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

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

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[Intervention Review]

Management of people with early- or very early-stage hepatocellular carcinoma: an attempted network meta-analysis

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ABSTRACT

Background

Hepatocellular carcinoma (primary liver cancer) is classified in many ways. The Barcelona Clinic Liver Cancer (BCLC) group staging classifies the cancer based on patient's life expectancy. People with very early- or early-stage hepatocellular carcinoma have single tumour or three tumours of maximum diameter of 3 cm or less, Child-Pugh status A to B, and performance status 0 (fully functional). Management of hepatocellular carcinoma is uncertain.

Objectives

To assess the comparative benefits and harms of different interventions used in the treatment of early or very early hepatocellular carcinoma through a network meta-analysis and to generate rankings of the available interventions according to their safety and efficacy. However, it was not possible to assess whether the potential effect modifiers were similar across different comparisons. Therefore, we did not perform the network meta-analysis and instead assessed the benefits and harms of different interventions versus each other or versus sham or no intervention using standard Cochrane methodology.

Search methods

We searched CENTRAL, MEDLINE, Embase, Science Citation Index Expanded, and trials registers to September 2016 to identify randomised clinical trials (RCTs) on hepatocellular carcinoma.

Selection criteria

We included only RCTs, irrespective of language, blinding, or publication status, in participants with very early- or early-stage hepatocellular carcinoma, irrespective of the presence of cirrhosis, portal hypertension, aetiology of hepatocellular carcinoma, size and number of the tumours, and future remnant liver volume. We excluded trials including participants who were previously liver transplanted. We considered interventions compared with each other, sham, or no intervention.

Data collection and analysis

We calculated the odds ratio, mean difference, rate ratio, or hazard ratio with 95% confidence intervals using both fixed-effect and random-effects models based on available-participant analysis with Review Manager 5. We assessed the risk of bias according to Cochrane, controlled risk of random errors with Trial Sequential Analysis using Stata, and the quality of the evidence using GRADE.

Main results

Eighteen trials met the inclusion criteria for this review. Four trials (593 participants; 574 participants included for one or more analyses) compared surgery versus radiofrequency ablation in people with early hepatocellular carcinoma, eligible to undergo surgery. Fourteen trials (2533 participants; 2494 participants included for various analyses) compared different non-surgical interventions in people with early hepatocellular carcinoma, not eligible to undergo surgery. Overall, the quality of evidence was low or very low for all outcomes for both comparisons.

Surgery versus radiofrequency ablation

The majority of participants had cirrhotic livers, and the hepatocellular carcinoma was of viral aetiology. The trials did not report the participants' portal hypertension status or whether they received adjuvant antiviral treatment or adjuvant immunotherapy. The average follow-up ranged from 29 months to 42 months (3 trials).

There was no evidence of a difference in all-cause mortality at maximal follow-up for surgery versus radiofrequency ablation (hazard ratio 0.80, 95% confidence interval (CI) 0.60 to 1.08; 574 participants; 4 trials; I^2 = 68). Cancer-related mortality was lower in the surgery group (20/115 (17.4%)) than in the radiofrequency ablation group (43/115 (37.4%)) (odds ratio 0.35, 95% CI 0.19 to 0.65; 230 participants; 1 trial). Serious adverse events (number of participants) was higher in the surgery group (14/60 (23.3%)) than in the radiofrequency ablation group (1/60 (1.7%)) (odds ratio 17.96, 95% CI 2.28 to 141.60; 120 participants; 1 trial). The number of serious adverse events was higher in the surgery group (adjusted rate 11.3 events per 100 participants) than in the radiofrequency ablation group (3/186 (1.6 events per 100 participants)) (rate ratio 7.02, 95% CI 2.29 to 21.46; 391 participants; 2 trials; I^2 = 0%). None of the trials reported health-related quality of life. One trial was funded by a party with vested interests; three trials were funded by parties without any vested.

Non-surgical interventions

The majority of participants had cirrhotic livers, and the hepatocellular carcinoma was of viral aetiology. Most trials did not report the portal hypertension status of the participants, and none of the trials reported whether the participants received adjuvant antiviral treatment or adjuvant immunotherapy. The average follow-up ranged from 6 months to 37 months (11 trials). Trial participants, who were not eligible for surgery, were treated with radiofrequency ablation, laser ablation, microwave ablation, percutaneous acetic acid injection, percutaneous alcohol injection, a combination of radiofrequency ablation with systemic chemotherapy, a combination of radiofrequency ablation with percutaneous alcohol injection, a combination of transarterial chemoembolisation with percutaneous alcohol injection, or a combination of transarterial chemoembolisation with radiofrequency ablation.

The mortality at maximal follow-up was higher in the percutaneous acetic acid injection (hazard ratio 1.77, 95% CI 1.12 to 2.79; 125 participants; 1 trial) and percutaneous alcohol injection (hazard ratio 1.49, 95% CI 1.18 to 1.88; 882 participants; 5 trials; I^2 = 57%) groups compared with the radiofrequency ablation group. There was no evidence of a difference in all-cause mortality at maximal follow-up for any of the other comparisons. The proportion of people with cancer-related mortality at maximal follow-up was higher in the percutaneous alcohol injection group (adjusted proportion 16.8%) compared with the radiofrequency ablation group (20/232 (8.6%)) (odds ratio 2.18, 95% CI 1.22 to 3.89; 458 participants; 3 trials; I^2 = 0%). There was no evidence of a difference in any of the comparisons that reported serious adverse events (number of participants or number of events). None of the trials reported health-related quality of life. Five trials were funded by parties without any vested interest; the source of funding was not available in the remaining trials.

Authors' conclusions

The evidence was of low or very low quality. There was no evidence of a difference in all-cause mortality at maximal follow-up between surgery and radiofrequency ablation in people eligible for surgery. All-cause mortality at maximal follow-up was higher with percutaneous acetic acid injection and percutaneous alcohol injection than with radiofrequency ablation in people not eligible for surgery. There was no evidence of a difference in all-cause mortality at maximal follow-up for the other comparisons. High-quality RCTs designed to assess clinically important differences in all-cause mortality and health-related quality of life, and having an adequate follow-up period (approximately five years) are needed.

PLAIN LANGUAGE SUMMARY

Treatment of very early- or early-stage primary liver cancer (hepatocellular carcinoma)

Background

Hepatocellular carcinoma (primary liver cancer) arises from the liver cells and is distinct from cancer arising from other parts of the body and spreading to the liver. The Barcelona Clinic Liver Cancer (BCLC) group staging classifies cancer based on patient's life expectancy. It is broadly based on the size of the cancer, number of cancers in the liver, how well the liver functions, and whether one's activities are affected by the cancer. People with very early- or early-stage hepatocellular carcinoma have single cancer or multiple small cancers confined to the liver, have good liver function, and no restriction of activities. There is significant uncertainty in the management of early-stage hepatocellular carcinoma. Therefore, we searched literature databases for randomised clinical trials (RCTs) on the topic until September 2016. We excluded trials in which participants had previously undergone liver transplantation. Apart from using standard Cochrane methods, which allow comparison of only two treatments at a time, we planned to use advanced methods described in full in the review.

Study characteristics of included trials

Four trials (593 participants; 574 participants included for one or more analyses) compared surgery (removal of part of the liver containing cancer) versus radiofrequency ablation (cancer destruction using heat generated by electric current) in people with early hepatocellular carcinoma, eligible to undergo surgery; and 14 trials (2533 participants; 2494 participants included for various analyses) compared different non-surgical interventions in people with early hepatocellular carcinoma, not eligible to undergo surgery.

Key results

Surgery versus radiofrequency ablation

The majority of participants had cirrhotic livers, and the hepatocellular carcinoma was of viral cause. The trials did not report the participants' portal hypertension status or whether they received adjuvant antiviral treatment or adjuvant immunotherapy. Three trials reported average follow-up (range 29 months to 42 months). One trial was funded by a party with vested interests; three trials were funded by parties without any vested..

In people eligible for surgery, there was no evidence of a difference in death between radiofrequency ablation and surgery; although there were fewer deaths due to cancer in the surgery group. There were more serious complications in the the surgery group than in the radiofrequency ablation group. None of the trials reported health-related quality of life.

Non-surgical interventions

The majority of participants had cirrhotic livers, and the hepatocellular carcinoma was of viral cause. Most trials did not report the portal hypertension status of the participants, and none reported whether the participants received adjuvant antiviral treatment or adjuvant immunotherapy. Eleven trials reported average follow-up (range 6 months to 37 months). Trial participants, who were not eligible for surgery, were treated with radiofrequency ablation, laser ablation (cancer destruction using laser), microwave ablation (cancer destruction using microwaves), percutaneous acetic acid injection (cancer destruction using vinegar), percutaneous alcohol injection (cancer destruction using alcohol), a combination of radiofrequency ablation with systemic chemotherapy, a combination of radiofrequency ablation with percutaneous alcohol injection, a combination of transarterial chemoembolisation (blocking the artery supplying the cancer with beads containing chemotherapy drugs) with percutaneous alcohol injection, or a combination of transarterial chemoembolisation with radiofrequency ablation. Five trials were funded by parties without any vested interest; the source of funding was not available in the remaining trials.

In people not eligible for surgery, the percentage of people who died during the follow-up period was higher in the percutaneous acetic acid injection and percutaneous alcohol injection groups than in the radiofrequency ablation group. There was no evidence of any difference in the percentage of people who died between any of the remaining comparisons. The percentage of people who died because of cancer was also higher in the percutaneous alcohol injection group than in the radiofrequency ablation group. There was no evidence of any difference in the percentage of people who died because of cancer between any of the remaining comparisons. None of the trials reported health-related quality of life at any time point.

Quality of evidence

The overall quality of evidence was low or very low because of the way trials were conducted. Therefore, the conclusions made could overestimate the benefits or underestimate the harms of a given treatment. Further high-quality RCTs are needed.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Surgery versus radiofrequency ablation for people with early- or very early-stage hepatocellular carcinoma

Patient or population: people with early- or very early-stage hepatocellular carcinoma eligible for surgery
Settings: secondary or tertiary care
Intervention: surgery
Control: radiofrequency ablation

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Radiofrequency ablation	Surgery			
All-cause mortality at maximal follow-up Follow-up: 29 months to 42 months	**300 per 1000**	**248 per 1000** (193 to 320)	**HR 0.80** (0.60 to 1.08)	574 (4 trials)	⊕◯◯◯ **very low**[1,2,3,4]
Cancer-related mortality at maximal follow-up Follow-up: 42 months	**374 per 1000**	**173 per 1000** (102 to 280)	**OR 0.35** (0.19 to 0.65)	230 (1 trial)	⊕⊕◯◯ **low**[1,2]
Serious adverse events (number of participants) Follow-up: postprocedural (very short term)	**17 per 1000**	**233 per 1000** (37 to 706)	**OR 17.96** (2.28 to 141.6)	120 (1 trial)	⊕⊕◯◯ **low**[1,2]
Serious adverse events (number of events) Follow-up: postprocedural (very short term)	**108 per 1000**	**758 per 1000** (247 to 2318)	**Rate ratio 7.02** (2.29 to 21.46)	391 (2 trials)	⊕⊕◯◯ **low**[1,2]
Health-related quality of life	None of the trials reported this outcome.				

*The basis for the **assumed risk** for all-cause mortality is the approximate control group proportions at two to three years reported in the Kaplan-Meier curves in the trials that reported mortality at maximal-follow-up. We have assumed proportional hazards. The basis for the **assumed risk** for other outcomes is based on the mean control group proportion. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **HR:** hazard ratio; **OR:** odds ratio; **RR:** rate ratio

GRADE Working Group grades of evidence

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

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

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level because of within-study risk of bias: there was unclear or high risk of bias in the trial(s).

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

[3]Downgraded one level because of imprecision: the confidence intervals overlapped clinically significant effect and clinically insignificant effect.

[4]Downgraded one level because of inconsistency: there was substantial unexplained heterogeneity.

BACKGROUND

Description of the condition

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

Description of the intervention

Several classifications of hepatocellular carcinoma have been proposed, including clinical staging classifications, histopathological classifications, and molecular classifications (Wu 1996; Henderson 2003; Van Deusen 2005; Cillo 2006; Nanashima 2006; van Malenstein 2011a). Of these, the Barcelona Clinic Liver Cancer (BCLC) staging system, Llovet 1999 and Llovet 2003, and the Milan criteria, Mazzaferro 1996, are commonly used and are important classification systems for determining the management of hepatocellular carcinoma. Appendix 1 and Appendix 2 show these classification systems in detail. Stage 0 (very early hepatocellular carcinoma) and stage A (early hepatocellular carcinoma) of BCLC staging correspond approximately to tumours falling within the Milan criteria 1, although stage A of the BCLC staging system includes single tumour of any size, while to fall within Milan criteria 1 a single tumour should be less than 5 cm. This review examined the treatment options for people with very early hepatocellular carcinoma (single nodule less than 2 cm in diameter, Child-Pugh A cirrhosis, and performance status 0 (fully functional)) and early hepatocellular carcinoma (single tumour or two or three lesions less than 3 cm in diameter with no evidence of vascular invasion or extrahepatic spread, Child-Pugh A or B cirrhosis, and performance status 0) (stages 0 and A of the BCLC staging system). A separate review covers the treatment options for people with intermediate hepatocellular carcinoma (large multinodular tumours with no evidence of vascular invasion or extrahepatic spread; stage B BCLC staging system, Child-Pugh A or B cirrhosis, and performance status 0) (Roccarina 2017). There are currently no Cochrane systematic reviews that cover all of the treatments for advanced hepatocellular carcinoma (vascular invasion or extrahepatic spread; stage C BCLC staging system) or end-stage hepatocellular carcinoma (poor performance status or Child-Pugh C liver functional status; stage D BCLC staging system).

Various treatments are aimed at curing hepatocellular carcinoma. These can be broadly classified as surgical (liver resection and liver transplantation), ablative techniques, and transarterial embolisation (TAE) or transarterial chemoembolisation (TACE).

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

Ablation is usually in the form of radiofrequency ablation (Bruix 2011; EASL 2012; Asham 2013), however other modalities exist such as chemical ablation using percutaneous alcohol injections, percutaneous acetic acid injections, and thermal ablations such as microwave ablation, laser (light amplification by stimulated emission of radiation) ablation, cryoablation (tissue ablation by freezing), high-intensity focused ultrasound, and irreversible electroporation (NanoKnife) (Head 2004; Germani 2010; Sindram 2010; Chan 2013a). Complications related to radiofrequency ablation include mortality, liver failure, bleeding, liver abscess, bile duct injuries, and tumour dissemination through the needle tract ('seeding') or into the peritoneum (Chan 2013a; McDermott 2013). Transarterial embolisation involves embolisation of the hepatic artery without using any chemotherapeutic agents, while TACE involves injection of a chemotherapeutic agent prior to embolisation of the hepatic artery (Pleguezuelo 2008; Oliveri 2011). Major complications of TAE and TACE include mortality, liver failure, liver and splenic abscesses, acute cholecystitis, damage to the bile ducts, renal failure, and severe upper gastrointestinal bleeding (Pleguezuelo 2008; Oliveri 2011).

How the intervention might work

Liver resection and liver transplantation work by removing the cancer. Chemical ablations using alcohol injections and acetic acid injections work by destruction of cancer tissue by the chemicals used (Sindram 2010). Thermal ablations cause destruction of cancer tissue by heat or cold (Sindram 2010). Transarterial embolisation and TACE cause ischaemia to the tumour, thereby inducing tumour necrosis (Pleguezuelo 2008; Oliveri 2011). Transarterial chemoembolisation combines the effect of chemotherapy agents, which inhibit the tumour, with the effect of ischaemia on the tumour, although the main effect of TACE may be due to the ischaemia rather than the chemotherapy delivered via the artery (Pleguezuelo 2008).

Why it is important to do this review

Current guidelines on the management of hepatocellular carcinoma by the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) recommend the following for people with early and very early hepatocellular carcinoma (Bruix 2011; EASL 2012).

- Liver resection for single tumour provided that the portal pressure and bilirubin levels are normal.
- Liver transplantation for two or three nodules less than 3 cm or a single nodule in the presence of increased portal pressure or abnormal bilirubin levels provided that there are no associated diseases that preclude liver transplantation.
- Radiofrequency ablation for two or three nodules less than 3 cm or a single nodule in the presence of increased portal pressure or abnormal bilirubin levels in the presence of associated diseases that preclude liver transplantation.

