of affected people.

We reviewed the evidence about the effect of cryotherapy in destroying cancer metastases in the liver. We searched for studies assessing the effect of cryotherapy in comparison with no treatment or any other treatment in people with liver metastases from cancer of any location. We aimed to assess the effect of cryotherapy on the risk of death, quality of life, and adverse events (side effects caused by the treatment).

Study characteristics

We last searched for evidence in June 2018. We included only one trial conducted in Ukraine, and participants' primary cancer was colorectal (bowel) cancer in 66% of instances, but there were also people with stomach, breast, skin, and other tumours. All of them had cancer spread to the liver. In this trial, 123 participants were allocated at random to receive either cryotherapy (63 people) or conventional surgery (affected parts of the liver were removed; 60 people).

Funding

Cryotherapy for liver metastases (Review)

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The trial did not provide information on funding.

Key results

The trial was at high risk of bias. The participants were followed for up to 10 years (minimum five months). The trial reported that the mortality at 10 years was 81% (51/63) in the cryotherapy group and 92% (55/60) in the conventional surgery group. We judged the evidence as low-certainty evidence. We found no evidence of a difference in proportion of participants with recurrence of the malignancy in the liver: 86% (54/63) of the participants in the cryotherapy group and 95% (57/60) of the participants in the conventional surgery group developed a new malignancy (low-certainty evidence). The frequency of reported complications was similar between the cryotherapy group and the conventional surgery group, except for postoperative pain. Both insignificant and pronounced pain were reported to be more common in the cryotherapy group while intense pain was reported to be more common in the conventional surgery group. However, it was not reported whether there was any evidence of a difference. The frequency of unwanted effects (adverse events or complications) was mostly similar in both groups, but pain intensity and frequency seemed to differ between the groups. There were no intervention-related mortality or bile leakages. The trial did not provide data on quality of life; cancer mortality, and time to progression of liver metastases.

Reliability of the evidence

The evidence for the effectiveness of cryotherapy versus conventional surgery in people with liver metastases is of low certainty. We are uncertain about our estimate and cannot determine whether cryotherapy compared with conventional surgery is beneficial or harmful. We found no evidence for the benefits or harms of cryotherapy compared with no intervention, or versus systemic treatments.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Cryotherapy for liver metastasis

Cryotherapy for liver metastasis

Patient or population: people with liver metastases

Settings: hospital

Intervention: cryotherapy

Comparison: conventional surgery

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Conventional surgery ^a	Cryotherapy ^b				
All-cause mortality Follow-up: 10 years	917 per 1000	807 per 1000 (706 to 935)	RR 0.88 (0.77 to 1.02)*	123 (1 RCT)	⊕⊕⊕⊖ Low ^{1,2}	—
Cancer mortality	Outcome not reported					
All adverse events and complications Follow-up: up to 10 years	Similar frequency of reported adverse events in both groups, except for postoperative pain (insignificant and pronounced pain reported to be more common in the cryotherapy group, intense pain reported to be more common in the control group), but no evidence of a difference reported and numbers of participants not reported. No intervention-related mortality and no bile leakage. Similar numbers of participants had uneventful postoperative course in both groups (RR 1.15, 95% CI 0.90 to 1.45).					
Health-related quality of life	Outcome not reported					
Recurrence of liver metastases Number of participants developing recurrences of liver metastases Follow-up: up to 10 years	950 per 1000	855 per 1000 (760 to 959)	RR 0.90 (0.80 to 1.01)	123 (1 RCT)	⊕⊕⊕⊖ Low ^{1,2}	—
Time to progression of liver metastases	Outcome not reported					

Tumour response measures

Measured in terms of the carcinoembryonic antigen level in 69% of participants, and the results in the form of a graph were reported for 30% of participants. The carcinoembryonic antigen level was lower in the cryotherapy group, and faster decreased to normal values in comparison with the control group ($P < 0.05$).

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

CI: confidence interval; **RR:** risk ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence

High certainty: further research is very unlikely to change our confidence in the estimate of effect.

Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low certainty: 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 certainty: we are very uncertain about the estimate.

^aConsisted of wedge resection of one of more metastases (40% of participants), anatomic lobectomy (28% of participants), right bisegmentectomy (5% of participants), right trisegmentectomy (3% of participants), extended left-sided lobectomy (2% of participants), and extended right-sided lobectomy (2% of participants), or only exploratory laparotomy (20% of participants).

^bConsisted of cryoexcision (46% of participants), cryoresection (32% of participants), and cryodestruction (22% of participants).

¹Downgraded one level because of risk of bias: the trial did not describe sequence generation, allocation concealment, and blinding. The reporting of outcome data was incomplete, and the information to assess 'selective reporting bias' was insufficient as the study protocol was not found.

²Downgraded one level because of imprecision due to low number of participants and low number of events, and confidence interval crossing the line of no effect.

BACKGROUND

Description of the condition

The liver is affected by two of the most common groups of malignant tumours: primary liver tumours and liver metastases from colorectal carcinoma (Chakedis 2017; Forner 2018). Primary liver tumours arise from malignant cells within the liver, and hepatocellular carcinoma represents the most common form of primary liver cancer (Forner 2018). Liver metastases are significantly more common than primary liver cancers (Bilchik 2000). Long-term survival rates reported for patients after radical surgical treatment is approximately 50%. However, R0 resection is not feasible in the majority of patients (Nordlinger 2013). Liver metastases commonly originate from cancers of the lung, stomach, colon and rectum, and endometrium (Hugh 1997). In 35% of people with colorectal cancer, liver metastases are found on preoperative imaging, and 8% to 30% will subsequently develop liver metastases (Hugh 1997). Colorectal cancer is the second most common cancer in Europe, and its prevalence is rising (Ferlay 2013). Globally, the age-adjusted annual incidence rate for colorectal cancer is 23.6 per 100,000 in men and 16.3 per 100,000 in women (GCO 2018). Very high incidence is observed in North America (age-adjusted 26.2 per 100,000), Australia and New Zealand (age-adjusted 36.7), northern Europe (age-adjusted 32.1), and western Europe (age-adjusted 28.8) (GCO 2018). Lower incidences are observed in Africa (age-adjusted from 6.4 in Western Africa to 13.4 in Southern Africa) and South-Central Asia (age-adjusted 4.9). Globally, age-adjusted mortality for colorectal cancer is 8.9 per 100,000; it is higher in the countries with a higher incidence, and lower in the countries with a lower incidence (GCO 2018). In 2013, approximately 414,000 men and 357,000 women globally died of colorectal cancer, making it the fourth cause of cancer death in men and the third in women (Global Burden of Disease Cancer Collaboration 2017). In the USA, approximately 51,370 Americans die of colorectal cancer each year, accounting for approximately 9% of all cancer deaths (Jemal 2010). In the USA, five-year survival after the diagnosis of colorectal cancer is 64.5% (Noone 2018). In all high-income countries analysed together, the estimated survival was 55% (Parkin 2005), while in low and middle income countries analysed together it was 39% (Parkin 2005), with the lowest rate reported for Sub-Saharan Africa (13% for male and 14% for female). In Europe, relative survival rate for five years was 57% for colon cancer and 56% for rectum cancer (Holleczek 2015). Although there has been an improvement in long-term survival since the 2000s, according to CONCORD-3 analysis, there are still significant disparities in colorectal cancer treatment outcomes worldwide (CONCORD-3).

Globally, lung cancer has been the most common cancer in the world. For lung cancer, the age-standardised incidence rate is 22.5 per 100,000 people and mortality rate is 18.6 per 100,000 people of both sexes and the highest estimated age-standardised incidence rates are observed in Polynesia (38.1 per 100,000) (GCO 2018). Lung cancer is the most common cause of death from cancer worldwide; every fifth cancer patient dies from lung cancer (1.76 million deaths, 18.4% of the total) (GCO 2018). In all high-income countries analysed together, estimated survival after the diagnosis of lung cancer is 12% in men and women (Torre 2016).

Endometrial cancer is the most common gynaecological malignancy mostly affecting women in the postmenopausal age group. Diagnoses of endometrial cancer have increased worldwide in recent years (Siegel 2016). For instance, in 2016 an estimated

60,050 women were diagnosed with this type of cancer in the USA, with an estimated 10,470 deaths related to the disease. It accounts for 26.0 new cases per 100,000 women per year and 4.6 deaths per 100,000 women per year (SEER). For uterine cancer, 66.9% are diagnosed at the local stage. However, in one third of women, lymph node or distant metastases are present. The five-year relative survival rate in women with distant metastases is 16% (SEER).

Although the incidence has declined over the last decades, almost 0.8 million new patients with stomach cancer were estimated to have occurred in 2018 (GCO 2018). Standardised incidence rates are higher in men than in women, ranging from 4.7 in Eastern Africa to 32.1 in Eastern Asia per 100,000 men, and from 4.0 in Eastern Africa to 13.2 in Eastern Asia per 100,000 women (GCO 2018). Thanks to improvements in surgical techniques, radiotherapy, and introduction of neoadjuvant therapy regimens, overall survival after gastric cancer treatment has improved over the last two decades (Song 2017).

For people with liver metastases, surgical resection may cure the disease, but only limited number of them qualify for resection (Bilchik 2000; Bipat 2007). Other options for people with unresectable liver metastases include chemotherapy delivered intra-arterially (5-fluorouracil), called 'regional chemotherapy'; systemic chemotherapy (5-fluorouracil, irinotecan, oxaliplatin, leucovorin, capecitabine); or monoclonal antibodies (such as bevacizumab or cetuximab) (Riemsma 2009). Additional methods include local tumour ablative techniques, transarterial (chemo)embolisation, percutaneous ethanol injection, microwave coagulation, laser-induced thermotherapy, radiofrequency ablation, and cryosurgical ablation (Riemsma 2009).

Description of the intervention

For people who cannot undergo surgical resection of the liver due to extent of the disease (unresectable liver metastases), local tumour ablative techniques were developed which use various types of energy to destroy cancer lesions (Bilchik 2000; Mala 2006). One of them is cryotherapy (also called cryosurgery, cryoablation, or cryosurgical ablation) and can be performed percutaneously, laparoscopically, or during open surgery (Mala 2006). It involves destruction of tumour cells by freezing them (Baust 2014).

How the intervention might work

Cryotherapy is performed using an image-guided cryoprobe which delivers liquid nitrogen or argon gas to the tumour tissue (Mala 2006; Baust 2014). Freezing is associated with formation of ice crystals, which directly damage cells, including cancer cells. Then the tumour is thawed, and the procedure is repeated (Mala 2006; Baust 2014). Cryolesion, which is an effect of the procedure, is characterised by central necrosis surrounded by tissue in the process of inflammation and peripheral zone, in which cells are not fully damaged (Mala 2006; Baust 2014). Freezing also causes damage to the microvascular system supplying the tumour through damage to endothelium – it may result in oedema, inflammation, and thrombosis (Mala 2006; Baust 2014).

Why it is important to do this review

In people with liver metastases, local or regional treatment methods can provide local control, but it is uncertain what the long-term outcomes of some of these therapies are. Systematic

reviews may help to establish the effectiveness of interventions, and the trade-off between the benefits and harms associated with different non-surgical ablation methods for the treatment of all forms of malignant liver tumours (primary and metastatic). Systematic reviews published so far focus mostly on primary liver tumours or colorectal cancer liver metastases and include studies up to April 2006 (Llovet 2003; Decadt 2004; Lopez 2006; Marlow 2006; Sutherland 2006). There is one Cochrane Review entitled 'Resection versus no intervention or other surgical interventions for colorectal cancer liver metastases' (Fedorowicz 2008), which includes one trial comparing conventional surgery and cryogenic surgery. However, there is no review comparing cryotherapy with either no intervention, other ablation methods, or systemic treatments in people with liver metastases from any primary site. A review published in 2011 aimed at assessing the long-term outcomes and complications of various ablative therapies used in the management of people with liver metastases of colorectal cancer (Pathak 2011). It included 26 studies on cryotherapy and one of them was the randomised trial included in our review. However, the authors analysed the data for the cohort of people receiving cryotherapy without taking into account the comparison with surgical resection. We expected to find further randomised trials for inclusion in our review update.

