Cochrane
Library

Cochrane Database of Systematic Reviews

Percutaneous ethanol injection for liver metastases (Review)

Swierz MJ, Storman D, Riemsma RP, Wolff R, Mitus JW, Pedziwiatr M, Kleijnen J, Bala MM

Swierz MJ, Storman D, Riemsma RP, Wolff R, Mitus JW, Pedziwiatr M, Kleijnen J, Bala MM.
Percutaneous ethanol injection for liver metastases.
Cochrane Database of Systematic Reviews 2020, Issue 2. Art. No.: CD008717.
DOI: [10.1002/14651858.CD008717.pub3](https://doi.org/10.1002/14651858.CD008717.pub3).

www.cochranelibrary.com

Percutaneous ethanol injection for liver metastases (Review)

Copyright © 2020 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	4
BACKGROUND	6
OBJECTIVES	7
METHODS	7
RESULTS	10
Figure 1.	11
Figure 2.	12
Figure 3.	13
Figure 4.	14
DISCUSSION	15
AUTHORS' CONCLUSIONS	15
ACKNOWLEDGEMENTS	16
REFERENCES	17
CHARACTERISTICS OF STUDIES	21
APPENDICES	23
WHAT'S NEW	35
CONTRIBUTIONS OF AUTHORS	35
DECLARATIONS OF INTEREST	35
SOURCES OF SUPPORT	36
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	36
INDEX TERMS	36

[Intervention Review]

Percutaneous ethanol injection for liver metastases

Mateusz J Swierz¹, Dawid Storman², Robert P Riemsma³, Robert Wolff³, Jerzy W Mitus⁴, Michal Pedziwiatr⁵, Jos Kleijnen^{3,6}, Malgorzata M Bala⁷

¹Department of Hygiene and Dietetics, Systematic Reviews Unit, Jagiellonian University Medical College, Krakow, Poland. ²Department of Hygiene and Dietetics, Systematic Reviews Unit, Jagiellonian University Medical College, Department of Adult Psychiatry, University Hospital, Krakow, Poland. ³Kleijnen Systematic Reviews Ltd, York, UK. ⁴Department of Surgical Oncology, The Maria Skłodowska-Curie Institute, Oncology Center, Krakow Branch; Department of Anatomy, Jagiellonian University Medical College, Krakow, Poland. ⁵2nd Department of General Surgery, Jagiellonian University Medical College, Krakow, Poland. ⁶School for Public Health and Primary Care (CAPHRI), Maastricht University, Maastricht, Netherlands. ⁷Chair of Epidemiology and Preventive Medicine, Department of Hygiene and Dietetics; Systematic Reviews Unit, Jagiellonian University Medical College, Krakow, Poland

Contact: Mateusz J Swierz, Department of Hygiene and Dietetics, Systematic Reviews Unit, Jagiellonian University Medical College, Krakow, Poland. mefiu11@onet.eu.

Editorial group: Cochrane Hepato-Biliary Group.

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 2, 2020.

Citation: Swierz MJ, Storman D, Riemsma RP, Wolff R, Mitus JW, Pedziwiatr M, Kleijnen J, Bala MM. Percutaneous ethanol injection for liver metastases. *Cochrane Database of Systematic Reviews* 2020, Issue 2. Art. No.: CD008717. DOI: [10.1002/14651858.CD008717.pub3](https://doi.org/10.1002/14651858.CD008717.pub3).

Copyright © 2020 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

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 or other extrahepatic primary cancers. Liver metastases are significantly more common than primary liver cancer, and the reported long-term survival rate after radical surgical treatment is approximately 50%. However, R0 resection (resection for cure) is not feasible in the majority of patients; therefore, other treatments have to be considered. One of these is percutaneous ethanol injection (PEI), which causes dehydration and necrosis of tumour cells, accompanied by small-vessel thrombosis, leading to tumour ischaemia and destruction of the tumour.

Objectives

To assess the beneficial and harmful effects of percutaneous ethanol injection (PEI) compared with no intervention, other ablation methods, or systemic treatments in people with liver metastases.

Search methods

We searched the following databases up to 10 September 2019: the Cochrane Hepato-Biliary Group Controlled Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library; MEDLINE Ovid; Embase Ovid; Science Citation Index Expanded; Conference Proceedings Citation Index – Science; Latin American Caribbean Health Sciences Literature (LILACS); and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). We also searched clinical trials registers such as ClinicalTrials.gov, the International Clinical Trials Registry Platform (ICTRP), and the US Food and Drug Administration (FDA) (17 September 2019).

Selection criteria

Randomised clinical trials assessing beneficial and harmful effects of percutaneous ethanol injection and its comparators (no intervention, other ablation methods, systemic treatments) for liver metastases.

Data collection and analysis

We followed standard methodological procedures as outlined by Cochrane. We extracted information on participant characteristics, interventions, study outcomes, study design, and trial methods. Two review authors performed data extraction and assessed risk of bias independently. We assessed the certainty of evidence by using GRADE. We resolved disagreements by discussion.

Main results

We identified only one randomised clinical trial comparing percutaneous intratumour ethanol injection (PEI) in addition to transcatheter arterial chemoembolisation (TACE) versus TACE alone. The trial was conducted in China and included 48 trial participants with liver metastases: 25 received PEI plus TACE, and 23 received TACE alone. The trial included 37 male and 11 female participants. Mean participant age was 49.3 years. Sites of primary tumours included colon (27 cases), stomach (12 cases), pancreas (3 cases), lung (3 cases), breast (2 cases), and ovary (1 case). Seven participants had a single tumour, 15 had two tumours, and 26 had three or more tumours in the liver. The bulk diameter of the tumour on average was 3.9 cm, ranging from 1.2 cm to 7.6 cm.

Participants were followed for 10 months to 43 months. The trial reported survival data after one, two, and three years. In the PEI + TACE group, 92%, 80%, and 64% of participants survived after one year, two years, and three years; in the TACE alone group, these percentages were 78.3%, 65.2%, and 47.8%, respectively. Upon conversion of these data to mortality rates, the calculated risk ratio (RR) for mortality at last follow-up when PEI plus TACE was compared with TACE alone was 0.69 (95% confidence interval (CI) 0.36 to 1.33; very low-certainty evidence) after three years of follow-up. Local recurrence was 16% in the PEI plus TACE group and 39.1% in the TACE group, resulting in an RR of 0.41 (95% CI 0.15 to 1.15; very low-certainty evidence). Forty-five out of a total of 68 tumours (66.2%) shrunk by at least 25% in the PEI plus TACE group versus 31 out of a total of 64 tumours (48.4%) in the TACE group. Trial authors reported some adverse events but provided very few details. We did not find data on time to mortality, failure to clear liver metastases, recurrence of liver metastases, health-related quality of life, or time to progression of liver metastases.

The single included trial did not provide information on funding nor on conflict of interest.

Authors' conclusions

Evidence for the effectiveness of PEI plus TACE versus TACE in people with liver metastases is of very low certainty and is based on one small randomised clinical trial at high risk of bias. Currently, it cannot be determined whether adding PEI to TACE makes a difference in comparison to using TACE alone. Evidence for benefits or harms of PEI compared with no intervention, other ablation methods, or systemic treatments is lacking.

PLAIN LANGUAGE SUMMARY

Percutaneous ethanol injection for liver metastases

Is local destruction of the cancer that spread to the liver with percutaneous ethanol injection beneficial?

Review question

What is the effect of using percutaneous ethanol injection (PEI) to destroy any cancer metastases in the liver? Metastases are new cancer sites that are found in parts of the body other than the site of the original cancer. We were looking for any randomised trial (a study in which patients are allocated to groups by a play of chance) assessing effects of PEI in people with metastases in the liver from cancer of any location compared with no PEI with or without co-interventions. We looked at effects of PEI on risk of death, progression of disease, health-related quality of life, and adverse events (unwanted effects caused by the intervention).

Background

When cancer spreads in the body (metastasis), one of the most common sites of metastasis is the liver. Besides cancers of the liver (primary liver cancer), liver metastases from colorectal cancer are the most common cancers affecting the liver. More than half of people who have cancer spread to the liver die of complications. Metastases in the liver can be destroyed by several different methods, one of them being PEI. This procedure is performed under ultrasound or computed tomography guidance; a special needle is placed at the cancer site and is subsequently used to inject alcohol with the goal of killing cancer tissues. Ultrasound and computed tomography are imaging procedures. Alcohol induces tumour destruction by drawing water out of tumour cells (dehydrating them), thereby altering (denaturing) the structure of the cellular proteins.

Search results and study characteristics

We last searched for evidence on 10 September 2019. We included only one randomised trial comparing percutaneous intratumour ethanol injection in combination with transcatheter arterial chemoembolisation (TACE; a liver-directed treatment whereby chemotherapy is administered through the catheter directly to blood vessels supplying the tumour) to TACE alone. Forty-eight people with liver metastases were included; 25 received PEI with TACE, and 23 received TACE alone. Primary tumours were colon, stomach, pancreas, lung, breast, and ovary cancers.

The included study did not provide information on funding nor on conflict of interest.

Key results

Results of one small randomised clinical trial do not show beneficial or harmful effects of adding percutaneous intratumour ethanol injection to TACE in people with liver metastases with respect to mortality or local recurrence in comparison with TACE alone. Participants were followed for between 10 and 43 months. The tumour necrosis was larger in the combined treatment group. Trial authors reported some adverse events but gave very few details. We found no data on time to mortality, failure to clear liver metastases, recurrence of liver metastases, health-related quality of life, or time to progression of liver metastases.

