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Transcatheter arterial chemoembolisation followed by three-dimensional conformal radiotherapy versus transcatheter arterial chemoembolisation alone for primary hepatocellular carcinoma in adults (Review)

Lu L, Zeng J, Wen Z, Tang C, Xu N

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[Intervention Review]

Transcatheter arterial chemoembolisation followed by three-dimensional conformal radiotherapy versus transcatheter arterial chemoembolisation alone for primary hepatocellular carcinoma in adults

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ABSTRACT

Background

Hepatocellular carcinoma, also called malignant hepatoma, is a primary malignancy of the liver. Despite regular surveillance conducted in high-risk populations, most people with hepatocellular carcinoma are diagnosed at an advanced stage. Consequently, only a minority of people with the disease are suitable for surgical resection when diagnosed.

Objectives

To compare the beneficial and harmful effects of transcatheter arterial chemoembolisation (TACE) followed by three-dimensional conformal radiotherapy (3-DCRT) versus TACE alone in adults with primary hepatocellular carcinoma, considered unsuitable for surgical resection.

Search methods

We searched The Cochrane Hepato-Biliary Group Controlled Trials Register, CENTRAL, MEDLINE, Embase, LILACS, Science Citation Index Expanded, and Conference Proceedings Citation Index – Science up to 31 May 2018. We checked reference lists for all included studies and related reviews for further relevant articles.

Selection criteria

We included all randomised clinical trials comparing TACE followed by 3-DCRT versus TACE alone in people with primary hepatocellular carcinoma.

Data collection and analysis

We used standard methodological procedures as suggested by Cochrane. We presented the results of the fixed-effect model in the absence of statistical heterogeneity. Otherwise, we reported the results from the random-effects model meta-analysis. We assessed risk of bias of the included trials using bias risk domains and presented the review results incorporating the methodological quality of the trials using GRADE. Our main conclusions were based on the analysis up to three years' follow-up.

Main results

We identified eight randomised clinical trials (632 participants) that fulfilled our inclusion criteria. All eight trials were at high risk of bias, and we rated the evidence as low to very low certainty. The mean age ranged from 16 years to 78 years. The proportion of men ranged from 60% to 75% and the proportion of people with stage III primary hepatocellular carcinoma ranged from 22% to 85%. The median follow-up duration was 12 months (2 months to 38 months).

TACE followed by 3-DCRT compared with TACE alone may have reduced all-cause mortality at three years' follow-up (risk ratio (RR) 0.80, 95% confidence interval (CI) 0.73 to 0.88; 552 participants; 7 trials; low-certainty evidence). TACE followed by 3-DCRT compared with TACE alone may reduce the proportion of participants without tumour response (complete response plus partial response) (RR 0.49, 95% CI 0.39 to 0.61; 632 participants; 8 trials; low-certainty evidence). Data, from one trial on health-related quality of life, favoured the TACE followed by 3-DCRT group, but the provided data were ill-defined (very low-certainty evidence). None of the trials reported serious adverse events. The results on non-serious adverse events were as follows: TACE followed by 3-DCRT compared with TACE alone showed no difference in the results for proportion of participants with leukopenia (RR 1.12, 95% CI 0.92 to 1.34; 438 participants; 5 trials; very low-certainty evidence) and serum transaminases elevation (RR 1.67, 95% CI 0.66 to 4.27; 280 participants; 4 trials; very low-certainty evidence). However, the proportion of participants with total bilirubin elevation was larger in the TACE followed by 3-DCRT group than in the TACE alone group (RR 2.69, 95% CI 1.34 to 5.40; 172 participants; 2 trials; very low-certainty evidence). The rate of participants with serum alpha-fetoprotein (AFP) without decline or normalisation was significantly lower in the TACE followed by 3-DCRT group than in the TACE group, but these data were from one trial only ($Chi^2 = 7.24$, $P = 0.007$; very low-certainty evidence).

Authors' conclusions

TACE followed by 3-DCRT may be associated with lower all-cause mortality and increased tumour response, despite the increased toxicity expressed by a higher rise of total bilirubin. Our review findings should be considered with caution because of the methodological weaknesses in the included trials, resulting in low- to very low-certainty evidence. Data on serious adverse events and health-related quality of life are lacking. We are also very much uncertain in the results of the reported non-serious adverse events. High-quality trials are needed to assess further the role of TACE followed by 3-DCRT for unresectable hepatocellular carcinoma.

PLAIN LANGUAGE SUMMARY

Transcatheter arterial chemoembolisation followed by three-dimensional conformal radiotherapy for primary hepatocellular carcinoma

Background

Hepatocellular carcinoma, also called malignant hepatoma, is a primary liver cancer. Despite regular surveillance conducted in high-risk populations, most people with hepatocellular carcinoma are diagnosed at an advanced stage. Consequently, a minority of the people with the disease are suitable for surgical resection (removal). Since transcatheter arterial chemoembolisation (TACE; a procedure to restrict the blood supply to a tumour) was introduced as a palliative (to relieve symptoms and improve quality of life) treatment in people with unresectable liver cancer, it has become one of the most common forms of intervention. More recently, the modern radiation technology of three-dimensional conformal radiotherapy (3-DCRT), which shapes the radiation beams to the shape of the tumour, has been used to improve the adverse effects of conventional radiotherapy. It is predicted that the combination of TACE followed by 3-DCRT could enhance the treatment effect for hepatocellular carcinoma. To date, little is known about the benefits and harms of the combination of TACE followed by 3-DCRT, and current studies are still controversial for the efficacy of the combination of TACE followed by 3-DCRT compared with TACE alone. The aim of this Cochrane systematic review was to compare the benefits and harms of TACE followed by 3-DCRT versus TACE alone in people with primary hepatocellular carcinoma, considered to be unsuitable for surgical removal.

Study characteristics

The review authors searched the medical literature in order to clarify the role of the combination of TACE followed by 3-DCRT for the treatment of primary hepatocellular carcinoma, and to compare their benefits and harms with TACE alone. We collected and analysed data from randomised clinical trials (clinical studies where people are randomly put into one of two or more treatment groups) of people with primary hepatocellular carcinoma who were able to receive TACE or 3-DCRT. Evidence is current to May 2018.

Key results and quality of evidence

The review included eight trials with 632 participants. All trials were at high risk of bias. TACE followed by 3-DCRT appeared to be superior to TACE in improving death from any cause and tumour response, despite an increased toxicity expressed by a higher rise of total

bilirubin (measured by a blood test to see how well the liver is working). No trials reported serious side effects. One trial reported health-related quality of life (a measure of a person's satisfaction with their life and health), but this was ill-defined. The review findings were uncertain because the included trials had methodological weaknesses. More high-quality randomised clinical trials are needed to confirm or complete the review findings.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. TACE followed by 3-DCRT compared to TACE for primary hepatocellular carcinoma

TACE followed by 3-DCRT compared to TACE for primary hepatocellular carcinoma

Patient or population: primary hepatocellular carcinoma

Setting: hospitalised in China

Intervention: TACE followed by 3-DCRT

Comparison: TACE

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with TACE	Risk with TACE+3-DCRT				
All-cause mortality: at 3 years Follow-up: mean 17 months	**Study population**		**RR 0.80** (0.73 to 0.88)	552 (7 RCTs)	⊕⊕⊖⊖ **Low**[a]	—
	853 per 1000	683 per 1000 (623 to 751)				
Proportion of participants without tumour response (CR+PR) Follow-up: mean 18 months	**Study population**		**RR 0.49** (0.39 to 0.61)	632 (8 RCTs)	⊕⊕⊖⊖ **Low**[a]	—
	495 per 1000	243 per 1000 (193 to 302)				
Serious adverse events	None of the trials reported data on serious adverse events.				⊕⊖⊖⊖ **Very low**[a,b]	—
Health-related quality of life	Health-related quality of life was significantly better in the TACE followed by 3-DCRT group than in the TACE alone group (Chi^2 = 4.479, P = 0.034)			66 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,b]	—
Non-serious adverse events: leukopenia Follow-up: mean 13.2 months	**Study population**		**RR 1.12** (0.92 to 1.34)	438 (5 RCTs)	⊕⊖⊖⊖ **Very low**[a,c]	—
	475 per 1000	532 per 1000 (437 to 636)				
Non-serious adverse events: serum transaminases elevation Follow-up: mean 7.5 month	**Study population**		**RR 1.67** (0.66 to 4.27)	280 (4 RCTs)	⊕⊖⊖⊖ **Very low**[a,d,e,f]	—
	328 per 1000	549 per 1000 (217 to 1000)				

Non-serious adverse events: total bilirubin elevation Follow-up: mean 6 months	**Study population**		**RR 2.69** (1.34 to 5.40)	172 (2 RCTs)	⊕⊖⊖⊖ **Very low**[a,g]	—
	108 per 1000	292 per 1000 (145 to 586)				
Proportion of participants without serum AFP normalisation	The rate of participants with serum AFP without decline or normalisation was a significantly lower in the TACE followed by 3-DCRT group than in the TACE alone group ($Chi^2 = 7.24$, $P = 0.007$)			96 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,b]	—

*__The risk in the intervention group__ (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).

3-DCRT: three-dimensional conformal radiotherapy; **AFP:** alpha fetoprotein; **CI:** confidence interval; **CR:** complete response; **PR:** partial response; **RCT:** randomised clinical trial; **RR:** risk ratio; **TACE:** transcatheter arterial chemoembolisation.

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

[a]Downgraded two levels for risk of bias: most of the included RCTs had unclear risk of concealment of allocation, non-blinded assessment of outcomes, attrition bias, and other bias.
[b]Downgraded one level for imprecision: we were unable to combine the data in an overall analysis due to lack of data.
[c]Downgraded one level for heterogeneity: the heterogeneity test showed that variation existed in point estimates due to among-study differences.
[d]Downgraded one level for heterogeneity: the heterogeneity test showed that large variation ($I^2 = 88\%$) existed in point estimates due to among-study differences.
[e]Downgraded two levels for imprecision: the sample size was less than 300 (280 participants), the number of events not high (108 events), and the confidence intervals of the pooled RR clearly crossed the line of no effect and appreciable harm.
[f]Downgraded one level for publication bias; based on the funnel plot.
[g]Downgraded one level for imprecision: the sample size was less than 300 (172 participants).