OBJECTIVES

To assess the beneficial and harmful effects of cryotherapy compared with no intervention, other ablation methods, or systemic treatments in people with liver metastases.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised clinical trials assessing the beneficial and harmful effects of cryotherapy and its comparators, irrespective of publication status, language, or blinding. By choosing this strategy, we were aware that we put more focus on potential benefits and may have overlooked late occurring or rare harms which are often missed in randomised clinical trials (Storebø 2018). If we demonstrated benefits from using cryotherapy in people with liver metastasis, then a systematic review of adverse events of cryotherapy in people with liver metastasis ought to be launched (Storebø 2018). However, we considered quasi-randomised and other controlled studies, identified in the search results and if relevant to the review topic, only for the reporting of data on harm.

Types of participants

People with liver metastases, no matter the location of the primary tumour.

Types of interventions

Experimental intervention

Cryotherapy.

Control intervention

No intervention, other ablation methods (such as ablation with ethanol, microwave, radiofrequency, photocoagulation with laser, chemoembolisation, radioembolisation, and embolisation), or

systemic treatments (such as chemotherapy, immunotherapy, and radiotherapy).

Cointerventions were allowed if provided equally to the experimental and control groups of the individual randomised trial.

Types of outcome measures

Primary outcomes

- All-cause mortality at last follow-up, and time to mortality (counted from the start of treatment).
- Cancer mortality.
- All adverse events and complications, separately and in total. The International Conference on Harmonisation (ICH) Guidelines defined adverse events as serious and non-serious (ICH-GCP 1997). A serious fatal or non-fatal adverse event was any event that led to death, was life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability, and any important medical event which may have jeopardised the person or required intervention to prevent it. All other adverse events were considered non-serious.

Secondary outcomes

- Health-related quality of life.
- Participants with failure to clear liver metastases or recurrence of liver metastases.
- Time to progression of liver metastases.
- Tumour response measures (complete response, partial response, stable disease, disease progression).

The outcomes were analysed at the last follow-up.

Search methods for identification of studies

Electronic searches

We searched The Cochrane Hepato-Biliary Group Controlled Trials Register (maintained and searched internally by the CHBG Information Specialist via the Cochrane Register of Studies Web; June 2018), Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (2018, Issue 5), MEDLINE Ovid (1946 to June 2018), Embase Ovid (1974 to June 2018), LILACS (Bireme; 1982 to June 2018), Science Citation Index Expanded (Web of Science; 1900 to June 2018), Conference Proceedings Citation Index – Science (Web of Science; 1990 to June 2018), and CINAHL (EBSCOhost; 1981 to June 2018) (Royle 2003). We also searched the World Health Organization (WHO) International Clinical Trials Registry Platform (WHO 2018) (search date 21 June 2018). For this update, we also searched clinicaltrials.gov (search date 16 February 2019).

Originally, one global search was used for all non-surgical ablation methods for primary malignant liver tumours and liver metastases. These search strategies with the time spans of the searches are given in [Appendix 1](#). Individual search strategies were performed for the updated searches. These strategies with the time spans of the searches are presented in [Appendix 2](#).

In addition, we assessed all US Food and Drug Administration (FDA) approvals and investigational device exemptions for inclusion as found on www.fda.gov/ (last search 22 June 2018) (keywords

used: cryotherapy, cryoablation, cryosurgery, cryotechnology, cryoextirpation, cryoresection, cryodestruction, ablation).

Searching other resources

For additional relevant studies, we searched reference lists of reviews (such as [Schwartz 2004](#) and [Lopez 2006](#)), Health Technology Assessment (HTA) reports (such as [Marlow 2006](#)), all Cochrane Reviews, and the trial that we included.

Data collection and analysis

Selection of studies

Two review authors in pairs (RR, RW, JWM, MP, DS, MJS, and MMB) independently evaluated titles and abstracts of the retrieved search results with references. We resolved any differences in opinion by discussion or, if necessary, by consulting a third review author (JK, RR, RW, or MMB). For titles and abstracts that were of potential relevance to our review, we retrieved full papers. Two review authors in pairs (RR, RW, JWM, MP, DS, MJS, and MMB) independently assessed these papers, and we resolved the differences in opinion, if any.

Data extraction and management

We extracted available relevant information on PICOT (participant characteristics, interventions, comparisons, study outcomes, and time of follow-up) as well as other trial data that we needed, including information on the design and methodology of the trials. We used a data extraction form, previously developed for another review on non-surgical ablation methods. RR, MMB, MJS, JWM, MP, DS, or RW extracted data from the retrieved study publications and added study information to either included or excluded studies. Another review author (RW, JWM, MP, DS, or MJS) checked all extracted data. Two review authors (MMB, RR) performed the quality assessment of the trial independently.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias of the included trial (MMB, RR), based on the domains described below ([Schulz 1995](#); [Moher 1998](#); [Kjaergaard 2001](#); [Gluud 2008](#); [Wood 2008](#); [Higgins 2011](#); [Savović 2012a](#); [Savović 2012b](#); [Hrobjartsson 2013](#); [Hrobjartsson 2014a](#); [Hrobjartsson 2014b](#); [Savović 2018](#)).

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 planned to only include 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 planned to only include such studies for assessment of harms.

Blinding of participants and personnel

- Low risk of bias: either of the following: no blinding or incomplete blinding, but the review authors judged that the outcome was unlikely to have been 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: either 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: either of the following: no blinding or incomplete blinding, and the outcome was likely to have been 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 have been influenced by lack of blinding.

Blinded outcome assessment

- Low risk of bias: either 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: either 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: either 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: all-cause mortality, adverse events, and failure to clear liver metastases or recurrence of liver metastases. If the original trial protocol was available, the outcomes were 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, we did not consider those outcomes to be reliable.

- Unclear risk of bias: the study authors did not report all predefined outcomes fully, or it was unclear whether the study authors recorded data on these outcomes or not.
- High risk of bias: the study authors did not report one or more predefined outcomes.

Other bias

- Low risk of bias: the trial appeared free of other factors that could have put it at risk of bias.
- Unclear risk of bias: the trial may or may not have been free of other factors that could have put it at risk of bias.
- High risk of bias: there were other factors in the trial that could have put it at risk of bias.

We judged a trial to be at an overall low risk of bias if assessed as having a low risk of bias in all the above domains. We judged a trial to be at a high overall risk of bias if assessed as having an unclear or high risk of bias in one or more of the above domains. We resolved any differences in opinion through discussion, and in the case of unsettled disagreements, a third review author adjudicated (JK, RR, RW, or MMB).

Measures of treatment effect

For dichotomous variables, we planned to calculate the relative risk (RR) with 95% confidence interval (CI). For continuous variables, we planned to calculate the standardised mean difference (for outcomes such as quality of life when different scales could be used) with 95% CI. For outcomes such as hazard ratio for death, we planned to use the generic inverse variance method for the meta-analysis. We planned to calculate pooled estimates using the random-effects model (DerSimonian 1986) and the fixed-effect model (Mantel 1959; Greenland 1985). We planned to present both results if there were discrepancies in the results. If not, we planned to report the random-effects model. We planned to measure the quantity of heterogeneity using the I^2 statistic (Higgins 2011). However, we could not follow our plan completely as we identified only one trial for inclusion in our review.

Dealing with missing data

We analysed data using the intention-to-treat principle, that is, we included in the analysis the total number of randomised participants.

Assessment of heterogeneity

We planned to check if the included trials were similar enough to combine their results before commencing statistical pooling of the data. We planned to assess heterogeneity using the χ^2 and I^2 statistic methods (Higgins 2011). We planned to discuss any plausible, possible causes of heterogeneity.

Data synthesis

We followed the instructions given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and we planned to use Review Manager 5 for the analyses (Review Manager 2014).

As only one trial fulfilled the review inclusion criteria, we presented the results in a narrative way. We planned to calculate the relevant measures of effect of the included trial, that is, hazard ratios and risk ratios. Whenever possible, we planned to calculate hazard ratios using the methods described by Parmar and Tierney (Parmar 1998). We planned to extract information on, for example, hazard rates, P values, events, ratios, curve data, and information on follow-up, from the publications to enter them into a Microsoft Office Excel 2003 spreadsheet in order to calculate log hazard ratios and their standard errors (Thierney 2007). As we identified only one trial, meta-analyses and statistical methods were not possible. If data could not be meta-analysed statistically, for example in the case of extreme heterogeneity, we planned to present results in a forest plot, without the estimate, in order to show the variance of the effects (Egger 1997). We planned to include cross-over trials, if identified, using the results of the first period only (before cross-over), as if they were parallel trials. In cases without heterogeneity but yet with meta-analysis not being possible, we planned to present the results in a narrative way, including text, tables, and figures to summarise the data and to allow the reader to judge the results based on the differences and similarities of the included trials and their risk of bias assessment. We planned to group the trials by intervention, participant characteristics, and outcomes, and to describe the most important characteristics of the trials including a detailed review of the methodological shortcomings of a trial.

We planned to use funnel plots to identify any possible small-trial biases, such as publication bias (Egger 1997). Furthermore, we planned to discuss the possible implications of our findings if bias was present. None of this was possible due to lack of data.

Where possible, we planned to examine apparent significant beneficial and harmful intervention effects with Trial Sequential Analysis (Thorlund 2011; TSA 2011; Wetterslev 2017) in order to evaluate if these apparent effects could have been caused by random error ('play of chance') (Brok 2008; Wetterslev 2008; Brok 2009; Thorlund 2009; Wetterslev 2009; Thorlund 2010; Wetterslev 2017). We did not carry out such analysis as only one trial was included.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses, where possible, based on prognostic indicators such as age, sex, tumour size, location of primary tumour, and use of any cointerventions. We also planned to do subgroup analysis with low risk of bias versus high risk of bias studies as defined in the [Risk of bias in included studies](#) section.

Sensitivity analysis

We planned to summarise the separate outcomes after intervention at six months or less, six to 12 months, and one year or more. However, we lacked data for sensitivity analyses.

'Summary of findings' tables

We used the GRADE system to evaluate the certainty of the evidence of our primary (all-cause mortality; cancer mortality; all adverse events and complications) and secondary outcomes (health-related quality of life; participants with failure to clear liver metastases or recurrence of liver metastases; time to progression of liver metastases; tumour response measures) (GRADEpro GDT). We considered the within-study risk of bias (methodological

quality) based on individual domains as well as the overall assessment, indirectness of evidence (population, intervention, control, outcomes), unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses); imprecision of effect estimate, and risk of publication bias ([GRADEpro GDT](#)). We defined the levels of certainty in the evidence as 'high', 'moderate', 'low', or 'very low'.

- **High certainty:** further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate certainty:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low certainty:** 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 certainty:** we are very uncertain about the estimate.

RESULTS

Description of studies

See: [Characteristics of included studies](#) table.

Results of the search

Up to 2017, we carried out the searches for this review as global search for a full review of non-surgical ablation methods in people with liver metastases or primary malignant liver tumours ([Riemsma 2009](#)), and the search produced 13,409 references. After excluding duplicates, we screened 13,382 references. Based on titles and abstracts, we found 13,047 references irrelevant for the current review, resulting in 335 full papers to be retrieved. We found one trial that met the inclusion criteria for the present review ([Korpan 1997](#)). We excluded 334 references because they were not randomised clinical trials (150), they examined another intervention not relevant for this review (141), the population was not relevant for this review (29), the comparison was not relevant for this review (13), and authors examined outcomes not relevant for this review (one). We identified no ongoing trials.

Since we did not run separate searches for non-randomised studies, we only checked the eligibility of the studies which came up with searches for randomised studies and none of these studies was eligible for inclusion.

Summary of the searches is provided in [Figure 1](#).

Figure 1. Flow chart of identification of randomised trials for inclusion in the first published review version. RCT: randomised clinical trial.

When updating the search in June 2018, we found 615 new references, and after removing the duplicates, we screened 460 references. We retrieved seven full-text publications, but we excluded them because of study design (four were not randomised clinical trials); the population was not relevant for this review (one trial); the examined intervention was not relevant for this review

(one trial); and the comparison was not relevant for this review (one trial).

We identified no new trials within the updated searches (Figure 2). We identified no ongoing trials with control groups on the WHO platform (WHO 2018) and the clinicaltrials.gov/ either.

Figure 2. Flow chart of identification of randomised trials for inclusion in the current review.