However, it should be noted that people with hepatocellular carcinoma must compete with other people waiting for liver transplantation. In 2012, pre-transplant deaths occurred at the rate of 5.8 deaths per 100 waitlist years in the USA (SRTR 2012), and in the financial year to the end of March 2014, 12% of people on the liver transplant waiting list in the UK died or became too unwell to be transplanted (NHSBT 2014). This indicates an organ shortage necessitating an organ allocation policy. The Milan criteria are now used for organ allocation in many countries. In the USA, eligible people with hepatocellular carcinoma are given exceptional status to limit their presence on the waiting list, as waiting increases the chance of tumour progression or dissemination (OPTN 2014). To be considered eligible for liver transplantation, people with hepatocellular carcinoma must fulfil the Milan criteria as well as having a minimum tumour size of 2 cm if they have a single tumour and a minimum tumour size of 1 cm each if they have two or three lesions (OPTN 2014). There thus appears to be a discrepancy in the recommendations by AASLD and EASL regarding organ allocation policy concerning people with early or very early hepatocellular carcinoma. Network meta-analysis allows the combination of the direct and indirect evidence and permits ranking of different interventions in terms of the different outcomes (Salanti 2011; Salanti 2012). No network meta-analysis on the different interventions for early or very early hepatocellular carcinoma has been performed. This systematic review and attempted network meta-analysis intended to provide the best level of evidence for the role of different treatment options used for people with early or very early hepatocellular carcinoma.

OBJECTIVES

To assess the comparative benefits and harms of different interventions used in the treatment of early or very early hepatocellular carcinoma through a network meta-analysis and to generate rankings of the available interventions according to their safety and efficacy. However, it was not possible to assess whether the potential effect modifiers were similar across different comparisons. Therefore, we did not perform the network meta-analysis and instead assessed the benefits and harms of different interventions versus each other or versus sham or no intervention using standard Cochrane methodology.

When more trials become available with adequate description of potential effect modifiers, we will attempt to conduct network meta-analysis in order to generate rankings of the available interventions according to their safety and efficacy. Therefore, we have retained the planned methodology for network meta-analysis in Appendix 3. Once data appear allowing for the conduct of network

meta-analysis, Appendix 3 will be moved back into the Methods section.

METHODS

Criteria for considering studies for this review

Types of studies

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

Types of participants

We included randomised clinical trials with participants with early or very early hepatocellular carcinoma irrespective of the presence of cirrhosis, size of tumour(s), and number of tumours (provided that they met the criteria of early or very early hepatocellular carcinoma (i.e. BCLC stages 0 and A)), presence or absence of portal hypertension, aetiology of hepatocellular carcinoma, and the future remnant liver volume. We excluded randomised clinical trials in which participants were previously liver transplanted.

Types of interventions

We planned to include any of the following interventions that are possible treatments for early or very early hepatocellular carcinoma, either alone or in combination tested versus each other or versus sham or no intervention.

Some of the interventions that we considered were:

- liver resection;
- liver transplantation;
- radiofrequency ablation;
- microwave ablation;
- other ablations (laser ablation, cryoablation, high-intensity focused ultrasound, irreversible electroporation);
- alcohol injection;
- acetic acid injection;
- TAE;
- TACE.

The above list is not exhaustive. If we identified interventions of which were unaware, we considered them as eligible and included them in the review if they are used primarily for the treatment of hepatocellular carcinoma. If liver resection or liver transplantation is combined with ablation, TAE, or TACE, we planned to categorise the intervention as liver resection or liver transplantation, because liver resection and liver transplantation are the major components in such interventions, with ablation, TAE, or TACE playing an exclusively supportive role to liver resection or liver transplantation. However, we planned to exclude such interventions from a sensitivity analysis (see Sensitivity analysis). If we found a sufficient number of trials (at least one in each category) on one or more of the other methods of ablation (laser ablation, cryoablation, high-intensity focused ultrasound, irreversible electroporation), we considered the specific method of ablation with sufficient trials as a separate intervention (node).

Types of outcome measures

We assessed the comparative benefits and harms of available interventions aimed at treating people with early or very early hepatocellular carcinoma for the following outcomes.

Primary outcomes

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

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

Secondary outcomes

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

Search methods for identification of studies

Electronic searches

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

Searching other resources

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

Data collection and analysis

Selection of studies

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

Data extraction and management

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

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

If available, we planned to obtain separate data for people with and without cirrhosis; single tumour less than 5 cm compared to single tumour 5 cm or greater compared to multiple tumours; presence compared to absence of portal hypertension; and viral versus non-viral aetiology. We contacted the authors for unclear or missing information. If there was any doubt as to whether trials shared the same participants, completely or partially (by identifying common authors and centres), we planned to contact the trial authors to clarify whether the trial report was duplicated. Any differences in opinion were resolved through discussion.

Assessment of risk of bias in included studies

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

Allocation sequence generation

- Low risk of bias: sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were adequate if performed by an independent person not otherwise involved in the trial.
- Uncertain risk of bias: the method of sequence generation was not specified.
- High risk of bias: the sequence generation method was not random.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. Allocation was controlled by a central and independent randomisation unit. The allocation sequence was unknown to the investigators (e.g. if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Uncertain risk of bias: the method used to conceal the allocation was not described so that intervention allocations may have been foreseen in advance of, or during, enrolment.
- High risk of bias: the allocation sequence was likely to be known to the investigators who assigned the participants.

Blinding of participants and personnel

- Low risk of bias: blinding was performed adequately, or the care that participants received was not likely to be influenced by lack of blinding.
- Uncertain risk of bias: there was insufficient information to assess whether blinding was likely to induce bias on the results.
- High risk of bias: no blinding or incomplete blinding, and the care that participants received was likely to be influenced by lack of blinding.

Blinding of outcome assessors

- Low risk of bias: blinding was performed adequately, or the assessment of outcomes was not likely to be influenced by lack of blinding.
- Uncertain risk of bias: there was insufficient information to assess whether blinding was likely to induce bias on the results.
- High risk of bias: no blinding or incomplete blinding, and the assessment of outcomes 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. Sufficient methods, such as multiple imputation, were employed to handle missing data.
- Uncertain risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias on the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

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

For-profit bias

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

Other bias

- Low risk of bias: the trial appeared to be free of other components (e.g. inappropriate control or dose or administration of control) that could put it at risk of bias.

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

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

Measures of treatment effect

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

Unit of analysis issues

Cluster randomised clinical trials

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

Cross-over randomised clinical trials

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

Trials with multiple treatment groups

We collected data for all trial intervention groups that met the inclusion criteria.

Dealing with missing data

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

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

Assessment of heterogeneity

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

We used the I^2 test and Chi^2 test for heterogeneity, and overlapping of CIs to assess heterogeneity. If we identified substantial heterogeneity (clinical, methodological, or statistical), we planned to explore and address heterogeneity in a subgroup analysis (see Subgroup analysis and investigation of heterogeneity section).

Assessment of reporting biases

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

We also considered selective reporting as evidence of reporting bias.

Data synthesis

We performed the meta-analyses according to the recommendations of Cochrane (Higgins 2011), using the software package Review Manager 5 (RevMan 2014). We used a random-effects model and a fixed-effect model (DerSimonian 1986; DeMets 1987). In the case of a discrepancy between the two models, we reported both results; otherwise, we reported only the results from the fixed-effect model.

Calculation of required information size and Trial Sequential Analysis

For calculation of the required information size, see Appendix 5. We performed Trial Sequential Analysis to control the risk of random errors when at least two trials were included for all-cause mortality at maximal follow-up and health-related quality of life, the two outcomes that determine whether the treatment should be given (Wetterslev 2008; Thorlund 2011; TSA 2011). We used an alpha error as per guidance of Jakobsen 2014, power of 90% (beta error of 10%), a relative risk reduction of 20%, a control group proportion observed in the trials, and the heterogeneity observed in the meta-analysis. As the only outcome was mortality at maximal follow-up, which is a time-to-event outcome, we performed the Trial Sequential Analysis using Stata/SE 14.2 employing methods suggested by Miladinovic 2013.

Subgroup analysis and investigation of heterogeneity

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

- Trials at low risk of bias compared to trials at high risk of bias.
- People with and without cirrhosis.
- Very early compared to early hepatocellular carcinoma.
- Presence compared to absence of portal hypertension.
- Viral aetiology compared to non-viral aetiology.
- Use of immunotherapy or antiviral therapy as adjuvant therapy compared to no use.

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

Sensitivity analysis

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

Presentation of results and GRADE assessments

We have reported all-cause mortality, cancer-related mortality, serious adverse events, and health-related quality of life, the outcomes that determine the management of people with early- or very early-stage hepatocellular carcinoma, in a 'Summary of findings' table format, downgrading the quality of evidence for risk of bias, inconsistency, indirectness, imprecision, and publication bias using GRADE (Guyatt 2011). We have presented only comparisons in which at least two trials were included for one or more of these outcomes.

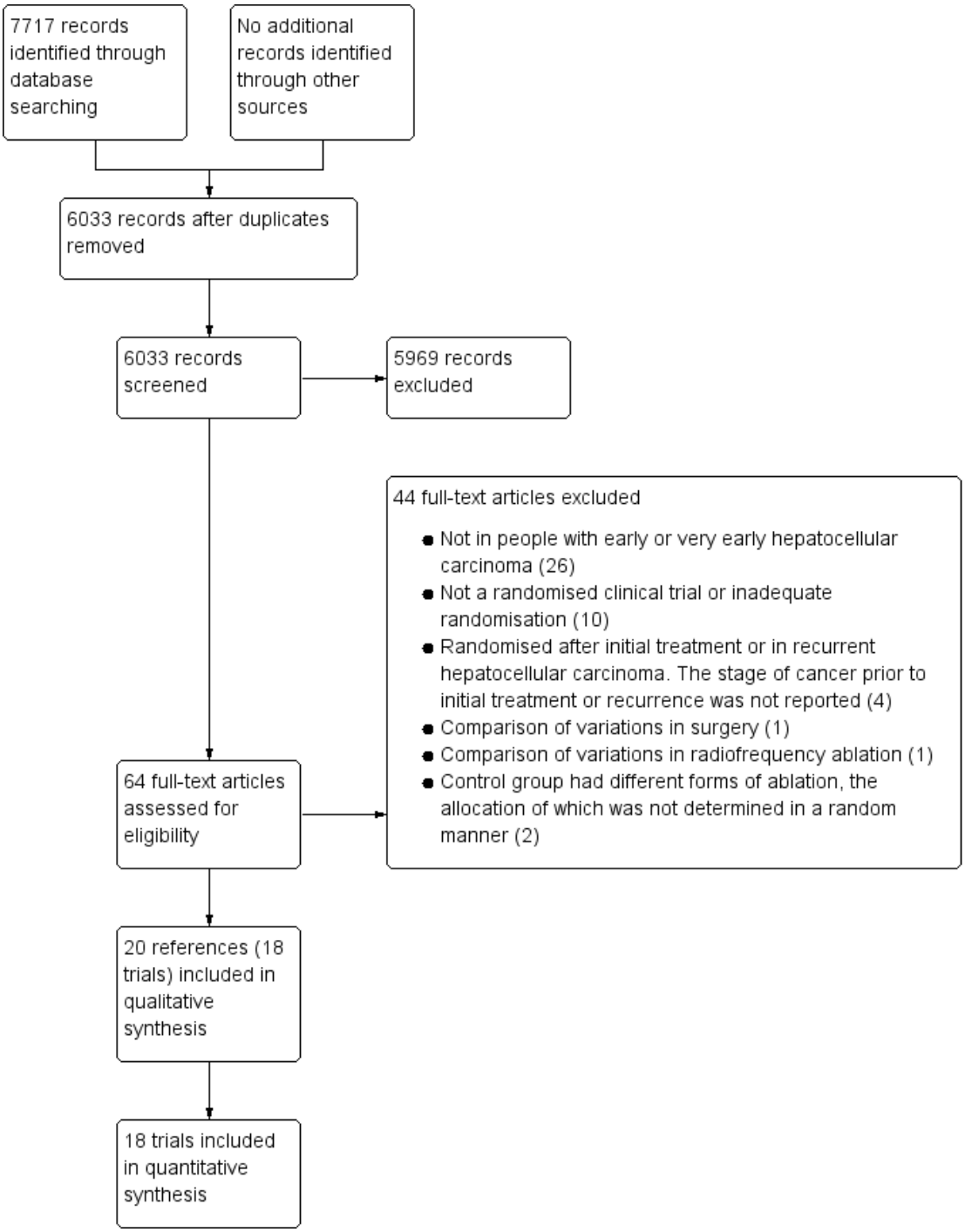
RESULTS

Description of studies

Results of the search

We identified 7717 references through electronic searches of CENTRAL (N = 615), MEDLINE (N = 3753), Embase (N = 809), Science Citation Index Expanded (N = 2277), World Health Organization International Clinical Trials Registry Platform (N = 85), and ClinicalTrials.gov (N = 178). After removing 1684 duplicates, we obtained 6033 references. We then excluded 5969 clearly irrelevant references through screening titles and reading abstracts. We retrieved 64 references for further assessment. We identified no references through scanning reference lists of the identified randomised trials. We excluded 44 references for the reasons listed in the Characteristics of excluded studies table. A total of 20 references (18 trials) met the inclusion criteria. The reference flow is summarised in the study flow diagram (Figure 1).

Figure 1. Study flow diagram.



Included studies

Eighteen trials met the inclusion criteria for this review: four trials (593 participants; 574 participants included for one or more analyses) compared surgery versus radiofrequency ablation in people with early hepatocellular carcinoma who were eligible to undergo surgery, while 14 trials (2533 participants; 2494 participants included for various analyses) compared different non-surgical interventions in people with early hepatocellular carcinoma who were not eligible to undergo surgery (this was clear from the inclusion criteria in the trials). We have listed the comparisons included in the trials and the follow-up period in the trials in Table 1.

Participants eligible for surgery

All four included trials compared surgery with radiofrequency ablation (Chen 2006; Huang 2010; Fang 2014; Lee 2014). It should be noted that none of the trials included liver transplantation or sham treatment or no treatment as one of the comparison groups. The average age in the trials that reported this information ranged from 51 years to 56 years. The proportion of females in the trials that reported this information ranged from 18.6% to 28.7%. Three trials included participants with and without cirrhosis (Chen 2006; Huang 2010; Fang 2014). The fourth trial did not report the cirrhosis status of participants (Lee 2014). The proportion of participants who had cirrhosis was 61.7% and 84.2% in the two trials that reported this information (Huang 2010; Fang 2014). One trial included participants with early hepatocellular carcinoma but did not include participants with very early hepatocellular carcinoma (Lee 2014). The remaining trials did not report the proportion of participants with very early hepatocellular carcinoma. The proportion of participants with viral aetiology was 89.2% and 93.5% in the two trials that reported this information (Huang 2010; Fang 2014). The remaining two trials did not report this information (Chen 2006; Lee 2014). None of the trials reported the proportion of participants who received adjuvant antiviral therapy or adjuvant immunotherapy. The mean or median follow-up in the trials ranged from 29 months to 42 months in the three trials that provided this information (Chen 2006; Huang 2010; Fang 2014).

Source of funding

Three trials did not receive any additional funding or were funded by parties without any vested interest in the results (Chen 2006; Huang 2010; Fang 2014). One trial was funded by a party with vested interest in the results (Lee 2014).

Participants not eligible for surgery

Fourteen trials included only participants who were not eligible for surgery and compared various non-surgical interventions: radiofrequency ablation, laser ablation, microwave ablation, percutaneous acetic acid injection, percutaneous alcohol injection, a combination of radiofrequency ablation with systemic chemotherapy, a combination of radiofrequency ablation with percutaneous alcohol injection, a combination of transarterial chemoembolisation with percutaneous alcohol injection, or a combination of transarterial chemoembolisation with radiofrequency ablation. None of the trials included sham treatment or no treatment as one of the comparison groups. The average age in the trials that reported this information ranged from 49 years to 72 years. The proportion of females in the trials that reported this information ranged from 11.1% to 42.3%. Eight trials only included participants who had cirrhosis (Bolondi 1996; Shibata 2002; Lencioni 2003; Lin 2005; Brunello 2008; Giorgio 2011; Orlacchio 2014; Costanzo 2015). The proportion of participants with cirrhosis was 85.3% and 88.5% in the two trials that included both cirrhotic and non-cirrhotic participants and reported the proportion of participants with cirrhosis (Koda 2001; Shiina 2005; Huang 2010; Fang 2014). The remaining four trials did not report this information (Gan 2004; Chen 2005; Aikata 2006; El Kady 2013). One trial included participants with early hepatocellular carcinoma, but did not include participants with very early hepatocellular carcinoma (El Kady 2013). The proportion of participants with very early hepatocellular carcinoma in the only trial that reported this information was 25% (Giorgio 2011). The remaining trials did not report the proportion of participants with very early hepatocellular carcinoma. Only one trial reported the proportion of participants with portal hypertension (all 30 participants in this trial had portal hypertension) (Orlacchio 2014). One trial included hepatocellular carcinoma of viral aetiology only (Giorgio 2011). The proportion of participants with viral aetiology ranged from 80.4% to 98.6% in the remaining seven trials that reported this information (Koda 2001; Shibata 2002; Lencioni 2003; Lin 2005; Shiina 2005; Brunello 2008; Orlacchio 2014). None of the trials reported the proportion of participants who received adjuvant antiviral therapy or adjuvant immunotherapy. The mean or median follow-up in the trials ranged from 6 months to 37 months in the 11 trials that provided this information (Bolondi 1996; Koda 2001; Shibata 2002; Lencioni 2003; Gan 2004; Lin 2005; Shiina 2005; Brunello 2008; Giorgio 2011; El Kady 2013; Orlacchio 2014).