Quality of evidence

We judged the evidence to be of very low certainty because the identified study was at high risk of bias, had a relatively small sample size, described few events overall, and reported inconclusive results.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Percutaneous ethanol injection compared to no intervention, other ablation methods, or systemic treatment for liver metastases

Percutaneous ethanol injection compared to no intervention, other ablation methods, or systemic treatment for liver metastases

Patient or population: patients with liver metastases

Setting: hospital

Intervention: percutaneous ethanol injection (PEI) added to transcatheter arterial chemoembolisation (TACE)

Comparison: transcatheter arterial chemoembolisation (TACE)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Risk with TACE	Risk with PEI + TACE				
Mortality at last follow-up: 3 years	522 per 1000	360 per 1000 (187 to 695)	RR 0.69 (0.36 to 1.33)**	48 (1 RCT)	⊕⊕⊕⊕ Very low ^{a,b}	The trial reported survival data after 1, 2, and 3 years. This was 92%, 80%, and 64% in the PEI + TACE group, and 78.3%, 65.2%, and 47.8% in the TACE group. We converted data into mortality and calculated an RR for mortality at 3 years' follow-up
Time to mortality	Outcome not reported					
Health-related quality of life	Outcome not reported					
Failure to clear liver metastases or recurrence of liver metastases	Study population		RR 0.41 (0.15 to 1.15)**	48 (1 RCT)	⊕⊕⊕⊕ Very low ^{a,c}	
	391 per 1000	160 per 1000 (58 to 450)				
Time to progression of liver metastases	Outcome not reported					

Tumour response measures	Outcome not reported by a number of patients, but number of tumours shrunk by at least 25%. This was 45 out of 68 tumours (66.2%) in PEI + TACE group and 31 out of 64 (48.4%) in TACE group	48 (1 RCT)	⊕⊕⊕⊕ Very low ^{a,d}
Serious adverse events and complications	Trial authors reported some adverse events but provided very few details. No complications related to the conduct of the interventional therapy were reported		

***The risk in the intervention group (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).

**Calculated using the Review Manager calculator.

CI: confidence interval; RCT: randomised clinical trial; RR: risk ratio

GRADE Working Group grades of evidence.

- **High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- **Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aDowngraded by two levels due to within-study risk of bias: the trial did not describe allocation concealment or blinding.

^bDowngraded by two levels due to imprecision: 95% CI including both benefit and harm and a small sample size - the optimal information size (OIS) is not reached (calculated OIS = 147). Only 48 respondents were included in the two relevant intervention groups (intervention = 25, control = 23).

^cDowngraded by two levels due to imprecision: 95% CI including both benefit and harm and a small sample size - the optimal information size (OIS) is not reached (calculated OIS = 58). Only 48 respondents were included in the two relevant intervention groups (intervention = 25, control = 23).

^dDowngraded by two levels due to imprecision: inability to calculate the effect of intervention due to wrong unit of analysis issue and a small sample size. Only 48 respondents were included in the two relevant intervention groups (intervention = 25, control = 23).

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 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% 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; this rate is higher in countries with a higher incidence and lower in 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 leading cause of cancer death among men and the third among 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 diagnosis of colorectal cancer is 64.5% (Howlader 2018). In all high-income countries analysed together in 2005, estimated survival was 55% (Parkin 2005), and 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 patients). In Europe, the relative survival rate for five years was 57% for colon cancer and 56% for rectal cancer (Holleczeck 2015). Although improvement in long-term survival has been reported since the 2000s, CONCORD-3 analysis shows 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 the mortality rate is 18.6 per 100,000 people of both sexes; 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 of lung cancer (1.76 million deaths; 18.4% of the total) (GCO 2018). In all high-income countries analysed together, estimated survival after diagnosis of lung cancer is 12% among 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 in the USA were diagnosed with this type of cancer, with an estimated 10,470 deaths related to the disease. Endometrial cancer accounts for 26.0 new cases per 100,000 women per year and 4.6 deaths per 100,000 women per year (Howlader 2018). In all, 66.9% of women with uterine cancer receive the diagnosis 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% (Howlader 2018).

Although the incidence has declined over past decades, almost 0.8 million new cases of 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 to 32.1 in Eastern Asia per 100,000 men, and from 4.0 to 13.2 in Eastern Asia per 100,000 women (GCO 2018). Thanks to improvements in surgical techniques and radiotherapy and the introduction of neoadjuvant therapy regimens, overall survival after gastric cancer treatment has improved over the past two decades (Song 2017).

For people with liver metastases, surgical resection may cure the disease, but only a limited number of these patients 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); and 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

Percutaneous ethanol injection (PEI) is a technique whereby pure alcohol is injected into liver cancers. This causes dehydration, denaturation, and necrosis of tumour cells accompanied by small-vessel thrombosis, leading to tumour ischaemia and destruction (EASL 2018). PEI is performed with a very thin needle that is placed through the skin (percutaneously) into the tumour, usually under ultrasound or computed tomography (CT) visual guidance, to inject ethanol into liver cancer cells. These injections are repeated on separate days. PEI is well established for treatment of nodular-type hepatocellular carcinoma (HCC), resulting in complete necrosis in 90% of tumours smaller than 2 cm. However, for most tumours 2 cm or larger, PEI is associated with incomplete necrosis and a high local recurrence rate, which may reach as high as 49% (EASL 2018). Although data are available for PEI application in liver tumours, this treatment is mainly limited to HCC; data regarding liver metastases are limited, given that PEI is an uncommon, optional treatment with limited indications for use (mainly for small liver metastases when surgery is contraindicated) (Qian 2011; Revel-Mouroz 2017). Percutaneous acetic acid injection (PAI) has been used as an alternative to PEI; however, PAI has not offered substantial advantages when compared to PEI (Ohnishi 1996; Ohnishi 1998; EASL 2018). Common contraindications for PEI and PAI are cirrhosis with poor liver function (Child C cirrhosis), complete portal vein thrombosis, and massive ascites.

How the intervention might work

All local ablative techniques offer the advantages of preserving the uninvolved liver parenchyma and eliminating the morbidity and mortality associated with major hepatic surgery. Percutaneous local ablative therapies are currently considered as the preferred option for early unresectable HCC (Weis 2015). Among percutaneous local ablative therapies for HCC, meta-analyses of randomised clinical trials have favoured radiofrequency ablation over PEI in terms of survival and recurrence (EASL 2018). However, strong evidence shows that PEI is an option in some cases for which thermal ablation is not technically feasible, especially in small tumours (EASL 2018). No such data are available regarding PEI for liver metastases.

Why it is important to do this review

For people with liver metastases, local or regional treatment methods can provide local control, but the long-term outcomes of some of these interventions are uncertain. Systematic reviews may help to establish the trade-off between benefits and harms associated with different non-surgical methods for treatment of all forms of malignant liver tumours (primary and metastases). Systematic reviews published so far focus mostly on primary liver tumours or colorectal cancer liver metastases and include mainly retrospective studies (Llovet 2003; Decadt 2004; Marlow 2006; Sutherland 2006; Li 2017; Kacmaz 2019). There is one Cochrane Review entitled "Percutaneous ethanol injection or percutaneous acetic acid injection for early hepatocellular carcinoma", which was last updated in 2015 (Schoppmeyer 2009; Weis 2015). However, no systematic reviews have compared PEI with no intervention, other ablation methods, or systemic treatments in people with liver metastases. Therefore, a systematic review focusing on all types of malignant liver metastases is warranted.

OBJECTIVES

To assess the beneficial and harmful effects of percutaneous ethanol injection (PEI) 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 PEI versus no intervention, other ablation methods, or systemic treatment, 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 rare harms, which are often missed in randomised clinical trials (Storebø 2018). Relevant quasi-randomised and other controlled studies that were identified in the searches were considered only for reporting of data on harms.

Types of participants

Patients with liver metastases, irrespective of the primary location of the tumour.

Types of interventions

Experimental intervention

Percutaneous ethanol injection (PEI).

Control intervention

No intervention, other ablation methods (such as ablation with cryotherapy, microwave, radiofrequency, photocoagulation with laser, embolisation, chemoembolisation, and radioembolisation), or systemic treatments (such as chemotherapy, immunotherapy, and radiotherapy).

Co-interventions were allowed if provided equally to experimental and control groups in individual randomised trials.

Types of outcome measures

Primary outcomes

- Mortality at last follow-up
- Time to mortality
- Health-related quality of life

Secondary outcomes

- 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)
- Any adverse events or complications - 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, or resulted in persistent or significant disability, and any important medical event that may have jeopardised the person or required intervention to prevent it. All other adverse events were considered non-serious

We planned to extract data at the longest 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; in September 2019); the Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 9), in the Cochrane Library; MEDLINE Ovid (1946 to September 2019); Embase Ovid (1974 to September 2019); Science Citation Index Expanded (Web of Science; 1900 to September 2019); Conference Proceedings Citation Index - Science (Web of Science; 1990 to September 2019); Latin American Caribbean Health Sciences Literature (LILACS; Bireme; 1982 to September 2019); and the Cumulative Index to Nursing and Allied Health Literature (CINAHL; EBSCOhost; 1981 to September 2019) (Royle 2003).

Up to 5 June 2017, we carried out searches for this review as a global search for a full review of non-surgical ablation methods in people with liver metastases or primary malignant liver tumours (Riemsma 2009). These search strategies with time spans are given

in [Appendix 1](#). When updating the searches on 9 July 2018, we developed new individual search strategies, given in [Appendix 2](#). In addition, we searched the clinical trials register World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; www.who.int/ictip/en/), as well as all US Food and Drug Administration (FDA) approvals and investigational device exemptions as found on www.fda.gov/.

For the current update, we reran the searches on 10 September 2019. We searched WHO, FDA, and clinicaltrials.gov registers on 17 September 2019 (keywords used: liver ethanol, ethanol injection, percutaneous ethanol injection).