Figure 2. (Continued)

Included studies

We included one randomised trial comparing two groups: cryotherapy and conventional surgery ([Korpan 1997](#)). The trial included 123 consecutive people with solitary, or multiple unilobar, or bilobar liver metastases. Sixty-three participants received cryotherapy, and the procedures included cryoexcirpation (46% of participants), cryoresection (32% of participants), and cryodestruction (22% of participants).

Hepatic cryoresection used a self-constructed cryogenic clamp or cryoscalpel, and the margin of the resection was preliminarily frozen using cryosurgical systems, while cryoexcirpation and cryodestruction used 5, 10, 15, 20, 35, 45, or 55 mm in diameter probes of roughly disc design with two or three cycles for each lesion.

Sixty participants received conventional surgery, and the procedures included wedge resection of metastases (40% of participants), anatomic lobectomy (28% of participants), right bisegmentectomy (5% of participants), right trisegmentectomy (3% of participants), extended left-sided lobectomy (2% of participants), and extended right-sided lobectomy (2% of participants). Twenty per cent of the participants had only an exploratory laparotomy.

The trial included 36 women and 87 men. The primary sites for the metastases were: colon and rectum (66.6%; 16% Duke scale A, 35%

B, 49% C), stomach (7.3%), breast (6.5%), skin (melanoma; 4.9%), ovary (ovarian adenocarcinoma; 4.1%), uterus (3.3%), kidney (3.3%), intestines (1.6%), pancreas (1.6%), and unknown (0.8%). The diagnosis was confirmed by histological assessment. Mean age was 41.3 years and symptoms were present in 21% of the participants. The mean size of the tumour was 3.1 cm. Thirty per cent of the participants had one metastasis, 37% had two metastases, and the remaining 33% had three or more metastases. The participants were followed up to 10 years (minimum five months in the conventional surgery group, six months in the cryotherapy group).

Funding: the trial did not provide information on funding.

Excluded studies

We excluded studies mainly because of their study design, interventions, and population which did not fulfil the inclusion criteria of our review (see [Characteristics of excluded studies](#)).

Regarding report of harm, we found no study that contained data on harm of relevance to this review.

Risk of bias in included studies

Overall, we assessed the risk of bias of the included trial as high. For an overview of the methodological quality of the included trial, see [Figure 3](#) and [Figure 4](#).

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): Pain	Blinding of participants and personnel (performance bias): Objective outcomes	Blinding of outcome assessment (detection bias): Objective outcomes	Blinding of outcome assessment (detection bias): Pain	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Korpan 1997	?	?	?	+	+	?	?	?	?

Figure 4. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Allocation

Trial participants were stratified according to age, sex, disease, primary lesions, metastatic liver tumours, and disease-free interval. However, there was no information to assess sequence generation or allocation concealment (unclear risk of bias).

Blinding

The study did not provide information about blinding.

We judged that for subjective outcomes such as pain, lack of blinding might have influenced the results. However, it is unlikely that the lack of blinding would have influenced the objective outcomes: mortality, recurrence of liver metastasis, tumour response, and complications.

Incomplete outcome data

There was insufficient information to assess whether there were any missing data in the trial as patient flow was not described. The trial provided only the number of participants with an outcome analysed (unclear risk of bias).

Selective reporting

There was insufficient information to assess whether there was selective reporting as no protocol was available (unclear risk of bias).

Other potential sources of bias

It was not possible to assess whether the trial was free of other bias (unclear risk of bias).

Effects of interventions

See: [Summary of findings for the main comparison Cryotherapy for liver metastasis](#)

One trial compared cryotherapy versus conventional surgery (123 participants; [Summary of findings for the main comparison](#)).

Primary outcomes

All-cause mortality at last follow-up

The trial reported that the mortality at 10 years was 81% (51/63) in the cryotherapy group and 92% (55/60) in the conventional surgery group (RR 0.88, 95% CI 0.77 to 1.02; low-certainty evidence) (our calculation using the Review Manager calculator). As this was based on only one trial, and given that the number of events was high, we checked the result using Fisher's exact test which produced a two-sided P value of 0.117, confirming no evidence of a difference (Fisher 1922).

The study reported survival after 3, 5, and 10 years. On the basis of the provided information on the number of participants surviving, we calculated mortality (3 years: 40% in the cryotherapy group versus 49% in the conventional surgery group; 5 years: 56% in the cryotherapy group versus 64% in the conventional surgery group; 10 years: 81% in the cryotherapy group versus 92% in the conventional surgery group).

The trial did not report time to mortality.

Cancer mortality

The trial did not report cancer mortality.

All adverse events and complications, separately and in total

The frequency of reported adverse events was similar between the cryotherapy and the conventional surgery groups, except for postoperative pain. Both insignificant and pronounced pain was more common in the cryotherapy group while intense pain was more common in the control group. The authors did not report evidence of a difference regarding pain and they did not provide numbers of trial participants. There was no intervention-related mortality or bile leakage. Other reported complications are described in [Table 1](#). There were similar numbers of participants with uneventful postoperative course in both groups (47 (75%) in the cryotherapy group versus 39 (65%) in the conventional surgery group).

group; RR calculated using Review Manager 5 calculator 1.15, 95% CI 0.90 to 1.45).

Secondary outcomes

Health-related quality of life

The trial did not report quality of life.

Participants with failure to clear liver metastases or recurrence of liver metastases

The trial reported recurrence rates during follow-up of up to 10 years. Recurrence in the liver occurred in 54/63 (86%) participants in the cryotherapy group and 57/60 (95%) participants in the conventional surgery group (RR calculated using Review Manager 5 calculator 0.90, 95% CI 0.80 to 1.01; low-certainty evidence). As this was based on only one trial, and given that the number of events was high, we checked the result using Fisher's exact test which produced a two-sided P value of 0.1274, confirming that there was no evidence of difference (Fisher 1922).

Time to progression of liver metastasis

The trial did not report time to progression of liver metastasis.

Tumour response measures (complete response, partial response, stable disease, disease progression)

The trial measured tumour response in terms of the carcinoembryonic antigen level in 69% of participants, and presented the results in the form of a graph for 30% of participants. The carcinoembryonic antigen level was lower in the cryotherapy group and decreased faster to normal values in comparison with the control group ($P < 0.05$).

Certainty of the evidence

We created a 'Summary of findings' table for all the primary and secondary outcomes reported in the review. We assessed the evidence as at low certainty because of the risk of bias in the trial (downgraded one level for within study risk of bias) and imprecision (downgraded one level for small sample size and wide CIs including benefit and harm). We could not assess indirectness, heterogeneity, or publication bias since there was only one included trial (Summary of findings for the main comparison).

DISCUSSION

Summary of main results

On the basis of one randomised clinical trial at high risk of bias, cryotherapy compared with conventional surgery showed no evidence of difference in terms of people's survival or recurrence of liver metastases from various primary sites. We found no trials assessing cryotherapy compared to no intervention.

Overall completeness and applicability of evidence

The search strategy was very wide as it was designed for all non-surgical ablation interventions. Additionally, by searching the reference lists of the included trial and by checking recent review articles, we made sure that no relevant studies were overlooked.

Quality of the evidence

The trial did not provide sufficient details to judge the quality of the randomisation process, allocation concealment, or presence of blinding. It was also not possible to assess incomplete outcome data and selective outcome reporting bias. Therefore, the main limitation of this review was the certainty of the available evidence, which was low, due to concerns regarding risk of bias (downgraded one level for all outcomes) and due to imprecision – small sample size and wide CIs including both benefit and harm (downgraded one level).

Analyses with Trial Sequential Analysis (Thorlund 2011; TSA 2011; Wetterslev 2017) have shown that apparent significant beneficial and harmful intervention effects may in fact have been caused by random error ('play of chance') (Brok 2008; Wetterslev 2008; Brok 2009; Thorlund 2009; Wetterslev 2009; Thorlund 2010; Wetterslev 2017). This was not formally assessed in this review. Accordingly, any significant results, had they been found, need to be interpreted with caution because some of the results may have been caused by random error.

Potential biases in the review process

The process of the review was rigorous. The review was preceded by a peer reviewed and published protocol in which all review methods were described and followed during the review preparation. All of us, the review authors, were trained and experienced in review preparation. We extracted all relevant for the review data which we subsequently rechecked in order to ensure the reliability of the review results. We performed comprehensive searches for published and unpublished studies. However, because only one trial was found, we may suspect publication bias which we cannot assess formally because the minimum number for assessment of publication bias is 10 trials (Higgins 2011). An important issue is also the reporting bias because the identified and included trial lacked a protocol (Chan 2004).

Agreements and disagreements with other studies or reviews

Five reviews assessed the efficacy of cryotherapy for colorectal cancer liver metastases. A National Institute for Health and Care Excellence (NICE) guidance, based on a review of evidence (using the same randomised clinical trial plus two non-randomised studies), and which we assessed to be of inadequate quality, recommended cryotherapy for the treatment of liver metastases only in exceptional circumstances (such as consent and audit or research) (NICE 2010). One Cochrane Review assessed the effects of surgical resection of colorectal cancer liver metastases in comparison with no intervention or other surgical interventions (Fedorowicz 2008). It included the same randomised trial as our review, and the authors concluded that there is limited evidence to support the use of single surgical or non-surgical approaches for the management of people with liver metastases of colorectal cancer. Two other systematic reviews on all ablative methods or only on cryotherapy were identified with the literature searches. One of them, published in 1997, aimed to compare hepatic cryosurgery and surgical resection in people with liver metastases of colorectal cancer with regard to long-term survival. It included 13 studies, all of which were case series (Tandan 1997). The authors concluded that in people with resectable liver metastases from colorectal cancer, cryosurgery may offer some

advantages over surgical resection; however, current evidence does not support the use of this intervention outside clinical trials. The review was published before the randomised trial included in our review was published. Another review, published in 2011, aimed to assess the long-term effects of various ablative therapies, which are used in the management of people with liver metastases of colorectal cancer (Pathak 2011). It included 26 studies on cryotherapy and one of them was the randomised trial included in our review. However, the authors analysed the data for the cohort of people receiving cryotherapy without a comparison with surgical resection. Wu 2015 aimed to assess efficacy of cryotherapy compared with radiofrequency ablation in people with all types of liver malignancies. Wu 2015 included seven studies, one randomised clinical trial and six non-randomised clinical trials, enrolling people with hepatocellular carcinoma or liver metastases, and all study data were meta-analysed together. They concluded that those two methods have similar effects for mortality and local tumour progression, but cryotherapy has higher risk of complications. The authors also concluded that further properly designed randomised clinical trials with large sample size are warranted.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence for the effectiveness of cryotherapy compared with conventional surgery in people with liver metastases relies on one randomised clinical trial with a high risk of bias. Our confidence in the results is limited due to the risk of bias and imprecision, and therefore, it cannot be determined whether cryotherapy compared with conventional surgery is either beneficial or harmful. Further studies are likely to change our confidence and the results. We found no evidence for any benefits or harms of cryotherapy compared with no intervention, or versus systemic treatments.

Implications for research

There is a need for further randomised clinical trials of cryotherapy versus no intervention, other ablation methods, or systemic treatments in people with liver metastases. These trials should be large enough to assess major clinical outcomes such as all-cause mortality, adverse events, and quality of life. To ensure appropriate study samples, multicentre trials are likely to be required. The trials ought to be conducted in a way ensuring low risk of random errors and low risk of systematic error (bias), designed according to the SPIRIT statement (SPIRIT 2013a; SPIRIT 2013b), and reported according to the CONSORT Statement (www.consort-statement.org).

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Korpan 1997

Methods	<p>Study type: randomised clinical trial</p> <p>Location: Ukraine, single centre, University hospital</p> <p>Time frame: 1983 to 1992</p> <p>Inclusion criteria: consecutive patients with single or multiple hepatic metastases in 1 lobe or both lobes of the liver. The diagnosis was confirmed by histological assessment.</p> <p>Follow-up: up to 10 years</p>
Participants	<p>Total number of participants: 123</p> <p>Primary sites:</p> <ul style="list-style-type: none"> • colorectal 82 (66%; in Dukes scale: A (16%), B (35%), C (49%)); • stomach 9 (7.3%); • breast 8 (6.5%); • skin 6 (4.9%); • ovarian adenocarcinoma 5 (4.1%);

Cryotherapy for liver metastases (Review)

Korpan 1997 (Continued)

- uterus 4 (3.3%);
- kidney 4 (3.3%);
- intestines 2 (1.6%);
- pancreas 2 (1.6%);
- unknown 1 (0.8%).