Source of funding

Five trials did not receive any special funding or received funding from parties without vested interest in the results (Brunello 2008;

Giorgio 2011; El Kady 2013; Orlacchio 2014; Costanzo 2015).
The source of funding was not reported in the remaining trials.

Excluded studies

None of the trials met the inclusion criteria.

Risk of bias in included studies

The risk of bias is summarised in Figure 2, Figure 3, and Table 2.
None of the trials was at low risk of bias for all domains; hence, we considered all trials to be at high risk of bias.

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

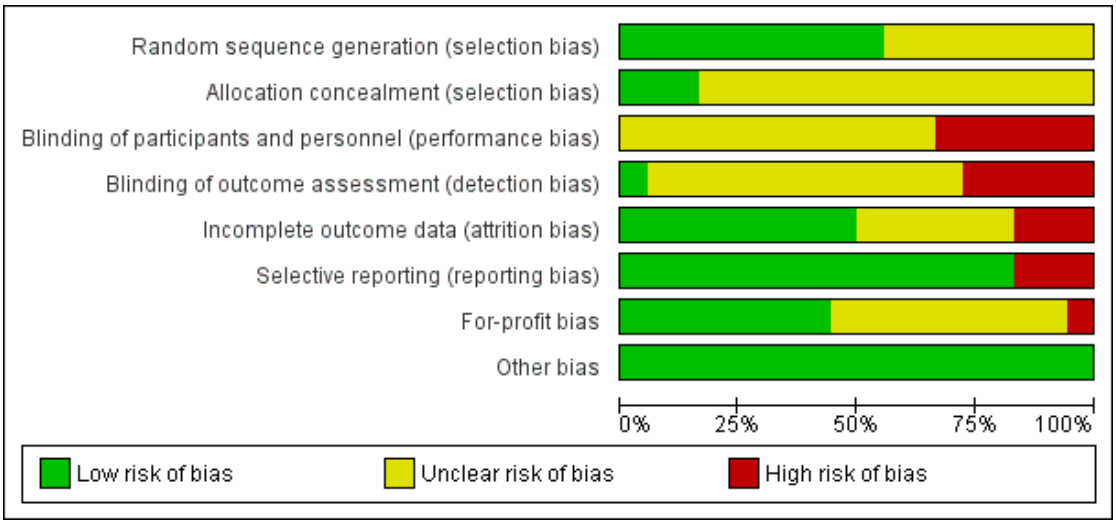
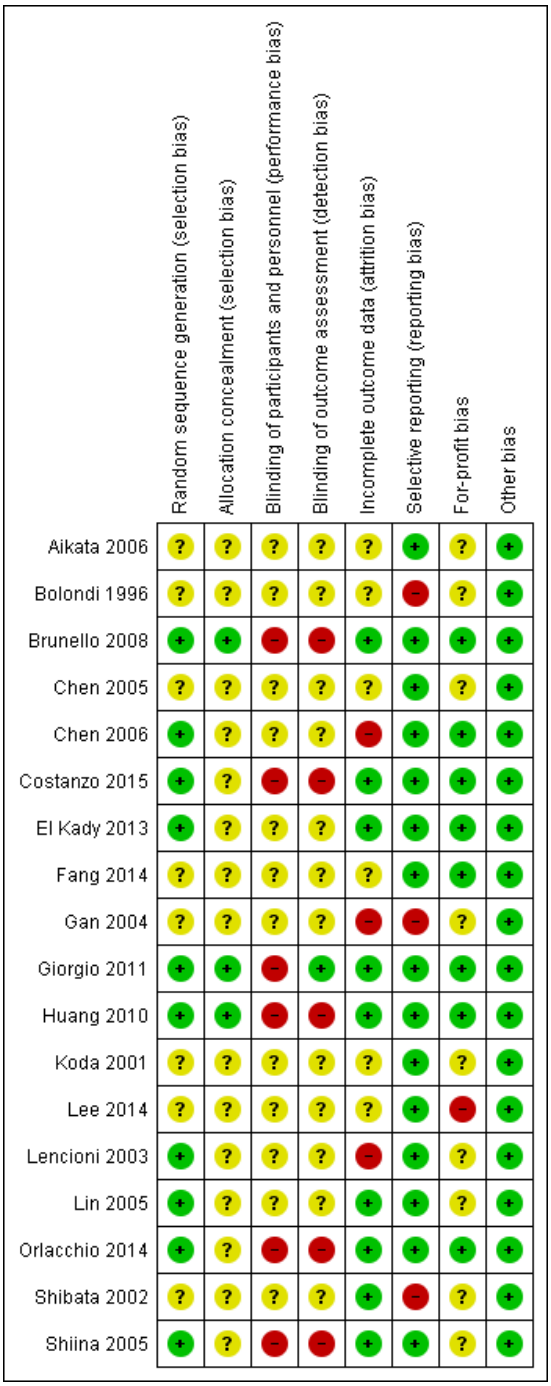


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Surgery versus radiofrequency ablation

Two trials were at low risk of bias for random sequence generation (Chen 2006; Huang 2010). The remaining trials were at unclear risk of bias for random sequence generation. One trial was at low risk of bias for allocation concealment (Huang 2010). The remaining trials were at unclear risk of bias for allocation concealment. We considered one trial that was at low risk of bias for random sequence generation and allocation concealment to be at low risk of allocation bias (Huang 2010).

Non-surgical interventions

Eight trials were at low risk of bias for random sequence generation (Lencioni 2003; Lin 2005; Shiina 2005; Brunello 2008; Giorgio 2011; El Kady 2013; Orlacchio 2014; Costanzo 2015); none of the trials was at high risk of bias for random sequence generation; and six trials were at unclear risk of bias for random sequence generation (Bolondi 1996; Koda 2001; Shibata 2002; Gan 2004; Chen 2005; Aikata 2006).

Two trials were at low risk of bias for allocation concealment (Brunello 2008; Giorgio 2011); none of the trials was at high risk of bias for allocation concealment; and 12 trials were at unclear risk of bias for allocation concealment (Bolondi 1996; Koda 2001; Shibata 2002; Lencioni 2003; Gan 2004; Chen 2005; Lin 2005; Shiina 2005; Aikata 2006; El Kady 2013; Orlacchio 2014; Costanzo 2015).

Overall, two trials were at low risk of selection bias (Brunello 2008; Giorgio 2011); no trials were at high risk of selection bias; and 12 trials were at unclear risk of selection bias (Bolondi 1996; Koda 2001; Shibata 2002; Lencioni 2003; Gan 2004; Chen 2005; Lin 2005; Shiina 2005; Aikata 2006; El Kady 2013; Orlacchio 2014; Costanzo 2015).

Blinding

Surgery versus radiofrequency ablation

One trial was at high risk of bias for blinding of participants and healthcare providers (Huang 2010). The remaining trials were at unclear risk of bias for blinding of participants and healthcare providers. One trial was at high risk of bias for blinding of outcome assessors (Huang 2010). The remaining trials were at unclear risk of bias for blinding of outcome assessors. Overall, one trial was at high risk of performance bias and detection bias. The remaining trials were at unclear risk of performance bias and detection bias.

Non-surgical interventions

Five trials were at high risk of bias for blinding of participants and health professionals (Shiina 2005; Brunello 2008; Giorgio 2011; Orlacchio 2014; Costanzo 2015); the remaining nine trials were at unclear risk of bias for blinding of participants and health professionals (Bolondi 1996; Koda 2001; Shibata 2002; Lencioni 2003; Gan 2004; Chen 2005; Lin 2005; Aikata 2006; El Kady 2013).

The trials had the same risk of bias for blinding of outcome assessors domain as for the blinding of participants and health professionals domain.

Incomplete outcome data

Surgery versus radiofrequency ablation

One trial was at low risk of bias for incomplete outcome data (attrition bias) (Huang 2010). One trial was at high risk of bias for incomplete outcome data (attrition bias) (Chen 2006). The remaining trials were at unclear risk of bias for incomplete outcome data (attrition bias).

Non-surgical interventions

Eight trials were at low risk of bias for incomplete outcome data (attrition bias) (Shibata 2002; Lin 2005; Shiina 2005; Brunello 2008; Giorgio 2011; El Kady 2013; Orlacchio 2014; Costanzo 2015); two trials were at high risk of bias for incomplete outcome data (attrition bias) (Lencioni 2003; Gan 2004); and four trials were at unclear risk of bias for incomplete outcome data (attrition bias) (Bolondi 1996; Koda 2001; Chen 2005; Aikata 2006).

Selective reporting

Surgery versus radiofrequency ablation

All four trials were at low risk of bias for selective reporting (reporting bias) (Chen 2006; Huang 2010; Fang 2014; Lee 2014).

Non-surgical interventions

Eleven trials were at low risk of bias for selective reporting (reporting bias) (Koda 2001; Lencioni 2003; Chen 2005; Lin 2005; Shiina 2005; Aikata 2006; Brunello 2008; Giorgio 2011; El Kady 2013; Orlacchio 2014; Costanzo 2015); three trials were at high risk of bias for selective reporting (reporting bias) (Bolondi 1996; Shibata 2002; Gan 2004); and none of the trials was at unclear risk of bias for selective reporting (reporting bias).

Other potential sources of bias

Surgery versus radiofrequency ablation

For-profit bias: Three trials did not receive any additional funding or were funded by parties without any vested interest in the results (Chen 2006; Huang 2010; Fang 2014). One trial was funded by parties with vested interest in the results (Lee 2014).
We noted no other bias in any of the trials.

Non-surgical interventions

For-profit bias: Five trials were at low risk of for-profit bias (Brunello 2008; Giorgio 2011; El Kady 2013; Orlacchio 2014; Costanzo 2015); none of the trials was at high risk of for-profit bias; nine trials were at unclear risk of for-profit bias (Bolondi 1996; Koda 2001; Shibata 2002; Lencioni 2003; Gan 2004; Chen 2005; Lin 2005; Shiina 2005; Aikata 2006).
All the trials were at low risk of other bias.

Effects of interventions

See: **Summary of findings for the main comparison** Surgery versus radiofrequency ablation for people with early- or very early-stage hepatocellular carcinoma; **Summary of findings 2** Percutaneous alcohol injection versus radiofrequency ablation for people with early- or very early-stage hepatocellular carcinoma; **Summary of findings 3** Laser ablation versus radiofrequency ablation for people with early- or very early-stage hepatocellular carcinoma; **Summary of findings 4** Transarterial embolisation plus radiofrequency ablation versus radiofrequency ablation for people with early- or very early-stage hepatocellular carcinoma; **Summary of findings 5** Transarterial embolisation plus percutaneous alcohol injection versus percutaneous alcohol injection for people with early- or very early-stage hepatocellular carcinoma

Surgery versus radiofrequency ablation

Mortality at maximal follow-up

A total of four trials including 574 participants reported mortality at maximal follow-up (Chen 2006; Huang 2010; Fang 2014; Lee 2014). There was no evidence of difference in mortality at maximal follow-up between the groups (hazard ratio (HR) 0.80, 95% confidence interval (CI) 0.60 to 1.08; 574 participants; 4 trials; I^2 = 68) (Analysis 1.1).

Cancer-related mortality at maximal follow-up

One trial including 230 participants reported cancer-related mortality at maximal follow-up (Huang 2010). The cancer-related mortality was lower in the surgery group (20/115 (17.4%)) than in the radiofrequency ablation group (43/115 (37.4%)) (odds ratio (OR) 0.35, 95% CI 0.19 to 0.65; 230 participants; 1 trial) (Analysis 1.2).

Mortality (< 1 year)

None of the trials reported this outcome.

Mortality (> 1 year)

One trial including 230 participants reported mortality (> 1 year) (Huang 2010). The mortality (> 1 year) was lower in the surgery group (28/115 (24.3%)) than in the radiofrequency ablation group (52/115 (45.2%)) (OR 0.39, 95% CI 0.22 to 0.68; 230 participants; 1 trial) (Analysis 1.3).

Serious adverse events (number of participants)

One trial including 120 participants reported serious adverse events (number of participants) (Fang 2014). The serious adverse events (number of participants) was higher in the surgery group (14/60 (23.3%)) than in the radiofrequency ablation group (1/60 (1.7%)) (OR 17.96, 95% CI 2.28 to 141.60; 120 participants; 1 trial) (Analysis 1.4).

Serious adverse events (number of events)

Two trials including 391 participants reported number of serious adverse events (Chen 2006; Huang 2010). The number of serious adverse events was higher in the surgery group (adjusted rate: 11.3 events per 100 participants) than in the radiofrequency ablation group (3/186 (1.6 events per 100 participants)) (rate ratio 7.02, 95% CI 2.29 to 21.46; 391 participants; 2 trials; I^2 = 0%) (Analysis 1.5).

Any adverse events (number of participants)

Two trials including 183 participants reported any adverse events (number of participants) (Fang 2014; Lee 2014). The adverse events (number of participants) was higher in the surgery group than in the radiofrequency ablation group using the fixed-effect model (OR 3.83, 95% CI 1.70 to 8.60; 183 participants; 2 trials; I^2 = 76%); there was no evidence of difference between the groups (surgery: adjusted proportion: 35.2% versus radiofrequency ablation: 11/94 (11.7%)) using the random-effects model (OR 4.09, 95% CI 0.61 to 27.41; 183 participants; 2 trials; I^2 = 76%) (Analysis 1.6).

Any adverse events (number of events)

Two trials including 391 participants reported number of any adverse events (Chen 2006; Huang 2010). The number of any adverse events was higher in the surgery group (adjusted rate: 47.5 events per 100 participants) than in the radiofrequency ablation group (20/186 (10.8 events per 100 participants)) (RR 4.42, 95% CI 2.74 to 7.15; 391 participants; 2 trials; I^2 = 0%) (Analysis 1.7).

Health-related quality of life

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

Hepatocellular carcinoma recurrence (local or distal)

Three trials including 413 participants reported hepatocellular carcinoma recurrence (local or distal) (Huang 2010; Fang 2014; Lee 2014). The hepatocellular carcinoma recurrence (local or distal) was lower in the surgery group (adjusted proportion: 41.2%) than in the radiofrequency ablation group (119/209 (56.9%)) (OR 0.53, 95% CI 0.35 to 0.78; 413 participants; 3 trials; I^2 = 36%) (Analysis 1.8).

Hepatocellular carcinoma recurrence (recurrence in the liver)

Two trials including 350 participants reported hepatocellular carcinoma recurrence (recurrence in liver) (Huang 2010; Fang 2014). The proportion of people with hepatocellular carcinoma recurrence (recurrence in liver) was lower in the surgery group (adjusted proportion: 29.7%) than in the radiofrequency ablation group (81/175 (46.3%)) (OR 0.49, 95% CI 0.31 to 0.78; 350 participants; 2 trials; I^2 = 6%) (Analysis 1.9).

Length of hospital stay

Three trials including 530 participants reported the length of hospital stay (Chen 2006; Huang 2010; Fang 2014). The length of hospital stay was longer in the surgery group than in the radiofrequency ablation group (mean difference (MD) 8.42 days, 95% CI 7.84 to 9.01; 530 participants; 3 trials; I^2 = 86%) (Analysis 1.10).

Overall summary of comparisons in which there was some evidence of difference

- Cancer-related mortality was lower in the surgery group than in the radiofrequency ablation group (OR 0.35, 95% CI 0.19 to 0.65; 230 participants; 1 trial).
- Mortality (> 1 year) was lower in the surgery group than in the radiofrequency ablation group (OR 0.39, 95% CI 0.22 to 0.68; 230 participants; 1 trial).
- Serious adverse events (number of participants) and number of serious adverse events was higher in the surgery group than in the radiofrequency ablation group (OR 17.96, 95% CI 2.28 to 141.60; 120 participants; 1 trial and RR 7.02, 95% CI 2.29 to 21.46; 391 participants; 2 trials; I^2 = 0%).
- Number of any adverse events was higher in the surgery group than in the radiofrequency ablation group (RR 4.42, 95% CI 2.74 to 7.15; 391 participants; 2 trials; I^2 = 0%).
- The proportion of people with hepatocellular carcinoma recurrence (local or distal) and hepatocellular carcinoma recurrence (recurrence in liver) was lower in the surgery group than in the radiofrequency ablation group (OR 0.53, 95% CI 0.35 to 0.78; 413 participants; 3 trials; I^2 = 36% and OR 0.49, 95% CI 0.31 to 0.78; 350 participants; 2 trials; I^2 = 6%).
- Length of hospital stay was longer in the surgery group than in the radiofrequency ablation group (MD 8.42 days, 95% CI 7.84 to 9.01; 530 participants; 3 trials; I^2 = 86%).