BACKGROUND

Description of the condition

Hepatocellular carcinoma, also called malignant hepatoma, is a primary malignancy of the liver. It is the fifth most common neoplasm worldwide and its incidence is increasing (Venook 2010; Ferlay 2015). It is the second leading cause of cancer-related death (El-Serag 2014). Most people with hepatocellular carcinoma develop malignancy secondary to either viral hepatitis infections (hepatitis B or hepatitis C) or cirrhosis (alcoholism being the most common cause of hepatic cirrhosis) (Kumar 2004).

Hepatocellular carcinoma exhibits two main global patterns: one in North America and Western Europe where the prevalence of chronic hepatitis C virus is increasing, and another in non-Western countries, such as those in sub-Saharan Africa, Central and Southeast Asia, and the Amazon basin where the prevalence of chronic hepatitis B is high (El-Serag 2001; Lodato 2006). Epidemiological data show that the incidence of hepatocellular carcinoma is changing around the world following aetiology; it is increasing in many high-income countries, whereas it is declining in low-income countries (McGlynn 2001). Usually, there are more men than women who develop hepatocellular carcinoma, and the women are usually between 30 years and 50 years of age (Kumar 2004). Yearly, 610,000 people die of hepatocellular carcinoma worldwide (WHO 2009), and about half of these deaths occur in China. Hepatocellular carcinoma is one of the deadliest cancers in China, where chronic hepatitis B is found to be the cause in 90% of the deaths. With the introduction of hepatitis B virus vaccination, the incidence of hepatocellular carcinoma has been decreasing in low-income countries (Lodato 2006). In Japan, 90% of hepatocellular carcinomas are associated with hepatitis C. Food infected with *Aspergillus flavus* (especially peanuts and corns stored during prolonged wet seasons), which produces aflatoxin, poses another risk factor for hepatocellular carcinoma. However, most malignant tumours of the liver discovered in people from Western countries are metastases from tumours elsewhere, and hepatocellular carcinoma is generally seen as a rare cancer (Lodato 2006). Hepatocellular carcinoma is one of the few types of cancer that has increased in frequency and mortality in the USA (Mittal 2013) and Europe (Deuffic 1998).

Hepatocellular carcinoma at its early stages is often non-symptomatic. As the cancer grows, symptoms may include pain in the upper abdomen on the right side, which may extend to the back and shoulder, or cause swollen abdomen (bloating), weight loss, loss of appetite, loss of the sensation of being full, fatigue, nausea and vomiting, jaundice, or fever. Mostly, these symptoms happen in stages III or IV of the disease. Diagnosis of hepatocellular carcinoma may involve physical examination such as examination of the liver, spleen, or any lumps; ascites; and jaundice. It may also entail an alpha-fetoprotein (AFP) test, computer tomography scan, ultrasound, magnetic resonance imaging, angiogram, or biopsy (El-Serag 2008). Despite regular surveillance conducted in high-risk populations, most people with hepatocellular carcinoma are diagnosed at an advanced stage. Consequently, a minority of people with the disease are suitable for surgical resection. The recurrence rates are as high as 65% to 80% within five years, even for those people who undergo surgical resection (Li 2013), which results in a five-year survival of about 40% (Cha 2005).

Description of the intervention

People with early-stage cancer (20% to 30% of people with hepatocellular carcinoma) are considered suitable for treatments such as liver resection, liver transplantation, percutaneous ablation, percutaneous ethanol injection, and radiofrequency ablation (Llovet 2004; Cabrera 2010). Since transcatheter arterial chemoembolisation (TACE) was introduced as a palliative treatment in people with unresectable hepatocellular carcinoma, it has become one of the most common forms of intervention (Takayasu 2006); and it is considered a standard treatment option for people with unresectable hepatocellular carcinoma (Kothary 2007). In addition, TACE is usually performed as a temporary treatment while waiting for a liver transplant, or for people for whom surgical or percutaneous ablative treatment is contraindicated. TACE involves the injection of anticancer drugs (doxorubicin, epirubicin, or cisplatin) and iodised oil (Lipiodol Ultra-Fluide, Laboratoires Guerber, Aulnay-sous-Bois, France) (^{131}I-lipiodol radiotherapy) into the hepatic artery, followed by the administration of embolic agents (Nakamura 1990; Bronowicki 1994). Currently, TACE is considered the standard of care for people with intermediate-stage hepatocellular carcinoma presenting with Child-Pugh class A and B liver function, and large or multinodular hepatocellular carcinoma without cancer-related symptoms, macrovascular invasion, or extrahepatic metastasis (Murata 2014).

These treatment recommendations occur irrespective of the fact that a Cochrane systematic review has been unable to identify high-quality evidence in support of TACE (Oliveri 2011).

Since the early 2000s, the modern radiation technology of three-dimensional conformal radiotherapy (3-DCRT) has been applied in clinics to improve the shortcomings of conventional radiotherapy. Radiotherapy for hepatocellular carcinoma has resulted in unsatisfactory outcomes since the late 1980s because of the liver's poor tolerance to irradiation (Liang 2005). 3-DCRT is aided by a computerised treatment-planning system which has enabled the tight conformation of a high-dose volume to hepatocellular carcinoma lesions in three dimensions. Thus, 3-DCRT has made it possible to escalate the irradiation dose to focal hepatocellular carcinoma without causing undue dose-limiting toxicity in neighbouring non-cancerous liver tissues. Therefore, it spares non-cancerous liver tissue from excess damage, and has increasingly been recognised as a potentially curative option for people with hepatocellular carcinoma (Lawrence 1990; Feng 2011).

How the intervention might work

TACE is appropriate for hepatocellular carcinoma, as the hepatic artery delivers 99% of the blood supply to hepatic tumours (Murata 2014). TACE seems to improve survival compared with the best supportive care in meta-analyses of randomised trials (Cammà 2002; Llovet 2003); and in two individual clinical trials (Llovet 2002; Lo 2002). The antitumour effect of TACE is greater than that of other anticancer drugs (Yoshikawa 1994); or iodised oil alone (Takayasu 1987; Yamagami 2014). As stated above, we lack high-quality evidence in support of TACE (Oliveri 2011).

With advances in 3-DCRT, local radiation of the liver has become safer (Robertson 1993); and its efficacy is better than in conventional radiotherapy (Matsuura 1998). 3-DCRT has shown favourable outcomes in local control and survival, with a median

survival time of 10 months to 25 months (Yu 2014); and a three-year survival of around 30% for people with hepatocellular carcinoma (Lee 2013). Several series that employed 3-DCRT have reported a dose-response relation in radiotherapy for liver cancers with better response rates and prolonged hepatic control in groups that received higher radiotherapy doses (Robertson 1993; Seong 2000).

The inadequacy of single TACE in inducing complete tumour necrosis has also been well documented (Sasaki 1987), and TACE is usually repeated at regular intervals. Nevertheless, repeated TACE frequently becomes ineffective due to tumour progression. As most primary liver tumours have dual blood supplies, it is easy to re-form the collateral circulation in lesions with the residual tumour cells after TACE (Ikeda 1991; Cheng 2000). It is predicted that the combination of TACE and 3-DCRT could enhance treatment effects for hepatocellular carcinoma. It was reported that the one-year survival rate for the combination of TACE followed by 3-DCRT was 73%, two-year survival rate was 53%, and three-year survival rate was 35%, which was higher than the TACE alone group (one-year survival rate 60%, two-year survival rate 31%, and three-year survival rate 14%) (Zou 2014).

The rationale for combined TACE and 3-DCRT was based on the following three considerations. First, with the iodised oil injection by TACE, the deposit of iodine would have made the margin of the median gross tumour volume clearer, making gross tumour volume delineation more accurate, and 3-DCRT plan verification easier. Second, after TACE, the tumour burden becomes less and the number of tumour cells decreases. This would make it easier for 3-DCRT to control the malignancy. Third, the 3-DCRT radiosensitivity of hepatocellular carcinoma still exists when 3-DCRT begins several weeks after TACE (Zhou 2007).

Why it is important to do this review

To date, little is known about the benefits and harms of the combination of TACE and 3-DCRT, and only few clinical studies have been conducted. Some were in favour of the combination of TACE and 3-DCRT (Shim 2005; Koo 2010), while another showed that the survival rates of people with combined TACE and 3-DCRT were similar to those with TACE alone (Chia-Hsien 2001). Despite the publication of further studies on the use of TACE followed by 3-DCRT in people with primary hepatocellular carcinoma, we found no systematic reviews or meta-analyses with randomised clinical trials comparing the combination of TACE followed by 3-DCRT versus TACE alone.

OBJECTIVES

To compare the beneficial and harmful effects of transcatheter arterial chemoembolisation (TACE) followed by three-dimensional conformal radiotherapy (3-DCRT) versus TACE alone in adults with primary hepatocellular carcinoma, considered unsuitable for surgical removal.

METHODS

Criteria for considering studies for this review

Types of studies

We considered all randomised clinical trials investigating a combination of TACE and 3-DCRT versus TACE alone for inclusion, whether they were double-blind, single-blind, or open-label, and regardless of publication status, language, and length of the trial. In addition, we scanned quasi-randomised and other observational studies which were retrieved with the searches for randomised clinical trials to identify reports on harm. By not searching specifically for harms in observational studies, we are aware that we, in the present systematic review, may have been biased towards assessing benefits and ignoring harms (see Storebø 2018).

Types of participants

Participants older than 18 years diagnosed with hepatocellular carcinoma based on their pathological findings in at least one lesion with or without other laboratory evidence such as B-ultrasound, computed tomography, or AFP. Furthermore, diagnosis had to conform to the following criteria.

- Participants had not received any anticancer therapy.
- Karnofsky score was 69 or less (Park 2014).
- Child-Pugh grade of liver function was A or B (Liang 2015).
- Number of white blood cell 4.0×10^9/L or greater.
- Model for end-stage liver disease (MELD) score less than 10.
- There were no contraindications (vascular or adjacent organ involvement, involvement with lymph nodes, distant metastasis, jaundice and ascites, cardiopulmonary dysfunction, coagulation disorders) of TACE and 3-DCRT.

Types of interventions

We included trials comparing TACE followed by 3-DCRT versus TACE alone in people with primary hepatocellular carcinoma.

Types of outcome measures

We sought to measure the following outcomes at the end of treatment, as well as at maximal follow-up.