Number of metastases in the liver lobes:

- multiple unilobar 47 (38%);
- multiple bilobar 39 (32%);
- solitary 37 (30%).

Mean size of the tumour: 3.1 cm

- number of tumours < 3 cm 81;
- number of tumours > 3 cm 42.

Number of tumours, number of participants (%):

- 1 metastasis 37 (30%);
- 2 metastases 46 (37%);
- ≥ 3 metastases 40 (33%).

Mean age: 41.3 (SD 12.1) years

Men: 71% (87 men, 36 women)

Symptoms: 21%

Interventions	<p>2 treatment groups</p> <p>Group 1: cryotherapy (63 participants)</p> <p>Group 2: conventional surgery without cryotechnology (60 participants)</p> <p>Cryotherapy included: cryoextirpation (46%), cryoresection (32%), cryodestruction (22%)</p> <p>Conventional surgery included: wedge resection of metastases (40%), anatomic lobectomy (28%), right bisegmentectomy (5%), right trisegmentectomy (3%), extended left-sided lobectomy (2%), extended right-sided lobectomy (2%), and exploratory laparotomy (20%)</p> <p>Treatment following the intervention: systemic chemotherapy (5-fluorouracil 12 mg/kg and 500 mL 0.9% NaCl or 5% glucose, once a week, for 6 weeks)</p>
Outcomes	<p>Number of deaths after 10 years</p> <p>3-, 5-, 10-year survival</p> <p>Disease-free survival rate</p> <p>Failure or recurrence rates</p> <p>Tumour response measures (carcinoembryonic antigen level)</p> <p>Adverse events or complications (intervention-related mortality, systemic infection (pneumonia), wound infection, pleural effusion, fever, pain, intervention-related bleeding, other (Intensive care unit treatment, subphrenic abscess))</p>
Notes	
Risk of bias	

Korpan 1997 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were stratified and randomised into 2 treatment groups. Stratification was according to age, sex, disease, primary lesions, metastatic liver tumours, and disease-free interval.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) Pain	Unclear risk	Not described. For subjective outcomes such as pain, lack of blinding may have influenced the results.
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Not described. For objective outcomes such as mortality, recurrence, tumour response, and complications, lack of blinding was unlikely to influence the outcomes.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Not described. For subjective outcome such as pain, lack of blinding may have influenced the results.
Blinding of outcome assessment (detection bias) Pain	Unclear risk	Not described. For objective outcomes such as mortality, recurrence, tumour response, and complications, lack of blinding was unlikely to influence the outcomes.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No participant flow was described; however, it appeared as if all included participants were analysed.
Selective reporting (reporting bias)	Unclear risk	Insufficient information, as no protocol was available.
Other bias	Unclear risk	Insufficient information

SD: standard deviation

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Agarwala 2004	Irrelevant for the review intervention
Akinwande 2014	Not a randomised clinical trial
Akinwande 2015	Not a randomised clinical trial
Alberts 2007	Not a randomised clinical trial
Allen-Mersh 1994	Irrelevant for the review intervention
Allen-Mersh 2000	Irrelevant for the review intervention
An 1993	Not a randomised clinical trial

Study	Reason for exclusion
Andersson 1989	Pharmacokinetic study
Aoki 1991	Not a randomised clinical trial
Aprile 2015	Not a randomised clinical trial
Arai 1990	Irrelevant for the review intervention
Arciero 2008	Not a randomised clinical trial
Arita 2005	Irrelevant for the review intervention
Asahara 1998	Not a randomised clinical trial
Avey 2008	Not a randomised clinical trial
Bacher 2002	Irrelevant for the review intervention
Baldwin 2002	Not a randomised clinical trial
Beger 1991	Not a randomised clinical trial
Bengmark 1983	Not a randomised clinical trial
Bergsland 2000	Irrelevant for the review population
Brown 2009	Not a randomised clinical trial
Bushnell 2003	Not a randomised clinical trial
Campos 1993	Not a randomised clinical trial
Cao 2012	Not a randomised clinical trial
Cao 2014	Irrelevant for the review intervention
Cascinu 1998	Not a randomised clinical trial
Chang 1987	Irrelevant for the review intervention
Chen 2001	Not a randomised clinical trial
Chen 2002	Irrelevant for the review intervention
Chen 2004	Irrelevant for the review intervention
Chen 2008	Irrelevant for the review population
Cheng 2001	Not a randomised clinical trial
Civalleri 1986	Not a randomised clinical trial
Civalleri 1996	Not a randomised clinical trial
Civalleri 1997	Not a randomised clinical trial

Study	Reason for exclusion
Correa-Gallego 2014	Not a randomised clinical trial
Cortesi 1994a	Irrelevant for the review intervention
Cortesi 1994b	Irrelevant for the review intervention
Cosimelli 1990	Irrelevant for the review intervention
Cosimelli 1991	Irrelevant for the review intervention
Cosimelli 1996	Irrelevant for the review intervention
Cosimelli 2010	Not a randomised clinical trial
Cui 2003	Irrelevant for the review population
D'Orazio 2002	Irrelevant for the review intervention
Dalla 1997	Irrelevant for the review intervention
Daly 1985	Not a randomised clinical trial
Daly 1987	Irrelevant for the review intervention
De Baere 2010	Not a randomised clinical trial
Debaere 2010	Not a randomised clinical trial
Deleporte 2010	Not a randomised clinical trial
Ding 2013	Not a randomised clinical trial
Du 2002	Irrelevant for the review population
Du 2016	Irrelevant for the review intervention
Dudeck 2011	Irrelevant for the review comparison
Earlam 1997	Irrelevant for the review intervention
Endoh 1987	Not a randomised clinical trial
Engelman 2014	Not a randomised clinical trial
Eschelman 2011	Irrelevant for the review intervention
Fahy 2006	Not a randomised clinical trial
Falcone 2007	Irrelevant for the review intervention
Fiorentini 1994	Irrelevant for the review intervention
Fiorentini 2004	Irrelevant for the review intervention
Fiorentini 2006	Irrelevant for the review intervention

Study	Reason for exclusion
Fiorentini 2010a	Irrelevant for the review intervention
Fiorentini 2010b	Irrelevant for the review intervention
Fiorentini 2011	Irrelevant for the review intervention
Fiorentini 2012a	Irrelevant for the review comparison
Fiorentini 2012b	Irrelevant for the review intervention
Fiorentini 2012c	Irrelevant for the review comparison
Fiorentini 2012d	Irrelevant for the review intervention
Fischer 2011	Irrelevant for the review intervention
Flamen 2010	Irrelevant for the review intervention
Focan 1994	Irrelevant for the review intervention
Focan 1995	Irrelevant for the review intervention
Fong 2012	Not a randomised clinical trial
Fortuny 1975	Irrelevant for the review intervention
Foubert 2014	Not a randomised clinical trial
Friedman 1988	Irrelevant for the review intervention
Fujii 1997	Not a randomised clinical trial
Fujii 2005	Not a randomised clinical trial
Gaitanis 2011	Irrelevant for the review population
Gambato 2015	Not a randomised clinical trial
Gananadha 2002	Not a randomised clinical trial
Gao 2013	Irrelevant for the review population
Gassel 1998a	Irrelevant for the review intervention
Gassel 1998b	Irrelevant for the review intervention
Ge 2000	Not a randomised clinical trial
Gerard 1988	Not a randomised clinical trial
Gerard 1991	Irrelevant for the review intervention
Geschwind 2010	Not a randomised clinical trial
Giantonio 2005	Irrelevant for the review population

Study	Reason for exclusion
Gibbs 2010	Not a randomised clinical trial
Gillams 2001	Not a randomised clinical trial
Gillams 2015	Not a randomised clinical trial
Goldberg 2002	Irrelevant for the review intervention
Gonen 2003	Irrelevant for the review intervention
Gootjes 2015	Irrelevant for the review comparison
Grage 1979	Irrelevant for the review intervention
Gray 2001	Irrelevant for the review intervention
Groeschl 2014	Not a randomised clinical trial
Hafstrom 1998	Irrelevant for the review intervention
Halappa 2013	Not a randomised clinical trial
Han 2000	Irrelevant for the review population
Hao 2000	Irrelevant for the review population
Hashimoto 1989	Not a randomised clinical trial
Hashimoto 1997	Not a randomised clinical trial
Hasuike 1996	Irrelevant for the review intervention
Hayashibe 2007	Not a randomised clinical trial
He 2002	Not a randomised clinical trial
Hendlisz 2010a	Irrelevant for the review intervention
Hendlisz 2010b	Irrelevant for the review intervention
Hildebrandt 2000	Not a randomised clinical trial
Hiraki 2015	Not a randomised clinical trial
Hirokawa 2011	Not a randomised clinical trial
Hohn 1985	Irrelevant for the review intervention
Hohn 1989	Irrelevant for the review intervention
Holting 1991	Irrelevant for the review comparison
Horiguchi 1992	Not a randomised clinical trial
Hottenrott 1989	Irrelevant for the review intervention

Study	Reason for exclusion
Huang 1998	Not a randomised clinical trial
Huang 2000	Not a randomised clinical trial
Huang 2006	Irrelevant for the review intervention
Hubert 2007	Not a randomised clinical trial
Hughes 2016	Irrelevant for the review intervention
Hunt 1990	Irrelevant for the review intervention
Iezzi 2014	Not a randomised clinical trial
Illing 2010	Not a randomised clinical trial
Jacobsen 1995	Not a randomised clinical trial
Jones 2012	Not a randomised clinical trial
Joosten 2005	Not a randomised clinical trial
Julianov 2006	Not a randomised clinical trial
Junhui 1999	Irrelevant for the review intervention
Kairaluoma 1988	Not a randomised clinical trial
Karanicolas 2013	Not a randomised clinical trial
Kemeny 1985	Irrelevant for the review intervention
Kemeny 1986a	Irrelevant for the review intervention
Kemeny 1986b	Irrelevant for the review intervention
Kemeny 1987	Irrelevant for the review intervention
Kemeny 1992	Irrelevant for the review intervention
Kemeny 1993	Irrelevant for the review intervention
Kemeny 1995	Not a randomised clinical trial
Kemeny 1999a	Irrelevant for the review intervention
Kemeny 1999b	Irrelevant for the review intervention
Kemeny 2002	Irrelevant for the review intervention
Kemeny 2003	Irrelevant for the review intervention
Kemeny 2006	Irrelevant for the review intervention
Kennedy 2010	Not a randomised clinical trial

Study	Reason for exclusion
Kerr 2003	Irrelevant for the review intervention
Khan 2010	Not a randomised clinical trial
King 2013	Not a randomised clinical trial
Kiriyaama 1990	Not a randomised clinical trial
Kitchin 2014	Not a randomised clinical trial
Kondo 1995	Irrelevant for the review intervention
Korpan 2014	Irrelevant for the review population
Kosaka 2003	Not a randomised clinical trial
Ku 1997	Not a randomised clinical trial
Kurokawa 2000	Not a randomised clinical trial
Kurokohchi 2002	Irrelevant for the review intervention
Kurokohchi 2007	Irrelevant for the review intervention
Kusunoki 2000	Not a randomised clinical trial
Kwon 2003	Irrelevant for the review intervention
Labianca 2004	Irrelevant for the review intervention
Lange 1974	Irrelevant for the review intervention
Lange 1985	Irrelevant for the review intervention
Lee 2016	Not a randomised clinical trial
Leonard 2004	Not a randomised clinical trial
Lewis 2012	Not a randomised clinical trial
Li 1994	Irrelevant for the review intervention
Li 2014	Not a randomised clinical trial
Li 2015	Irrelevant for the review population
Liang 2005	Irrelevant for the review intervention
Liang 2007	Irrelevant for the review intervention
Liapi 2007	Not a randomised clinical trial
Lin 2005	Irrelevant for the review intervention
Link 1999	Not a randomised clinical trial