Subgroup analyses

Because of the paucity of data, we did not perform any subgroup analyses.

Sensitivity analysis

Because of the paucity of data, we did not perform a sensitivity analysis of imputing information based on different scenarios, that is it was unclear whether there were any postrandomisation dropouts in many trials, as well as to which group these postrandomisation dropouts belonged even when the number of postrandomisation dropouts was reported. We did not impute standard deviation, therefore we did not perform a sensitivity analysis to assess the impact of imputing the standard deviation.

We performed a sensitivity analysis excluding the trial in which 19 participants from the radiofrequency ablation group were excluded because they underwent surgical resection (Chen 2006). As it was not possible to perform a sensitivity analysis for the primary outcome of mortality at maximal follow-up by imputing the information based on different scenarios (this being a time-to-event outcome), we performed a post hoc sensitivity analysis by excluding this trial. Excluding this trial did not alter the conclusions (Analysis 1.11).

Reporting bias

We did not assess reporting bias by creating a funnel plot because of the few trials included for each comparison.

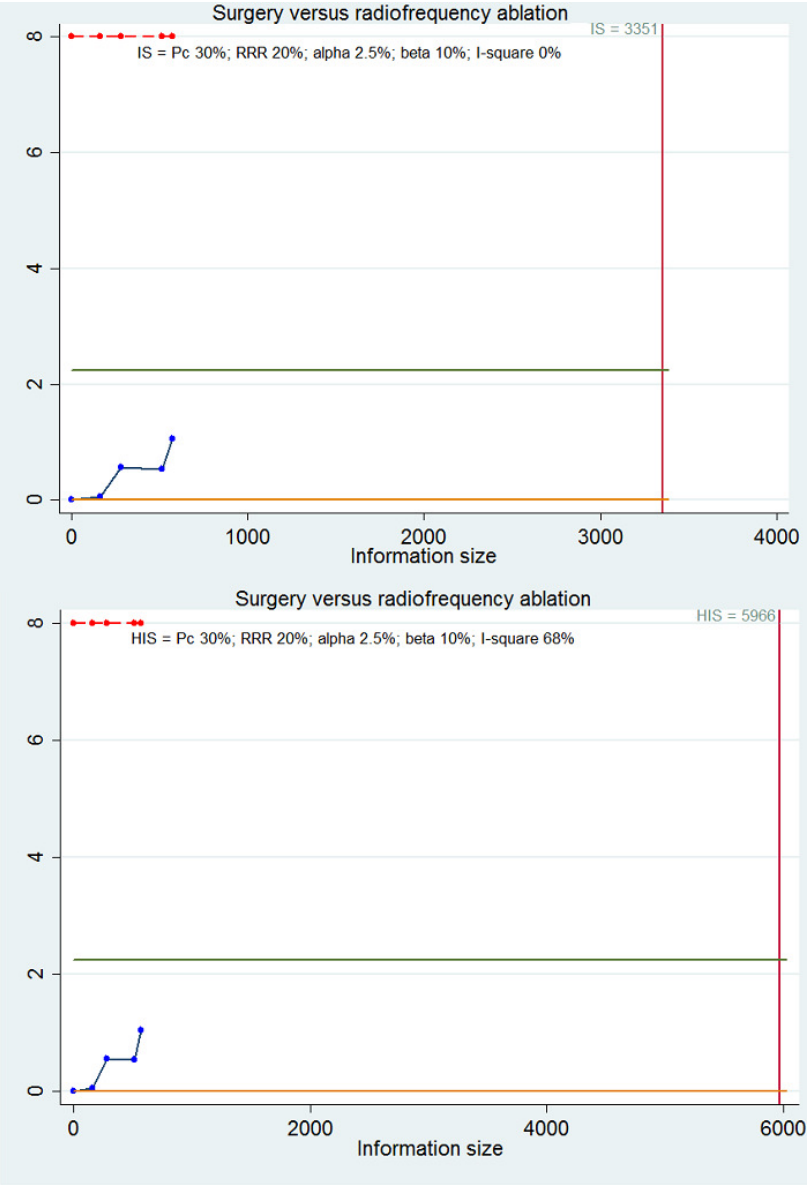
Using fixed-effect model versus random-effects model

The interpretation of results was not altered based on the model used for analysis for any of the analyses.

Trial Sequential Analysis

We performed a Trial Sequential Analysis for all-cause mortality at maximal follow-up. As shown in Figure 4, the cumulative Z-curves (blue lines) did not cross any of the trial sequential monitoring boundaries (red lines). They did not cross the conventional alpha boundary of 2.5% (green lines) either, suggesting a high risk of random error.

Figure 4. Trial Sequential Analysis of all-cause mortality at maximal follow-up for surgery versus radiofrequency ablation. We used an alpha error of 2.5%, power of 90% (beta error of 10%), a relative risk reduction (RRR) of 20% (upper figure) and that observed in trials (20%) (lower figure), control group proportion (Pc) observed in the trials (30% mortality in about 2 to 3 years), and I2 of 0% (upper figure) and that observed in the trials (I2 = 68%) (lower figure). The accrued sample size (574) is only a fraction of the information size (IS) (3351 trial participants) or heterogeneity-adjusted information size (HIS) (5966 trial participants). As shown in all the comparisons, the cumulative Z-curves (blue line) do not cross any of the trial sequential monitoring boundaries (red lines), and neither do they cross the conventional alpha boundary of 2.5% (green line).



Quality of the evidence

The overall quality of the evidence was low or very low for all outcomes (Summary of findings for the main comparison). All of the trials were at high risk of bias. However, for all-cause mortality, the issue of bias due to blinding does not arise; therefore, we downgraded the quality of the evidence one level for all-cause mortality and two levels for the remaining comparisons. There was no issue of indirectness, as all of the outcomes were clinical outcomes and only direct comparisons were used. The sample size was small (all comparisons downgraded one level) and the confidence intervals overlapped clinically significant effect and clinically insignificant effect for most comparisons (downgraded one level). In addition, there was substantial heterogeneity for some of the outcomes, resulting in further downgrading by one level. We did not explore publication bias because of the few trials included in this review.

Comparison of non-surgical interventions

Mortality at maximal follow-up

Ten trials including 1417 participants reported mortality at maximal follow-up (Bolondi 1996; Koda 2001; Lencioni 2003; Chen 2005; Lin 2005; Shiina 2005; Aikata 2006; Brunello 2008; Giorgio 2011; Costanzo 2015).

Mortality at maximal follow-up was higher in the percutaneous acetic acid injection group (HR 1.77, 95% CI 1.12 to 2.79; 125 participants; 1 trial) and the percutaneous alcohol injection group (HR 1.49, 95% CI 1.18 to 1.88; 882 participants; 5 trials; I^2 = 57%) than in the radiofrequency ablation group. There was no evidence of difference in any of the remaining comparisons (Analysis 2.1).

Cancer-related mortality at maximal follow-up

Five trials including 717 participants reported cancer-related mortality at maximal follow-up across all comparisons (Koda 2001; Lencioni 2003; Lin 2005; Shiina 2005; Costanzo 2015). Cancer-related mortality at maximal follow-up was higher in the percutaneous alcohol injection group (adjusted proportion: 16.8%) than in the radiofrequency ablation group (20/232 (8.6%)) (OR 2.18, 95% CI 1.22 to 3.89; 458 participants; 3 trials; I^2 = 0%). There was no evidence of difference in any of the remaining comparisons (Analysis 2.2).

Mortality (< 1 year)

Two trials including 74 participants reported mortality (< 1 year) (El Kady 2013; Orlacchio 2014). There were no deaths within one year in either trial.

Mortality (> 1 year)

Six trials including 852 participants reported mortality (> 1 year) across all comparisons (Koda 2001; Lencioni 2003; Lin 2005; Shiina 2005; Brunello 2008; Costanzo 2015). Mortality (> 1 year) was higher in the percutaneous alcohol injection group (adjusted proportion: 29.7%) than in the radiofrequency ablation group (62/302 (20.5%)) (OR 1.69, 95% CI 1.15 to 2.49; 598 participants; 4 trials; I^2 = 0%). There was no evidence of difference in any of the remaining comparisons (Analysis 2.3).

Serious adverse events (number of participants)

Eleven trials including 934 participants reported serious adverse events (number of participants) across all comparisons (Koda 2001; Shibata 2002; Lencioni 2003; Gan 2004; Chen 2005; Lin 2005; Aikata 2006; Brunello 2008; El Kady 2013; Orlacchio 2014; Costanzo 2015). There was no evidence of difference in any of the comparisons (Analysis 2.4).

Serious adverse events (number of events)

Two trials including 278 participants reported number of serious adverse events across all comparisons (Shiina 2005; Aikata 2006). There was no evidence of difference in any of the comparisons (Analysis 2.5).

Any adverse events (number of participants)

Three trials including 611 participants reported any adverse events (number of participants) across all comparisons (Lin 2005; Brunello 2008; Giorgio 2011). There was no evidence of difference in any of the comparisons (Analysis 2.6).

Any adverse events (number of events)

Six trials including 732 participants reported number of any adverse events across all comparisons (Koda 2001; Lencioni 2003; Shiina 2005; El Kady 2013; Orlacchio 2014; Costanzo 2015). The number of any adverse events was lower in the TACE plus percutaneous alcohol injection group (adjusted rate: 438.5 events per 100 participants) than in the percutaneous alcohol injection group (215/26 (826.9 events per 100 participants)) (RR 0.53, 95% CI 0.42 to 0.67; 52 participants; 1 trial). There was no evidence of difference in any of the remaining comparisons (Analysis 2.7).

Health-related quality of life

None of the trials reported this outcome.

Hepatocellular carcinoma recurrence (local or distal)

Three trials including 511 participants reported hepatocellular carcinoma recurrence (local or distal) across all comparisons (Shiina 2005; Brunello 2008; Costanzo 2015). The proportion of people with hepatocellular carcinoma recurrence (local or distal) was higher in the percutaneous alcohol injection group (adjusted proportion: 68.3%) than in the radiofrequency ablation group (110/188 (58.5%)) (OR 1.58, 95% CI 1.02 to 2.45; 371 participants; 2 trials; I^2 = 0%). There was no evidence of difference in any of the remaining comparisons (Analysis 2.8).

Hepatocellular carcinoma recurrence (recurrence in liver)

Four trials including 439 participants reported hepatocellular carcinoma recurrence (recurrence in liver) across all comparisons (Gan 2004; Shiina 2005; El Kady 2013; Costanzo 2015). There was no evidence of difference in any of the comparisons (Analysis 2.9).

Length of hospital stay

One trial including 232 participants reported the length of hospital stay across all comparisons (Shiina 2005). The length of hospital stay was longer in the percutaneous alcohol injection group than in the radiofrequency ablation group in this trial (MD 15.30 days, 95% CI 13.23 to 17.37; 232 participants; 1 trial).

Overall summary of comparisons in which there was some evidence of difference

- Mortality at maximal follow-up was higher in the percutaneous acetic acid injection group (HR 1.77, 95% CI 1.12 to 2.79; 125 participants; 1 trial) and the percutaneous alcohol injection group (HR 1.49, 95% CI 1.18 to 1.88; 882 participants; 5 trials; I^2 = 57%) than in the radiofrequency ablation group.
- Cancer-related mortality at maximal follow-up was higher in the percutaneous alcohol injection group than in the radiofrequency ablation group (OR 2.18, 95% CI 1.22 to 3.89; 458 participants; 3 trials; I^2 = 0%).
- Mortality (> 1 year) was higher in the percutaneous alcohol injection group than in the radiofrequency ablation group (OR 1.69, 95% CI 1.15 to 2.49; 598 participants; 4 trials; I^2 = 0%).
- Number of any adverse events was lower in the TACE plus percutaneous alcohol injection group than the percutaneous alcohol injection group (RR 0.53, 95% CI 0.42 to 0.67; 52 participants; 1 trial).
- The proportion of people with hepatocellular carcinoma recurrence (local or distal) was higher in the percutaneous alcohol injection group than in the radiofrequency ablation group (OR 1.58, 95% CI 1.02 to 2.45; 371 participants; 2 trials; I^2 = 0%).
- Length of hospital stay was longer in the percutaneous alcohol injection group than in the radiofrequency ablation group (MD 15.30 days, 95% CI 13.23 to 17.37; 232 participants; 1 trial).

Subgroup analyses

Because of the paucity of data, we did not perform any subgroup analyses.

Sensitivity analysis

Because of the paucity of data, we did not perform a sensitivity analysis of imputing information based on different scenarios, and we did not perform a sensitivity analysis to assess the impact of imputing the standard deviation.

Reporting bias

We did not assess reporting bias by creating a funnel plot because of the few trials included for each comparison.

Using fixed-effect model versus random-effects model

The interpretation of results was not altered based on the model used for analysis.

Trial Sequential Analysis

The required sample size for identifying a 20% relative risk reduction in the different outcomes based on an alpha error of 5%, a beta error of 20%, and the control group (radiofrequency ablation) proportion observed across all trials were as follows.

- Cancer-related mortality at maximal follow-up (control group proportion: 9.6%): 6722 people
- Mortality < 1 year (control group proportion: 0%): not estimable
- Mortality > 1 year (control group proportion: 21.5%): 2648 people
- Serious adverse events (proportion) (control group proportion: 2.0%): 34,688 people
- Adverse events (proportion) (control group proportion: 6.6%): 10,066 people
- Hepatocellular carcinoma recurrence (local or distal) (control group proportion: 60.5%): 530 people
- Hepatocellular carcinoma recurrence (liver) (control group proportion: 49.5%): 790 people

The above mentioned are sample sizes uncorrected for heterogeneity. In the presence of heterogeneity of 25%, for example, the required information size for cancer-related mortality at maximal follow-up is 6772/(1 - 0.25) = 8963 people.

As seen in the various analyses, only a small fraction of the above sample sizes has been reached in the comparisons in which there was no evidence of difference, therefore one cannot rule out alpha and beta errors in any of these comparisons.

We performed a Trial Sequential Analysis for all-cause mortality at maximal follow-up for various comparisons. As shown in Figure 5 and Figure 6, the cumulative Z-curves (blue lines) did not cross any of the trial sequential monitoring boundaries (red lines) for any of the comparisons. They did not cross the conventional alpha boundary of 2.5% (green lines) either, suggesting a high risk of random error.

Figure 5. Trial Sequential Analysis of all-cause mortality at maximal follow-up for percutaneous alcohol injection versus radiofrequency ablation. We used an alpha error of 2.5%, power of 90% (beta error of 10%), a relative risk reduction (RRR) of 20% (upper figure) and that observed in trials (49%) (lower figure), control group proportion observed in the trials (Pc = 30% mortality in about 2 to 3 years), and heterogeneity of 0% (upper figure) and that observed in the trials (I2 = 57%) (lower figure). The accrued sample size (882 trial participants) is only a fraction of the information size (IS) (3351) or heterogeneity-adjusted information size (HIS) (970 trial participants). As shown in all the comparisons, the cumulative Z-curves (blue line) do not cross any of the trial sequential monitoring boundaries (red lines), and neither do they cross the conventional alpha boundary of 2.5% (green line).