Searching other resources

We searched reference lists of relevant reviews (such as [Li 2017](#) and [Kacmaz 2019](#)), Health Technology Assessment (HTA) reports (such as [Marlow 2006](#) and [Loveman 2014](#)), relevant Cochrane Reviews ([Weis 2015](#)), and the included trial.

Data collection and analysis

We performed the systematic review according to the recommendations of Cochrane ([Higgins 2011](#)).

Selection of studies

Two review authors in pairs independently screened titles and abstracts of identified studies. We resolved any differences in opinion by discussion or, if necessary, by consultation with a third review author. Full-text screening was performed in pairs by two independent review authors, and differences in opinion were resolved as mentioned above.

Data extraction and management

We extracted relevant data on participant characteristics, interventions, comparisons, study outcome measures, time of follow-up, and trial design and methods. We used a data extraction form that was previously developed for another review on non-surgical ablation methods. Data extraction was done in pairs by two independent review authors.

Assessment of risk of bias in included studies

Risk of bias in included studies was assessed based on the domains described below ([Schulz 1995](#); [Moher 1998](#); [Kjaergard 2001](#); [Gluud 2008](#); [Wood 2008](#); [Higgins 2011](#); [Savović 2012a](#); [Savović 2012b](#); [Hrobjartsson 2013](#); [Hrobjartsson 2014a](#); [Hrobjartsson 2014b](#); [Savović 2018](#)). This assessment was done separately for each trial and was then considered in relation to overall reliability of the evidence. This was done in pairs by two independent review authors.

Allocation sequence generation

- Low risk of bias: study authors performed sequence generation using computer random number generation or a random numbers 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: study authors did not specify the method of sequence generation
- High risk of bias: sequence generation method was not random

Allocation concealment

- Low risk of bias: participant allocations could not have been foreseen in advance of, or during, enrolment. A central and independent randomisation unit controlled allocation. 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: study authors did not describe the method used to conceal the allocation, so intervention allocations may have been foreseen before, or during, enrolment
- High risk of bias: it is likely that investigators who assigned participants knew the allocation sequence

Blinding of participants and personnel

- Low risk of bias: either of the following: no blinding or incomplete blinding, but 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

Blinding of outcome assessment

- Low risk of bias: either of the following: no blinding of outcome assessment, but 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: information was insufficient 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: results were likely to be biased due to missing data

Selective outcome reporting

- Low risk of bias: the trial reported the following pre-defined 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 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: study authors did not report all pre-defined outcomes fully, or it was unclear whether or not study authors recorded data on these outcomes
- High risk of bias: study authors did not report one or more pre-defined 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: other factors in the trial could have put it at risk of bias

We judged a trial to be at low overall risk of bias if assessed as having low risk of bias in all of the above domains. We judged a trial to be at high overall risk of bias if assessed as having unclear or high risk of bias in one or more of the above domains.

Measures of treatment effect

For dichotomous variables, we planned to calculate the risk ratio (RR) with 95% confidence interval (CI). For continuous variables, we planned to calculate the standardised mean difference with 95% CI for outcomes such as quality of life when different scales could be used. 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 sets of results if we noted discrepancies in the results. If not, we planned to report results of the random-effects model. However, we could not perform the planned analyses 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 the total number of randomised participants in the analyses.

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 χ^2 and I^2 statistical methods (Higgins 2011). We planned to discuss any plausible, possible causes of heterogeneity. However, this was not possible, as we identified only one trial for inclusion in our review.

Data synthesis

We followed the instructions given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). 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 relevant measures of effect for 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; Tierney 2007). We planned to extract from the publications information on, for example, hazard ratios, P values, events ratios, curve data, and follow-up, and enter them into a Microsoft Office Excel 2003 spreadsheet to calculate log hazard ratios and their standard errors (Tierney 2007). 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, to show the variance of effects (Egger 1997). We planned to include cross-over trials, if identified, using 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 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 differences and similarities of the included trials and their risk of bias assessments. We planned to group 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. As we identified only one trial, it was not possible to apply meta-analyses and statistical methods.

We planned to use funnel plots to identify 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.

When possible, we planned to examine apparent significant beneficial and harmful intervention effects using Trial Sequential Analysis (Thorlund 2011; TSA 2011; Wetterslev 2017) 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 an analysis, as only one trial was included.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses, when possible, based on prognostic indicators such as age, sex, tumour size, location of primary tumour, and use of any co-interventions. 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. We were not able to perform such analyses, as only one trial was included.

Sensitivity analysis

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

'Summary of findings' tables

We used the GRADE system to evaluate the certainty of evidence for our primary (mortality at last follow-up, time to mortality)

and secondary outcomes (failure to clear liver metastases or recurrence of liver metastases, time to progression of liver metastases, tumour response measures, health-related quality of life, any adverse events or complications) ([GRADEpro GDT](#)). We considered within-study risk of bias (methodological quality) based on individual domains, as well as 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 levels of certainty in the evidence as 'high', 'moderate', 'low', or 'very low'.

- High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

RESULTS

Description of studies

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

Results of the search

Up to 5 June 2017, we carried out searches for this review as a global search for a full review of non-surgical ablation methods in people with liver metastases or primary malignant liver tumours ([Riemsma 2009](#)). These search strategies with time spans are given in [Appendix 1](#); they 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 ([Liang 2007](#)). We excluded 334 references because they did not describe randomised clinical trials (149), they examined another intervention not relevant for this review (142), the population was not relevant for this review (29), the comparison was not relevant for this review (13), or study authors examined outcomes not relevant for this review (1). We identified no ongoing trials. We did not run separate searches for non-randomised studies; therefore we checked eligibility only for studies that came up during searches for randomised trials, and none of these studies was eligible for inclusion. A summary of the searches is provided in [Figure 1](#).

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

When updating the searches on 9 July 2018, we developed the new search strategies given in [Appendix 2](#). In addition, we searched the clinical trials registry WHO ICTRP (www.who.int/ictip/en/), as well as all US FDA approvals and investigational device exemptions as found on www.fda.gov/.

For the current update, we reran the searches on 10 September 2019. We searched WHO, FDA, and ClinicalTrials.gov databases on 17 September 2019. As outlined in indications for study flow diagrams in Cochrane systematic review updates, we reported cumulative results for updates ([Stovold 2014](#)). Altogether, with both updates considered (9 July 2018 and 10 September 2019), we found 4507 new references, of which 1630 were screened after 2877

duplicates were removed. We excluded 1625 references based on title and abstract; as a result, we screened five full-text publications. None of these studies matched the eligibility criteria. Four studies were excluded because of study design (not a randomised clinical

trial), as was one study because it was irrelevant for the review population. We did not identify any ongoing studies by searching the clinical trials registers. A summary of the updated searches is provided in [Figure 2](#).

Figure 2. Flow chart for identification of randomised trials for inclusion in the updates. RCT: randomised clinical trial.

Included studies

We included one randomised trial comparing percutaneous intratumour ethanol injection (PEI) plus transcatheter arterial chemoembolisation (TACE) versus TACE alone ([Liang 2007](#)). Forty-eight patients with liver metastases were included; 25 received PEI plus TACE, and 23 received TACE alone.

The trial included 37 male and 11 female participants. Mean age was 49.3 years, with an age range of 34 to 81 years. Participants were followed for between 10 months and 43 months. The trial was performed between November 1998 and April 2003.

Sites of the primary tumours included colon (27 cases), stomach (12 cases), pancreas (3 cases), lung (3 cases), breast (2 cases), and ovary (1 case). Seven participants had a single tumour in the liver, 15 had two tumours, and 26 had three or more tumours. Among the 48 participants, nine had metastases in organs other than the liver. The total number of liver metastases in the PEI + TACE group was 68, and 64 in the TACE group. Tumour bulk diameter on average was 3.9

cm, ranging from 1.2 to 7.6 cm. Primary cancers were established by surgical resection and histopathological examination. Metastases were diagnosed during treatment or re-examination by ultrasound B, computed tomography (CT), or magnetic resonance imaging (MRI); in nine participants, metastases were established by liver puncture biopsy.

The included trial did not provide information on funding nor on conflict of interest.

Excluded studies

We excluded studies because of their study design, or because they were irrelevant for the review population, irrelevant for the review intervention, irrelevant for the review comparison, or irrelevant for the review outcomes (see [Characteristics of excluded studies](#)).

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

Risk of bias in included studies

Overall, we judged the trial to be at high risk of bias. For an overview of the methodological quality of the included trial, see [Figure 3](#)

and [Figure 4](#), and for trial characteristics and details of risk of bias judgements, see [Characteristics of included studies](#).

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

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

Allocation

The trial was described as a randomised clinical trial. However, data regarding sequence generation or allocation concealment were insufficient (unclear risk of bias).

Blinding

Information was insufficient to assess whether participants, physicians, or outcome assessors were properly blinded (unclear risk of bias).

Incomplete outcome data

We judged the analysis methods as appropriate. The trial did not report any data to be missing (low risk of bias).

Selective reporting

Information was insufficient 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 biases (unclear risk of bias).

Effects of interventions

See: [Summary of findings for the main comparison Percutaneous ethanol injection compared to no intervention, other ablation methods, or systemic treatment for liver metastases](#)

One trial compared PEI plus TACE versus TACE (48 participants; [Summary of findings for the main comparison](#)).

We summarised the results in a narrative way.

Primary outcomes

Mortality at last follow-up

The trial reported survival data after one, two, and three years. In the PEI plus TACE group, 92% (23/25 participants), 80% (20/25), and

64% (16/25) of participants survived after one, two, and three years, respectively; these percentages were 78.3% (18/23 participants), 65.2% (15/23), and 47.8% (11/23) for participants in the TACE alone group. Conversion of these into mortality resulted in the following mortality rates: in the PEI plus TACE group, 8% (2/25 participants), 20% (5/25), and 36% (9/25) of participants died after one, two, and three years, respectively; these percentages were 21.7% (5/23 participants), 34.8% (8/23), and 52.2% (12/23) for participants in the TACE alone group.