Study	Reason for exclusion
Link 2001	Not a randomised clinical trial
Liu 2003	Irrelevant for the review population
Liu 2006	Irrelevant for the review intervention
Liu 2007	Not a randomised clinical trial
Liu 2009	Irrelevant for the review population
Liu 2015	Irrelevant for the review population
Livraghi 1997	Not a randomised clinical trial
LiXue 2007	Irrelevant for the review intervention
Lorenz 1995	Not a randomised clinical trial
Lorenz 1998a	Irrelevant for the review intervention
Lorenz 1998b	Irrelevant for the review intervention
Lorenz 1998c	Irrelevant for the review intervention
Lorenz 2000	Irrelevant for the review intervention
Lupo 2007	Irrelevant for the review intervention
Lygidakis 1995	Irrelevant for the review intervention
Lygidakis 1996	Irrelevant for the review intervention
Lygidakis 2001a	Irrelevant for the review intervention
Lygidakis 2001b	Irrelevant for the review intervention
Madden 1993	Irrelevant for the review intervention
Maire 2012	Irrelevant for the review intervention
Malinovskii 2003	Not a randomised clinical trial
Martin 1990	Irrelevant for the review intervention
Martin 2012	Not a randomised clinical trial
Martin-II-Robert 2006	Not a randomised clinical trial
Martinelli 1994	Irrelevant for the review comparison
Matsuoka 2006	Not a randomised clinical trial
Mavligit 1990	Irrelevant for the review intervention
Mayo 2011	Not a randomised clinical trial

Study	Reason for exclusion
McArdle 2001	Irrelevant for the review intervention
Melichar 2002	Not a randomised clinical trial
Memon 2012	Not a randomised clinical trial
Meng 2003	Irrelevant for the review intervention
Mocellin 2007	Not a randomised clinical trial
Moeslein 2012	Irrelevant for the review intervention
Monna 1982	Not a randomised clinical trial
Mori 1996	Not a randomised clinical trial
Mori 1999	Not a randomised clinical trial
Mori 2000	Not a randomised clinical trial
Moroz 2001	Irrelevant for the review intervention
Murthy 2010	Irrelevant for the review comparison
Nakashima 1992	Not a randomised clinical trial
Naredi 2003	Irrelevant for the review intervention
NCT00043004	Irrelevant for the review intervention
NCT01867918	Irrelevant for the review intervention
NCT02843802	Irrelevant for the review population
Newlands 1976	Irrelevant for the review population
Nielsen 2014	Not a randomised clinical trial
Nishizaki 1995	Irrelevant for the review population
Niu 2013	Not a randomised clinical trial
Ohgashi 1991	Not a randomised clinical trial
Okuno 1999	Irrelevant for the review intervention
Okuyama 1992	Not a randomised clinical trial
Ong 1976	Irrelevant for the review intervention
Order 1991	Irrelevant for the review intervention
Osuga 2012	Not a randomised clinical trial
Oussoultzoglou 2006	Not a randomised clinical trial

Study	Reason for exclusion
Patt 1997	Not a randomised clinical trial
Peng 1993	Not a randomised clinical trial
Pingpank 2010	Irrelevant for the review comparison
Pohlen 2006	Not a randomised clinical trial
Power 2010	Irrelevant for the review comparison
Pulatov 2003	Not a randomised clinical trial
Quesada 2016	Irrelevant for the review intervention
Rauchfuss 2015	Not a randomised clinical trial
Reid 2000	Not a randomised clinical trial
Ricke 2010a	Not a randomised clinical trial
Ricke 2010b	Not a randomised clinical trial
Riesener 1998	Not a randomised clinical trial
Romano 2012	Not a randomised clinical trial
Rougier 1992	Irrelevant for the review intervention
Rudroff 1999	Irrelevant for the review intervention
Ruers 2010a	Irrelevant for the review intervention
Ruers 2010b	Irrelevant for the review intervention
Ruers 2011a	Irrelevant for the review intervention
Ruers 2011b	Irrelevant for the review intervention
Ruutiainen 2007	Not a randomised clinical trial
Safi 1989a	Not a randomised clinical trial
Safi 1989b	Irrelevant for the review comparison
Saitsu 2006	Not a randomised clinical trial
Salim 1993	Irrelevant for the review intervention
Salman 2002	Irrelevant for the review intervention
Schmitz 1990	Irrelevant for the review intervention
Schulman 1994	Irrelevant for the review population
Seki 1996	Not a randomised clinical trial

Study	Reason for exclusion
Seki 1999	Not a randomised clinical trial
Shang 2007	Irrelevant for the review intervention
Shankar 2004	Not a randomised clinical trial
Shibata 2000a	Not a randomised clinical trial
Shibata 2000b	Irrelevant for the review intervention
Shiiba 1993a	Irrelevant for the review intervention
Shiiba 1993b	Irrelevant for the review intervention
Shimomatsuya 2006	Not a randomised clinical trial
Simoni 1986	Not a randomised clinical trial
Soemarno 2002	Irrelevant for the review comparison
Stagg 1984	Irrelevant for the review intervention
Stattner 2013	Not a randomised clinical trial
Stein 2011	Irrelevant for the review intervention
Stojanovic 2010	Not a randomised clinical trial
Sun 2010	Irrelevant for the review population
Suzuki 2005	Irrelevant for the review intervention
Taguchi 1992	Irrelevant for the review intervention
Taguchi 1993	Not a randomised clinical trial
Takada 2002	Not a randomised clinical trial
Takada 2003	Not a randomised clinical trial
Takano 1989	Not a randomised clinical trial
Takano 1994	Not a randomised clinical trial
Takano 1998	Not a randomised clinical trial
Tam 2011	Not a randomised clinical trial
Tanada 1996	Not a randomised clinical trial
Tanemura 1996	Not a randomised clinical trial
Taniguchi 1988	Not a randomised clinical trial
Tarazov 2000	Irrelevant for the review intervention

Study	Reason for exclusion
Tilli 2011	Irrelevant for the review intervention
Tono 1994	Irrelevant for the review intervention
Tono 1995	Irrelevant for the review intervention
Tono 2000	Irrelevant for the review intervention
Tono 2006	Irrelevant for the review intervention
Topal 2003	Not a randomised clinical trial
Tsuji 1995	Not a randomised clinical trial
Tsuji 1999	Not a randomised clinical trial
Uchino 1993	Irrelevant for the review intervention
Uemura 1996	Not a randomised clinical trial
Vadot 2013	Irrelevant for the review population
Valpione 2015	Not a randomised clinical trial
Van 2004	Irrelevant for the review intervention
Van Nieuwenhovc 2007	Irrelevant for the review intervention
Virgolini 2002	Not a randomised clinical trial
Visvanathan 2014	Not a randomised clinical trial
Wagman 1990	Irrelevant for the review intervention
Walter 2012	Not a randomised clinical trial
Wang 1992	Irrelevant for the review population
Wang 1993	Irrelevant for the review intervention
Wang 1994	Irrelevant for the review intervention
Wang 1998	Irrelevant for the review population
Wiley 1989	Irrelevant for the review comparison
Xie 2000	Irrelevant for the review comparison
Xin 2001	Not a randomised clinical trial
Xju 2000	Irrelevant for the review population
Xu 2002	Irrelevant for the review population
Xu 2005	Not a randomised clinical trial

Study	Reason for exclusion
Xu 2006	Irrelevant for the review intervention
Xu 2007	Irrelevant for the review intervention
Xu 2012	Percutaneous microwave coagulation therapy plus transarterial chemoembolisation versus transarterial chemoembolisation
Xu 2013	Not a randomised clinical trial
Xu 2015	Irrelevant for the review intervention
Xue 1995	Irrelevant for the review population
Yamada 1988	Irrelevant for the review intervention
Yamada 1999	Irrelevant for the review intervention
Yamamura 1993	Not a randomised clinical trial
Yamamura 1994	Not a randomised clinical trial
Yamashita 1990	Not a randomised clinical trial
Yamashita 1992	Irrelevant for the review intervention
Yang 2012	Irrelevant for the review population
Yasuda 1994	Not a randomised clinical trial
Yayoi 1995	Not a randomised clinical trial
Yongxiang 2001	Irrelevant for the review population
Yukawa 2001	Not a randomised clinical trial
Yunxue 1999	Irrelevant for the review population
Zager 2011	Irrelevant for the review intervention
Zhang 1997	Not a randomised clinical trial
Zhang 2004	Irrelevant for the review intervention
Zheng 1998	Irrelevant for the review intervention
Zheng 2013	Irrelevant for the review intervention
Zhong 2008	Irrelevant for the review intervention
Zhou 2003	Not a randomised clinical trial
Zhu 1998	Irrelevant for the review intervention

ADDITIONAL TABLES

Table 1. Adverse events in participants with liver metastases treated with cryotherapy versus conventional surgery

Korpan 1997	Conventional surgery	Cryotherapy	RR (95% CI)^a
Complications	12 (20%)	6 (10%)	0.48 (0.19 to 1.19)
Systemic infection (pneumonia)	2 (3%)	3 (5%)	1.43 (0.25 to 8.25)
Wound infection (septic wound)	1 (2%)	2 (3%)	1.9 (0.18 to 20.46)
Pleural effusion	3 (5%)	0	0.14 (0.007 to 2.58)
Intervention-related bleeding	2 (3%)	0	0.19 (0.009 to 3.89)
ICU treatment (blood, plasma, human albumin)	21 (35%)	16 (25%)	0.73 (0.42 to 1.25)
Other (subphrenic abscess)	4 (7%)	0	0.11 (0.006 to 1.9)
Pain severity at day 5 postoperation			
• Pronounced	9% ^b	17% ^b	—
• Intense	29% ^b	0	—
• Insignificant	62% ^b	83% ^b	—

^aCalculated using Review Manager 5 calculator.

^bOnly percentages provided by the authors.

CI: confidence interval; ICU: Intensive care unit; RR: risk ratio.

APPENDICES

Appendix 1. Search strategies for the main review and update up to 2017

Database	Time span	Search strategy
Cochrane Hepato-Biliary Group Controlled Trials Register	29 September 2017	((liver or hepatic or hepatocellular* or hepato-cellular*) AND (cancer* or neoplasm* or malign* or carcinoma* or tumor*)) OR ((metastasis* or secondary* or spread or advanced) AND (liver or hepatic))) and (Ablation* OR (injection* and (ethanol or acetic acid))) or PEI or PAI
Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	5 June 2017	((liver or hepatic or hepatocellular* or hepato-cellular*) AND (cancer* or neoplasm* or malign* or carcinoma* or tumor*)) OR ((metastasis* or secondary* or spread or advanced) AND (liver or hepatic))) and (radiofrequency* or radiofrequency* or rfa or rf OR Ablation* OR (injection* and (ethanol or acetic acid))) or PEI or PAI OR Yttrium Radioisotopes OR selective internal radiation* OR radioembolisation* OR radio-embolisation* OR sir-sphere* OR therasphere* OR (yttrium* or 90y* or radiolabel*) AND microsphere*) OR Embolisation OR Embolisation OR ((transcatheter or transarterial) and (embolisation* or chemoembolisation*)) or TAE or TACE or lipiodolisation or lipiodol embolisation OR lipiodol or HAI or arterial

(Continued)

infusion or targeted chemotherapy OR ((transcatheter or transarterial) and chemoinfusion) OR Iodized Oil OR thermotherapy OR Hyperthermia OR Microwaves or coagulation OR cryosurgery)

MEDLINE Ovid	1950 to 5 June 2017	1 exp Carcinoma, Hepatocellular/
		2 exp Liver Neoplasms/
		3 hcc.mp.
		4 ((liver or hepatic or hepatocellular\$ or hepato-cellular\$) adj5 (cancer\$ or neoplas\$ or malign\$ or carcinom\$ or tumo\$)).mp.
		5 1 or 2 or 3 or 4
		6 exp Neoplasm Metastasis/
		7 (metasta* or secundar* or spread or advanced).mp.
		8 6 or 7
		9 exp Neuroendocrine Tumors/
		10 exp Apudoma/
		11 exp Carcinoid Tumour/
		12 exp Adenoma, Islet Cell/
		13 exp Insulinoma/
		14 exp Carcinoma, Islet Cell/
		15 exp Gastrinoma/
		16 exp Glucagonoma/
		17 exp Somatostatinoma/
		18 exp Vipoma/
		19 exp Multiple Endocrine Neoplasia/
		20 exp Pancreatic Neoplasms/
		21 exp Malignant Carcinoid Syndrome/
		22 (neuroendocrine tumour or neuroendocrine tumours or neuroendocrine tumour or neuroendocrine tumours or adenoma or adenomas or apudoma or apudomas or carcinoid or carcinoids).mp.
		23 (argentaffinoma or argentaffinomas or somatostatinoma or somatostatinomas or islet cell tumour or islet cell tumours or island cell tumour or island cell tumours or nesidioblastoma).mp.
		24 (nesidioblastomas or insulinoma or insulinomas or multiple endocrine neoplasia or multiple endocrine adenopathy or multiple endocrine adenopathies or multiple endocrine adenomatoses).mp.
		25 (multiple endocrine adenomatosis or familial endocrine adenomatoses or familial endocrine adenomatosis or multiple endocrine neoplasms or vipoma or vipomas or diarrheogenic tumour).mp.
		26 (diarrheogenic tumours or diarrheogenic tumour or diarrheogenic tumours or VIP secreting tumour or VIP secreting tumours or VIP secreting tumour or VIP secreting tumours).mp.