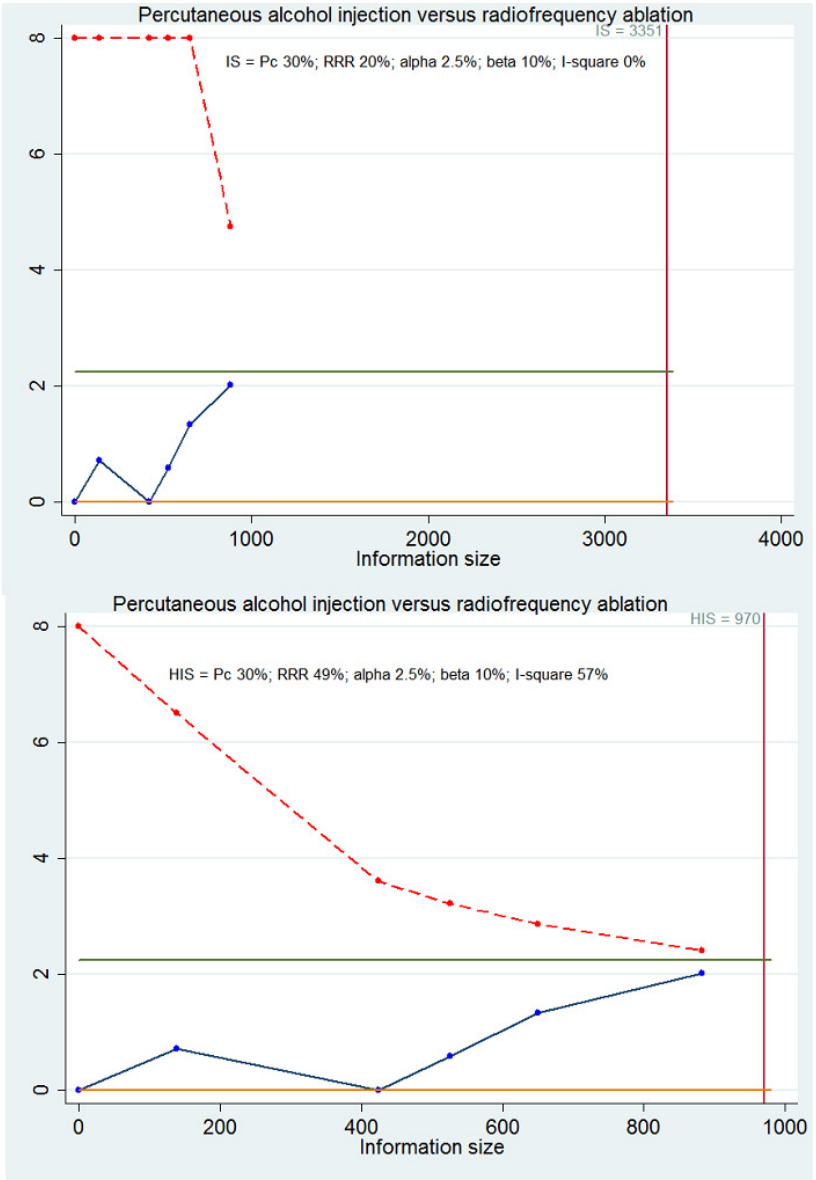
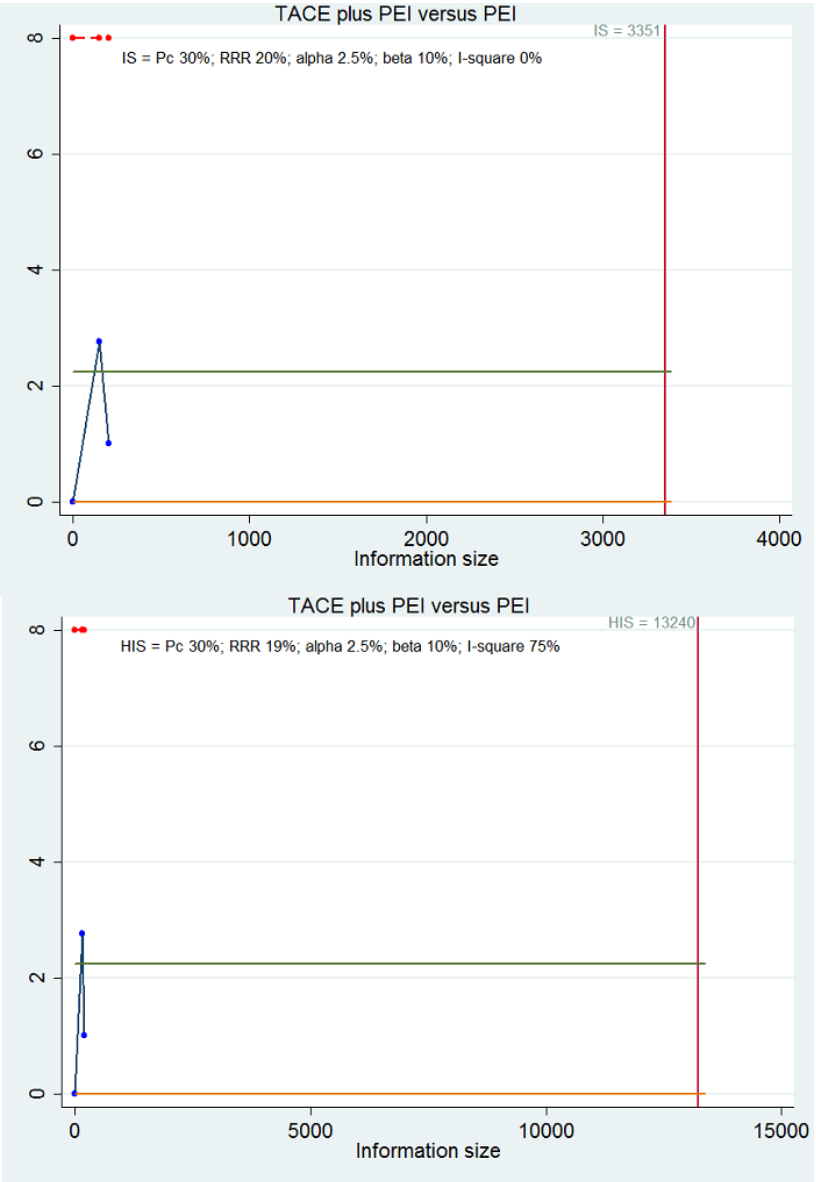


Figure 6. Trial Sequential Analysis of all-cause mortality at maximal follow-up for transarterial chemoembolisation (TACE) versus percutaneous alcohol injection (PAI) versus PAI. We used an alpha error of 2.5%, power of 90% (beta error of 10%), a relative risk reduction (RRR) of 20% (upper figure) and that observed in trials (lower figure), control group proportion observed in the trials (30% mortality in about 2 to 3 years), and heterogeneity of 0% (upper figure) and that observed in the trials (I2 = 75%) (lower figure). The accrued sample size (202 trial participants) is only a fraction of the information size (IS) (3351) or heterogeneity-adjusted information size (HIS) (13,240 trial participants). As shown in all the comparisons, the cumulative Z-curves (blue line) do not cross any of the trial sequential monitoring boundaries (red lines). They crossed the conventional alpha boundary of 2.5% (green line).



Quality of the evidence

As for the surgery versus radiofrequency ablation comparison, the overall quality of the evidence was also low or very low for all outcomes for the comparison of non-surgical interventions (Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5). All of the trials were at high risk of bias. As before, we downgraded the quality of the evidence one level for all-cause mortality and two levels for the remaining comparisons for risk of bias; one level for imprecision because of small sample size (all comparisons); one level for imprecision because the confidence intervals overlapped clinically significant effect and clinically insignificant effect for most comparisons; and one level for comparisons with substantial heterogeneity.

ADDITIONAL SUMMARY OF FINDINGS [*Explanation*]

Percutaneous alcohol injection versus radiofrequency ablation for people with early- or very early-stage hepatocellular carcinoma

Patient or population: people with early- or very early-stage hepatocellular carcinoma ineligible for surgery
Settings: secondary or tertiary care
Intervention: percutaneous alcohol injection
Control: radiofrequency ablation

Outcomes	Illustrative risks* (95% CI)		Relative effect (95% CI)	No. of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Radiofrequency ablation	Percutaneous alcohol injection			
Mortality at maximal follow-up Follow-up: 23 months to 37 months	**300 per 1000**	**447 per 1000** (354 to 564)	**HR 1.49** (1.18 to 1.88)	882 (5 trials)	⊕◯◯◯ **very low**[1,2,3]
Cancer-related mortality at maximal follow-up Follow-up: 23 months to 37 months	**96 per 1000**	**188 per 1000** (115 to 292)	**OR 2.18** (1.22 to 3.89)	458 (3 trials)	⊕⊕◯◯ **low**[1,2]
Serious adverse events (number of participants) Follow-up: 23 months to 36 months	**20 per 1000**	**13 per 1000** (4 to 47)	**OR 0.67** (0.19 to 2.40)	365 (3 trials)	⊕◯◯◯ **very low**[1,2,3]
Serious adverse events (number of events) Follow-up: 37 months	**34 per 1000**	**26 per 1000** (6 to 118)	**Rate ratio 0.78** (0.17 to 3.47)	232 (1 trial)	⊕◯◯◯ **very low**[1,2,3]
Health-related quality of life	None of the trials reported this outcome.				

*The basis for the **assumed risk** for all-cause mortality is the approximate control group proportions at two to three years reported in the Kaplan-Meier curves in the trials that reported mortality at maximal-follow-up. We have assumed proportional hazards. The basis for the **assumed risk** for other outcomes is based on the mean control group proportion. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **HR:** hazard ratio; **OR:** odds ratio; **RR:** rate ratio

GRADE Working Group grades of evidence

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

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

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level because of within-study risk of bias: there was unclear or high risk of bias in the trial(s).

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

[3]Downgraded one level because of imprecision: the confidence intervals overlapped clinically significant effect and clinically insignificant effect.

Laser ablation versus radiofrequency ablation for people with early- or very early-stage hepatocellular carcinoma

Patient or population: people with early- or very early-stage hepatocellular carcinoma ineligible for surgery
Settings: secondary or tertiary care
Intervention: laser ablation
Control: radiofrequency ablation

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Radiofrequency ablation	Laser ablation			
Mortality at maximal follow-up Follow-up: not stated	**300 per 1000**	**468 per 1000** (262 to 731)	**HR 1.77** (0.85 to 3.68)	140 (1 trial)	⊕◯◯◯ **very low**[1,2,3]
Cancer-related mortality at maximal follow-up Follow-up: not stated	**96 per 1000**	**118 per 1000** (49 to 258)	**OR 1.26** (0.49 to 3.27)	140 (1 trial)	⊕◯◯◯ **very low**[1,2,3]
Serious adverse events (number of participants) Follow-up: 12 months in 1 trial and not stated in another trial	**20 per 1000**	**20 per 1000** (1 to 250)	**OR 1.00** (0.06 to 16.31)	170 (2 trials)	⊕◯◯◯ **very low**[1,2,3]
Serious adverse events (number of events)	None of the trials reported this outcome.				
Health-related quality of life	None of the trials reported this outcome.				

*The basis for the **assumed risk** for all-cause mortality is the approximate control group proportions at two to three years reported in the Kaplan-Meier curves in the trials that reported mortality at maximal-follow-up. We have assumed proportional hazards. The basis for the **assumed risk** for other outcomes is based on the mean control group proportion. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **HR:** hazard ratio; **OR:** odds ratio

GRADE Working Group grades of evidence

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

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

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level because of within-study risk of bias: there was unclear or high risk of bias in the trial(s).

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

[3]Downgraded one level because of imprecision: the confidence intervals overlapped clinically significant effect and clinically insignificant effect.

Transarterial embolisation plus radiofrequency ablation versus radiofrequency ablation for people with early- or very early-stage hepatocellular carcinoma

Patient or population: people with early- or very early-stage hepatocellular carcinoma ineligible for surgery
Settings: secondary or tertiary care
Intervention: transarterial embolisation plus radiofrequency ablation
Control: radiofrequency ablation

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Radiofrequency ablation	Transarterial embolisation plus radiofrequency ablation			
Mortality at maximal follow-up Follow-up: not stated	**300 per 1000**	**329 per 1000** (157 to 602)	**HR 1.12** (0.48 to 2.58)	44 (1 trial)	⊕◯◯◯ **very low**[1,2,3]
Cancer-related mortality at maximal follow-up	None of the trials reported this outcome.				
Serious adverse events (number of participants) Follow-up: 6 months in 1 trial and not stated in another trial	**20 per 1000**	**41 per 1000** (4 to 341)	**OR 2.11** (0.18 to 25.35)	84 (2 trials)	⊕◯◯◯ **very low**[1,2,3]
Serious adverse events (number of events) Follow-up: not stated	There were no events in either group.			44 (1 trial)	⊕◯◯◯ **very low**[1,2,3]
Health-related quality of life	None of the trials reported this outcome.				

*The basis for the **assumed risk** for all-cause mortality is the approximate control group proportions at two to three years reported in the Kaplan-Meier curves in the trials that reported mortality at maximal-follow-up. We have assumed proportional hazards. The basis for the **assumed risk** for other outcomes is based on the mean control group proportion. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **HR:** hazard ratio; **OR:** odds ratio

GRADE Working Group grades of evidence

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

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

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level because of within-study risk of bias: there was unclear or high risk of bias in the trial(s).

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

[3]Downgraded one level because of imprecision: the confidence intervals overlapped clinically significant effect and clinically insignificant effect.

Transarterial embolisation plus percutaneous alcohol injection versus percutaneous alcohol injection for people with early- or very early-stage hepatocellular carcinoma

Patient or population: people with early- or very early-stage hepatocellular carcinoma ineligible for surgery
Settings: secondary or tertiary care
Intervention: transarterial embolisation plus percutaneous alcohol injection
Control: percutaneous alcohol injection

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Percutaneous alcohol injection	Transarterial embolisation plus percutaneous alcohol injection			
Mortality at maximal follow-up Follow-up: 19 months to 30 months	**300 per 1000**	**251 per 1000** (207 to 302)	**HR 0.81** (0.65 to 1.01)	202 (2 trials)	⊕◯◯◯ **very low**[1,2,3,4]
Cancer-related mortality at maximal follow-up Follow-up: 30 months	**192 per 1000**	**16 per 1000** (0 to 251)	**OR 0.07** (0.00 to 1.41)	52 (1 trial)	⊕◯◯◯ **very low**[1,2,3]
Serious adverse events (number of participants) Follow-up: 30 months	**1 per 1000**	**5 per 1000** (0 to 106)	**OR 5.41** (0.25 to 118.34)	52 (1 trial)	⊕◯◯◯ **very low**[1,2,3]
Serious adverse events (number of events)	None of the trials reported this outcome.				
Health-related quality of life	None of the trials reported this outcome.				

*The basis for the **assumed risk** for all-cause mortality is the approximate control group proportions at two to three years reported in the Kaplan-Meier curves in the trials that reported mortality at maximal-follow-up. We have assumed proportional hazards. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **OR:** odds ratio

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

[1]Downgraded one level because of within-study risk of bias: there was unclear or high risk of bias in the trial(s).
[2]Downgraded one level because of imprecision: the sample size was small.
[3]Downgraded one level because of imprecision: the confidence intervals overlapped clinically significant effect and clinically insignificant effect.
[4]Downgraded one level because of inconsistency: there was substantial unexplained heterogeneity.

DISCUSSION

Summary of main results

We included a total of 18 trials in this review. Four trials (593 participants; 574 participants included for one or more analyses) compared surgery versus radiofrequency ablation in people with early hepatocellular carcinoma who were eligible to undergo surgery (Chen 2006; Huang 2010; Fang 2014; Lee 2014), while 14 trials (2533 participants; 2494 participants included for various analyses) compared different non-surgical interventions in people with early hepatocellular carcinoma who were not eligible to undergo surgery (Bolondi 1996; Koda 2001; Shibata 2002; Lencioni 2003; Gan 2004; Chen 2005; Lin 2005; Shiina 2005; Aikata 2006; Brunello 2008; Giorgio 2011; El Kady 2013; Orlacchio 2014; Costanzo 2015). Non-surgical interventions compared in the trials that included participants not eligible for surgery included radiofrequency ablation, laser ablation, microwave ablation, percutaneous acetic acid injection, percutaneous alcohol injection, a combination of radiofrequency ablation with systemic chemotherapy, a combination of radiofrequency ablation with percutaneous alcohol injection, a combination of transarterial chemoembolisation with percutaneous alcohol injection, and a combination of transarterial chemoembolisation with radiofrequency ablation.

Surgery versus radiofrequency ablation

There was no evidence of difference in mortality at maximal follow-up between surgery and radiofrequency ablation. Of the outcomes in which at least two trials were included, the proportion of people with hepatocellular carcinoma recurrence (local or distal) and hepatocellular carcinoma recurrence (recurrence in liver) were lower in the surgery group than in the radiofrequency ablation group (OR 0.53, 95% CI 0.35 to 0.78; 413 participants; 3 trials; I^2 = 36% and OR 0.49, 95% CI 0.31 to 0.78; 350 participants; 2 trials; I^2 = 6%), while the numbers of serious adverse events and any adverse events were lower in the radiofrequency ablation group than in the surgery group (RR 7.02, 95% CI 2.29 to 21.46; 391 participants; 2 trials; I^2 = 0% and RR 4.42, 95% CI 2.74 to 7.15; 391 participants; 2 trials; I^2 = 0%). In addition, the length of hospital stay was shorter in the radiofrequency ablation group than in the surgery group (MD 8.42 days, 95% CI 7.84 to 9.01; 530 participants; 3 trials; I^2 = 86%). Overall, it appears that surgery offers lower cancer recurrence but radiofrequency ablation is less invasive. Clearly, lower cancer recurrence is more important to most patients than fewer complications or quicker recovery, unless the difference in health-related quality of life compensates for the lower cancer recurrence. As none of the trials reported health-related quality of life, we are unable to comment on this. In addition, it should be noted the trial sequential monitoring boundaries were not crossed for cancer recurrence (Figure 5), indicating that there is a high risk of random error in these outcomes. Furthermore, it should be noted that lower cancer recurrence by itself does not mean that the survival is longer, for example patients may be able to undergo additional treatments after cancer recurrence and the overall survival may be improved. There was no evidence of difference in mortality at maximal follow-up between surgery and radiofrequency ablation. This may be due to additional treatments that people might have received after cancer recurrence, or is more likely due to the short follow-up period in the trials. The average follow-up period in the three trials that reported this information was between 29 months and 42 months (Table 1). However, the Kaplan-Meier curves in the trials suggest that most deaths occur beyond three to four years. Trials of longer follow-up and adequate sample size are needed to determine whether radiofrequency ablation provides equivalent survival in people with early- or very early-stage hepatocellular carcinoma who are eligible for surgery. Consequently, there is lot of uncertainty around this issue.