The risk ratio (RR) for mortality at last follow-up considering PEI plus TACE versus TACE comparison was 0.69 (95% CI 0.36 to 1.33) after three-year follow-up (calculated using the Review Manager calculator).

Time to mortality

Time to mortality was not reported.

Health-related quality of life

Health-related quality of life was not reported.

Secondary outcomes

Failure to clear liver metastases or recurrence of liver metastases

The local recurrence rate was 16% (4/25 participants) in the PEI plus TACE group and 39.1% (9/23) in the TACE group, resulting in an RR of 0.41 (95% CI 0.15 to 1.15) (calculated using the Review Manager calculator).

Time to progression of liver metastases

Time to progression of liver metastases was not reported.

Tumour response measures

Forty-five out of 68 tumours in total (66.2%) shrunk by at least 25% in the PEI plus TACE group versus 31 out of 64 tumours in total (48.4%) in the TACE group.

Any adverse events or complications

Study authors reported adverse events with very few details.

Different levels of burning and painful sensations in the liver region were described in most PEI plus TACE participants, and symptoms like feeling drunk were reported in a few participants. These symptoms disappeared with or without special treatment. No complications related to the conduct of the interventional therapy were reported.

Different serious levels of fever, pain in the liver region, nausea, and vomiting occurred in all 48 participants in the TACE alone group (no specific information provided in the article). All disappeared within two to five days after treatment.

Certainty of the evidence

We created [Summary of findings for the main comparison](#) for all [Primary outcomes](#) and [Secondary outcomes](#) reported in the review. We assessed the evidence as of very low certainty because of risk of bias in the trial (downgraded by two levels due to within-study risk of bias: the trial did not describe allocation concealment nor blinding) and imprecision (downgraded by two levels for small sample size, not reaching the optimal information size (calculated OIS for outcomes ranged from 58 to 147), and wide CIs including both benefit and harm). We could not assess indirectness, heterogeneity, or publication bias because there was only one included trial.

DISCUSSION

Summary of main results

Evidence for the benefits and harms of PEI plus TACE versus TACE in people with liver metastases is based on one, small randomised trial at high risk of bias. Results do not show beneficial or harmful effects of adding percutaneous intratumour ethanol injection (PEI) to transcatheter arterial chemoembolisation (TACE) in people with liver metastases with respect to mortality or local recurrence in comparison with TACE alone. Participants were followed for between 10 months and 43 months. Tumour necrosis was larger in the PEI plus TACE group. Study authors reported some adverse events but provided very few details. We found no evidence on time to mortality, health-related quality of life, failure to clear liver metastases, recurrence of liver metastases, or time to progression of liver metastases.

Overall completeness and applicability of evidence

Both primary and update search strategies were comprehensive and included a wide range of databases and registers. We additionally searched reference lists of the included trial and of relevant review articles.

Quality of the evidence

The included trial did not provide sufficient details to judge the quality of the randomisation process, allocation concealment, presence of blinding, and selective reporting. Therefore, the main limitation of this review is the certainty of available evidence, which was very low because of risk of bias in the trial (downgraded by two levels due to within-study risk of bias: the trial did not describe allocation concealment or blinding) and imprecision (downgraded by two levels for small sample size not reaching the optimal

information size (OIS) and wide confidence intervals (CIs) including both benefit and harm).

Analyses through 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. In a similar vein, the lack of observed effect cannot be taken as proof of no effect, as we simply have too few data.

Potential biases in the review process

The process of the review was rigorous. The review was preceded by publication of a protocol with all review methods described. All review authors were appropriately trained and had previous experience in review preparation. We performed comprehensive searches for both published and unpublished studies. We extracted all relevant data and assessed both risk of bias in the included study and overall certainty of evidence. However, because only one trial was found, we may suspect publication bias, which we cannot assess formally because the minimum number for reasonable assessment of publication bias is 10 trials ([Higgins 2011](#)). Another important issue is reporting bias because the included trial lacked a protocol ([Chan 2004](#)).

Agreements and disagreements with other studies or reviews

We found no other reviews of PEI for people with liver metastases. Consensus on management of metastatic colorectal cancer in Central America and the Caribbean did not provide any guidance on use of PEI, and evidence was based on the previous version of our review ([Lopez 2018](#)).

Management of hepatocellular carcinoma (HCC) has been addressed by the European Association for the Study of the Liver (EASL) through clinical practice guidelines. The treatment of choice is dependent on the Barcelona Clinic Liver Cancer (BCLC) staging system. A preferred treatment option for very early-stage (0) and early-stage (A) HCC - not suitable for surgery - is radiofrequency ablation (RFA) ([EASL 2018](#)). There is a strong recommendation that in cases where RFA is not technically feasible, especially for tumours smaller than 2 cm, PEI is a viable option. Complete necrosis in 90% of tumours smaller than 2 cm has been reported for use of PEI in nodular-type HCC ([EASL 2018](#)). We should refrain from applying these conclusions to the use of PEI for liver metastases, as no convincing evidence is available.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence for the benefits and harms of percutaneous intratumour ethanol injection in people with liver metastases relies on one randomised clinical trial at high risk of bias, comparing PEI plus TACE versus TACE alone. Our confidence in the results is limited due to risk of bias and imprecision; therefore, it cannot be determined whether PEI in addition to TACE versus no intervention or placebo is either beneficial or harmful. Further randomised clinical trials

are likely to change our confidence and the results. We found no evidence showing any benefits or harms of PEI compared with no intervention, other ablation methods, or versus systemic treatments.

Implications for research

Good quality, large randomised clinical trials of PEI (alone or in combination) for people with liver metastases are highly needed. As the quality of the included trial was unsatisfactory, it is important that the randomisation process, blinding methods, and results are clearly described. Future trials ought to be conducted in a way that ensures low risk of random error and low risk of systematic error (bias). Trial authors should follow the SPIRIT statements (SPIRIT 2013a; SPIRIT 2013b), and they should report results of their trials according to the CONSORT statement (www.consort-statement.org).

ACKNOWLEDGEMENTS

We would like to thank Dimitrinka Nikolova for help and Christian Gluud for advice on preparing this systematic review.

Peer Reviewers of the protocol of the review: Thomas Karlas, Germany, and Hans Christian Spangenberg, Germany.

Peer Reviewer of the previous review and the current review: Janus Christian Jakobsen, Denmark.

Contact Editor: Emil Eik Nielsen, Denmark.

Sign-off Editor: Christian Gluud, Denmark.

Cochrane Abdomen and Endocrine Network Associate Editor: Liz Bickerdike, UK.

Cochrane Review Group funding acknowledgement: the Danish State is the largest single funder of the Cochrane Hepato-Biliary Group through its investment in the Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Denmark. Disclaimer: the views and opinions expressed in this review are those of the authors and do not necessarily reflect those of the Danish State or the Copenhagen Trial Unit.

REFERENCES

References to studies included in this review

Liang 2007 {published data only}

Liang YC, Li ZY, Yang JZ, Lin J, Li ZY, Ke X. Transcatheter arterial chemoembolisation combined with CT guided percutaneous intratumor ethanol injection for liver metastases. *Chinese Journal of Interventional Imaging and Therapy* 2007;**4**(1):49-51.

References to studies excluded from this review

Andersson 1989 {published data only}

Andersson M, Aronsen KF, Balch C, Domellof L, Eksborg S, Hafstrom L, et al. Pharmacokinetics of intra-arterial mitomycin C with or without degradable starch microspheres (DSM) in the treatment of non-resectable liver cancer. *Acta Oncologica* 1989;**28**(2):219-22.

Dudeck 2011 {published data only}

Dudeck O, Bulla K, Wieners G, Ruehl R, Ulrich G, Amthauer H, et al. Embolization of the gastroduodenal artery before selective internal radiotherapy: a prospectively randomized trial comparing standard pushable coils with fibered interlock detachable coils. *Cardiovascular and Interventional Radiology* 2011;**34**(1):74-80.

Fiorentini 2012a {published data only}

Fiorentini G, Aliberti C, Coschiera P, Cantore M, Mulazzani L, Catalano V. Trans arterial hepatic embolization (TACE) adopting polyvinyl alcohol microspheres preloaded with irinotecan (DEBIRI) versus systemic therapy (FOLFIRI) for liver metastases (LM) from colorectal cancer (CRC): a randomized study of efficacy, toxicity and quality of life. *Journal of Vascular and Interventional Radiology* 2012;**23**(6):853.e15.

Fiorentini 2012b {published data only}

Fiorentini G, Aliberti C, Tilli M, Coschiera P, Mambrini A, Giordani P, et al. Hepatic arterial embolization adopting polyvinyl alcohol microspheres preloaded with irinotecan versus systemic chemotherapy for hepatic metastases from colorectal cancer: a phase III clinical research trial of activity and quality of life. *Journal of Clinical Oncology* 2012;**30**(Suppl 4):587.

Gootjes 2015 {published data only}

Gootjes EC, Buffart TE, Tol MP, Burger J, Grunhagen DJ, Van Der Stok EP, et al. The ORCHESTRA trial: a phase III trial of adding tumor debulking to systemic therapy versus systemic therapy alone in (mCRC) multi-organ metastatic colorectal cancer. *Journal of Clinical Oncology* 2015;**33**(Suppl 1):15.

Holting 1991 {published data only}

Holting T, Frohmuller S, Aulenbacher P, Peukert M, Schlag P. Locoregional versus systemic chemotherapy in metastatic colorectal cancer – efficacy of an additive immunotherapy with rubratin. A prospective randomized pilot study. *Onkologie* 1991;**14**(5):406-10.