Primary outcomes

- All-cause mortality (death from any cause). We calculated one-year, two-year, and three-year all-cause mortality. We drew primary conclusions based on three-year all-cause mortality, as the longer the follow-up period, the stronger the evidence.
- Proportion of participants without tumour response: according to the World Health Organization (WHO) Handbook for reporting the results of cancer treatment (Spieth 2003), the responses were assessed as follows:
  - complete response (CR), complete disappearance or 100% necrosis of all tumours with no evidence of new lesions;
  - partial response (PR), more than 50% reduction or more than 50% necrosis (or both) of all measurable lesions with no evidence of new lesions;
  - progressive disease (PD), more than 25% enlargement of all measurable lesions or appearance of new lesions;
  - stable disease (SD), no change.
- Serious adverse events: we used the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice's definition of a serious adverse event (ICH-GCP 1997); that was, any untoward medical occurrence that resulted in death, was life threatening, required hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability or incapacity, or was a congenital anomaly or birth defect. We considered all other adverse events as non-serious.

Secondary outcomes

- Health-related quality of life as reported in the trials.
- Non-serious adverse events, such as abdominal pain, fatigue, poor appetite, nausea, vomiting, fever, leukopenia, thrombocytopenia, MELD score, etc. We analysed the following non-serious adverse events separately: proportion of participants with leukopenia, with serum transaminases elevation, and with total bilirubin elevation.
- Proportion of participants without serum AFP normalisation.

Search methods for identification of studies

Electronic searches

We searched the The Cochrane Hepato-Biliary Group Controlled Trials Register (May 2018; Cochrane Hepato-Biliary Group Module), the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (2018, Issue 4), MEDLINE Ovid (1946 to May 2018), Embase Ovid (1974 to May 2018), LILACS (1982 to May 2018; Bireme), Science Citation Index Expanded (1900 to May 2018; Web of Science), and Conference Proceedings Citation Index – Science (1990 to May 2018; Web of Science) (Royle 2003). We checked reference lists of all included studies and related reviews manually for further related articles. Appendix 1 provided the search strategies with the time spans of the searches.

Searching other resources

We searched the reference lists of the identified trials to identify further relevant trials.

We also searched online trial registries such as ClinicalTrials.gov (clinicaltrials.gov/), European Medicines Agency (EMA; www.ema.europa.eu/ema/), WHO International Clinical Trials Registry Platform (www.who.int/ictrp), and the Food and Drug Administration (FDA; www.fda.gov), as well as pharmaceutical company sources, for ongoing or unpublished trials.

Data collection and analysis

We performed the review according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and the Cochrane Hepato-Biliary Group Module. We used the Cochrane statistical software Review Manager 5, for data entry and analysis (Review Manager 2014).

Selection of studies

Two review authors (LL and JZ) independently identified the trials for inclusion. We listed the excluded studies with their reasons for exclusion. We resolved disagreements by discussion with the other author (WZ). We collated multiple reports of the same study, so that each study rather than each report was the unit of interest in the review.

Data extraction and management

Two review authors (LL and JZ) independently extracted the following data from each trial.

- Year and language of publication.
- Country.
- Year trial was conducted.
- Inclusion and exclusion criteria.
- Sample size.
- Population characteristics such as age, sex ratio, Karnofsky score and Child-Pugh grade of liver function.
- For TACE, use of drugs for chemotherapy and embolisation.
- For 3-DCRT, use of irradiation such as dosage, frequency, and range.
- Treatment measures for adverse effects.
- Outcomes (see Primary outcomes; Secondary outcomes).
- Methodological quality and bias risk.
- Sample size calculation.
- Intention-to-treat (ITT) analysis.

We sought missing information or clarification of unclear information by contacting the authors of the individual trials. We resolved any differences in opinion through discussion.

Assessment of risk of bias in included studies

Two review authors (LL; JZ) independently assessed the risk of bias for each included trial according to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), the Cochrane Hepato-Biliary Group Module, and methodological studies (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Savović 2012a; Savović 2012b; Lundh 2017; Savović 2018).

We used the following definitions in the assessment of risk of bias.

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, or throwing dice were adequate if performed by an independent person not otherwise involved in the trial.
- Unclear risk of bias: method of sequence generation was not specified.
- High risk of bias: sequence generation method was not random.

Allocation concealment

- Low risk of bias: participant allocations could not have been foreseen in advance of, or during, enrolment. Allocation was controlled by a central and independent randomisation unit. Allocation sequence was unknown to the investigators (e.g. whether the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Unclear risk of bias: 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: allocation sequence was likely known to the investigators who assigned the participants.

Blinding of participants and personnel

- Low risk of bias: any of the following: no blinding or incomplete blinding, but the review authors judged this outcome unlikely to have been influenced by lack of blinding (mortality) (Wood 2008; Savović 2012a; Savović 2012b); or blinding of participants and key study personnel was ensured, and it was unlikely that the blinding could have been broken.

- Unclear risk of bias: any of the following: insufficient information to permit judgement of 'low risk' or 'high risk'; or the trial did not address this outcome.
- High risk of bias: any of the following: no blinding or incomplete blinding, and the outcome was likely to have been influenced; or blinding of key study participants and personnel was attempted, but likely could have been broken, thus influencing the outcome.

Blinding of outcome assessment

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

Incomplete outcome data

- Low risk of bias: missing data were unlikely to have made treatment effects depart from plausible values. Sufficient methods, such as multiple imputation, were employed to handle missing data.
- Unclear risk of bias: there was insufficient information to assess whether missing data, in combination with the method used to handle missing data, were likely to have induced bias in the results.
- High risk of bias: the results were likely to have been biased due to missing data.

Selective outcome reporting

- Low risk of bias: the trial reported the following predefined outcomes: all-cause mortality, tumour response assessments, and serious 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 have been those enumerated in the original protocol if the trial protocol was registered before or at the time it began. If the trial protocol was registered after the trial began, those outcomes were not considered reliable.
- Unclear risk of bias: not all predefined outcomes were reported in full, or it was unclear whether data on these outcomes had been recorded or not.
- High risk of bias: one or more predefined outcomes was not reported.

Other bias

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

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

Measures of treatment effect

We performed the meta-analyses according to Cochrane recommendations (Higgins 2011) and the Cochrane Hepato-Biliary Group Module. We used the Review Manger 5 software package provided by Cochrane (Review Manager 2014). For dichotomous variables, we calculated the risk ratio (RR) with a 95% confidence interval (CI). For continuous variables, we calculated the mean difference with a 95% CI.

Unit of analysis issues

We took into account the group of participants per intervention group in the randomised clinical trials with parallel-group design. In the case of cross-over trials, we planned to use the data from the first trial period only. We did not expect to find cluster-randomised trials. For trials with multiple intervention groups, we planned to include the groups in which our experimental and control interventions were compared. We planned to divide the control group into two or more to avoid double-counting in case it was a common comparator.

Dealing with missing data

We considered participants with completely missing data as treatment failures and performed ITT analyses. If data for any participant were obtained at any point before the measured time point, this observation was carried forward.

Assessment of heterogeneity

We explored heterogeneity using the Chi^2 test with significance set at a P value of 0.10 or less, and measured the extent of heterogeneity using the I^2 statistic (Higgins 2002). We interpreted I^2 values as follows:

- probably not important: 0% to 40%;
- possible moderate heterogeneity: 30% to 60%;
- possible substantial heterogeneity: 50% to 90%;
- considerable heterogeneity: 75% to 100%.

Assessment of reporting biases

We used visual asymmetry on a funnel plot to explore reporting bias when at least 10 randomised clinical trials were identified in a particular field (Egger 1997; Macaskill 2001). In addition, we performed the linear regression approach described by Egger to determine the funnel plot asymmetry if the result of a funnel plot was unclear (Egger 1997).

Data synthesis

Meta-analysis

We performed our meta-analyses in accordance with Cochrane's recommendations (Higgins 2011), and used Review Manager 5 software for our analyses (Review Manager 2014). We evaluated

all missing data using ITT analyses. We treated missing data as treatment failures.

We expressed binary outcomes using RR with 95% CI. If the results were statistically significant according to our Trial Sequential Analysis (see 'Trial Sequential Analysis' below), we calculated the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH) using fixed-effect and random-effects models (DerSimonian 1986; DeMets 1987). We interpreted the results according to Jakobsen 2014. If there is absence of statistical heterogeneity or only one trial was included, the fixed-effect and the random-effects models would show identical results. We presented the results of the fixed-effect model in this situation. If there was substantial statistical heterogeneity, we reported the results from the random-effects meta-analysis. We presented unavailable data and inappropriate data using descriptive means.

Trial Sequential Analysis

We applied Trial Sequential Analysis as cumulative meta-analyses are at risk of producing random errors due to sparse data and repetitive testing of the accumulating data (Brok 2008; Wetterslev 2008; Brok 2009; Thorlund 2009; Wetterslev 2009; Thorlund 2010). To minimise random errors, we calculated the required information size (i.e. the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) (Wetterslev 2008). We calculated the required information size adjusted for diversity, since the heterogeneity adjustment with the I^2 statistic underestimated the required information size (Wetterslev 2008; Wetterslev 2009). In our meta-analysis, we performed Trial Sequential Analysis to maintain an overall 2.5% risk of a type I error and 20% of type II error (a power of 80%) (Wetterslev 2009). On the basis of the required information size, we constructed trial sequential monitoring boundaries (Lan 1983; Wetterslev 2008; Thorlund 2011). These boundaries determined the statistical inference one may draw regarding the cumulative meta-analysis that had not reached the required information size; if the trial sequential monitoring boundary for benefit or harm was crossed before the required information size was reached, firm evidence may have been established, and further trials may have turned out to be superfluous. In contrast, if the boundary had not been surpassed, it was probably necessary to continue doing trials in order to detect or reject a certain intervention effect. This could be determined by assessing whether the cumulative Z-curve crossed the trial sequential boundaries for futility. If futility boundaries had been crossed, then further trials may have been unnecessary (TSA 2011). We conducted Trial Sequential Analysis using software from The Copenhagen Trial Unit (Thorlund 2011; TSA 2011; Wetterslev 2017).

Subgroup analysis and investigation of heterogeneity

We performed the following subgroup analyses.

- Trials at low bias risk compared to trials at high bias risk.
- With TACE, different drugs used in chemotherapy and embolisation.
- With 3-DCRT, different dosage, frequency, and range in irradiation.
- Presence or absence of chronic liver disease.
- Aetiology of the chronic liver disease.