Non-surgical interventions

In people who were not eligible for surgery, mortality at maximal follow-up was higher in the percutaneous acetic acid injection group (HR 1.77, 95% CI 1.12 to 2.79; 125 participants; 1 trial) and the percutaneous alcohol injection group (HR 1.49, 95% CI 1.18 to 1.88; 882 participants; 5 trials; I^2 = 57%) than in the radiofrequency ablation group. There was no evidence of a difference in mortality at maximal follow-up for any of the other comparisons.

Among the remaining outcomes, for the comparisons in which at least two trials were included, the only outcomes with evidence of difference were cancer-related mortality at maximal follow-up, which was higher in the percutaneous alcohol injection group than in the radiofrequency ablation group (OR 2.18, 95% CI 1.22 to 3.89; 458 participants; 3 trials; I^2 = 0%); mortality (> 1 year), which was higher in the percutaneous alcohol injection group than in the radiofrequency ablation group (OR 1.69, 95% CI 1.15 to 2.49; 598 participants; 4 trials; I^2 = 0%); and hepatocellular carcinoma recurrence (local or distal), which was again higher in the percutaneous alcohol injection group than in the radiofrequency ablation group (OR 1.58, 95% CI 1.02 to 2.45; 371 participants; 2 trials; I^2 = 0%). Overall, it appears that radiofrequency ablation provides better cancer control and survival than percutaneous alcohol injection. However, it should be noted that there is a high risk of random error as shown by the Trial Sequential Analysis (Figure 4).

Because of the risk of bias, short period of follow-up, and small samples in the trials, resulting in high risk of random errors, it is not possible to say with certainty how people with early hepatocellular carcinoma should be managed.

Overall completeness and applicability of evidence

This review included only people with very early- or early-stage hepatocellular carcinoma, that is BCLC A stage (single tumour or three tumours of maximum diameter of 3 cm or less, Child-Pugh status A to B, and performance status 0). This review is therefore applicable only to people with very early- or early-stage hepatocellular carcinoma. The findings of the comparison between surgical resection and radiofrequency ablation are applicable only to people who are eligible for surgical resection, while the findings of the comparison between non-surgical interventions are applicable only to people who are not eligible for surgical resection.

The participants in the trials included in this review had viral or non-viral aetiologies and cirrhotic or non-cirrhotic livers. Hence, the review is applicable to people with viral or non-viral aetiologies and people with cirrhotic and non-cirrhotic livers. The proportion of people with portal hypertension was not clearly reported in any of the trials, except Orlacchio 2014, although a proportion of participants had features suggestive of portal hypertension such as oesophageal varices or ascites. It therefore appears that the findings of the review are applicable to people with portal hypertension. The proportion of people who received adjuvant antiviral or immunotherapy was also not reported, consequently it is unclear whether the findings of the review are applicable to people who receive such therapy.

Quality of the evidence

The overall quality of the evidence was low or very low for all outcomes included in the comparison of surgery versus radiofrequency ablation in people who are eligible for surgery and the comparison of various non-surgical interventions in people who were not eligible for surgery. All of the trials were at high risk of bias. As the issue of blinding may not arise for all-cause mortality, we downgraded the quality of the evidence one level for all-cause mortality and two levels for the remaining comparisons. Indirectness was not an issue, as all of the outcomes were clinical outcomes, and only direct comparisons were used. The sample sizes were small (all comparisons downgraded one level), and the confidence intervals overlapped clinically significant effect and clinically insignificant effect for most comparisons (downgraded one level). In addition, there was substantial heterogeneity for some of the outcomes, resulting in further downgrading by one level. We did not explore publication bias because of the few trials included in this review; this could have led to one further downgrading.

The average follow-up period in the different trials varied. The Kaplan-Meier curves in some of the trials that provided this information suggest that most deaths occur beyond three to four years in people with early or very early hepatocellular carcinoma. The short period of follow-up in the trials and the variability in the follow-up is another limitation of this review.

Potential biases in the review process

We selected a range of databases and used no language restrictions. At least two review authors independently selected the trials and extracted the data, thereby minimising errors. We conducted the systematic review according to the guidance found in the *Cochrane Handbook for Systematic Reviews of Interventions (*Higgins 2011*)*. We included only randomised clinical trials, which provide the best estimates of treatment effect, in this review. These are the strengths of the review process.

As discussed in the previous section, the quality of the evidence was low or very low, which was mainly due to the risk of bias and sparse data. This is the major limitation of this review. In addition, we have not included non-randomised studies in this review. In general, the participants included randomised clinical trials are carefully selected, while those seen in the clinic have multiple comorbidities. As a result, the complication rates reported in this review may be lower than those in actual clinical practice. Furthermore, it is possible that none of the participants in the randomised clinical trials developed rare complications because of the small sample sizes in the trials included in this review.

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

We planned to perform a network meta-analysis. However, it was not possible to assess whether the potential effect modifiers were similar across different comparisons, and performing a network meta-analysis in this scenario can be misleading. We therefore did not perform the network meta-analysis, and instead assessed the comparative benefits and harms of different interventions using standard Cochrane methodology.

Agreements and disagreements with other studies or reviews

There has been one network meta-analysis, Lan 2016, and several systematic reviews comparing the different interventions included in this topic (Liu 2010; Zhou 2010; Xu 2012b; Shen 2013; Dong 2014; Fu 2014; Qi 2014; Yi 2014; He 2016). We disagree with the network meta-analysis that the combination therapy of TACE and radiofrequency ablation is the most effective strategy for early-stage hepatocellular carcinoma (Lan 2016), because the comparison of TACE and radiofrequency ablation versus radiofrequency ablation alone was based on two small trials at high risk of bias

(Aikata 2006; El Kady 2013), and only one of these trials reported mortality at maximal follow-up (Aikata 2006). We are unable to comment on the findings of Weis 2015 on comparisons between percutaneous acetic acid injection and percutaneous alcohol injection because we were unable to obtain the data for the participants who met early-stage hepatocellular carcinoma according to BCLC criteria (it should be noted that many authors defined hepatocellular carcinoma as early despite not meeting the BCLC 0 or BCLC A criteria). We also disagree with the authors who concluded that surgery was better than radiofrequency ablation in people with early-stage hepatocellular carcinoma (Liu 2010; Zhou 2010; Xu 2012b; Dong 2014; Qi 2014; Yi 2014; He 2016). We agree with the authors who concluded that radiofrequency ablation was better than percutaneous ablation in people with early-stage hepatocellular carcinoma (Shen 2013), although some uncertainty remains around this issue. The possible reasons for the differences in conclusions from other studies include restricting trials to randomised clinical trials only and taking the risk of random errors, systematic errors, and heterogeneity into account while arriving at conclusions.

We agree with Fu 2014 that further trials on surgery versus radiofrequency ablation are required to determine the relative benefits and harms of surgery and radiofrequency ablation.

Several systematic reviews also exist in other patient groups of hepatocellular carcinoma. Oliveri 2011 found there was no evidence to support or refute TACE or TAE in people with unresectable hepatocellular carcinoma. We agree that there is insufficient evidence to support or refute one treatment over the other. However, we disagree with Weis 2013 that surgery offered better survival than radiofrequency ablation. The difference in conclusions may be due to two additional trials that we included in this review. We are unable to comment on the findings of Abdel-Rahman 2016 on the role of radioembolisation in people with unresectable hepatocellular carcinoma because the trials included in this review did not belong to early stage.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence was of low or very low quality. In people who are eligible for surgery, there was no evidence of difference in all-cause mortality at maximal follow-up between surgery and radiofrequency ablation. In people who are not eligible for surgery, all-cause mortality at maximal follow-up was higher with percutaneous acetic acid injection and percutaneous alcohol injection than with radiofrequency ablation. There was no evidence of difference in all-cause mortality at maximal follow-up in other comparisons.

Implications for research

High-quality randomised clinical trials designed to measure clinically important differences in all-cause mortality and following the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials), Chan 2013b, and CONSORT guidelines, Schulz 2010, are needed. Future trials on early hepatocellular carcinoma should follow up participants for at least four to five years because most deaths occur beyond three years. They should also include other patient-oriented outcomes such as health-related quality of life.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Aikata 2006

Methods	Randomised clinical trial
Participants	Country: Japan Number randomised: 44 Postrandomisation dropouts: not stated Revised sample size: 44 Average age: not stated Females: not stated Cirrhosis: not stated Very early HCC: not stated Portal hypertension: not stated Viral aetiology: not stated Immunotherapy/antiviral adjuvant therapy: not stated Average follow-up period in months (for all groups): not stated Criteria for early or very early HCC and other inclusion criteria: • < 3 cm solitary hypervascular nodules
Interventions	Participants were randomly assigned to 2 groups: Group 1: TACE plus radiofrequency ablation (n = 21). Further details: cisplatinum TACE, internally cooled electrode (brand not stated) for radiofrequency ablation. Group 2: Radiofrequency ablation (n = 23). Further details: internally cooled electrode (brand not stated)
Outcomes	The outcomes reported were: • mortality, • adverse events.
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.

Aikata 2006 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	Low risk	Comment: important clinical outcomes were reported.
For-profit bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other bias noted.

Bolondi 1996

Methods	Randomised clinical trial
Participants	Country: Italy Number randomised: 150 Postrandomisation dropouts: not stated Revised sample size: 150 Average age: not stated Females: not stated Cirrhosis: 150 (100%) Very early HCC: not stated Portal hypertension: not stated Viral aetiology: not stated Immunotherapy/antiviral adjuvant therapy: not stated Average follow-up period in months (for all groups): mean: 19 months Criteria for early or very early HCC and other inclusion criteria: • < 5 cm unifocal lesions
Interventions	Participants were randomly assigned to 2 groups: Group 1: PEI plus TACE (n = 66). Further details not available for TACE or PEI. Group 2: PEI (n = 84). Further details not available.
Outcomes	The outcomes reported were: mortality.
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.

Bolondi 1996 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	High risk	Comment: important clinical outcomes expected to be measured in such trials were not reported
For-profit bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other bias noted.

Brunello 2008

Methods	Randomised clinical trial
Participants	Country: Italy Number randomised: 139 Postrandomisation dropouts: 0 (0%) Revised sample size: 139 Average age: 70 years Females: 47 (33.8%) Cirrhosis: 139 (100%) Very early HCC: not stated Portal hypertension: not stated Viral aetiology: 114 (82%) Immunotherapy/antiviral adjuvant therapy: not stated Average follow-up period in months (for all groups): all participants: 36 months Criteria for early or very early HCC and other inclusion criteria: • 1 to 3 nodules, < 3 cm diameter • Child-Pugh class A or B Exclusion criteria: • Hypovascular HCC • Lesions not detectable by ultrasound • Lesions close to the gallbladder, hilum of liver, colon, or stomach • Venous invasion • Metastatic disease • Liver transplantation

Brunello 2008 (*Continued*)

Interventions	Participants were randomly assigned to 2 groups: Group 1: PEI (n = 69). Further details: 2 to 20 mL ethanol (95%). Group 2: radiofrequency ablation (n = 70). Further details: Cool-tip or StarBurst system for radiofrequency ablation
Outcomes	The outcomes reported were: • mortality, • adverse events, • HCC recurrence.
Notes	Authors provided additional information in February 2017.

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "computerized random generator"
Allocation concealment (selection bias)	Low risk	Quote: "closed, sequentially numbered envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "the healthcare providers were blinded until the opening of the sealed envelopes containing the assignation from the randomized list. The same for the patients, who were informed about their treatment (PEI or RF) after the opening of the envelope and were thereafter scheduled for the appropriate treatment" (author replies)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: after treatment, evaluations of computed tomography by a "blinded" observer were considered not feasible because of different radiological signs produced by the 2 techniques
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: important clinical outcomes were reported.
For-profit bias	Low risk	Quote: "The work of Eva Pagano was supported by the Compagnia di San Paolo."
Other bias	Low risk	Comment: no other bias noted.

Chen 2005

Methods	Randomised clinical trial
Participants	Country: China Number randomised: 86 Postrandomisation dropouts: not stated Revised sample size: 86 Average age: 49 years Females: 13 (15.1%) Cirrhosis: not stated Very early HCC: not stated Portal hypertension: not stated Viral aetiology: not stated Immunotherapy/antiviral adjuvant therapy: not stated Average follow-up period in months (for all groups): not stated Criteria for early or very early HCC and other inclusion criteria: • Single nodule < 5 cm
Interventions	Participants were randomly assigned to 2 groups: Group 1: radiofrequency ablation plus PEI (n = 45). Further details: radiofrequency ablation using RF 2000 (RadioTherapeutics), PEI with absolute alcohol: volume 1 to 2 times the tumour diameter. Group 2: radiofrequency ablation (n = 41). Further details: radiofrequency ablation using RF 2000 (RadioTherapeutics)
Outcomes	The outcomes reported were: • mortality, • adverse events.
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.

Chen 2005 (*Continued*)

Selective reporting (reporting bias)	Low risk	Comment: important clinical outcomes were reported.
For-profit bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other bias noted.

Chen 2006

Methods	Randomised clinical trial
Participants	Country: China Number randomised: 180 Postrandomisation dropouts: 19 (10.6%) Revised sample size: 180 Average age: 51 years Females: 30 (16.7%) Cirrhosis: not stated Very early HCC: not stated Portal hypertension: not stated Viral aetiology: not stated Immunotherapy/antiviral adjuvant therapy: not stated Average follow-up period in months (for all groups): mean: 29 months Criteria for early or very early HCC and other inclusion criteria: • Single nodule < 5 cm • No vascular involvement • No extrahepatic metastases • Child-Pugh class A
Interventions	Participants were randomly assigned to 2 groups: Group 1: surgery (n = 90). Further details: open surgical resection. Group 2: radiofrequency ablation (n = 71). Further details: radiofrequency ablation using RF 2000 or LeVeen (RadioTherapeutics)
Outcomes	The outcomes reported were: • mortality, • adverse events, • length of hospital stay.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was done by using random numbers generated from a computer in a central registry for this study"

Chen 2006 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: important clinical outcomes were reported.
For-profit bias	Low risk	Quote: "Supported by the grant of Sciences and Technology Committee of Guangdo Province, China, 2002."
Other bias	Low risk	Comment: no other bias noted.

Costanzo 2015

Methods	Randomised clinical trial
Participants	Country: Italy Number randomised: 140 Postrandomisation dropouts: 0 (0%) Revised sample size: 140 Average age: 70 years Females: 40 (28.6%) Cirrhosis: 140 (100%) Very early HCC: not stated Portal hypertension: not stated Viral aetiology: not stated Immunotherapy/antiviral adjuvant therapy: not stated Average follow-up period in months (for all groups): not stated Criteria for early or very early HCC and other inclusion criteria: • Milan criteria • Child A or B • No vascular invasion • No distant metastases
Interventions	Participants were randomly assigned to 2 groups: Group 1: laser (n = 70). Further details: laser: EchoLaser, Elesta s.r.l. Group 2: radiofrequency ablation (n = 70). Further details: radiofrequency ablation: Cool-tip, Valleylab

Costanzo 2015 (*Continued*)

Outcomes	The outcomes reported were: • mortality, • cancer-related mortality, • adverse events, • HCC recurrence.
Notes	Authors provided additional information in February 2017.

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated random numbers"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: blinding of participants and personnel was not performed (author replies)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: blinding of outcome assessors was not performed (author replies)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: important clinical outcomes were reported.
For-profit bias	Low risk	Comment: no special source of funding (author replies)
Other bias	Low risk	Comment: no other bias noted.