Martinelli 1994 {published data only}

Martinelli DJ, Wadler S, Bakal CW, Cynamon J, Rozenblit A, Haynes H, et al. Utility of embolization or chemoembolization as second-line treatment in patients with advanced or recurrent colorectal carcinoma. *Cancer* 1994;**74**(6):1706-12.

Murthy 2010 {published data only}

Murthy R, Mahvash A, Avritscher R, Erwin W, Chasen B, Eng C. Yttrium microspheres with cetuximab plus irinotecan for patients with advanced colorectal cancer metastases to liver. *Journal of Clinical Oncology* 2010;**28**(15 Suppl):TPS197.

Pingpank 2010 {published data only}

Pingpank JF, Hughes MS, Alexander HR, Faries MB, Zager JS, Royal R, et al. A phase III random assignment trial comparing percutaneous hepatic perfusion with melphalan (PHP-mel) to standard of care for patients with hepatic metastases from metastatic ocular or cutaneous melanoma. *Journal of Clinical Oncology* 2010;**28**(Suppl):18.

Power 2010 {published data only}

Power DG, Capanu M, Patel D, Gewirtz A, Jarnagin WR, Fong Y, et al. Unexpected increased biliary toxicity when systemic bevacizumab is added to hepatic arterial infusion. *Journal of Clinical Oncology* 2010;**15**(Suppl):3559.

Safi 1989 {published data only}

Safi F, Bittner R, Roscher R, Schuhmacher K, Gaus W, Beger GH. Regional chemotherapy for hepatic metastases of colorectal carcinoma (continuous intraarterial versus continuous intraarterial/intravenous therapy). Results of a controlled clinical trial. *Cancer* 1989;**64**(2):379-87.

Soemarno 2002 {published data only}

Soemarno A, Akbar N, Noer S, Soewandhi. Long term survival rates after transcatheter arterial chemoembolization (TACE) and percutaneous ethanol. *Journal of Hepatology* 2002;**36**:220.

Wiley 1989 {published data only}

Wiley AL Jr, Wirtanen GW, Stephenson JA, Ramirez G, Demets D, Lee JW. Combined hepatic artery 5-fluorouracil and irradiation of liver metastases. A randomized study. *Cancer* 1989;**64**(9):1783-9.

Xie 2000 {published data only}

Xie L, Pang R, Jin Y, Xiang S, Li H. Effects of hepatic artery chemotherapeutic embolization combined with perfusing LAK cells into hepatic artery after radical operation of liver cancer. *Chung Hua Kan Tsang Ping Tsa Chih* 2000;**8**(3):142-3.

Additional references

Bilchik 2000

Bilchik AJ, Wood TF, Allegra D, Tsioulas GJ, Chung M, Rose DM, et al. Cryosurgical ablation and radiofrequency ablation for unresectable hepatic malignant neoplasms: a proposed algorithm. *Archives of Surgery* 2000;**135**(6):657-64.

Bipat 2007

Bipat S, van Leeuwen MS, Ijzermans JN, Comans EF, Planting AS, Bossuyt PM, et al. Evidence-based guideline on management of colorectal liver metastases in the Netherlands. *Netherlands Journal of Medicine* 2007;**65**(1):5-14.

Brok 2008

Brok J, Thorlund K, Gluud C, Wetterslev J. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. *Journal of Clinical Epidemiology* 2008;**61**:763-9.

Brok 2009

Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently conclusive meta-analyses may be inconclusive - trial sequential analysis adjustment for random error risk in conclusive neonatal meta-analyses. *International Journal of Epidemiology* 2009;**38**:287-98.

Chakedis 2017

Chakedis J, Squires MH, Beal EW, Hughes T, Lewis H, Paredes A, et al. Update on current problems in colorectal liver metastasis. *Current Problems in Surgery* 2017;**54**(11):554-601.

Chan 2004

Chan AW, Hróbjartsson A, Haahr MT, Gøtzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. *JAMA* 2004;**291**:2457-65.

CONCORD-3

Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Nikšić M, et al. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet* 2018;**391**(10125):1023-75.

Decadt 2004

Decadt B, Siriwardena AK. Radiofrequency ablation of liver tumours: systematic review. *Lancet Oncology* 2004;**5**:550-60.

DerSimonian 1986

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**(3):177-88.

EASL 2018

European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. *Journal of Hepatology* 2018;**69**:182-236.

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical Research Ed.)* 1997;**315**:629-34.

Ferlay 2013

Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *European Journal of Cancer* 2013;**49**:1374-403.

Forner 2018

Forner A, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet* 2018;**391**:1301-14.

GCO 2018

Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer; 2018. gco.iarc.fr/today/data/factsheets/cancers/10_8_9-Colorectum-fact-sheet.pdf (accessed 19 December 2018).

Global Burden of Disease Cancer Collaboration 2017

Global Burden of Disease Cancer Collaboration. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. *JAMA Oncology* 2017;**3**(4):524-48.

Gluud 2008

Gluud LL, Thorlund K, Gluud C, Woods L, Harris R, Sterne JA. Correction: reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. *Annals of Internal Medicine* 2008;**149**(3):219.

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime). GRADEpro GDT. Version accessed 4 December 2018. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Greenland 1985

Greenland S, Robins JM. Estimation of a common effect parameter from sparse follow-up data. *Biometrics* 1985;**41**:55-68.

Higgins 2011

Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Holleczer 2015

Holleczer B, Rossi S, Domenic A, Innos K, Minicozzi P, Francisci S, et al. EURO-CARE-5 Working Group. On-going improvement and persistent differences in the survival for patients with colon and rectum cancer across Europe 1999-2007 - results from the EURO-CARE-5 study. *European Journal of Cancer* 2015;**51**(15):2158-68.

Howlader 2018

Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, et al. SEER Cancer Statistics Review, 1975-2016, 2018. seer.cancer.gov/csr/1975_2016/ (accessed 6 March 2019).

Hrobjartsson 2013

Hrobjartsson A, Thomsen AS, Emanuelsson F, Tendal B, Hilden J, Boutron I, et al. Observer bias in randomized clinical trials with measurement scale outcomes: a systematic review of trials with both blinded and nonblinded assessors. *Canadian Medical Association Journal* 2013;**185**(4):201-11.

Hrobjartsson 2014a

Hrobjartsson A, Emanuelsson F, Skou Thomsen AS, Hilden J, Brorson S. Bias due to lack of patient blinding in clinical trials. A systematic review of trials randomizing patients to blind and nonblind sub-studies. *International Journal of Epidemiology* 2014;**43**(4):1272-83.

Hrobjartsson 2014b

Hrobjartsson A, Thomsen AS, Emanuelsson F, Tendal B, Rasmussen JV, Hilden J, et al. Observer bias in randomized clinical trials with time-to-event outcomes: systematic review of trials with both blinded and non-blinded outcome assessors. *International Journal of Epidemiology* 2014;**43**(3):937-48.

Hugh 1997

Hugh TS, Poston GJ. The aetiology and management of hepatic metastases. *Australian and New Zealand Journal of Surgery* 1997;**67**(7):400-9.

ICH-GCP 1997

International Conference on Harmonisation Expert Working Group. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. ICH harmonised tripartite guideline. Guideline for good clinical practice CFR & ICH Guidelines. Vol. **1**, Philadelphia (PA): Barnett International/PAREXEL, 1997.

Jemal 2010

Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA: A Cancer Journal for Clinicians* 2010;**60**(5):277-300.

Kacmaz 2019

Kacmaz E, Heidsma CM, Besselink MGH, Dreijerink KMA, Klumpen H-J, Van Dijkum EJMN, et al. Treatment of liver metastases from midgut neuroendocrine tumours: a systematic review and meta-analysis. *Journal of Clinical Medicine* 2019;**8**(3):403.

Kjaergard 2001

Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. *Annals of Internal Medicine* 2001;**135**:982-9.

Li 2017

Li Z, Zhang K, Lin SM, Mi DH, Cao N, Wen ZZ, et al. Radiofrequency ablation combined with percutaneous ethanol injection for hepatocellular carcinoma: a systematic review and meta-analysis. *International Journal of Hyperthermia* 2017;**33**(3):237-46.

Llovet 2003

Llovet JM, Bruix J, for the Barcelona Clinic Liver Cancer Group. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. *Hepatology (Baltimore, Md.)* 2003;**37**:429-42.

Lopez 2018

López RI, Castro JL, Cedeño H, Cisneros D, Corrales L, González-Herrera I, et al. Consensus on management of metastatic colorectal cancer in Central America and the Caribbean: San

José, Costa Rica, August 2016. *ESMO Open* 2018;**3**(3):e000315. [DOI: [10.1136/esmoopen-2017-000315](https://doi.org/10.1136/esmoopen-2017-000315)]

Loveman 2014

Loveman E, Jones J, Clegg AJ, Picot J, Colquitt JL, Mendes D, et al. The clinical effectiveness and cost-effectiveness of ablative therapies in the management of liver metastases: systematic review and economic evaluation. *Health Technology Assessment* 2014;**18**(7):1-283.

Mantel 1959

Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *Journal of the National Cancer Institute* 1959;**22**:719-48.

Marlow 2006

Marlow NE, et al. A systematic review of radiofrequency ablation for the treatment of liver tumours (update) ASERNIP-S report no. 56. www.surgeons.org/media/17297/RFAupdate.pdf 2006 (accessed 12 July 2018).

Moher 1998

Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses?. *Lancet* 1998;**352**:609-13.

Nordlinger 2013

Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, et al. EORTC Gastro-Intestinal Tract Cancer Group, Cancer Research UK, Arbeitsgruppe Lebermetastasen und-tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO), Australasian Gastro-Intestinal Trials Group (AGITG), Fédération Francophone de Cancérologie Digestive (FFCD). Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncology* 2013;**14**:1208-15.