Sensitivity analysis

We assessed the robustness of our analyses by performing a sensitivity analysis, excluding studies from the overall analysis of high risk of bias due to lack of allocation concealment, blinding, or incomplete reporting of primary outcome. We compared the GRADE assessment of imprecision with that obtained with Trial Sequential Analysis (Jakobsen 2014; Castellini 2018).

'Summary of findings' tables

We presented the evidence in Summary of findings for the main comparison using GRADEpro software in accordance with the principles of the GRADE system (Guyatt 2011a). This was done to assess the certainty of the body of evidence associated with specific outcomes such as all-cause mortality, recent objective response of hepatocellular carcinoma, and serious adverse events in our review.

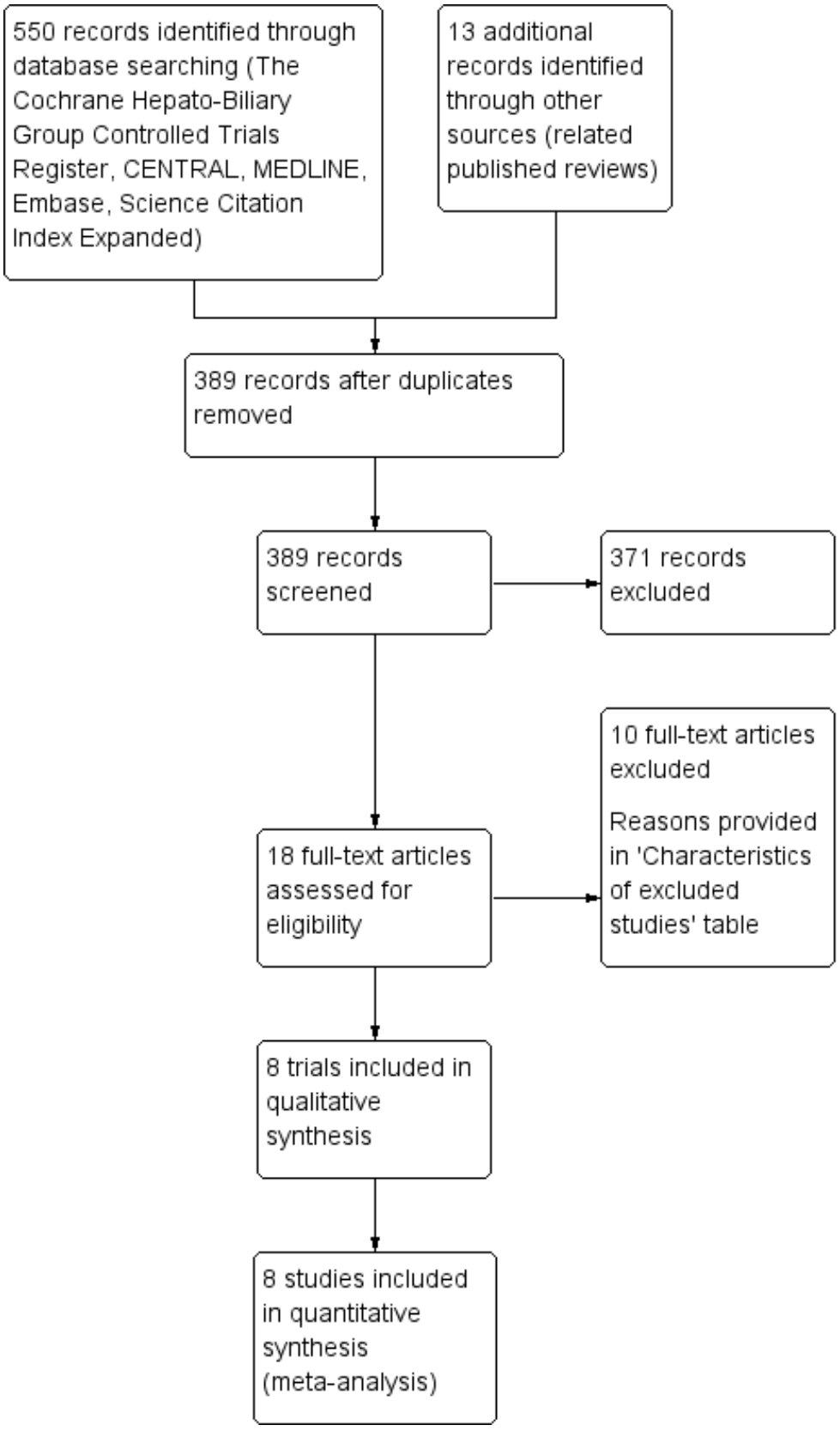
The GRADE approach defined the certainty in a body of evidence as the extent to which one could be confident that an estimate of effect or association was close to the quantity of specific interest. According to GRADE, the certainty in a body of evidence included five factors regarding limitations in the design and implementation of available studies suggesting high likelihood of bias: indirectness of evidence (population, intervention, control, outcomes); unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses); imprecision of results (wide CIs); and high probability of publication bias (Balshem 2011; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2011h; Guyatt 2013a; Guyatt 2013b; Guyatt 2013c; Guyatt 2013d; Mustafa 2013; Guyatt 2017).

RESULTS

Description of studies

The search identified 550 reports (Figure 1).

Figure 1. Study flow diagram.



Results of the search

Electronic literature searches revealed two hits in The Cochrane Hepato-Biliary Group Controlled Trials Register, 12 hits in the Cochrane Central Register of Controlled Trials (CENTRAL), 104 hits in MEDLINE, 212 hits in Embase, zero hits in LILACS, and 220 hits in Science Citation Index Expanded and Conference Proceedings Citation Index – Science. Appendix 1 shows the search strategies. Thirteen reports consisted of additional reports on published reviews (Zou 2014; Bai 2016). After removing duplicates, 389 reports remained. We excluded 371 irrelevant reports based on the title, abstract, or both. We retrieved and read the full-text of 18 reports, and finally included eight trials (eight reports).

Included studies

Eight trials satisfied our inclusion criteria (Zhao 2006; Shang 2007; Xiao 2008; Ning 2009; Liao 2010; Gong 2011; Xiao 2011; Chen 2014).

Characteristics of included studies

We summarised the characteristics of the eight included trials in the Characteristics of included studies table.

Study design

All trials were parallel group randomised clinical trials.

Funding

Only one trial was supported by a grant from the local science and technology bureau (Liao 2010). Other trials did not provide any data on funding.

Participants

There were 632 participants with primary hepatocellular carcinoma. The mean age ranged from 16 years to 78 years. The proportion of men ranged from 60% to 75%, and the proportion of people with stage III primary hepatocellular carcinoma ranged from 22% to 85%. The proportion of people with tumour size greater than 10 cm was 45% in one trial (Chen 2014), and with greater than 3 cm size ranging from 40% to 100% in five trials (Zhao 2006; Shang 2007; Xiao 2008; Liao 2010; Xiao 2011). The proportion of people with a single tumour was 68% to 75% in two trials (Xiao 2011; Chen 2014), the proportion with Child-Pugh class A ranged from 65% to 71% in two trials (Xiao 2008; Liao 2010), and the proportion with AFP greater than 400 µg/L ranged from 41% to 100% in three trials (Zhao 2006; Shang 2007; Xiao 2011). Accordingly, these participants would mostly likely be considered unsuitable for surgical resection.

Interventions

People underwent two courses (Zhao 2006; Shang 2007; Xiao 2008; Ning 2009; Gong 2011; Xiao 2011; Chen 2014) or three to five courses (Liao 2010) of TACE with one-month interval. 3-DCRT was delivered one to four weeks after the last course of TACE, if liver function tests were normal. The sum of the radiation doses in 3-DCRT received by each individual ranged from 30 Gray (Gy) to 66 Gy with 2 Gy/day to 5 Gy/day and 3 days/week to 5 days/week.

Comparisons

All eight trials compared TACE followed by 3-DCRT versus TACE alone. The chemotherapy included 5-fluorouracil (750 mg to 1250 mg) (Zhao 2006; Shang 2007; Xiao 2008; Ning 2009; Liao 2010; Gong 2011; Chen 2014), cisplatin (40 mg to 120 mg) (Zhao 2006; Shang 2007; Xiao 2008; Ning 2009; Liao 2010; Gong 2011; Xiao 2011; Chen 2014), adriamycin (30 mg to 100 mg) (Shang 2007; Xiao 2008; Liao 2010; Xiao 2011), hydroxyl radical (15 mg to 20 mg) (Zhao 2006; Ning 2009), and mitomycin C (6 mg to 14 mg) (Ning 2009; Chen 2014). Embolisation therapy: peripheral embolisation was performed by iodine oil emulsion, and central embolisation was performed by gelfoam.

Outcomes

All trials reported all-cause mortality and tumour response. Duration of therapy and embolisation were similar in the two intervention groups. No trial reported serious adverse events. Only one trial reported the rate of participants without decline or normalisation of AFP (Zhao 2006), and another trial provided some information on health-related quality of life (Ning 2009). Five trials reported non-serious adverse events (Zhao 2006; Shang 2007; Xiao 2008; Liao 2010; Chen 2014).

Excluded studies

See Characteristics of excluded studies table.

We excluded 10 observational studies (Chia-Hsien 2001; Zeng 2004; Guo 2005; Liang 2005; Shim 2005; Chung 2006; You 2007; Zhang 2009; Koo 2010; Lu 2015).

Risk of bias in included studies

See Figure 2 and Figure 3.