El Kady 2013

Methods	Randomised clinical trial
Participants	Country: Egypt Number randomised: 40 Postrandomisation dropouts: 0 (0%) Revised sample size: 40 Average age: 52 years Females: 11 (27.5%) Cirrhosis: not stated Very early HCC: 0 (0%) Portal hypertension: not stated Viral aetiology: not stated

El Kady 2013 (*Continued*)

	Immunotherapy/antiviral adjuvant therapy: not stated Average follow-up period in months (for all groups): 6 Criteria for early or very early HCC and other inclusion criteria: • Single nodule > 3 cm • No portal vein involvement • No extrahepatic metastasis
Interventions	Participants were randomly assigned to 2 groups: Group 1: TACE plus radiofrequency ablation (n = 20). Further details: TACE using 50 mg of adriamycin or cisplatin and 10 mL of ethiodised oil (Lipiodol), radiofrequency ablation with RITA 1500X RF generator and RITA StarBurst XL(RITA Medical Systems, Mountain View, CA, USA). Group 2: radiofrequency ablation (n = 20). Further details: radiofrequency ablation with RITA 1500X RF generator and RITA StarBurst XL(RITA Medical Systems, Mountain View, CA, USA)
Outcomes	The outcomes reported were: • mortality, • adverse events, • HCC recurrence.
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized (computer-based randomization) into two groups"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "After assigning the patients to the groups there were no drop-outs, as the patient was assigned and managed on the same day" (author replies)
Selective reporting (reporting bias)	Low risk	Comment: important clinical outcomes were reported.
For-profit bias	Low risk	Quote: "The conduct of the research (collection, analysis, and interpretation of data) and preparation of the article were totally funded by the authors"

El Kady 2013 (*Continued*)

Other bias	Low risk	Comment: no other bias noted.

Fang 2014

Methods	Randomised clinical trial
Participants	Country: China Number randomised: 120 Postrandomisation dropouts: not stated Revised sample size: 120 Average age: 53 years Females: 32 (26.7%) Cirrhosis: 101 (84.2%) Very early HCC: not stated Portal hypertension: not stated Viral aetiology: 107 (89.2%) Immunotherapy/antiviral adjuvant therapy: not stated Average follow-up period in months (for all groups): mean: 40 months Criteria for early or very early HCC and other inclusion criteria: • ≤ 3 lesions, ≤ 3 cm • Child-Pugh class A or B • No vascular invasion • No distant metastases • No clinically significant portal hypertension
Interventions	Participants were randomly assigned to 2 groups: Group 1: surgery (n = 60). Further details: surgery, not stated whether open or laparoscopic resection. Group 2: radiofrequency ablation (n = 60). Further details: radiofrequency ablation with Tyco radiofrequency ablation device, Valleylab
Outcomes	The outcomes reported were: • mortality, • adverse events, • HCC recurrence, • length of hospital stay.
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.

Fang 2014 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	Low risk	Comment: important clinical outcomes were reported.
For-profit bias	Low risk	Quote: "This work was fully supported by grants from Zhejiang Science and Technology Agency funding 2010C13025-1 (H.M. Pan), National Natural Science Foundation of China 81272593 (H.M. Pan), Zhejiang Provincial Natural Science Foundation of China LY13H160013 (Y. Fang) and Zhejiang Provincial Natural Science Foundation of China LQ13H160009 (W. Chen)"
Other bias	Low risk	Comment: no other bias noted.

Gan 2004

Methods	Randomised clinical trial
Participants	Country: China Number randomised: 38 Postrandomisation dropouts: 11 (28.9%) Revised sample size: 27 Average age: 53 years Females: 3 (11.1%) Cirrhosis: not stated Very early HCC: not stated Portal hypertension: not stated Viral aetiology: not stated Immunotherapy/antiviral adjuvant therapy: not stated Average follow-up period in months (for all groups): all participants were followed up for 12 months Criteria for early or very early HCC and other inclusion criteria: • 1 to 2 nodules, ≤ 3 cm • No portal vein involvement • No distant metastases • Life expectancy > 3 months
Interventions	Participants were randomly assigned to 2 groups: Group 1: radiofrequency ablation plus systemic chemotherapy (n = 15). Further details: radiofrequency ablation with RF 2000 (RadioTherapeutics); chemother-

Gan 2004 (*Continued*)

	apy with epirubicin 50 mg, cisplatin 40 mg, and floxuridine 500 mg. Group 2: radiofrequency ablation (n = 12). Further details: radiofrequency ablation: RF 2000 (RadioTherapeutics)
Outcomes	The outcomes reported were: • adverse events, • HCC recurrence.
Notes	Reasons for postrandomisation dropouts: follow-up less than 1 year

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: important clinical outcomes expected to be measured in such trials were not reported
For-profit bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other bias noted.

Giorgio 2011

Methods	Randomised clinical trial
Participants	Country: Italy Number randomised: 285 Postrandomisation dropouts: 0 (0%) Revised sample size: 285 Average age: 70 years Females: 78 (27.4%) Cirrhosis: 285 (100%) Very early HCC: 71 (24.9%)

Giorgio 2011 (*Continued*)

	Portal hypertension: not stated Viral aetiology: 285 (100%) Immunotherapy/antiviral adjuvant therapy: not stated Average follow-up period in months (for all groups): mean: 37 months Criteria for early or very early HCC and other inclusion criteria: • Single nodule, ≤ 3 cm
Interventions	Participants were randomly assigned to 2 groups: Group 1: PEI (n = 143). Further details: PEI using 4 to 20 mL of 95% ethanol depending upon tumour volume. Group 2: radiofrequency ablation (n = 142). Further details: radiofrequency ablation generator details not stated
Outcomes	The outcomes reported were: • mortality, • adverse events.
Notes	Although mortality was reported, this was a severely biased estimate, as 14 people who could not undergo radiofrequency ablation were excluded. We therefore did not use the survival information Authors provided additional information in February 2017.

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "random number generator"
Allocation concealment (selection bias)	Low risk	Quote: "The person randomising the patient were unaware of what the next treatment allocation was. It was used a centralised randomisation service to ensuring allocation concealment. So it was not possible for the investigators to know the allocation sequence in advance" (author replies)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The patients and healthcare providers were not blinded due to the nature of the treatments used in to the study (PEI versus RFA)" (author replies)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The outcome assessors were blinded as they did not know the patient was referring to the results" (author replies)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: important clinical outcomes were reported.

Giorgio 2011 (*Continued*)

For-profit bias	Low risk	Quote: "The study was not funded. It was self-financed by the hospital" (author replies)
Other bias	Low risk	Comment: no other bias noted.

Huang 2010

Methods	Randomised clinical trial
Participants	Country: China Number randomised: 230 Postrandomisation dropouts: 0 (0%) Revised sample size: 230 Average age: 56 years Females: 66 (28.7%) Cirrhosis: 142 (61.7%) Very early HCC: not stated Portal hypertension: not stated Viral aetiology: 215 (93.5%) Immunotherapy/antiviral adjuvant therapy: not stated Average follow-up period in months (for all groups): median: 42 months Criteria for early or very early HCC and other inclusion criteria: • Milan criteria • Child A or B • No vascular invasion • No distant metastases
Interventions	Participants were randomly assigned to 2 groups: Group 1: surgery (n = 115). Further details: not stated whether open or laparoscopic resection. Group 2: radiofrequency ablation (n = 115). Further details: radiofrequency ablation using Cool-tip (Radionics)
Outcomes	The outcomes reported were: • mortality, • cancer-related mortality, • adverse events, • HCC recurrence, • length of hospital stay.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomization method with a computer"

Huang 2010 (*Continued*)

Allocation concealment (selection bias)	Low risk	Quote: "Physicians received the envelope for each patient in the registry sequence kept in a container given by the statistician and kept by the chief nurse of our center."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Because of the nature of the interventions, the double-blind technique was not used"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Because of the nature of the interventions, the double-blind technique was not used"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: important clinical outcomes were reported.
For-profit bias	Low risk	Quote: "This study has not received any support from industry or private corporations."
Other bias	Low risk	Comment: no other bias noted.

Koda 2001

Methods	Randomised clinical trial
Participants	Country: Japan Number randomised: 52 Postrandomisation dropouts: not stated Revised sample size: 52 Average age: 66 years Females: 22 (42.3%) Cirrhosis: 46 (88.5%) Very early HCC: not stated Portal hypertension: not stated Viral aetiology: 49 (94.2%) Immunotherapy/antiviral adjuvant therapy: not stated Average follow-up period in months (for all groups): mean: 30 Criteria for early or very early HCC and other inclusion criteria: • 1 to 3 nodules, ≤ 3 cm • No portal thrombosis • No extrahepatic metastases
Interventions	Participants were randomly assigned to 2 groups: Group 1: TACE plus PEI (n = 26). Further details: TACE using iodised oil, epirubicin hydrocholoride, and gelatin sponge; PEI using 1 to 12 mL absolute alcohol per session. Group 2: PEI (n = 26).

Koda 2001 (*Continued*)

	Further details: PEI using 1 to 12 mL absolute alcohol per session
Outcomes	The outcomes reported were: • mortality, • cancer-related mortality, • adverse events.
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Quote: "sealed-envelope method" Comment: further details were not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	Low risk	Comment: important clinical outcomes were reported.
For-profit bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other bias noted.

Lee 2014

Methods	Randomised clinical trial
Participants	Country: South Korea Number randomised: 63 Postrandomisation dropouts: not stated Revised sample size: 63 Average age: not stated Females: not stated Cirrhosis: not stated Very early HCC: 0 (0%) Portal hypertension: not stated

Lee 2014 (*Continued*)

	Viral aetiology: not stated Immunotherapy/antiviral adjuvant therapy: not stated Average follow-up period in months (for all groups): not stated Criteria for early or very early HCC and other inclusion criteria: • Single nodule 2 to 4 cm
Interventions	Participants were randomly assigned to 2 groups: Group 1: surgery (n = 29). Further details: not stated whether surgery was open or laparoscopic resection. Group 2: radiofrequency ablation (n = 34). Further details not available.
Outcomes	The outcomes reported were: • mortality, • adverse events, • HCC recurrence.
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	Low risk	Comment: important clinical outcomes were reported.
For-profit bias	High risk	Comment: grant/research support: Green Cross, Chong Kun Dang Pharm, Novartis, SK Chemicals
Other bias	Low risk	Comment: no other bias noted.

Lencioni 2003

Methods	Randomised clinical trial
Participants	Country: Italy Number randomised: 104 Postrandomisation dropouts: 2 (1.9%) Revised sample size: 102 Average age: 68 years Females: 36 (35.3%) Cirrhosis: 102 (100%) Very early HCC: not stated Portal hypertension: not stated Viral aetiology: 82 (80.4%) Immunotherapy/antiviral adjuvant therapy: not stated Average follow-up period in months (for all groups): mean: 23 months Criteria for early or very early HCC and other inclusion criteria: • Milan criteria • Child class A or B • No vascular invasion • No distant metastases
Interventions	Participants were randomly assigned to 2 groups: Group 1: PEI (n = 50). Further details: PEI using 2 to 10 mL 95% alcohol per session. Group 2: radiofrequency ablation (n = 52). Further details: radiofrequency ablation using 500L RITA Medical Systems
Outcomes	The outcomes reported were: • mortality, • cancer-related mortality, • adverse events.
Notes	Reasons for postrandomisation dropouts: 1. Tumour size > 5 cm. 2. Extrahepatic cancer identified retrospectively.

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated randomization list"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.

Lencioni 2003 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: important clinical outcomes were reported.
For-profit bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other bias noted.

Lin 2005

Methods	Randomised clinical trial
Participants	Country: Taiwan Number randomised: 187 Postrandomisation dropouts: 0 (0%) Revised sample size: 187 Average age: 61 years Females: 66 (35.3%) Cirrhosis: 187 (100%) Very early HCC: not stated Portal hypertension: not stated Viral aetiology: 184 (98.4%) Immunotherapy/antiviral adjuvant therapy: not stated Average follow-up period in months (for all groups): mean: 27 months Criteria for early or very early HCC and other inclusion criteria: • 1. 1 to 3 nodules, ≤ 3 cm • 2. No vascular invasion • 3. No extrahepatic metastases • 4. Child Pugh class A or B
Interventions	Participants were randomly assigned to 3 groups: Group 1: radiofrequency ablation (n = 62). Further details: radiofrequency ablation using RF 2000 (RadioTherapeutics). Group 2: PEI (n = 62). Further details: PEI using 2 to 10 mL absolute alcohol per session. Group 3: percutaneous acetic acid injection (n = 63). Further details: percutaneous acetic acid injection using 1 to 3 mL 50% acetic acid
Outcomes	The outcomes reported were: • mortality, • cancer-related mortality, • adverse events.

Lin 2005 (*Continued*)

Notes	

Risk of bias		***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "computer randomisation list"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: important clinical outcomes were reported.
For-profit bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other bias noted.

Orlacchio 2014

Methods	Randomised clinical trial
Participants	Country: Italy Number randomised: 30 Postrandomisation dropouts: 0 (0%) Revised sample size: 30 Average age: 72 years Females: 9 (30%) Cirrhosis: 30 (100%) Very early HCC: not stated Portal hypertension: 30 (100%) Viral aetiology: 27 (90%) Immunotherapy/antiviral adjuvant therapy: not stated Average follow-up period in months (for all groups): all participants were followed up for 12 months Criteria for early or very early HCC and other inclusion criteria: • Single nodule < 4 cm in diameter • Child-Pugh class A or B

Orlacchio 2014 (*Continued*)

Interventions	Participants were randomly assigned to 2 groups: Group 1: laser (n = 15). Further details: laser using EchoLaser XVG system. Group 2: radiofrequency ablation (n = 15). Further details: radiofrequency ablation using RF 3000, Boston Scientific Corporation
Outcomes	The outcomes reported were: • mortality, • adverse events.
Notes	Authors provided additional information in February 2017.

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomisation software was used to allocate each patient to a treatment group"
Allocation concealment (selection bias)	Unclear risk	Quote: "randomisation software was used to allocate each patient to a treatment group" Comment: further details were not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: participants and personnel were not blinded (based on author replies)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: outcome assessors were not blinded (based on author replies)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: important clinical outcomes were reported.
For-profit bias	Low risk	Comment: no special source of funding (author replies)
Other bias	Low risk	Comment: no other bias noted.

Shibata 2002

Methods	Randomised clinical trial
Participants	Country: Japan Number randomised: 72 Postrandomisation dropouts: 0 (0%) Revised sample size: 72

Shibata 2002 (*Continued*)

	Average age: 63 years Females: 22 (30.6%) Cirrhosis: 72 (100%) Very early HCC: not stated Portal hypertension: not stated Viral aetiology: 71 (98.6%) Immunotherapy/antiviral adjuvant therapy: not stated Average follow-up period in months (for all groups): mean: 18 months Criteria for early or very early HCC and other inclusion criteria: • 1 to 3 nodules, ≤ 3 cm or single nodule < 4 cm • No portal thrombosis • No extrahepatic metastases
Interventions	Participants were randomly assigned to 2 groups: Group 1: microwave ablation (n = 36). Further details: microwave ablation with Microtaze. Group 2: radiofrequency ablation (n = 36). Further details: radiofrequency ablation using RF2000 (Radionics)
Outcomes	The outcomes reported were: adverse events.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Quote: "sealed-envelope method" Comment: further details were not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: important clinical outcomes expected to be measured in such trials were not reported
For-profit bias	Unclear risk	Comment: this information was not available.

Shibata 2002 (*Continued*)

Other bias	Low risk	Comment: no other bias noted.

Shiina 2005

Methods	Randomised clinical trial
Participants	Country: Japan Number randomised: 232 Postrandomisation dropouts: 0 (0%) Revised sample size: 232 Average age: not stated Females: 66 (28.4%) Cirrhosis: 198 (85.3%) Very early HCC: not stated Portal hypertension: not stated Viral aetiology: 217 (93.5%) Immunotherapy/antiviral adjuvant therapy: not stated Average follow-up period in months (for all groups): median: 37 months Criteria for early or very early HCC and other inclusion criteria: • 1 to 3 nodules • No vascular invasion • No extrahepatic metastases • Child-Pugh class A or B
Interventions	Participants were randomly assigned to 2 groups: Group 1: PEI (n = 114). Further details: PEI using 0.5 mL to 1 mL per site (alcohol percentage not stated). Group 2: radiofrequency ablation (n = 118). Further details: radiofrequency ablation using CC-1 Cosman Coagulator (Radionics)
Outcomes	The outcomes reported were: • mortality, • cancer-related mortality, • adverse events, • HCC recurrence, • length of hospital stay.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated random numbers"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.

Shiina 2005 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Double-blind technique was not used because of the nature of the interventions"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Double-blind technique was not used because of the nature of the interventions"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: important clinical outcomes were reported.
For-profit bias	Unclear risk	Quote: "Grants-in-Aid from the Ministry of Education, Science, Sports, and Culture of Japan" Comment: not clear how the remaining part of the study was funded
Other bias	Low risk	Comment: no other bias noted.