(Continued)

27 (Pancreatic cholera or Verner-Morrison syndrome or Verner Morrison syndrome or watery diarrhoea syndrome or watery diarrhoea syndrome or WDHA or WDHH or neuroendocrine carcinoma or neuroendocrine carcinomas or carcinoid syndrome).mp.

28 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27

29 exp Colorectal Neoplasms/

30 ((colon\$ or rect\$ or colorect\$ or bowel or large intestin\$) adj5 neoplas\$).tw,mp.

31 ((colon\$ or rect\$ or colorect\$ or bowel or large intestin\$) adj5 cancer\$).tw,mp.

32 ((colon\$ or rect\$ or colorect\$ or bowel or large intestin\$) adj5 carcinoma\$).tw,mp.

33 ((colon\$ or rect\$ or colorect\$ or bowel or large intestin\$) adj5 tumo\$).tw,mp.

34 ((colon\$ or rect\$ or colorect\$ or bowel or large intestin\$) adj5 malignan\$).tw,mp.

35 ((colon\$ or rect\$ or colorect\$ or bowel or large intestin\$) adj5 adenocarcinoma\$).tw,mp.

36 29 or 30 or 31 or 32 or 33 or 34 or 35

37 exp Liver/

38 (liver or hepatic).mp.

39 37 or 38

40 28 or 36

41 8 and 39 and 40

42 5 or 41

43 randomized controlled trial.pt.

44 controlled clinical trial.pt.

45 randomized.ab.

46 placebo.ab.

47 randomly.ab.

48 trial.ab.

49 groups.ab.

50 43 or 44 or 45 or 46 or 47 or 48 or 49

51 humans.sh.

52 50 and 51

53 (rfta or radio-frequ\$ or radiofrequ\$ or rfa or rf).mp.

54 exp Catheter Ablation/

55 53 or 54

56 percutaneous.mp.

57 (ablati* and (therap* or treatment* or radiofrequenc* or cryo*)).mp.

58 ((injection* and (ethanol or acetic acid)) or PEI or PAI).mp.

(Continued)

59 57 or 58

60 56 and 59

61 exp Yttrium Radioisotopes/

62 selective internal radi\$.tw,mp.

63 radioemboli\$.tw,mp.

64 radio-emboli\$.tw,mp.

65 sir-sphere\$.tw,mp.

66 therasphere\$.tw,mp.

67 ((yttrium\$ or \$yttrium or 90y\$ or radiolabel\$) adj5 microsphere\$).tw,mp.

68 61 or 62 or 63 or 64 or 65 or 66 or 67

69 exp Chemoembolisation, Therapeutic/

70 exp Embolisation, Therapeutic/

71 (((transcatheter or transarterial) and (emboli* or chemoemboli*)) or TAE or TACE or lipiodolisation or lipiodol embolisation).mp.

72 exp Infusions, Intra-Arterial/

73 (lipiodol or HAI or arterial infusion or targeted chemotherapy).mp.

74 ((transcatheter or transarterial) and chemo-infusion).mp.

75 exp Iodized Oil/

76 69 or 70 or 71 or 72 or 73 or 74 or 75

77 thermotherapy.mp. or exp Hyperthermia, Induced/

78 exp Microwaves/ or coagulation therapy.mp. or exp Electrocoagulation/

79 exp Catheter Ablation/ or ablation.mp.

80 cryosurgery.mp. or exp Cryosurgery/

81 55 or 60 or 68 or 76 or 77 or 78 or 79 or 80

82 42 and 52 and 81

Embase Ovid	1974 to 5 June 2017	<p>1 Liver-Cell-Carcinoma#</p> <p>2 Liver-Tumour#</p> <p>3 hcc AND CLINICAL-TRIAL# AND HUMAN=YES</p> <p>4 (liver OR hepatic OR hepatocellular\$3 OR hepato-cellular\$3) NEAR (cancer\$3 OR neoplas\$3 OR malign\$5 OR carcinom\$3 OR tumo\$3) AND CLINICAL-TRIAL# AND HUMAN=YES</p> <p>5 1 OR 2 OR 3 OR 4</p> <p>6 Metastasis#</p> <p>7 metasta\$5 OR secondar\$3 OR spread OR advanced</p> <p>8 6 OR 7</p> <p>9 Neuroendocrine-Tumour#</p>
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(Continued)

- 10 Apudoma#
- 11 Carcinoid#
- 12 Pancreas-Islet-Cell-Tumour#
- 13 Insulinoma#
- 14 Pancreas-Islet-Cell-Carcinoma#
- 15 Gastrinoma#
- 16 Glucagonoma#
- 17 Somatostatinoma#
- 18 Vipoma#
- 19 Multiple-Endocrine-Neoplasia#
- 20 Pancreas-Tumour#
- 21 Carcinoid-Syndrome#
- 22 neuroendocrine ADJ tumour OR neuroendocrine ADJ tumours OR neuroendocrine ADJ tumour OR neuroendocrine ADJ tumours OR adenoma OR adenomas OR apudoma OR apudomas OR carcinoid OR carcinoids
- 23 argentaffinoma OR argentaffinomas OR somatostatinoma OR somatostatinomas OR islet ADJ cell ADJ tumour OR islet ADJ cell ADJ tumours OR island ADJ cell ADJ tumour OR island ADJ cell ADJ tumours OR nesidioblastoma
- 24 multiple ADJ endocrine ADJ adenomatosis OR familial ADJ endocrine ADJ adenomatoses OR familial ADJ endocrine ADJ adenomatosis OR multiple ADJ endocrine ADJ neoplasms OR vipoma OR vipomas OR diarrheogenic ADJ tumour
- 25 nesidioblastomas OR insulinoma OR insulinomas OR multiple ADJ endocrine ADJ neoplasia OR multiple ADJ endocrine ADJ adenopathy OR multiple ADJ endocrine ADJ adenopathies OR multiple ADJ endocrine ADJ adenomatoses
- 26 diarrheogenic ADJ tumours OR diarrheogenic ADJ tumour OR diarrheogenic ADJ tumours OR VIP ADJ secreting ADJ tumour OR VIP ADJ secreting ADJ tumours OR VIP ADJ secreting ADJ tumour OR VIP ADJ secreting ADJ tumours
- 27 Pancreatic ADJ cholera OR Verner-Morrison ADJ syndrome OR Verner ADJ Morrison ADJ syndrome OR watery ADJ diarrhoea ADJ syndrome OR watery ADJ diarrhoea ADJ syndrome OR WDHA OR WDHH OR neuroendocrine ADJ carcinoma OR neuroendocrine ADJ carcinomas OR carcinoid ADJ syndrome
- 28 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27
- 29 Colorectal-Tumour#
- 30 (colon\$5 OR rect\$5 OR colorect\$3 OR bowel OR large ADJ intestin\$5) NEAR neoplas\$5
- 31 (colon\$5 OR rect\$5 OR colorect\$3 OR bowel OR large ADJ intestin\$5) NEAR cancer\$3
- 32 (colon\$5 OR rect\$5 OR colorect\$3 OR bowel OR large ADJ intestin\$5) NEAR carcinoma\$5
- 33 (colon\$5 OR rect\$5 OR colorect\$3 OR bowel OR large ADJ intestin\$5) NEAR tumor\$5
- 34 (colon\$5 OR rect\$5 OR colorect\$3 OR bowel OR large ADJ intestin\$5) NEAR malignan\$5

(Continued)

- 35 (colon\$5 OR rect\$5 OR colorect\$3 OR bowel OR large ADJ intestin\$5) NEAR adenocarcinoma\$5
- 36 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35
- 37 Liver#
- 38 liver OR hepatic
- 39 37 OR 38
- 40 28 OR 36
- 41 8 AND 39 AND 40
- 42 5 OR 41
- 43 random\$7 OR factorial\$3 OR crossover\$3 OR cross ADJ over\$3 OR placebo\$3 OR double\$3 ADJ blind\$5 OR single\$3 ADJ blind\$5 OR assign\$7 OR allocat\$5 OR volunteer\$3
- 44 Crossover-Procedure#
- 45 Double-Blind-Procedure#
- 46 Randomized-Controlled-Trial#
- 47 Single-Blind-Procedure#
- 48 43 OR 44 OR 45 OR 46 OR 47
- 49 rfta OR radio-frequ\$7 OR radiofrequ\$7 OR rfa OR rf
- 50 Catheter-Ablation#
- 51 49 OR 50
- 52 percutaneous
- 53 ablati\$5 AND (therap\$5 OR treatment\$3 OR radiofrequenc\$3 OR cryo\$7)
- 54 injection\$3 AND (ethanol OR acetic ADJ acid) OR PEI OR PAI
- 55 53 OR 54
- 56 52 AND 55
- 57 Yttrium#
- 58 selective ADJ internal ADJ radi\$7 OR radioemboli\$7 OR radio-emboli\$7 OR sir-sphere\$5 OR therasphere\$5
- 59 (yttrium\$7 OR 90y\$7 OR radiolabel\$7) NEAR microsphere\$3
- 60 57 OR 58 OR 59
- 61 Chemoembolisation#
- 62 Artificial-Embolism#
- 63 (transcatheter OR transarterial) AND (emboli\$5 OR chemoemboli\$5) OR TAE OR TACE OR lipiodolisation OR lipiodol ADJ embolisation
- 64 Intraarterial-Drug-Administration#.DE.
- 65 lipiodol OR HAI OR arterial ADJ infusion OR targeted ADJ chemotherapy
- 66 (transcatheter OR transarterial) AND chemo-infusion

(Continued)

67 (transcatheter OR transarterial) AND chemo ADJ infusion

68 Iodinated-Poppyseed-Oil#.DE.

69 61 OR 62 OR 63 OR 64 OR 65 OR 66 OR 67 OR 68

70 Hyperthermic-Therapy

71 thermotherapy

72 Microwave-Radiation#

73 Cryocoagulation# OR Electrocoagulation# OR Laser-Coagulation#

74 coagulation ADJ therapy

75 Catheter-Ablation#

76 ablation

77 Cryosurgery#.W..DE.

78 70 OR 71 OR 72 OR 73 OR 74 OR 75 OR 76 OR 77

79 51 OR 56 OR 60 OR 69 OR 78

80 42 AND 48 AND 79

81 HUMAN=YES

82 80 AND 81

83 CLINICAL-TRIAL#

84 82 AND 83

Science Citation Index Expanded (Web of Science)	1970 to 5 June 2017	<p># 70 #69 AND #37 AND #30</p> <p># 69 #68 OR #67 OR #66 OR #65 OR #64 OR #54 OR #45 OR #40</p> <p># 68 TS=(cryosurgery OR cryo-surgery)</p> <p># 67 TS=(ablation*)</p> <p># 66 TS=(Microwaves* or Microwave-Radiation* OR coagulation therapy or Electrocoagulation* or Electro-coagulation* or Cryocoagulation* OR Laser-Coagulation* OR Cryo-coagulation*)</p> <p># 65 TS= (thermotherapy or Induced Hyperthermia or Hyperthermic Therapy)</p> <p># 64 #63 OR #62 OR #61 OR #60 OR #59 OR #58 OR #57 OR #56 OR #55</p> <p># 63 TS=Iodinated Poppyseed Oil</p> <p># 62 TS=Intra-arterial Drug Administration</p> <p># 61 TS=Artificial-Embolism</p> <p># 60 TS=Iodized Oil*</p> <p># 59 TS=((transcatheter or transarterial) and chemo-infusion)</p> <p># 58 TS=(lipiodol or HAI or arterial infusion or targeted chemotherapy)</p> <p># 57 TS=Intra-Arterial Infusion*</p>
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(Continued)