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

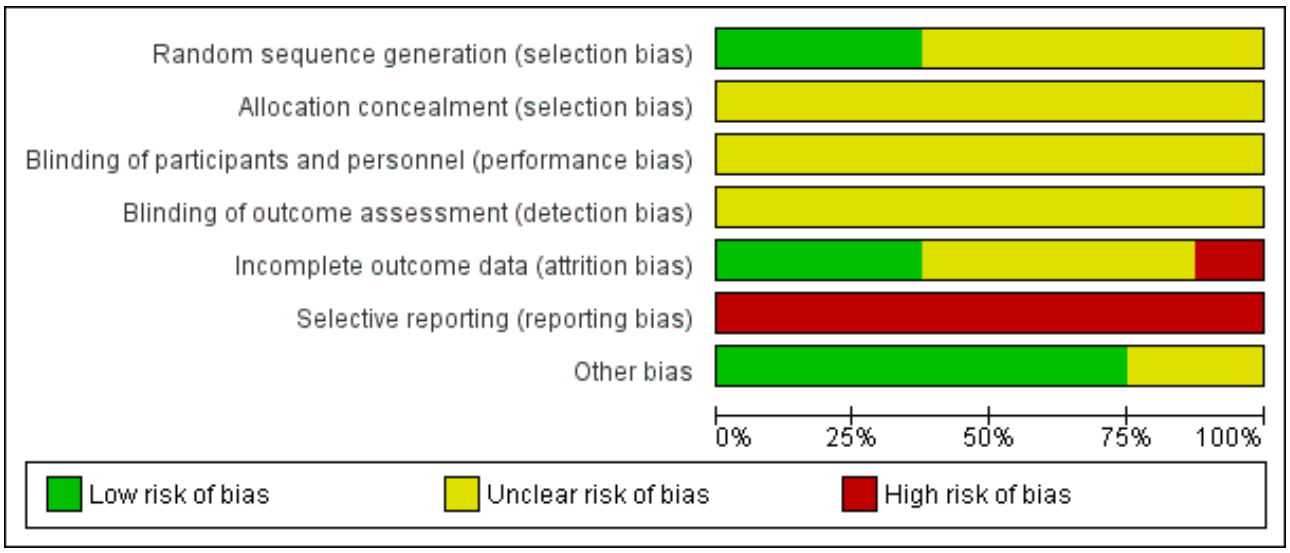
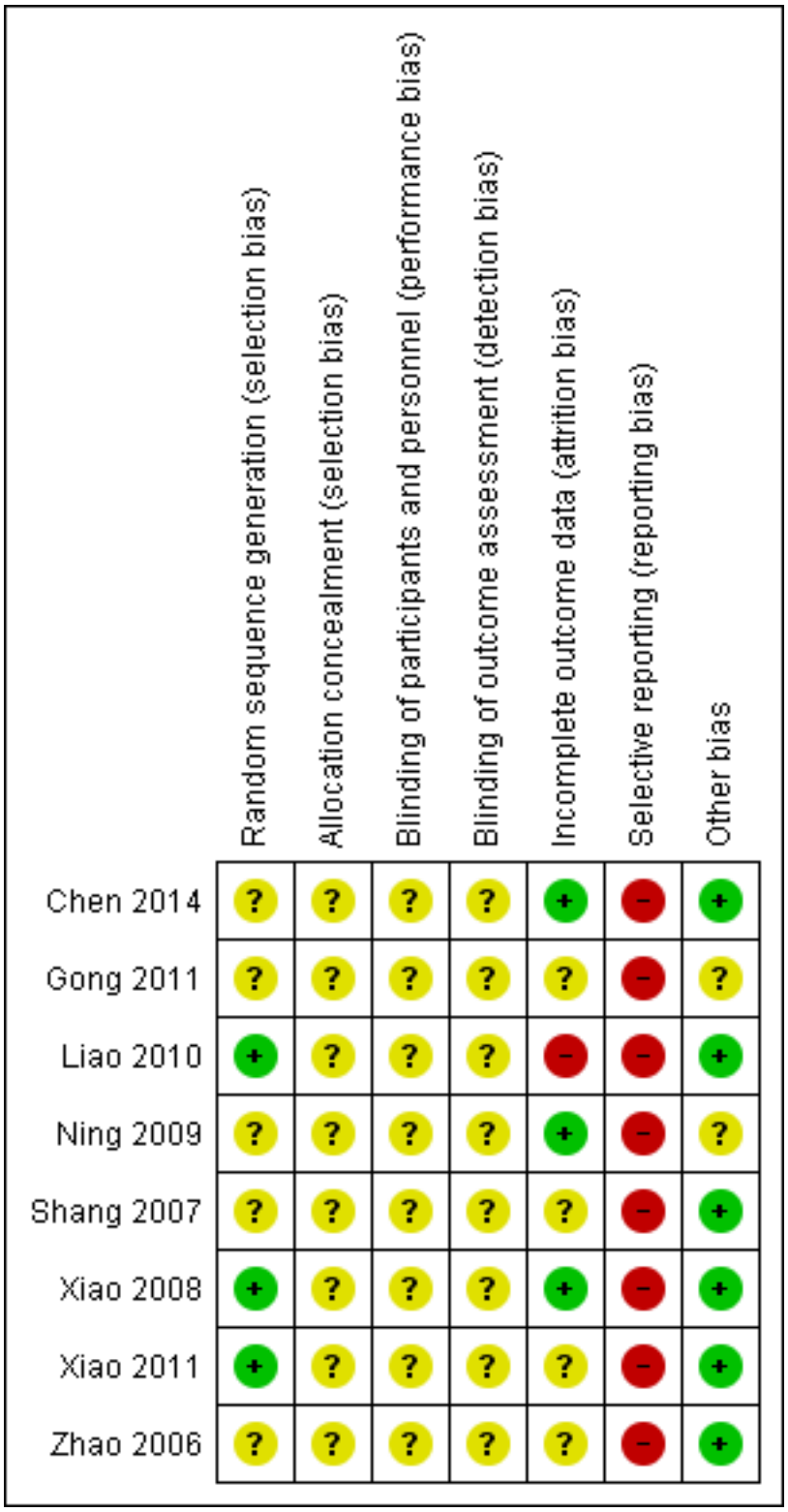


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



All trials were at high risk of bias (Zhao 2006; Shang 2007; Xiao 2008; Ning 2009; Liao 2010; Gong 2011; Xiao 2011; Chen 2014).

Allocation

Three trials performed random sequence generation using a random number table, and hence were at low risk of bias (Xiao 2008;

Liao 2010; Xiao 2011). The remaining five studies had unclear risk of bias, falling into the group of high risk of bias trials.

Allocation concealment had unclear risk of bias in all trials, as the trials provided no information.

Blinding

All trials were at unclear risk of bias for blinding of participants and investigators. Also, detection bias was unclear in all studies, hence all trials were at high overall risk of bias.

Incomplete outcome data

Three trials were at low risk of attrition bias, as they did not have any missing data after randomisation (Xiao 2008; Ning 2009; Chen 2014). One trial had high risk of bias because it did not account for participants with missing outcomes (Liao 2010). Other trials were at unclear risk of bias (Zhao 2006; Shang 2007; Gong 2011; Xiao 2011).

Selective reporting

All trials were at high risk of bias for selective reporting as none reported one clinically relevant outcome (serious adverse events); not all protocols were available.

Other potential sources of bias

We assessed six trials as having a low risk of bias regarding other potential sources of bias such as demographic and baseline characteristics of the randomised participants (Zhao 2006; Shang 2007; Xiao 2008; Liao 2010; Xiao 2011; Chen 2014), and we considered the remaining two trials as having unclear risk of bias because the trial authors did not provide the demographic and baseline characteristics of the randomised participants (Ning 2009; Gong 2011).

Effects of interventions

See: **Summary of findings for the main comparison** TACE followed by 3-DCRT compared to TACE for primary hepatocellular carcinoma

See Summary of findings for the main comparison.

Primary outcomes

All-cause mortality

At one-year, 85/319 (26.6%) participants treated with TACE followed by 3-DCRT and 155/313 (49.5%) participants treated with TACE died. There was a lower end of one-year all-cause mortality rate in the TACE followed by 3-DCRT group than in the TACE group (RR 0.54, 95% CI 0.44 to 0.66; 632 participants; 8 trials; Analysis 1.1). There was no trial heterogeneity (Chi^2 = 7.00, P = 0.43; I^2 = 0%).

By the end of the second year, all randomised clinical trials, except for Liao 2010, provided mortality data: 143/295 (48.5%) participants treated with TACE followed by 3-DCRT and 205/289 (70.9%) participants treated with TACE alone died (RR 0.68, 95% CI 0.60 to 0.78; 584 participants; 7 trials; Analysis 1.2). There was no trial heterogeneity (Chi^2 = 5.46, P = 0.49; I^2 = 0%).

By the end of the third year, all randomised clinical trials, except for Xiao 2011, provided mortality data: 191/279 (68.5%) participants treated with TACE followed by 3-DCRT and 233/273 (85.3%) participants treated with TACE died. (RR 0.80, 95% CI 0.73 to 0.88; 552 participants; 7 trials; Analysis 1.3). There was no trial heterogeneity (Chi^2 = 4.08, P = 0.67; I^2 = 0%).

Proportion of participants without tumour response (complete and partial)

All randomised clinical trials compared TACE followed by 3-DCRT versus TACE alone in participants without tumour response: 77/319 (24.1%) participants treated with TACE followed by 3-DCRT and 155/313 (49.5%) participants treated with TACE alone remained without tumour response (RR 0.49, 95% CI 0.39 to 0.61; 632 participants; 8 trials; Analysis 1.4). There was no trial heterogeneity (Chi^2 = 2.06, P = 0.96; I^2 = 0%).

Serious adverse events

No trials reported serious adverse events.

Secondary outcomes

Health-related quality of life

We could not perform an analysis of health-related quality of life as the information reported in the randomised clinical trials was insufficient. Only one trial reported scant data (Ning 2009). Health-related quality of life was significantly better in the TACE followed by 3-DCRT group than in the TACE group (Chi^2 = 4.479, P = 0.034).

Non-serious adverse events

There was no significant difference in the TACE followed by 3-DCRT group compared with the TACE alone group regarding the proportion of trial participants with leukopenia (RR 1.12, 95% CI 0.92 to 1.34; 438 participants; 5 studies; I^2 = 67%; Analysis 1.5) or the proportion of participants with serum transaminases elevation (RR 1.67, 95% CI 0.66 to 4.27; 280 participants; 4 trials; I^2 = 88%; Analysis 1.6). However, the proportion of participants with total bilirubin elevation was larger in the TACE followed by 3-DCRT group than in the TACE alone group (RR 2.69, 95% CI 1.34 to 5.40; 172 participants; 2 trials; I^2 = 0%; Analysis 1.7).

Table 1 reports types of adverse events.

Proportion of participants without serum AFP normalisation

We could not perform an analysis of serum AFP as the information reported in the randomised clinical trials was insufficient. Only one trial reported elevation in the level of AFP (Zhao 2006). The rate of participants with serum AFP without decline or normalisation was significantly lower in the TACE followed by 3-DCRT group than in the TACE group (Chi^2 = 7.24, P = 0.007).

Subgroup analyses

We could not perform the subgroup analysis of trials at low risk of bias and at high risk of bias because all of the trials were at high risk of bias. Due to data limitations, we could not perform subgroup analyses for the different drugs in TACE; different dosages, frequencies, and ranges in irradiation 3-DCRT; or aetiology of the chronic liver disease.