Ohnishi 1996

Ohnishi K, Nomura F, Ito S, Fujiwara K. Prognosis of small hepatocellular carcinoma (less than 3 cm) after percutaneous acetic acid injection: study of 91 cases. *Hepatology (Baltimore, Md.)* 1996;**23**(5):994-1002.

Ohnishi 1998

Ohnishi K, Yoshioka H, Ito S, Fujiwara K. Prospective randomized controlled trial comparing percutaneous acetic acid and percutaneous ethanol injection for small hepatocellular carcinoma. *Hepatology (Baltimore, Md.)* 1998;**27**(1):67-72.

Parkin 2005

Parkin DM, Bray F, Ferlay J, Pisani P. Global Cancer Statistics, 2002. *CA: A Cancer Journal for Clinicians* 2005;**55**(2):74-108.

Parmar 1998

Parmar MKB, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**:2815-34.

Qian 2011

Qian J. Interventional therapies of unresectable liver metastases. *Journal of Cancer Research and Clinical Oncology* 2011;**137**(12):1763–72.

Revel-Mouroz 2017

Revel-Mouroz P, Otal P, Jaffro M, Petermann A, Meyrignac O, Rabinel P, et al. Other non-surgical treatments for liver cancer. *Reports of Practical Oncology and Radiotherapy* 2017;**22**(2):181–92.

Review Manager 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Riemsma 2009

Riemsma R, Bala M, Wolff R, Kleijnen J. Non-surgical ablation methods for primary malignant liver tumours and liver metastases. www.zorginstituutnederland.nl/publicaties/standpunten/2009/05/19/verschillende-niet-chirurgische-locoregionale-interventies-bij-levertumoren-zijn-een-te-verzekeren-prestatie-rfa-nog-niet 2009 (accessed 12 March 2013):1–271.

Royle 2003

Royle P, Milne R. Literature searching for randomized controlled trials used in Cochrane reviews: rapid versus exhaustive searches. *International Journal of Technology Assessment in Health Care* 2003;**19**(4):591–603.

Savović 2012a

Savović J, Jones HE, Altman DG, Harris RJ, Jüni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. *Health Technology Assessment* 2012;**16**(35):1–82.

Savović 2012b

Savović J, Jones HE, Altman DG, Harris RJ, Jüni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. *Annals of Internal Medicine* 2012;**157**(6):429–38.

Savović 2018

Savović J, Turner RM, Mawdsley D, Jones HE, Beynon R, Higgins JP, et al. Association between risk-of-bias assessments and results of randomized trials in Cochrane Reviews: the ROBES Meta-Epidemiologic Study. *American Journal of Epidemiology* 2018;**187**(5):1113–22.

Schoppmeyer 2009

Schoppmeyer K, Weis S, Mössner J, Fleig WE. Percutaneous ethanol injection or percutaneous acetic acid injection for early hepatocellular carcinoma. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: [10.1002/14651858.CD006745.pub2](https://doi.org/10.1002/14651858.CD006745.pub2)]

Schulz 1995

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**(5):408–12.

Siegel 2016

Siegel RL, Miller KD, Jemal A. Cancer statistics 2016. *CA: A Cancer Journal for Clinicians* 2016;**66**:7–30.

Song 2017

Song Z, Wu Y, Yang J, Yang D, Fang X. Progress in the treatment of advanced gastric cancer. *Tumour Biology* 2017;**39**(7):1–6.

SPIRIT 2013a

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 Statement: defining standard protocol items for clinical trials. *Annals of Internal Medicine* 2013;**158**:200–7.

SPIRIT 2013b

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, et al. SPIRIT 2013 Explanation and elaboration: guidance for protocols of clinical trials. *BMJ (Clinical Research Ed.)* 2013;**346**:e7586.

Storebø 2018

Storebø OJ, Pedersen N, Ramstad E, Kielsholm ML, Nielsen SS, Krogh HB, et al. Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents – assessment of adverse events in non-randomised studies. *Cochrane Database of Systematic Reviews* 2018, Issue 5. [DOI: [10.1002/14651858.CD012069.pub2](https://doi.org/10.1002/14651858.CD012069.pub2)]

Stovold 2014

Stovold E, Beecher D, Foxlee R, Noel-Storr A. Study flow diagrams in Cochrane systematic review updates: an adapted PRISMA flow diagram. *Systematic Reviews* 2014;**3**:54.

Sutherland 2006

Sutherland LM, Williams JAR, Padbury RTA, Gotley DC, Stokes B, Maddern GJ. Radiofrequency ablation of liver tumors. A systematic review. *Archives of Surgery* 2006;**141**:181–90.

Thorlund 2009

Thorlund K, Devereaux PJ, Wetterslev J, Gyuatt G, Ioannidis JPA, Thabane L, et al. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses?. *International Journal of Epidemiology* 2009;**38**:276–86.

Thorlund 2010

Thorlund K, Anema A, Mills E. Interpreting meta-analysis according to the adequacy of sample size. An example using isoniazid chemoprophylaxis for tuberculosis in purified protein derivative negative HIV-infected individuals. *Clinical Epidemiology* 2010;**2**:57–66.

Thorlund 2011

Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, Gluud C. User manual for Trial Sequential Analysis (TSA). ctu.dk/tsa/files/tsa_manual.pdf 2011 (accessed 22 April 2019).

Tierney 2007

Tierney JF, Stewart LA, Gherzi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;**8**:16.

Torre 2016

Torre L, Siegel R, Jemal A. Lung cancer statistics. *Advances in Experimental Medicine and Biology* 2016;**893**:1-19.

TSA 2011 [Computer program]

Copenhagen Trial Unit. TSA - Trial Sequential Analysis. Version 0.9.5.10 Beta. Copenhagen: Copenhagen Trial Unit, 2011.

Weis 2015

Weis S, Franke A, Berg T, Mössner J, Fleig WE, Schoppmeyer K. Percutaneous ethanol injection or percutaneous acetic acid injection for early hepatocellular carcinoma. *Cochrane Database of Systematic Reviews* 2015, Issue 1. [DOI: [10.1002/14651858.CD006745.pub3](https://doi.org/10.1002/14651858.CD006745.pub3)]

Wetterslev 2008

Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *Journal of Clinical Epidemiology* 2008;**61**(1):64-75.

Wetterslev 2009

Wetterslev J, Thorlund K, Brok J, Gluud C. Estimating required information size by quantifying diversity in a random-effects meta-analysis. *BMC Medical Research Methodology* 2009;**9**:86.

Wetterslev 2017

Wetterslev J, Jakobsen JC, Gluud C. Trial Sequential Analysis in systematic reviews with meta-analysis. *BMC Medical Research Methodology* 2017;**17**(1):39.

Wood 2008

Wood L, Egger M, Gluud LL, Schulz KF, Jüni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ (Clinical Research Ed.)* 2008;**336**(7644):601-5.

References to other published versions of this review

Riemsma 2013

Riemsma RP, Bala MM, Wolff R, Kleijnen J. Percutaneous ethanol injection for liver metastases. *Cochrane Database of Systematic Reviews* 2013, Issue 5. [DOI: [10.1002/14651858.CD008717.pub2](https://doi.org/10.1002/14651858.CD008717.pub2)]

Riemsma 2010

Riemsma RP, Bala M, Wolff R, Kleijnen J. Percutaneous ethanol injection for liver metastases. *Cochrane Database of Systematic Reviews* 2010, Issue 9. [DOI: [10.1002/14651858.CD008717](https://doi.org/10.1002/14651858.CD008717)]

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Liang 2007

Methods	Study type: randomised clinical trial Location: China Study period: November 1998 - April 2003 Inclusion criteria: patients with liver metastases diagnosed during treatment or re-examination by ultrasound B, CT, or MRI, or by liver puncture biopsy. No further details reported
Participants	Total number of patients: 48 patients (11 females and 37 males) Primary tumour sites: colon 27, stomach 12, pancreas 3, lung 3, breast 2, ovary 1 Other metastases: 9 patients had other metastases, together with liver metastases Bulk diameter of the tumour: average 3.9 cm (ranging from 1.2 to 7.6 cm) Symptoms: 13 patients with symptoms (abdomen distension, pain in the upper right abdomen, latitude, low fever, nausea, etc.) and 35 patients without symptoms Child level before surgery: A 33, B 15 Mean age: 49.3 years
Interventions	Intervention group: Percutaneous intratumour ethanol injection + Transcatheter arterial chemoembolisation (n = 25) Control group: Transcatheter arterial chemoembolisation alone (n = 23)
Outcomes	1-, 2-, 3-year survival, local recurrence, tumour shrinking, adverse events
Notes	The trial was published in Chinese, and we used a translated version

Percutaneous ethanol injection for liver metastases (Review)

Liang 2007 (Continued)

Protocol: not reported

Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"48 liver metastases patients were randomised into two groups"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data reported
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Unclear risk	Not possible to assess whether the trial was free of other biases

CT: computed tomography.