HCC: hepatocellular carcinoma; PEI: percutaneous ethanol injection; RFA: radiofrequency ablation; TACE: transarterial chemoembolisation; TAE: transarterial embolisation

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

Study	Reason for exclusion
Abdelaziz 2014	Not in very early or early hepatocellular carcinoma
Azab 2011	Not in very early or early hepatocellular carcinoma
Casaccia 2015	Not a randomised clinical trial
Chen 2014	Not in very early or early hepatocellular carcinoma
Feng 2012	Not in very early or early hepatocellular carcinoma
Ferrari 2007	Not in very early or early hepatocellular carcinoma
Fukushima 2015	Not in very early or early hepatocellular carcinoma
Gallo 1998	Not in very early or early hepatocellular carcinoma
Goldberg 2002	Not in very early or early hepatocellular carcinoma

(*Continued*)

Habib 2002	Not in very early or early hepatocellular carcinoma
Hirakawa 2013	Variations in radiofrequency ablation
Hou 2009	Not in very early or early hepatocellular carcinoma
Huang 2005	Inadequate randomisation (groups were adjusted to equalise numbers)
Huo 2003	Not a randomised clinical trial
Hyun 2016	Not a randomised clinical trial
Kobayashi 2007	Not in very early or early hepatocellular carcinoma
Kuansheng 2011	Not in very early or early hepatocellular carcinoma
Lau 1999	Not in very early or early hepatocellular carcinoma
Lau 2008	Not in very early or early hepatocellular carcinoma
Lin 2004	Not in very early or early hepatocellular carcinoma
Livraghi 1999	Not a randomised clinical trial
Lo 2007	Not in very early or early hepatocellular carcinoma
Lu 2006a	In the control group, the ablation was performed with either radiofrequency ablation or microwave ablation and this was not determined at random
Mizuki 2010	Not in very early or early hepatocellular carcinoma
Muehlbacher 2014	Not in very early or early hepatocellular carcinoma
Ohnishi 1998	Not in very early or early hepatocellular carcinoma
Okusaka 2011	Recurrent hepatocellular carcinoma. Unable to determine disease stage prior to initial treatment
Peng 2012	Recurrent hepatocellular carcinoma. Unable to determine disease stage prior to initial treatment
Pinter 2015	Not in very early or early hepatocellular carcinoma
Shen 2005	Not in very early or early hepatocellular carcinoma
Shibata 2006	Not a randomised clinical trial
Shibata 2009	Not a randomised clinical trial

(*Continued*)

Shiozawa 2015	Not a randomised clinical trial
Sun 2016	Not a randomised clinical trial
van Malenstein 2011	Not in very early or early hepatocellular carcinoma
Wu 2015	Variations in surgical resection
Xu 2012a	Randomised after resection. Unable to determine disease stage prior to surgery
Xu 2013	Randomised after resection. Unable to determine disease stage prior to initial treatment
Xu 2015	Not in very early or early hepatocellular carcinoma
Yi 2014	In this randomised clinical trial, the decision to perform radiofrequency ablation or microwave ablation was not random
Yu 2014	Not in very early or early hepatocellular carcinoma
Yu 2016	Not in very early or early hepatocellular carcinoma
Zhang 2002	Not a randomised clinical trial
Zhang 2007	Not in very early or early hepatocellular carcinoma

DATA AND ANALYSES

Comparison 1. Surgery versus radiofrequency ablation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality at maximal follow-up	4	574	Hazard Ratio (Fixed, 95% CI)	0.80 [0.60, 1.08]
2 Cancer-related mortality at maximal follow-up	1	230	Odds Ratio (M-H, Fixed, 95% CI)	0.35 [0.19, 0.65]
3 Mortality (> 1 year)	1	230	Odds Ratio (M-H, Fixed, 95% CI)	0.39 [0.22, 0.68]
4 Serious adverse events (number of participants)	1	120	Odds Ratio (M-H, Fixed, 95% CI)	17.96 [2.28, 141.60]
5 Serious adverse events (number of events)	2	391	Rate Ratio (Fixed, 95% CI)	7.02 [2.29, 21.46]
6 Any adverse events (number of participants)	2	183	Odds Ratio (M-H, Random, 95% CI)	4.09 [0.61, 27.41]
7 Any adverse events (number of events)	2	391	Rate Ratio (Fixed, 95% CI)	4.42 [2.74, 7.15]
8 HCC recurrence (local or distal)	3	413	Odds Ratio (M-H, Fixed, 95% CI)	0.53 [0.35, 0.78]
9 HCC recurrence (recurrence in liver)	2	350	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.31, 0.78]
10 Length of hospital stay	3	530	Mean Difference (IV, Fixed, 95% CI)	8.42 [7.84, 9.01]
11 Mortality at maximal follow-up (sensitivity analysis)	3		Hazard Ratio (Fixed, 95% CI)	0.68 [0.47, 1.00]

Comparison 2. Non-surgical interventions

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality at maximal follow-up	10		Hazard Ratio (Fixed, 95% CI)	Subtotals only
1.1 Laser versus radiofrequency ablation	1	140	Hazard Ratio (Fixed, 95% CI)	1.77 [0.85, 3.68]
1.2 Percutaneous acetic acid injection versus radiofrequency ablation	1	125	Hazard Ratio (Fixed, 95% CI)	1.77 [1.12, 2.79]
1.3 Percutaneous alcohol injection versus radiofrequency ablation	5	882	Hazard Ratio (Fixed, 95% CI)	1.49 [1.18, 1.88]
1.4 Radiofrequency ablation plus percutaneous alcohol injection versus radiofrequency ablation	1	86	Hazard Ratio (Fixed, 95% CI)	0.66 [0.41, 1.06]

1.5 Transarterial chemoembolisation plus radiofrequency ablation versus radiofrequency ablation	1	44	Hazard Ratio (Fixed, 95% CI)	1.12 [0.48, 2.58]
1.6 Percutaneous alcohol injection versus percutaneous acetic acid injection	1	125	Hazard Ratio (Fixed, 95% CI)	1.15 [0.79, 1.65]
1.7 Transarterial chemoembolisation plus percutaneous alcohol injection versus percutaneous alcohol injection	2	202	Hazard Ratio (Fixed, 95% CI)	0.81 [0.65, 1.01]
2 Cancer-related mortality at maximal follow-up	5		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Laser versus radiofrequency ablation	1	140	Odds Ratio (M-H, Fixed, 95% CI)	1.26 [0.49, 3.27]
2.2 Percutaneous acetic acid injection versus radiofrequency ablation	1	125	Odds Ratio (M-H, Fixed, 95% CI)	2.42 [0.70, 8.31]
2.3 Percutaneous alcohol injection versus radiofrequency ablation	3	458	Odds Ratio (M-H, Fixed, 95% CI)	2.18 [1.22, 3.89]
2.4 Percutaneous alcohol injection versus percutaneous acetic acid injection	1	125	Odds Ratio (M-H, Fixed, 95% CI)	1.15 [0.43, 3.07]
2.5 Transarterial chemoembolisation plus percutaneous alcohol injection versus percutaneous alcohol injection	1	52	Odds Ratio (M-H, Fixed, 95% CI)	0.07 [0.00, 1.41]
3 Mortality (> 1 year)	6		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Laser versus radiofrequency ablation	1	140	Odds Ratio (M-H, Fixed, 95% CI)	1.51 [0.73, 3.12]
3.2 Percutaneous acetic acid injection versus radiofrequency ablation	1	124	Odds Ratio (M-H, Fixed, 95% CI)	1.96 [0.82, 4.72]
3.3 Percutaneous alcohol injection versus radiofrequency ablation	4	598	Odds Ratio (M-H, Fixed, 95% CI)	1.69 [1.15, 2.49]
3.4 Percutaneous alcohol injection versus percutaneous acetic acid injection	1	125	Odds Ratio (M-H, Fixed, 95% CI)	1.21 [0.54, 2.70]
3.5 Transarterial chemoembolisation plus percutaneous alcohol injection versus percutaneous alcohol injection	1	52	Odds Ratio (M-H, Fixed, 95% CI)	0.41 [0.11, 1.58]
4 Serious adverse events (number of participants)	11		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Laser versus radiofrequency ablation	2	170	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 16.31]

4.2 Microwave ablation versus radiofrequency ablation	1	72	Odds Ratio (M-H, Fixed, 95% CI)	4.38 [0.46, 41.22]
4.3 Percutaneous acetic acid injection versus radiofrequency ablation	1	125	Odds Ratio (M-H, Fixed, 95% CI)	0.13 [0.01, 2.65]
4.4 Percutaneous alcohol injection versus radiofrequency ablation	3	365	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.19, 2.40]
4.5 Radiofrequency ablation plus chemotherapy versus radiofrequency ablation	1	27	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.6 Radiofrequency ablation plus percutaneous alcohol injection versus radiofrequency ablation	1	86	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.7 Transarterial chemoembolisation plus radiofrequency ablation versus radiofrequency ablation	2	84	Odds Ratio (M-H, Fixed, 95% CI)	2.11 [0.18, 25.35]
4.8 Percutaneous alcohol injection versus percutaneous acetic acid injection	1	125	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.9 Transarterial chemoembolisation plus percutaneous alcohol injection versus percutaneous alcohol injection	1	52	Odds Ratio (M-H, Fixed, 95% CI)	5.41 [0.25, 118.34]
5 Serious adverse events (number of events)	2		Rate Ratio (Fixed, 95% CI)	Totals not selected
5.1 Percutaneous alcohol injection versus radiofrequency ablation	1		Rate Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Transarterial chemoembolisation plus radiofrequency ablation versus radiofrequency ablation	1		Rate Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Any adverse events (number of participants)	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Percutaneous acetic acid injection versus radiofrequency ablation	1	125	Odds Ratio (M-H, Fixed, 95% CI)	0.39 [0.10, 1.59]
6.2 Percutaneous alcohol injection versus radiofrequency ablation	3	548	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.43, 1.81]
6.3 Percutaneous alcohol injection versus percutaneous acetic acid injection	1	125	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.24]
7 Any adverse events (number of events)	6		Rate Ratio (Fixed, 95% CI)	Subtotals only
7.1 Laser versus radiofrequency ablation	2	170	Rate Ratio (Fixed, 95% CI)	0.83 [0.57, 1.20]

7.2 Percutaneous alcohol injection versus radiofrequency ablation	2	334	Rate Ratio (Fixed, 95% CI)	0.90 [0.71, 1.14]
7.3 Transarterial chemoembolisation plus radiofrequency ablation versus radiofrequency ablation	1	40	Rate Ratio (Fixed, 95% CI)	1.30 [0.78, 2.14]
7.4 Transarterial chemoembolisation plus percutaneous alcohol injection versus percutaneous alcohol injection	1	52	Rate Ratio (Fixed, 95% CI)	0.53 [0.42, 0.67]
8 HCC recurrence (local or distal)	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Laser versus radiofrequency ablation	1	140	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.44, 1.76]
8.2 Percutaneous alcohol injection versus radiofrequency ablation	2	371	Odds Ratio (M-H, Fixed, 95% CI)	1.58 [1.02, 2.45]
9 HCC recurrence (recurrence in liver)	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Laser versus radiofrequency ablation	1	140	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.39, 1.86]
9.2 Percutaneous alcohol injection versus radiofrequency ablation	1	232	Odds Ratio (M-H, Fixed, 95% CI)	1.70 [0.96, 3.00]
9.3 Radiofrequency ablation plus chemotherapy versus radiofrequency ablation	1	27	Odds Ratio (M-H, Fixed, 95% CI)	0.36 [0.07, 1.82]
9.4 Transarterial chemoembolisation plus radiofrequency ablation versus radiofrequency ablation	1	40	Odds Ratio (M-H, Fixed, 95% CI)	1.22 [0.35, 4.24]
10 Length of hospital stay	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.1 Percutaneous alcohol injection versus radiofrequency ablation	1	232	Mean Difference (IV, Fixed, 95% CI)	15.3 [13.23, 17.37]

ADDITIONAL TABLES

Table 1. Characteristics of included studies arranged according to intervention and control

Study name	Number of participants randomised	Postrandomisation dropouts	Number of participants for whom outcome was reported	Intervention(s)	Control	Average follow-up period (months)
In people who were eligible for surgery						**In people who for surgery**

Table 1. Characteristics of included studies arranged according to intervention and control *(Continued)*

Chen 2006	180	19	161	Surgery	Radiofrequency ablation	29
Huang 2010	230	0	230	Surgery	Radiofrequency ablation	42
Fang 2014	120	Not stated	120	Surgery	Radiofrequency ablation	40
Lee 2014	63	Not stated	63	Surgery	Radiofrequency ablation	Not stated
In people who were not eligible for surgery						**In people who v ble for surgery**
Bolondi 1996	150	Not stated	150	Percutaneous alcohol injection plus transarterial chemoembolisation	Percutaneous alcohol injection	19
Koda 2001	52	Not stated	52	Transarterial chemoembolisation plus percutaneous alcohol injection	Percutaneous alcohol injection	30
Lin 2005	187	0	187	Radiofrequency ablation	Percutaneous alcohol injection, percutaneous acetic acid injection	27
Orlacchio 2014	30	0	30	Laser	Radiofrequency ablation	12
Costanzo 2015	140	0	140	Laser	Radiofrequency ablation	Not stated
Shibata 2002	72	0	72	Microwave ablation	Radiofrequency ablation	18
Lencioni 2003	104	2	102	Percutaneous alcohol injection	Radiofrequency ablation	23
Shiina 2005	232	0	232	Percutaneous alcohol injection	Radiofrequency ablation	37

Table 1. Characteristics of included studies arranged according to intervention and control *(Continued)*

Brunello 2008	139	0	139	Percutaneous alcohol injection	Radiofrequency ablation	36
Giorgio 2011	285	0	285	Percutaneous alcohol injection	Radiofrequency ablation	37
Gan 2004	38	11	27	Radiofrequency ablation plus chemotherapy	Radiofrequency ablation	12
Chen 2005	86	Not stated	86	Radiofrequency ablation plus percutaneous alcohol injection	Radiofrequency ablation	Not stated
Aikata 2006	44	Not stated	44	Transarterial chemoembolisation plus radiofrequency ablation	Radiofrequency ablation	Not stated
El Kady 2013	40	0	40	Transarterial chemoembolisation plus radiofrequency ablation	Radiofrequency ablation	6

Table 2. Risk of bias in studies arranged according to intervention and control

Study name	Random sequence generation	Allocation concealment	Blinding of participants and health professionals	Blinding of outcome assessors	Incomplete outcome data bias	Selective outcome reporting	For-profit bias	Other bias
In people who were eligible for surgery								**In people who for surgery**
Chen 2006	Low	Unclear	Unclear	Unclear	High	Low	Low	Low
Huang 2010	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Fang 2014	Low	Low	High	High	Low	Low	Low	Low
Lee 2014	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High	Low

Table 2. Risk of bias in studies arranged according to intervention and control (*Continued*)

In people who were not eligible for surgery								In people who ble for surgery
Bolondi 1996	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low
Koda 2001	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Lin 2005	Low	Unclear	Unclear	Unclear	Low	Low	Unclear	Low
Orlacchio 2014	Low	Unclear	High	High	Low	Low	Low	Low
Costanzo 2015	Low	Unclear	High	High	Low	Low	Low	Low
Shibata 2002	Unclear	Unclear	Unclear	Unclear	Low	High	Unclear	Low
Lencioni 2003	Low	Unclear	Unclear	Unclear	High	Low	Unclear	Low
Shiina 2005	Low	Unclear	High	High	Low	Low	Unclear	Low
Brunello 2008	Low	Low	High	High	Low	Low	Low	Low
Giorgio 2011	Low	Low	Unclear	Low	Low	Low	Low	Low
Gan 2004	Unclear	Unclear	Unclear	Unclear	High	High	Unclear	Low
Chen 2005	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Aikata 2006	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
El Kady 2013	Low	Unclear	Unclear	Unclear	Low	Low	Low	Low

CONTRIBUTIONS OF AUTHORS

Avik Majumdar, Davide Roccarina, and Kurinchi Gurusamy selected the studies and extracted the data. Avik Majumdar completed the 'Characteristics of included studies' and 'Characteristics of excluded studies' tables. Kurinchi Gurusamy wrote the review. Avik Majumdar, Davide Roccarina, Emmanuel Tsochatzis, Brian Davidson, and Douglas Thorburn commented critically on the review. All review authors approved this version before publication.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- It was not possible to assess whether the potential effect modifiers were similar across different comparisons, therefore we did not perform the network meta-analysis and assessed the comparative benefits and harms of different interventions using standard Cochrane methodology. The methodology that we plan to use if we conduct a network meta-analysis in future is available in Appendix 3.

- We performed Trial Sequential Analysis in addition to the conventional method of assessing the risk of random errors using P value.

NOTES

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