Sensitivity analysis

We could not perform sensitivity analysis by excluding studies at high risk of bias. This was due to lack of allocation concealment and blinding of outcome assessment because all trials were at unclear or high risk of bias in these two domains.

We assessed the robustness of our analysis by including only those trials at low risk of bias in incomplete outcome data, and we found that these results did not change the conclusions. There were statistically significant differences for one-year all-cause mortality (RR 0.53, 95% CI 0.37 to 0.74; 284 participants; 3 studies; I^2 = 28%; Analysis 1.8), two-year all-cause mortality (RR 0.72, 95% CI 0.58 to 0.88; 284 participants; 3 studies; I^2 = 0%; Analysis 1.9), three-year all-cause mortality (RR 0.84, 95% CI 0.74 to 0.94; 284 participants; 3 studies; I^2 = 0%; Analysis 1.10), and the rate of participants without tumour response (complete and partial) (RR 0.48, 95% CI 0.33 to 0.68; 284 participants; 3 studies; I^2 = 0%; Analysis 1.11).

Risk of random error

In Trial Sequential Analysis (Figure 4; Figure 5; Figure 6; Figure 7), we individually calculated the diversity-adjusted required information size based upon a proportion of one-year all-cause mortality rate of 50%, two-year all-cause mortality rate of 70%, three-year all-cause mortality rate of 85%, and participants without complete and partial tumour response of 50% in the TACE group; relative risk reductions (RRR) of 20%; an alpha of 2.5% (α) and a beta of 20% (β). All cumulative Z-curves crossed the monitoring boundary. In summary, the analysis suggested that we have firm evidence to support the effect of TACE followed by 3-DCRT on the primary outcomes mentioned above. Results obtained by Trial Sequential Analysis indicated that the required information size had been reached for the primary outcomes mentioned above. If the Trial Sequential Analysis was used to assess imprecision, then we would not downgrade the certainty of the evidence by one level for imprecision in GRADE (see below).

Figure 4. Trial Sequential Analysis of transcatheter arterial chemoembolisation (TACE) followed by three-dimensional conformal radiotherapy (3-DCRT) versus TACE for primary hepatocellular carcinoma with the primary outcome of one-year all-cause mortality. The blue line (Z-curve) shows the cumulative meta-analysis adding the results of individual trials based on the year of publication. The horizontal green line represents the 2.5% level of significance. The monitoring boundaries (inward sloping red lines) show the significance level after adjusting for the cumulative analysis. The vertical red line shows the required information size (the number of participants needed to determine if firm evidence was established). We conducted the Trial Sequential Analysis with the alpha set to 2.5%, power to 80%, control group event proportion to 50%, relative risk reduction to 20%, and heterogeneity correction based on model variance. The diversity-adjusted required information size was 941 participants. The cumulative Z-curve crossed the monitoring boundary before reaching the heterogeneity-adjusted information size. In total, the cumulative meta-analysis included 319 participants in the TACE followed by 3-DCRT group and 313 in the TACE alone group. The cumulative Z-curve also crossed the monitoring boundary before reaching the adjusted information size when we increased the power to 90%. DARIS: Distributed and Reflective Informatics System.

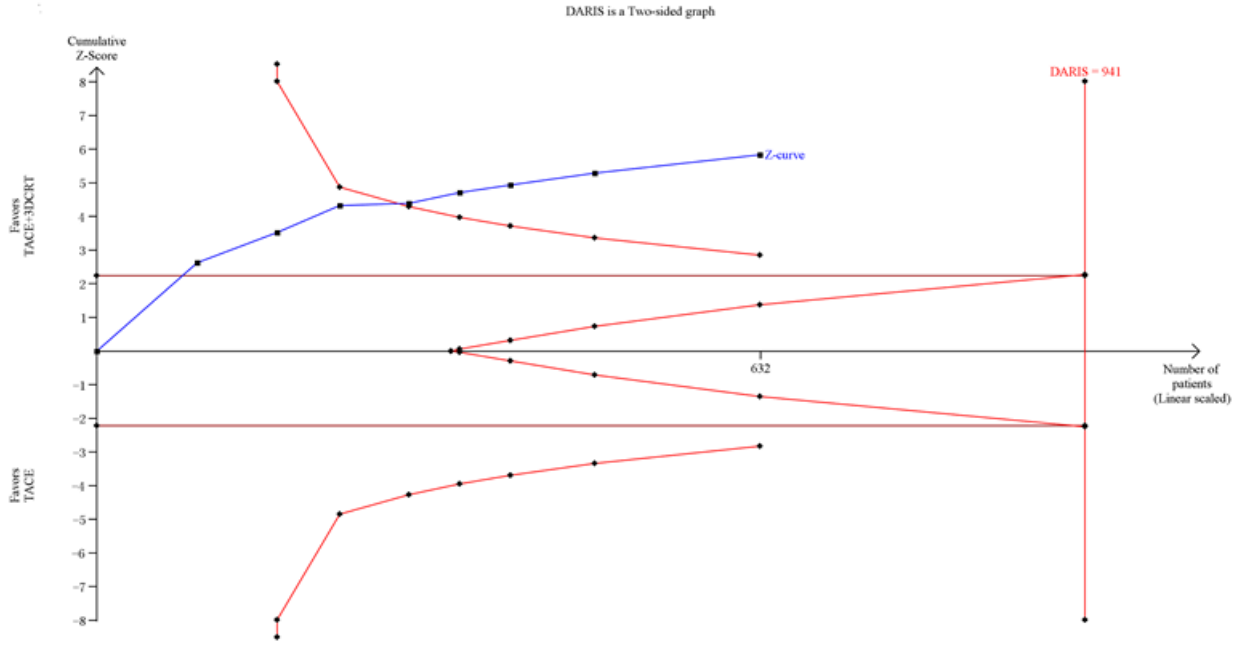


Figure 5. Trial Sequential Analysis of transcatheter arterial chemoembolisation (TACE) followed by three-dimensional conformal radiotherapy (3-DCRT) versus TACE alone for primary hepatocellular carcinoma with the primary outcome of two-year all-cause mortality. The blue line (Z-curve) shows the cumulative meta-analysis adding the results of individual trials based on the year of publication. The horizontal line represents the 2.5% level of significance. The monitoring boundaries (inward sloping red lines) show the significance level adjusting for the cumulative analysis. The vertical red line shows the required information size (the number of participants needed to determine if firm evidence was established). We conducted the Trial Sequential Analysis with the alpha set to 2.5%, power to 80%, control group event rate to 70%, relative risk reduction to 20%, and heterogeneity correction based on model variance. The diversity-adjusted required information size was 1155 participants (diversity adjusted). The cumulative Z-curve crossed the monitoring boundary before reaching the diversity-adjusted required information size. In total, the cumulative meta-analysis included 295 participants in the TACE followed by 3-DCRT group and 289 in the TACE alone group. The cumulative Z-curve also crossed the monitoring boundary before reaching the heterogeneity adjusted information size when we increased the power to 90%. DARIS: Distributed and Reflective Informatics System.

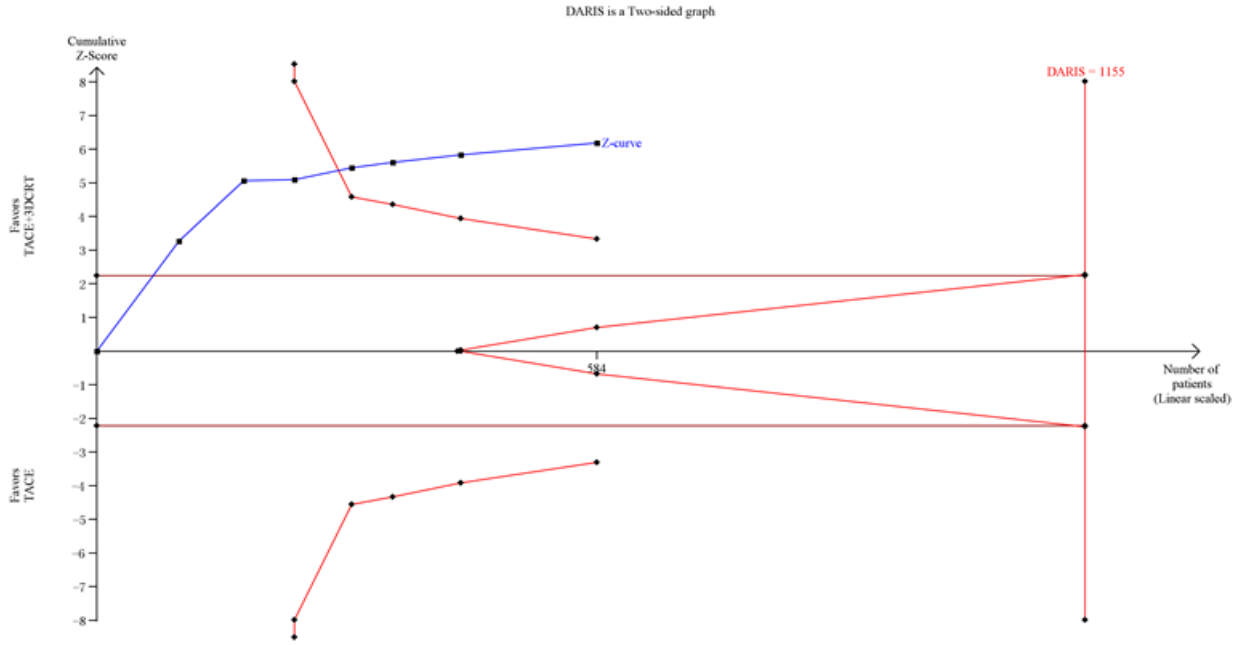


Figure 6. Trial Sequential Analysis of transcatheter arterial chemoembolisation (TACE) followed by three-dimensional conformal radiotherapy (3-DCRT)T versus TACE alone for primary hepatocellular carcinoma with the primary outcome of three-year all-cause mortality. The blue line (Z-curve) shows the cumulative meta-analysis adding the results of individual trials based on the year of publication. The horizontal green line represents the 2.5% level of significance. The monitoring boundaries (inward sloping red line) show the significance level adjusting for the cumulative analysis. The vertical red line shows the required information size (the number of participants needed to determine if firm evidence was established). We conducted the Trial Sequential Analysis with the alpha set to 5%, power to 80%, control group event rate to 85%, relative risk reduction to 20%, and heterogeneity correction based on model variance. The diversity-adjusted required information size was 237 participants. The cumulative Z-curve crossed the monitoring boundary before reaching the heterogeneity-adjusted information size. In total, the cumulative meta-analysis included 279 participants in the TACE followed by 3-DCRT group and 273 in the TACE alone group. The cumulative Z-curve also crossed the monitoring boundary before reaching the heterogeneity adjusted information size when we increased the power to 90%. DARIS: Distributed and Reflective Informatics System.