MRI: magnetic resonance imaging.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Andersson 1989	Irrelevant for the review outcomes: pharmacokinetic study
Dudeck 2011	Irrelevant for the review comparison
Fiorentini 2012a	Irrelevant for the review comparison
Fiorentini 2012b	Irrelevant for the review comparison
Gootjes 2015	Irrelevant for the review comparison
Holting 1991	Irrelevant for the review comparison
Martinelli 1994	Irrelevant for the review comparison
Murthy 2010	Irrelevant for the review comparison
Pingpank 2010	Irrelevant for the review comparison
Power 2010	Irrelevant for the review comparison
Safi 1989	Irrelevant for the review comparison

Study	Reason for exclusion
Soemarno 2002	Irrelevant for the review comparison
Wiley 1989	Irrelevant for the review comparison
Xie 2000	Irrelevant for the review comparison

APPENDICES

Appendix 1. Search strategies - primary searches on 5 June 2017

Database	Time span	Search strategy
Cochrane Hepato-Biliary Group Controlled Trials Register	accessed on 29 September 2017	(((liver or hepatic or hepatocellular* or hepato-cellular*) AND (cancer* or neoplasm* or malign* or carcinoma* or tumor*)) OR ((metasta* or secondar* or spread or advanced) AND (liver or hepatic))) and (Ablati* OR (injection* and (ethanol or acetic acid)) or PEI or PAI)
Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	up to 5 June 2017	(((liver or hepatic or hepatocellular* or hepato-cellular*) AND (cancer* or neoplasm* or malign* or carcinoma* or tumor*)) OR ((metasta* or secondar* or spread or advanced) AND (liver or hepatic))) and (rfta or radio-frequ* or radiofrequ* or rfa or rf OR Ablati* OR (injection* and (ethanol or acetic acid)) or PEI or PAI OR Yttrium Radioisotopes OR selective internal radi* OR radioemboli* OR radio-emboli* OR sir-sphere* OR therasphere* OR (yttrium* or 90y* or radiolabel*) AND microsphere*) OR Embolisation OR Embolisation OR ((transcatheter or transarterial) and (emboli* or chemoemboli*)) or TAE or TACE or lipiodolisation or lipiodol embolisation OR lipiodol or HAI or arterial 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 SP)	1946 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 secondar* 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/

(Continued)

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 adenomatosis 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 intestine\$) adj5 neoplas\$).tw,mp.
 31 ((colon\$ or rect\$ or colorect\$ or bowel or large intestine\$) adj5 cancer\$).tw,mp.
 32 ((colon\$ or rect\$ or colorect\$ or bowel or large intestine\$) adj5 carcinoma\$).tw,mp.
 33 ((colon\$ or rect\$ or colorect\$ or bowel or large intestine\$) adj5 tumor\$).tw,mp.
 34 ((colon\$ or rect\$ or colorect\$ or bowel or large intestine\$) adj5 malignan\$).tw,mp.
 35 ((colon\$ or rect\$ or colorect\$ or bowel or large intestine\$) 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 randomised 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.

(Continued)

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.
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 SP)	1974 to 5 June 2017	1 Liver-Cell-Carcinoma# 2 Liver-Tumour# 3 hcc AND CLINICAL-TRIAL# AND HUMAN=YES 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 5 1 OR 2 OR 3 OR 4 6 Metastasis# 7 metastas\$5 OR secundar\$3 OR spread OR advanced 8 6 OR 7 9 Neuroendocrine-Tumour# 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
------------------	---------------------	---

(Continued)

24 multiple ADJ endocrine ADJ adenomatosis OR familial ADJ endocrine ADJ adenomatosis 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 adenomatosis

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 tumo\$5

34 (colon\$5 OR rect\$5 OR colorect\$3 OR bowel OR large ADJ intestin\$5) NEAR malignan\$5

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 doubl\$3 ADJ blind\$5 OR singl\$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 microspheres\$3

60 57 OR 58 OR 59

61 Chemoembolisation#

62 Artificial-Embolism#

(Continued)

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
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 ([http://apps-
isiknowledge.com](http://apps.isiknowledge.com))

1900 to 5 June 2017

70 #69 AND #37 AND #30
69 #68 OR #67 OR #66 OR #65 OR #64 OR #54 OR #45 OR #40
68 TS=(cryosurgery OR cryo-surgery)
67 TS=(ablation*)
66 TS=(Microwaves* or Microwave-Radiation* OR coagulation therapy or
Electrocoagulation* or Electro-coagulation* or Cryocoagulation* OR Laser-Co-
agulation* OR Cryo-coagulation*)
65 TS= (thermotherapy or Induced Hyperthermia or Hyperthermic Therapy)
64 #63 OR #62 OR #61 OR #60 OR #59 OR #58 OR #57 OR #56 OR #55
63 TS=Iodinated Poppyseed Oil
62 TS=Intra-arterial Drug Administration
61 TS=Artificial-Embolism
60 TS=Iodized Oil*
59 TS=((transcatheter or transarterial) and chemo-infusion)
58 TS=(lipiodol or HAI or arterial infusion or targeted chemotherapy)
57 TS=Intra-Arterial Infusion*
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 (radiola-
bel* 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)

(Continued)

```
# 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 intestine* adenocarcinoma*)
# 24 TS=(colon* malignan* or rect* malignan* or colorect* malignan* or bowel malignan* or large intestine* malignan*)
# 23 TS=(colon* tumo* or rect* tumo* or colorect* tumo* or bowel tumo* or large intestine* tumo*)
# 22 TS=(colon* carcinoma* or rect* carcinoma* or colorect* carcinoma* or bowel carcinoma* or large intestine* carcinoma*)
# 21 TS=(colon* cancer* or rect* cancer* or colorect* cancer* or bowel cancer* or large intestine* cancer*)
# 20 TS=(colon* neoplas* or rect* neoplas* or colorect* neoplas* or bowel neoplas* or large intestine* 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 WDDH 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 hepatocellular* malign*)
# 7 TS=(liver tumo* or hepatic tumo* or hepatocellular* tumo* or hepatocellular* tumo*)
# 6 TS=(liver carcinom* or hepatic carcinom* or hepatocellular* carcinom* or hepatocellular* carcinom*)
# 5 TS=(liver neoplas* or hepatic neoplas* or hepatocellular* neoplas* or hepatocellular* neoplas*)
# 4 TS=(liver cancer* or hepatic cancer* or hepatocellular* cancer* or hepatocellular* cancer*)
# 3 TS=hcc
```

(Continued)

2 TS=Liver Neoplasms
1 TS=Hepatocellular Carcinoma

LILACS	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	S69 S67 and S68 Limiters - Exclude MEDLINE records S68 TX random* or placebo* or blind* or trial* or group* S67 S37 and S66 S66 S40 or S45 or S65 S65 S56 or S57 or S58 or S59 or S60 or S61 or S62 or S63 or S64 S64 TX cryosurgery S63 MM cryosurgery S62 TX ablation S61 MM catheter ablation S60 TX coagulation therapy S59 TX electrocoagulation S58 MM microwaves S57 TX thermotherapy S56 MM Hyperthermia, Induced S55 S49 or S50 or S51 or S52 or S53 or S54 S54 TX iodine oil S53 TX (trans?catheter or trans?arterial) and TX chemo-infusion S52 TX (lipiodol or HAI or arterial infusion or targeted chemotherapy) S51 MM Infusions, Intraarterial S50 TX (((transcatheter or transarterial) and (emboli* or chemoemboli*)) or TAE or TACE or lipiodolisation or lipiodol embolisation) S49 MM Embolization, Therapeutic S48 S46 or S47 S47 TX ((yttrium* or 90y* or radiolabel*)) and TX microsphere* S46 TX (yttrium radioisotope*) or (selective internal radi*) or radioemboli* or radio-emboli* or sir-sphere* or therasphere*

(Continued)

S45 S41 and S44

S44 S42 or S43

S43 TX ((injection* and (ethanol or acetic acid)) or PEI or PAI)

S42 TX (ablati* and (therap* or treatment* or radiofrequenc* or cryo*))

S41 TX percutaneous

S40 S38 or S39

S39 TX rfta or radio-frequ* or radiofrequ*

S38 MM catheter ablation

S37 S5 or S36

S36 S8 and S32 and S35

S35 S33 or S34

S34 TX liver or hepatic

S33 MM liver

S32 S28 or S31

S31 S29 or S30

S30 TX ((colon* or rect* or colorect* or bowel or large intestin*)) and TX ((neoplas* or cancer* or carcinoma* or tumo?r* or malignan* or adenocarcinoma*))

S29 MM colorectal neoplasms

S28 S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27

S27 TX 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*

S26 TX VIP secreting tumo?r*

S25 TX familial endocrine adenomatous* or diarrheogenic tumo?r*

S24 TX insulinoma* or (multiple endocrine AND (neoplasia or adenopath* or adenomatous* or neoplasm*))

S23 TX argentaaffinoma* or somatostatinoma* or islet cell tumo?r* or island cell tumo?r* or nesidioblastoma*

S22 TX ((neuroendocrine AND tumo?r*)) or TX (adenoma* OR apudoma* OR carcinoid*)

S21 TX malignant carcinoid syndrome Search modes

S20 TX apudoma* OR glucagonoma* OR somatostatinoma* OR vipoma*

S19 MM apudoma OR glucagonoma OR somatostatinoma

S18 MM glucagon

S17 MM gastrointestinal neoplasms

S16 MM endocrine gland neoplasms

(Continued)

S15 MM pancreatic neoplasms

S14 MM gastrinoma

S13 MM insulinoma

S12 MM carcinoma, islet cell

S11 MM adenoma, islet cell

S10 MM carcinoid tumor

S9 MM neuroendocrine tumors

S8 S6 or S7

S7 TX metasta* or secundar* or spread or advanced

S6 MM neoplasm metastasis

S5 S1 or S2 or S3 or S4

S4 TX (liver or hepatic or hepatocellular* or hepato-cellular*) and TX (cancer* or neoplas* or malign* or carcinom* or tumo*)