56 TS=((transcatheter or transarterial) and (emboli* or chemoemboli*)) or TAE or TACE or lipiodolisation or lipiodol embolisation)

55 TS=Embolisation

54 #53 OR #52 OR #51 OR #50 OR #49 OR #48 OR #47 OR #46

53 TS=Yttrium

52 TS=((yttrium* and microsphere*) or (90y* and microsphere*) or (radiolabel* and microsphere*))

51 TS=therasphere*

50 TS=sir-sphere*

49 TS=radio-emboli*

48 TS=radioemboli*

47 TS=selective internal radi*

46 TS=Yttrium Radioisotopes

45 #44 AND #41

44 #43 OR #42

43 TS=((injection* and (ethanol or acetic acid)) or PEI or PAI)

42 TS=(ablati* and (therap* or treatment* or radiofrequenc* or cryo*))

41 TS=percutaneous

40 #39 OR #38

39 TS=Catheter Ablation

38 TS=(rfta or radio-frequ* or radiofrequ* or rfa or rf)

37 #36 AND #35

36 TS=human*

35 #34 OR #33 OR #32 OR #31

34 TS=trial*

33 TS=random*

32 TS=groups

31 TS=placebo

30 #29 OR #10

29 #28 AND #27 AND #11

28 #26 OR #19

27 TS=(liver or hepatic)

26 #25 OR #24 OR #23 OR #22 OR #21 OR #20

25 TS=(colon* adenocarcinoma* or rect* adenocarcinoma* or colorect* adenocarcinoma* or bowel adenocarcinoma* or large intestin* adenocarcinoma*)

(Continued)

24 TS=(colon* malignan* or rect* malignan* or colorect* malignan* or bowel malignan* or large intestin* malignan*)

23 TS=(colon* tumo* or rect* tumo* or colorect* tumo* or bowel tumo* or large intestin*

tumo*)

22 TS=(colon* carcinoma* or rect* carcinoma* or colorect* carcinoma* or bowel carcinoma* or large intestin* carcinoma*)

21 TS=(colon* cancer* or rect* cancer* or colorect* cancer* or bowel cancer* or large intestin* cancer*)

20 TS=(colon* neoplas* or rect* neoplas* or colorect* neoplas* or bowel neoplas* or large intestin* neoplas*)

19 #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12

18 TS=(Gastrinoma or Glucagonoma or Somatostatinoma or Pancreatic Neoplasm*)

17 TS=(Pancreatic cholera or Verner-Morrison syndrome or Verner Morrison syndrome or watery diarrhoea syndrome or watery diarrhoea syndrome or WDHA or WDHH or neuroendocrine carcinoma or neuroendocrine carcinomas or carcinoid syndrome)

16 TS=(diarrheogenic tumours or diarrheogenic tumour or diarrheogenic tumours or VIP secreting tumour or VIP secreting tumours or VIP secreting tumour or VIP secreting tumours)

15 TS=(multiple endocrine adenomatosis or familial endocrine adenomatosis or familial endocrine adenomatosis or multiple endocrine neoplasms or vipoma or vipomas or diarrheogenic tumour)

14 TS=(nesidioblastomas or insulinoma or insulinomas or multiple endocrine neoplasia or multiple endocrine adenopathy or multiple endocrine adenopathies or multiple endocrine adenomatosis)

13 TS=(argentaffinoma or argentaffinomas or somatostatinoma or somatostatinomas or islet

cell tumour or islet cell tumours or island cell tumour or island cell tumours or

nesidioblastoma)

12 TS=(neuroendocrine tumour or neuroendocrine tumours or neuroendocrine tumour or neuroendocrine tumours or adenoma or adenomas or apudoma or apudomas or carcinoid or carcinoids)

11 TS=(Neoplasm Metastasis or metasta* or secundar* or spread or advanced)

10 #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1

9 TS=(Liver-Cell-Carcinoma or Liver Cell Carcinoma)

8 TS=(liver malign* or hepatic malign* or hepatocellular* malign* or hepato-cellular* malign*)

7 TS=(liver tumo* or hepatic tumo* or hepatocellular* tumo* or hepato-cellular* tumo*)

6 TS=(liver carcinom* or hepatic carcinom* or hepatocellular* carcinom* or hepato-cellular* carcinom*)

5 TS=(liver neoplas* or hepatic neoplas* or hepatocellular* neoplas* or hepato-cellular* neoplas*)

(Continued)

4 TS=(liver cancer* or hepatic cancer* or hepatocellular* cancer* or hepato-cellular* cancer*)

3 TS=hcc

2 TS=Liver Neoplasms

1 TS=Hepatocellular Carcinoma

LILACS (Bireme)	1982 to 5 June 2017	(Pt RANDOMIZED CONTROLLED TRIAL OR Pt CONTROLLED CLINICAL TRIAL OR Mh RANDOMIZED CONTROLLED TRIALS OR Mh RANDOM ALLOCATION OR Mh DOUBLE-BLIND METHOD OR Mh SINGLE-BLIND METHOD OR Pt MULTICENTER STUDY) OR ((tw ensaio or tw ensayo or tw trial) and (tw azar or tw acaso or tw placebo or tw control\$ or tw aleat\$ or tw random\$ or (tw duplo and tw cego) or (tw doble and tw ciego) or (tw double and tw blind)) and tw clinic\$)) AND NOT ((CT ANIMALS OR MH ANIMALS OR CT RABBITS OR CT MICE OR MH RATS OR MH PRIMATES OR MH DOGS OR MH RABBITS OR MH SWINE) AND NOT (CT HUMAN AND CT ANIMALS)) [Palavras] and (liver or hepatic) [Palavras]
CINAHL (EBSCO-host)	1981 to 5 June 2017	1 exp Carcinoma, Hepatocellular/ 2 exp Liver Neoplasms/ 3 hcc.mp. 4 ((liver or hepatic or hepatocellular\$ or hepato-cellular\$) adj5 (cancer\$ or neoplas\$ or malign\$ or carcinom\$ or tumor\$)).mp. 5 1 or 2 or 3 or 4 6 exp Neoplasm Metastasis/ 7 (metasta* or secundar* or spread or advanced).mp. 8 6 or 7 9 exp Neuroendocrine Tumors/ 10 Apudoma.mp. 11 exp Carcinoid Tumour/ 12 exp Adenoma, Islet Cell/ 13 exp INSULINOMA/ 14 exp Carcinoma, Islet Cell/ 15 exp GASTRINOMA/ 16 Glucagonoma.mp. or exp Glucagon/ 17 Somatostatinoma.mp. 18 Vipoma.mp. 19 exp Endocrine Gland Neoplasms/ or Multiple Endocrine Neoplasia.mp. 20 exp Pancreatic Neoplasms/ 21 Malignant Carcinoid Syndrome.mp. or exp Gastrointestinal Neoplasms/ 22 (neuroendocrine tumour or neuroendocrine tumours or neuroendocrine tumor or neuroendocrine tumors or adenoma or adenomas or apudoma or apudomas or carcinoid or carcinoids).mp.

(Continued)

23 (argentaftinoma or argentaftinomas or somatostatinoma or somatostatinomas or islet cell tumour or islet cell tumours or island cell tumour or island cell tumours or nesidioblastoma).mp.

24 (nesidioblastomas or insulinoma or insulinomas or multiple endocrine neoplasia or multiple endocrine adenopathy or multiple endocrine adenopathies or multiple endocrine adenomatoses).mp.

25 (multiple endocrine adenomatosis or familial endocrine adenomatoses or familial endocrine adenomatosis or multiple endocrine neoplasms or vipoma or vipomas or diarrheogenic tumour).mp.

26 (diarrheogenic tumours or diarrheogenic tumour or diarrheogenic tumours or VIP secreting tumour or VIP secreting tumours or VIP secreting tumour or VIP secreting tumours).mp.

27 (Pancreatic cholera or Verner-Morrison syndrome or Verner Morrison syndrome or watery diarrhoea syndrome or watery diarrhoea syndrome or WDHA or WDHH or neuroendocrine carcinoma or neuroendocrine carcinomas or carcinoid syndrome).mp.

28 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27

29 exp Colorectal Neoplasms/

30 ((colon\$ or rect\$ or colorect\$ or bowel or large intestin\$) adj5 neoplas\$).tw,mp.

31 ((colon\$ or rect\$ or colorect\$ or bowel or large intestin\$) adj5 cancer\$).tw,mp.

32 ((colon\$ or rect\$ or colorect\$ or bowel or large intestin\$) adj5 carcinoma\$).tw,mp.

33 ((colon\$ or rect\$ or colorect\$ or bowel or large intestin\$) adj5 tumo\$).tw,mp.

34 ((colon\$ or rect\$ or colorect\$ or bowel or large intestin\$) adj5 malignan\$).tw,mp.

35 ((colon\$ or rect\$ or colorect\$ or bowel or large intestin\$) adj5 adenocarcinoma\$).tw,mp.

36 29 or 30 or 31 or 32 or 33 or 34 or 35

37 exp LIVER/

38 (liver or hepatic).mp.

39 37 or 38

40 28 or 36

41 8 and 39 and 40

42 5 or 41

43 randomized controlled trial.pt.

44 controlled clinical trial.pt.

45 randomized.ab.

46 placebo.ab.

47 randomly.ab.

48 trial.ab.

49 groups.ab.

(Continued)

- 50 43 or 44 or 45 or 46 or 47 or 48 or 49
- 51 (rfta or radio-frequ\$ or radiofrequ\$ or rfa or rf).mp.
- 52 exp Catheter Ablation/
- 53 51 or 52
- 54 percutaneous.mp.
- 55 (ablati* and (therap* or treatment* or radiofrequenc* or cryo*)).mp.
- 56 ((injection* and (ethanol or acetic acid)) or PEI or PAI).mp.
- 57 55 or 56
- 58 54 and 57
- 59 Yttrium Radioisotopes.mp.
- 60 selective internal radi\$.tw,mp.
- 61 radioemboli\$.tw,mp.
- 62 radio-emboli\$.tw,mp.
- 63 sir-sphere\$.tw,mp.
- 64 therasphere\$.tw,mp.
- 65 ((yttrium\$ or \$yttrium or 90y\$ or radiolabel\$) adj5 microsphere\$).tw,mp.
- 66 59 or 60 or 61 or 62 or 63 or 64 or 65
- 67 exp Chemoembolisation, Therapeutic/
- 68 exp Embolisation, Therapeutic/
- 69 (((transcatheter or transarterial) and (emboli* or chemoemboli*)) or TAE or TACE or lipiodolisation or lipiodol embolisation).mp.
- 70 exp Infusions, Intraarterial/
- 71 (lipiodol or HAI or arterial infusion or targeted chemotherapy).mp.
- 72 ((transcatheter or transarterial) and chemo-infusion).mp.
- 73 Iodized Oil.mp.
- 74 67 or 68 or 69 or 70 or 71 or 72 or 73
- 75 exp Hyperthermia, Induced/
- 76 thermotherapy.mp.
- 77 exp MICROWAVES/
- 78 Electrocoagulation.mp.
- 79 coagulation therapy.mp.
- 80 exp Catheter Ablation/
- 81 ablation.mp.
- 82 cryosurgery.mp. or exp CRYOSURGERY/
- 83 53 or 58 or 66 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82

(Continued)