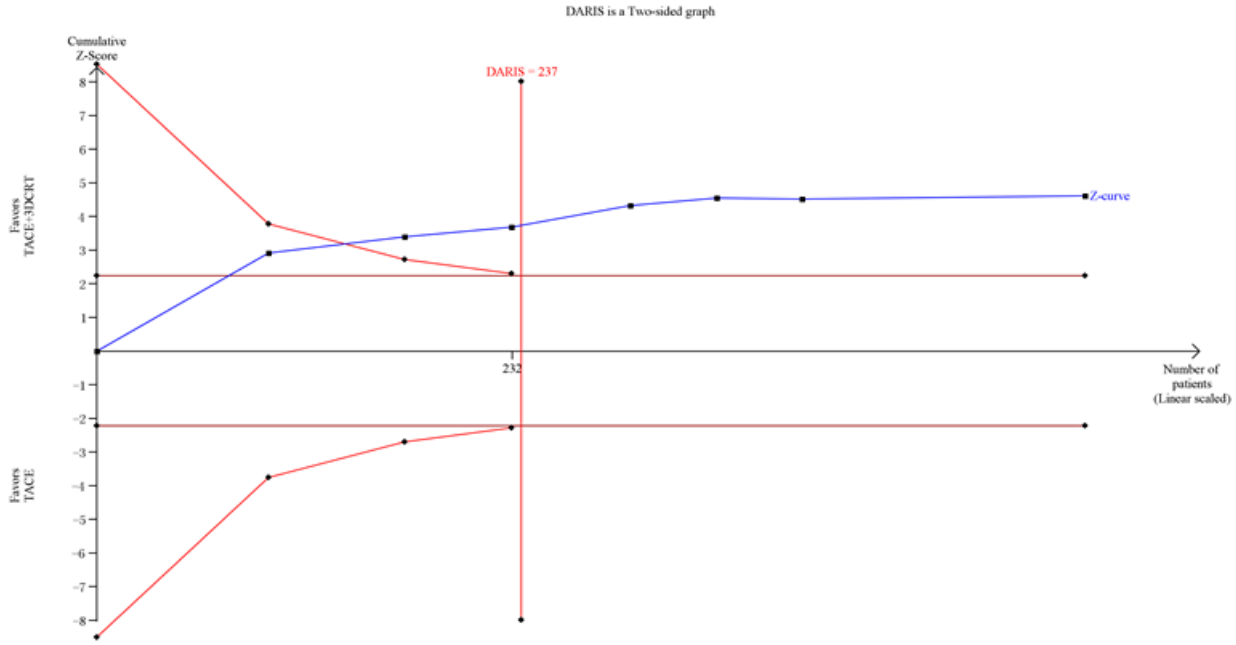
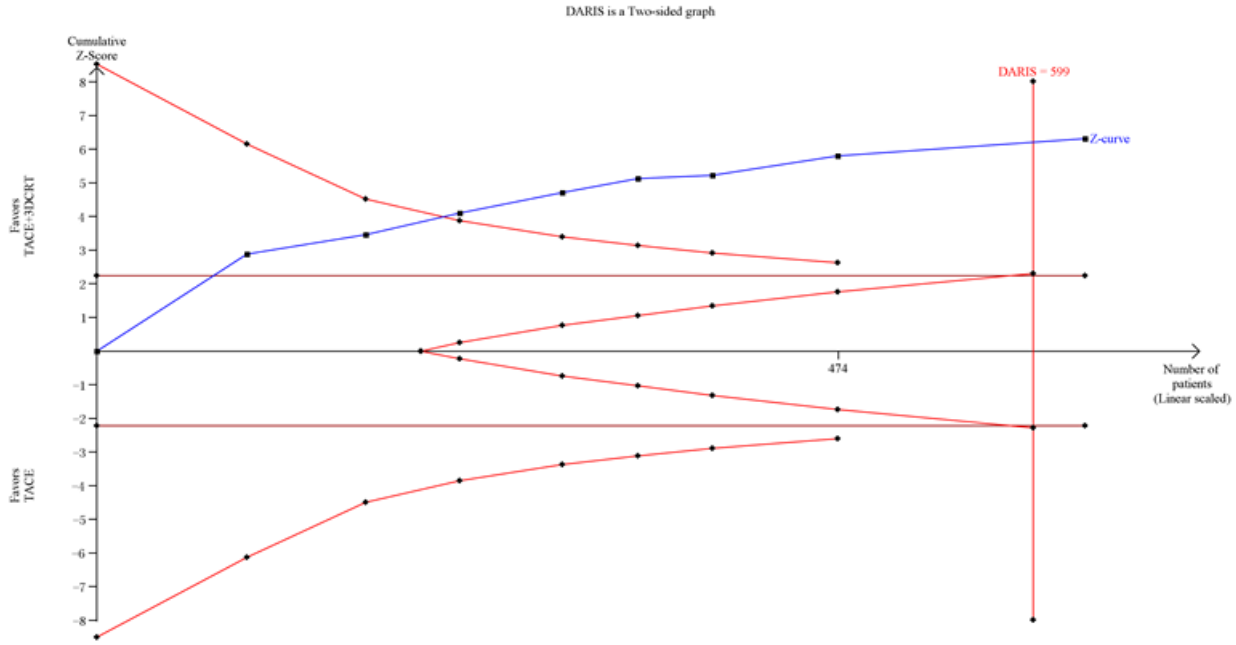


Figure 7. Trial Sequential Analysis of transcatheter arterial chemoembolisation (TACE) followed by three-dimensional conformal radiotherapy (3-DCRT) versus TACE alone for participants with primary hepatocellular carcinoma without complete or partial tumour response. The blue line (Z-curve) shows the cumulative meta-analysis adding the results of individual trials based on the year of publication. The horizontal green line represents the 2.5% level of significance. The monitoring boundary (inward sloping red line) shows the significance level after adjusting for the cumulative analysis. The vertical red line shows the required information size (the number of participants needed to determine if firm evidence was established). We conducted the Trial Sequential Analysis with the alpha set to 2.5%, power to 80%, control group event rate to 50%, relative risk reduction to 25%, and heterogeneity correction based on model variance. The estimated required information size was 599 participants (diversity adjusted). The cumulative Z-curve crossed the monitoring boundary before reaching the heterogeneity adjusted information size. In total, the cumulative meta-analysis included 319 participants in the TACE followed by 3-DCRT group and 313 in the TACE alone group. The cumulative Z-curve also crossed the monitoring boundary before reaching the heterogeneity adjusted information size when we increased the power to 90%. DARIS: Distributed and Reflective Informatics System.



GRADE assessment

Evidence as evaluated by the GRADE approach was of low certainty for the following outcomes: three-year all-cause mortality, and participants without tumour response (complete + partial). The GRADE evidence was of very-low certainty for health-related quality of life; non-serious adverse events (leukopenia, total bilirubin, and serum transaminases elevation) (Summary of findings for the main comparison).

DISCUSSION

Summary of main results

This review included eight randomised clinical trials comparing TACE followed by 3-DCRT versus TACE alone for primary hepatocellular carcinoma, with 632 participants included. Meta-analyses suggested that TACE followed by 3-DCRT compared with TACE alone seemed to have a beneficial effect on all-cause mortality and tumour response (CR+PR), without increasing most of the non-serious adverse events, but increasing the proportion of participants with elevated total bilirubin. There was no trial heterogeneity in the meta-analyses of primary outcomes. Trial Sequential Analysis showed that there was low risk of random error. The sensitivity analysis of GRADE and Trial Sequential Analysis assessments found that GRADE downgraded more often for imprecision. Our review findings should be interpreted with caution because of methodological weaknesses in the included trials, resulting in low to very low certainty of evidence.

Overall completeness and applicability of evidence

The trials included in this review compared the efficacy and safety of TACE followed by 3-DCRT versus TACE alone for people with primary hepatocellular carcinoma. The available randomised clinical trials allowed us to perform meta-analyses of our primary outcomes. The included trials addressed outcomes such as one-year all-cause mortality, two-year all-cause mortality, three-year all-cause mortality, and participants without complete and partial tumour response. There were no data for serious adverse events. Data were available for the declining rate of AFP in one trial (Zhao 2006), for thrombocytopenia in one trial (Shang 2007), for leukopenia in five trials (Zhao 2006; Shang 2007; Xiao 2008; Liao 2010; Chen 2014), for serum transaminases elevation in four trials

(Zhao 2006; Shang 2007; Xiao 2008; Liao 2010), and for total bilirubin elevation in two trials (Zhao 2006; Shang 2007). None of the trials compared different drugs in TACE, different classifications of 3-DCRT, and the aetiology of chronic liver disease for the primary outcome of all-cause mortality.

Participants in most of the trials were adults with Child-Pugh class A/B, with single tumours, and without severe complications or other concerns. Therefore, the data are most applicable to adults who have unresectable primary hepatocellular carcinoma and who are stable and well. In most trials, participants underwent two courses of TACE with a one-month interval, and 3-DCRT was delivered one week to four weeks after the last course of TACE, if liver function tests were normal. The sum of the radiation doses in 3-DCRT therapy ranged from 30 Gy to 66 Gy with 2 Gy/day to 5 Gy/day, 3 days/week to 5 days/week. The most common chemotherapies included 5-fluorouracil (750 mg to 1250 mg), cisplatin (40 mg to 120 mg), or adriamycin. Embolisation therapy included iodine oil emulsion and gelfoam.

All included trials were performed in inpatient centres in China; hepatocellular carcinoma is one of the most common cancers in China, but it is rare in North America and Europe (Lodato 2006). Although the findings in our review are likely applicable to medical practices in countries with a similar status of primary hepatocellular carcinoma, the question remains of how applicable this evidence is to medical practices in Western countries. In Western countries, chronic hepatitis C and alcoholism are the most common cause of hepatocellular carcinoma. In contrast, chronic hepatitis B is the main cause of hepatocellular carcinoma in China (Kumar 2004; Lodato 2006). Due to the data limitations, we could not perform subgroup analysis based on the aetiology of chronic liver disease. Thus, we were unable to determine the effect of TACE followed by 3-DCRT in relation to the aetiology of chronic liver disease or different countries.