S3 TX hcc

S2 MM liver neoplasms

S1 MM carcinoma, hepatocellular

Appendix 2. Updated search strategies - 9 July 2018 & 10 September 2019

Database	Time span	Search strategy
Cochrane Hepato-Biliary Group Controlled Trials Register	September 2019	(((ablati* or injection*) and (ethanol* or alcohol* or vinegar* or acetic acid*)) or PEI or PAI) 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	2019, Issue 9	<p>#1 MeSH descriptor: [Ethanol] explode all trees</p> <p>#2 MeSH descriptor: [Acetic Acid] explode all trees</p> <p>#3 MeSH descriptor: [Injections] explode all trees</p> <p>#4 (#1 or #2) and #3</p> <p>#5 ((ablati* or injection*) and (ethanol* or alcohol* or vinegar* or acetic acid*)) or PEI or PAI</p> <p>#6 #4 or #5</p> <p>#7 MeSH descriptor: [Carcinoma, Hepatocellular] explode all trees</p> <p>#8 MeSH descriptor: [Liver Neoplasms] explode all trees</p> <p>#9 ((liver or hepatic or hepatocellular* or hepato-cellular*) and (cancer* or neoplasm* or malign* or carcinoma* or tumo*))</p> <p>#10 #7 or #8 or #9</p>

(Continued)

		<p>#11 MeSH descriptor: [Neoplasm Metastasis] explode all trees</p> <p>#12 MeSH descriptor: [Liver] explode all trees</p> <p>#13 ((metasta* or secundar* or spread or advanced) and (liver or hepatic))</p> <p>#14 (#11 and #12) or #13</p> <p>#15 #6 and (#10 or #14)</p>
MEDLINE Ovid SP	1946 to September 2019	<ol style="list-style-type: none"> 1. exp ETHANOL/ 2. exp Acetic Acid/ 3. exp Injections/ 4. (1 or 2) and 3 5. (((ablati* or injection*) and (ethanol* or alcohol* or vinegar* or acetic acid*)) or PEI or PAI).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] 6. 4 or 5 7. exp Carcinoma, Hepatocellular/ 8. exp Liver Neoplasms/ 9. ((liver or hepatic or hepatocellular* or hepato-cellular*) and (cancer* or neoplasm* or malign* or carcinoma* or tumor*)).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] 10. 7 or 8 or 9 11. exp Neoplasm Metastasis/ 12. exp LIVER/ 13. ((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] 14. (11 and 12) or 13 15. 6 and (10 or 14) 16. (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] 17. 15 and 16
Embase Ovid SP	1974 to September 2019	<ol style="list-style-type: none"> 1. exp alcohol/ 2. exp acetic acid/ 3. exp injection/

(Continued)

4. (1 or 2) and 3
5. (((ablati* or injection*) and (ethanol* or alcohol* or vinegar* or acetic acid*)) or PEI or PAI).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]
6. 4 or 5
7. exp liver cell carcinoma/
8. exp liver tumor/
9. ((liver or hepatic or hepatocellular* or hepato-cellular*) and (cancer* or neoplasm* or malign* or carcinoma* or tumor*)).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]
10. 7 or 8 or 9
11. exp metastasis/
12. exp liver/
13. ((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]
14. (11 and 12) or 13
15. 6 and (10 or 14)
16. (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]
17. 15 and 16

Science Citation Index Expanded (Web of Science)	1900 to September 2019	#6 #5 AND #4 #5 TS=(random* or blind* or placebo* or meta-analys*) #4 #1 and (#2 or #3) #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 tumor*)) #1 TS((((ablati* or injection*) and (ethanol* or alcohol* or vinegar* or acetic acid*)) or PEI or PAI)
Conference Proceedings Citation Index – Science (Web of Science)	1990 to September 2019	#6 #5 AND #4 #5 TS=(random* or blind* or placebo* or meta-analys*) #4 #1 and (#2 or #3) #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 tumor*))

(Continued)

		#1 TS=((ablati* or injection*) and (ethanol* or alcohol* or vinegar* or acetic acid*)) or PEI or PAI)
LILACS (Bireme)	1982 to September 2019	(((ablati\$ or injection\$) and (ethanol\$ or alcohol\$ or vinegar\$ or acetic acid\$)) or PEI or PAI) [Words] and (((liver or hepatic or hepatocellular\$ or hepa-to-cellular\$) and (cancer\$ or neoplasm\$ or malign\$ or carcinoma\$ or tumo\$)) or ((metasta\$ or secondar\$ or spread or advanced) and (liver or hepatic))) [Words]
CINAHL (EBSCO host)	1981 to September 2019	<p>S32 S30 AND S31 Limiters - Exclude MEDLINE records</p> <p>S31 TX (random* OR placebo* OR blind* OR trial* OR group*)</p> <p>S30 S3 AND S6 AND S28 AND S29</p> <p>S29 TX ((percutaneous AND (ethanol OR acetic acid) AND injection*) OR PEI OR PAI)</p> <p>S28 S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27</p> <p>S27 TX ((colon* OR rect* OR colorect* OR bowel OR large intestin*) AND (neoplas* OR cancer* OR carcinoma* OR tumo?* OR malignan* OR adenocarcinoma*))</p> <p>S26 MM colorectal neoplasms</p> <p>S25 TX (Pancreatic cholera OR Verner-Morrison syndrome OR Verner Morrison syndrome OR watery diarrhoea syndrome OR WDHA OR WDHH OR neuroendocrine carcinoma*)</p> <p>S24 TX VIP secreting tumo?*</p> <p>S23 TX (familial endocrine adenomatos* OR diarrheogenic tumo?*)</p> <p>S22 TX (insulinoma* OR (multiple endocrine AND (neoplasia OR adenopath* OR adenomatos* OR neoplasm*)))</p> <p>S21 TX (argentaffinoma* OR somatostatinoma* OR islet cell tumo?* OR island cell tumo?* OR nesidioblastoma*)</p> <p>S20 TX ((neuroendocrine AND tumo?* OR (adenoma* OR apudoma* OR carcinoid*))</p> <p>S19 TX malignant carcinoid syndrome Search modes</p> <p>S18 TX (apudoma* OR glucagonoma* OR somatostatinoma* OR vipoma*)</p> <p>S17 MM (apudoma OR glucagonoma OR somatostatinoma)</p> <p>S16 MM glucagon</p> <p>S15 MM gastrointestinal neoplasms</p> <p>S14 MM endocrine gland neoplasms</p> <p>S13 MM pancreatic neoplasms</p> <p>S12 MM gastrinoma</p> <p>S11 MM insulinoma</p> <p>S10 MM carcinoma, islet cell</p> <p>S9 MM adenoma, islet cell</p>

(Continued)

S8 MM carcinoid tumor

S7 MM neuroendocrine tumors

S6 S4 OR S5

S5 TX (metasta* OR secundar* OR spread OR advanced)

S4 MM neoplasm metastasis

S3 S1 OR S2

S2 TX (liver OR hepatic)

S1 MM liver

WHAT'S NEW

Date	Event	Description
22 January 2020	Amended	This review will be updated again only if new published evidence is found through regular searches for trials.
30 September 2019	New citation required but conclusions have not changed	No new trials were identified.
15 September 2019	New search has been performed	Updated searches were conducted on 10 September 2019. No new trials were identified.

CONTRIBUTIONS OF AUTHORS

JK developed the concept for the project.

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

MJS, DS, JWM, and MP searched clinical trials registers.

MJS, DS, MMB, RR, JWM, MP, and RW performed the title and abstract screening.

MJS, DS, MMB, RR, JWM, MP, and RW performed the full-text screening.

MJS, MMB, and RR (originally checked the extracted data) performed data extraction.

MJS, MMB, RR, and RW performed the analyses.

MJS, MMB, and RR assessed the overall certainty of evidence.

MJS, DS, MMB, RR, JWM, MP, RW, and JK prepared the text of the review.

All review authors approved the review for publication.

DECLARATIONS OF INTEREST

MJS: none.

DS: none.

MMB: works as a freelancer for a company that does work for a number of pharmaceutical companies in an 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.

SOURCES OF SUPPORT

Internal sources

- Kleijnen Systematic Reviews Ltd (KSR), UK.

KSR funded updating of the review and producing Cochrane Reviews

External sources

- The Dutch Health Care Insurance Board (CVZ), 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 data on harm, from "Quasi-randomised and observational studies that will come up with the search, will be considered only for the report of data on harm" to "Relevant quasi-randomised and other controlled studies that were identified in the searches were considered only for reporting of data on harm"
- We removed the domains 'baseline imbalance' and 'early stopping of trials'. The argument for not considering baseline imbalance is that it may occur due to random error ('play of chance'), and that such random error is likely to be levelled out by conducting a meta-analysis of several trials. The argument for not considering early stopping is that such trials - although they may overestimate intervention effects - are likely to be counterbalanced by trials finding no significant difference. By solely excluding trials that are stopped early, one would bias the meta-analysis towards a neutral effect
- In the "Secondary outcomes" section, wording was changed from 'Failure or recurrence of tumours' to 'Failure to clear liver metastases or recurrence of liver metastases'
- 'Quality of life' was changed to 'Health-related quality of life' and was moved as a primary outcome
- We joined "Serious adverse events and complications, separately and in total" from the primary outcomes section and "Non-serious adverse events and complications" from the secondary outcomes section into "Any adverse events or complications" in the secondary outcomes section
- We removed the 'for profit bias' domain in risk of bias sections
- The included study has been extracted once again onto a separate extraction sheet and then compared with the previous extraction, so this has been done by two review authors independently (originally data extraction was done by one review author (MMB) and was checked by a second review author (RR))
- As the included study reported data on survival at each follow-up, this was reported as survival HR (hazard ratio) in the "Primary outcomes - Mortality at last follow-up" section in the previous version of the review. In the current version of the review, this was recalculated and presented as an RR (risk ratio) for mortality at last follow-up (three years)
- We were unable to perform the planned analyses due to lack of data

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Cutaneous; Chemoembolization, Therapeutic [methods]; Colorectal Neoplasms [pathology]; Ethanol [administration & dosage] [*therapeutic use]; Liver Neoplasms [*drug therapy] [secondary]; Randomized Controlled Trials as Topic

MeSH check words

Humans