84 42 and 52 and 83

Appendix 2. Search strategies for the update from 2018

Database	Time span	Search strategy
Cochrane Hepa-to-Biliary Group Controlled Trials Register	June 2018	(cryotherap* or cryosurg* or cryoablati*) AND (((liver or hepatic or hepatocellular* or hepato-cellular*) AND (cancer* or neoplasm* or malign* or carcinoma* or tumo*)) OR ((metasta* or secundar* or spread or advanced) AND (liver or hepatic)))
Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	2018, Issue 5	#1 MeSH descriptor: [Cryotherapy] explode all trees #2 MeSH descriptor: [Cryosurgery] explode all trees #3 cryotherap* or cryosurg* or cryoablati* #4 #1 or #2 or #3 #5 MeSH descriptor: [Carcinoma, Hepatocellular] explode all trees #6 MeSH descriptor: [Liver Neoplasms] explode all trees #7 ((liver or hepatic or hepatocellular* or hepato-cellular*) and (cancer* or neoplasm* or malign* or carcinoma* or tumo*)) #8 #5 or #6 or #7 #9 MeSH descriptor: [Neoplasm Metastasis] explode all trees #10 MeSH descriptor: [Liver] explode all trees #11 ((metasta* or secundar* or spread or advanced) and (liver or hepatic)) #12 #9 or #10 or #11 #13 #4 and #8 and #12
MEDLINE Ovid	1946 to June 2018	1. exp CRYOTHERAPY/ 2. exp CRYOSURGERY/ 3. (cryotherap* or cryosurg* or cryoablati*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 4. 1 or 2 or 3 5. exp Carcinoma, Hepatocellular/ 6. exp Liver Neoplasms/ 7. ((liver or hepatic or hepatocellular* or hepato-cellular*) and (cancer* or neoplasm* or malign* or carcinoma* or tumo*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 8. 5 or 6 or 7 9. exp Neoplasm Metastasis/ 10. exp LIVER/ 11. ((metasta* or secundar* or spread or advanced) and (liver or hepatic)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 12. 9 or 10 or 11 13. 4 and 8 and 12 14. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 15. 13 and 14
Embase Ovid	1974 to	1. exp cryotherapy/

(Continued)

	June 2018	2. (cryotherap* or cryosurg* or cryoablati*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 3. 1 or 2 4. exp liver cell carcinoma/ 5. exp liver tumor/ 6. ((liver or hepatic or hepatocellular* or hepato-cellular*) and (cancer* or neoplasm* or malign* or carcinoma* or tumo*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 7. 4 or 5 or 6 8. exp metastasis/ 9. exp liver/ 10. ((metasta* or secundar* or spread or advanced) and (liver or hepatic)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 11. 8 or 9 or 10 12. 3 and 7 and 11 13. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 14. 12 and 13
LILACS (Bireme)	1982 to June 2018	(cryotherap\$ or cryosurg\$ or cryoablati\$) [Words] and ((liver or hepatic or hepatocellular\$ or hepato-cellular\$) and (cancer\$ or neoplasm\$ or malign\$ or carcinoma\$ or tumo\$)) [Words] and ((metasta\$ or secundar\$ or spread or advanced) and (liver or hepatic)) [Words]
Science Citation Index Expanded (Web of Science)	1900 to 26 June 2018	#6 #5 AND #4 #5 TS=(random* or blind* or placebo* or meta-analys*) #4 #3 AND #2 AND #1 #3 TS=((metasta* or secundar* or spread or advanced) and (liver or hepatic)) #2 TS=((liver or hepatic or hepatocellular* or hepato-cellular*) and (cancer* or neoplasm* or malign* or carcinoma* or tumo*)) #1 TS=(cryotherap* or cryosurg* or cryoablati*)
Conference Proceedings Citation Index – Science (Web of Science)	1990 to June 2018	#6 #5 AND #4 #5 TS=(random* or blind* or placebo* or meta-analys*) #4 (#3 OR #2) AND #1 #3 TS=((metasta* or secundar* or spread or advanced) and (liver or hepatic)) #2 TS=((liver or hepatic or hepatocellular* or hepato-cellular*) and (cancer* or neoplasm* or malign* or carcinoma* or tumo*)) #1 TS=(cryotherap* or cryosurg* or cryoablati*)
CINAHL (EBSCO-host)	1981 to June 2018	1 exp Carcinoma, Hepatocellular/ 2 exp Liver Neoplasms/ 3 hcc.mp. 4 ((liver or hepatic or hepatocellular\$ or hepato-cellular\$) adj5 (cancer\$ or neoplas\$ or malign\$ or carcinom\$ or tumo\$)).mp.

(Continued)

- 5 1 or 2 or 3 or 4
- 6 exp Neoplasm Metastasis/
- 7 (metasta* or secundar* or spread or advanced).mp.
- 8 6 or 7
- 9 exp Neuroendocrine Tumors/
- 10 Apudoma.mp.
- 11 exp Carcinoid Tumour/
- 12 exp Adenoma, Islet Cell/
- 13 exp INSULINOMA/
- 14 exp Carcinoma, Islet Cell/
- 15 exp GASTRINOMA/
- 16 Glucagonoma.mp. or exp Glucagon/
- 17 Somatostatinoma.mp.
- 18 Vipoma.mp.
- 19 exp Endocrine Gland Neoplasms/ or Multiple Endocrine Neoplasia.mp.
- 20 exp Pancreatic Neoplasms/
- 21 Malignant Carcinoid Syndrome.mp. or exp Gastrointestinal Neoplasms/
- 22 (neuroendocrine tumour or neuroendocrine tumours or neuroendocrine tumour or neuroendocrine tumours or adenoma or adenomas or apudoma or apudomas or carcinoid or carcinoids).mp.
- 23 (argentaffinoma or argentaffinomas or somatostatinoma or somatostatinomas or islet cell tumour or islet cell tumours or island cell tumour or island cell tumours or nesidioblastoma).mp.
- 24 (nesidioblastomas or insulinoma or insulinomas or multiple endocrine neoplasia or multiple endocrine adenopathy or multiple endocrine adenopathies or multiple endocrine adenomatoses).mp.
- 25 (multiple endocrine adenomatosis or familial endocrine adenomatoses or familial endocrine adenomatosis or multiple endocrine neoplasms or vipoma or vipomas or diarrheogenic tumour).mp.
- 26 (diarrheogenic tumours or diarrheogenic tumour or diarrheogenic tumours or VIP secreting tumour or VIP secreting tumours or VIP secreting tumour or VIP secreting tumours).mp.
- 27 (Pancreatic cholera or Verner-Morrison syndrome or Verner Morrison syndrome or watery diarrhoea syndrome or watery diarrhoea syndrome or WDHA or WDHH or neuroendocrine carcinoma or neuroendocrine carcinomas or carcinoid syndrome).mp.
- 28 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
- 29 exp Colorectal Neoplasms/
- 30 ((colon\$ or rect\$ or colorect\$ or bowel or large intestin\$) adj5 neoplas\$).tw,mp.
- 31 ((colon\$ or rect\$ or colorect\$ or bowel or large intestin\$) adj5 cancer\$).tw,mp.

(Continued)

- 32 ((colon\$ or rect\$ or colorect\$ or bowel or large intestin\$) adj5 carcinoma\$).tw,mp.
- 33 ((colon\$ or rect\$ or colorect\$ or bowel or large intestin\$) adj5 tumo\$).tw,mp.
- 34 ((colon\$ or rect\$ or colorect\$ or bowel or large intestin\$) adj5 malignan\$).tw,mp.
- 35 ((colon\$ or rect\$ or colorect\$ or bowel or large intestin\$) adj5 adenocarcino-
ma\$).tw,mp.
- 36 29 or 30 or 31 or 32 or 33 or 34 or 35
- 37 exp LIVER/
- 38 (liver or hepatic).mp.
- 39 37 or 38
- 40 28 or 36
- 41 8 and 39 and 40
- 42 5 or 41
- 43 randomized controlled trial.pt.
- 44 controlled clinical trial.pt.
- 45 randomized.ab.
- 46 placebo.ab.
- 47 randomly.ab.
- 48 trial.ab.
- 49 groups.ab.
- 50 43 or 44 or 45 or 46 or 47 or 48 or 49
- 51 (rfta or radio-frequ\$ or radiofrequ\$ or rfa or rf).mp.
- 52 exp Catheter Ablation/
- 53 51 or 52
- 54 percutaneous.mp.
- 55 (ablati* and (therap* or treatment* or radiofrequenc* or cryo*)).mp.
- 56 ((injection* and (ethanol or acetic acid)) or PEI or PAI).mp.
- 57 55 or 56
- 58 54 and 57
- 59 Yttrium Radioisotopes.mp.
- 60 selective internal radi\$.tw,mp.
- 61 radioemboli\$.tw,mp.
- 62 radio-emboli\$.tw,mp.
- 63 sir-sphere\$.tw,mp.
- 64 therasphere\$.tw,mp.
- 65 ((yttrium\$ or \$yttrium or 90y\$ or radiolabel\$) adj5 microsphere\$).tw,mp.

(Continued)

66 59 or 60 or 61 or 62 or 63 or 64 or 65

67 exp Chemoembolisation, Therapeutic/

68 exp Embolisation, Therapeutic/

69 (((transcatheter or transarterial) and (emboli* or chemoemboli*)) or TAE or TACE or lipiodolisation or lipiodol embolisation).mp.

70 exp Infusions, Intraarterial/

71 (lipiodol or HAI or arterial infusion or targeted chemotherapy).mp.

72 ((transcatheter or transarterial) and chemo-infusion).mp.

73 Iodized Oil.mp.

74 67 or 68 or 69 or 70 or 71 or 72 or 73

75 exp Hyperthermia, Induced/

76 thermotherapy.mp.

77 exp MICROWAVES/

78 Electrocoagulation.mp.

79 coagulation therapy.mp.

80 exp Catheter Ablation/

81 ablation.mp.

82 cryosurgery.mp. or exp CRYOSURGERY/

83 53 or 58 or 66 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82

84 42 and 52 and 83

WHAT'S NEW

Date	Event	Description
29 October 2019	Amended	A sentence in the Plain language summary is simplified following a consumer request. It read: " Regarding adverse events and complications, separately and in total, our calculation showed no evidence of a difference in recurrence of the malignancy in the liver" and now it reads: " We found no evidence of a difference in proportion of participants with recurrence of the malignancy in the liver".

HISTORY

Protocol first published: Issue 3, 2011

Review first published: Issue 6, 2013

Date	Event	Description
26 June 2018	New search has been performed	Updated search, background, and methodological part of the review protocol
26 June 2018	New citation required but conclusions have not changed	No new trials fulfilled the inclusion criteria of the review; no change of overall conclusions

CONTRIBUTIONS OF AUTHORS

JK developed the concept for the project.

RR and JK formulated the search strategy and carried out searches.

MMB, RR, JWM, MP, DS, MJS, and RW performed study inclusion and data extraction.

MB, RR, and RW performed analyses.

MB, RR, JWM, MP, RW, DS, MJS, and JK prepared the text.

DECLARATIONS OF INTEREST

MMB: works as a freelancer for a company that does work for a number of pharmaceutical companies in unrelated indication; she was unaware of any conflict of interest.

RR, RW, and JK: all declare that the company they work for/own does work for a number of pharmaceutical companies in unrelated indications, and that they were unaware of any conflict of interest.

JWM: none.

MP: received speaking honoraria and travel grants from Nestle, Nutricia, Roche, and Johnson & Johnson. He is unaware of any conflict of interest.

DS: none.

MJS: none.

SOURCES OF SUPPORT

Internal sources

- Kleijnen Systematic Reviews (KSR) Ltd., UK.

KSR funded the updating of the review and producing Cochrane Reviews.

External sources

- The Dutch Health Care Insurance Board (currently ZIN – The National Health Care Institute (Zorginstituut Nederland)), Netherlands.

This systematic review was funded by the Dutch Health Care Insurance Board (CVZ). CVZ commissioned a systematic review of the effectiveness of non-surgical ablation methods for liver metastases.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- Amended inclusion criteria for Types of studies: Instead of " We will include all randomised clinical trials assessing the beneficial and harmful effects of percutaneous ethanol injection and its comparators, irrespective of publication status, language, or blinding. Quasi-randomised and observational studies that will come with the search, will be considered only for the report of harm.", it now reads "Randomised clinical trials assessing the beneficial and harmful effects of cryotherapy and its comparators, irrespective of publication status, language, or blinding. By choosing this strategy, we were aware that we put more focus on potential benefits and may have overlooked late occurring or rare harms which are often missed in randomised clinical trials ([Storebø 2018](#)). If we demonstrated benefits from using cryotherapy in people with liver metastasis, then a systematic review of adverse events of cryotherapy in people with liver metastasis ought to be launched ([Storebø 2018](#)). However, we considered quasi-randomised and other controlled studies, identified in the search results and if relevant to the review topic, only for the reporting of data on harm."
- Health-related quality of life moved to secondary outcomes.
- An error found in formulating the outcome "Time to progression to liver metastases" is now corrected and reads "Time to progression of liver metastases."
- We were unable to perform the planned analyses due to a lack of data.

INDEX TERMS**Medical Subject Headings (MeSH)**

*Cryotherapy [methods]; Colorectal Neoplasms [pathology]; Liver Neoplasms [*secondary] [*therapy]; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Humans