Quality of the evidence

All included trials were at high risk of bias for selective reporting and blinding (performance bias and detection bias). The GRADE assessment of certainty in the evidence for the analysed outcomes was low to very low because of concerns about the methodological limitations of the included trials (see Summary of findings for the main comparison). For all outcomes, we downgraded the certainty of the evidence by two levels for risk of bias. Some outcomes were downgraded by one level for imprecision and heterogeneity. A 'low' grade means that further research is likely to have an important impact on our confidence in the estimated effect, and it is likely to change the estimate. A 'very low' grade means that we are uncertain about the estimate. We downgraded the evidence for all outcomes, as most of the included randomised clinical trials had unclear risk of concealment of allocation, non-blinded assessment of outcomes, attrition bias, or other biases (Figure 2; Figure 3). All biases mentioned above may have affected outcome estimates and confidence. We acknowledge the uncertainty in our results for outcomes mentioned above, and anticipate that future high-quality trials may change the effect estimates presented in this review.

Potential biases in the review process

We performed a comprehensive literature search to find all relevant studies following the prespecified inclusion criteria of the published protocol (Lu 2016). Two review authors rigorously scanned the reports to avoid selection bias. One issue was reporting bias due to no protocol available for included trials. Thus, the extent of reporting bias could not be assessed, but it might be an issue. The other issue was the method of handling missing data. We considered all participants with entirely missing data as treatment failures and included them in their analysis on ITT basis. However, there are multiple ways to deal with missing data, and there are potential pitfalls with most methods.

Agreements and disagreements with other studies or reviews

We found two previous published meta-analyses comparing TACE followed by 3-DCRT with TACE alone for primary hepatocellular carcinoma that included prospective cohort or case-control studies, but no randomised clinical trials (Zou 2014; Bai 2016). Below are summaries of the results of these two meta-analyses.

- Zou 2014 included 10 prospective cohort or case-control studies in a meta-analysis. It observed that TACE followed by 3-DCRT significantly improved one-year, two-year, and three-year overall survival compared with TACE alone (one-year odds ratio (OR) 1.87, 95% CI 1.37 to 2.55; two-year OR 2.38, 95% CI 1.78 to 3.17; three-year OR 2.97, 95% CI 2.10 to 4.21). In addition, TACE followed by 3-DCRT was associated with a higher tumour response (OR 3.81, 95% CI 2.70 to 5.37) and declining AFP levels (OR 3.24, 95% CI 2.09 to 5.02). There was no significant heterogeneity or publication bias observed. There were no adverse events reported in the meta-analysis.
- Bai 2016 performed a meta-analysis of 17 case-control studies. The results showed that people with hepatocellular carcinoma receiving TACE followed by 3-DCRT had significantly increased overall survival rates when compared to people receiving TACE alone (one-year survival rate OR 1.95, 95% CI 1.54 to 2.47; two-year survival rate OR 1.87, 95% CI 1.49 to 2.34; three-year survival rate OR 2.00, 95% CI 1.52 to 2.64). There was significant improvement in the tumour response rate in the TACE followed by 3-DCRT group compared with the TACE alone group (OR 2.29, 95% CI 1.70 to 3.08). There was statistically significant heterogeneity in the two-year and three-year survival rates; there was significant publication bias in the one-year and three-year survival rates, as well as in tumour response. There were neither AFP nor adverse events reported in this meta-analysis.

In agreement with the present review, there was a beneficial effect on all-cause mortality and tumour response assessment for the TACE followed by 3-DCRT group compared with the TACE alone group. We believe that our review has more reliable results than previously published meta-analyses, as they included cohort or case-control studies with more confounding factors and bias affecting the accuracy of result estimates. We only used randomised clinical trials and followed our peer-reviewed published protocol.

AUTHORS' CONCLUSIONS

Implications for practice

Transcatheter arterial chemoembolisation (TACE) followed by three-dimensional conformal radiotherapy (3-DCRT) may be associated with lower all-cause mortality and increased tumour response, despite the increased toxicity expressed by a higher rise

of total bilirubin. Our review findings should be considered with caution because of the methodological weaknesses in the included trials, resulting in low- to very low-certainty evidence. Data on serious adverse events and health-related quality of life are lacking. We are also very much uncertain in the results of the reported non-serious adverse events.

Implications for research

This review identifies the need for conducting high-quality randomised clinical trials to evaluate the efficacy of TACE followed by 3-DCRT versus TACE alone. Randomised clinical trials assessing further the role of TACE followed by 3-DCRT in people with primary hepatocellular carcinoma are needed. The trials should be performed in people from different countries, with different aetiologies of the chronic liver disease, and the clinical outcomes should be prespecified. In addition, the trials should cover different drugs for TACE, and their dosages, frequency, and range in radiation. Such trials ought to be designed according to the SPIRIT Statements and reported according to the CONSORT Statements. Such trials ought to consider to stratify the participants according to etiology of hepatocellular carcinoma and disease severity. The different classifications of 3-DCRT should also be studied.

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CHARACTERISTICS OF STUDIES

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

Chen 2014

Methods	Study design: parallel randomised clinical trial Study duration: March 2000 to March 2009 Duration of follow-up: until the last follow-up visit or death from any cause, to December 2012
Participants	Country: China Setting: inpatient, 1 centre People with liver function Child-Pugh class A; ECOG PS 0–1; no cirrhosis, jaundice, or ascites; no severe illnesses except HCC; no history of liver radiotherapy; no contraindications for chemotherapy or radiotherapy; adequate bone marrow, renal, and cardiac function; expected survival > 3 months; aged 18–70 years Number: treatment group 80; control group 78 Mean age (range): treatment group 54 (22–72) years; control group 55 (18–76) years

Chen 2014 *(Continued)*

	Sex (M/F): treatment group 58/21; control group 60/70 Tumour size: treatment group > 10 cm, 36; ≤ 10 cm, 42; control group > 10 cm, 35; ≤ 10 cm, 45 Tumour lesions (single/multiple): treatment group 52/26; control group 56/24 Stage (III/IV): treatment group 40/39; control group 42/37
Interventions	Treatment group: 2 or 3 courses of TACE; 3-DCRT delivered 2 weeks after the last course of TACE if liver function tests were normal. Radiotherapy was designed with the CMS-Xi0 radiation treatment planning system. A Varian23EX linear accelerator used to deliver 6 MV high-energy X-ray radiotherapy. The sum of the radiation doses received by each participants ranged from 50 Gy to 62 Gy (median 58 Gy) with 2–2.5 Gy/day, 5 days/week. Control group: TACE comprised of hepatic arterial infusion chemotherapy and hepatic artery embolisation. 5-fluorouracil 750–1000 mg; cisplatin 40–60 mg; farmorubicin 40–80 mg; mitomycin 6–10 mg.
Outcomes	According to RECIST, treatment efficacy divided into CR, PR, SD, and PD; CR and PR considered as objective response Serum AFP levels served as complementary information for efficacy evaluation Response rate was the sum of CR+PR • 1-, 2-, and 3-year survival rates • Toxic effects according to the US NCI-CTC (common toxicity criteria)
Notes	Source of funding: not reported How to deal with adverse reactions (e.g. leukopenia, upper gastrointestinal haemorrhage) not reported No information on compliance and ITT/PP analysis Attempted to contact first author, but no reply has been received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "we carried out this randomized controlled trial to compare the efficacy of TACE in combination with 3-DCRT vs. TACE alone in cases of locally advanced unresectable HCC." Comment: no information of random sequence generated
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported for all outcomes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported for all outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 158 participants included in main analysis of all relevant outcomes

Chen 2014 *(Continued)*

Selective reporting (reporting bias)	High risk	1 predefined outcome (serious adverse events) not reported. Protocol not available
Other bias	Low risk	Demographic and baseline characters similar in both groups

Gong 2011

Methods	Study design: parallel randomised clinical trial Study duration: August 2005 to August 2011 Duration of follow-up: 3 years
Participants	Country: China Setting: inpatient, 1 centre People with HCC; no obvious bone marrow suppression; no liver or kidney function damage Number: treatment group 24; control group 24 Median age (range): 44 (31–60) years Sex (M/F): 36/12 Median tumour size (range): 7.3 cm (3–16 cm)
Interventions	Control group: 4 courses of TACE with 1-month interval. TACE comprised of hepatic arterial infusion chemotherapy and hepatic artery embolisation, cisplatin, fluorouracil, and iodine oil emulsion Treatment group: 2 courses of TACE with 1-month interval; 3-DCRT delivered 2 weeks after the last course of TACE, if liver function tests were normal. Radiotherapy: sum of radiation doses received by each participant was 40–60 Gy with 2–5 Gy/dose, 1 dose/day, 3–5 sessions/week
Outcomes	According to RECIST, treatment efficacy divided into CR, PR, SD, and PD; CR and PR considered objective response Response rate was the sum of CR+PR • 1-, 2-, and 3-year survival rates • Toxic effects
Notes	Source of funding: not reported Attempted to contact first author, without success

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned to a treatment group and to a control group." Comment: random allocation method not mentioned
Allocation concealment (selection bias)	Unclear risk	Not reported

Gong 2011 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported for all outcomes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported for all outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	1 predefined outcome (serious adverse events) not reported. Protocol not available
Other bias	Unclear risk	Demographic and baseline characteristics not presented per group.

Liao 2010

Methods	Study design: parallel randomised clinical trial Study duration: November 2005 to November 2007 Duration of follow-up: date of TACE therapy until the last follow-up visit (or death) up to November 2009 (median 12 months; range 2–38 months)
Participants	Country: China Setting: inpatient, 1 centre People with liver function Child-Pugh class A or B; ECOG PS 0–2; no distant metastasis; no obvious myelosuppression or renal damage Number: treatment group 24; control group 24 Mean age: treatment group 62 years; control group 63 years Sex (M/F): treatment group 15/9; control group 14/10 Tumour size: treatment group 3.5–11 cm; control group 3.8–11.5 cm Child-Pugh class (A/B): treatment group 17/7; control group 17/7 Stage (III/IV): treatment group 18/6; control group 16/8
Interventions	Control group: 3–5 courses of TACE with 1-month interval. TACE comprised hepatic arterial infusion chemotherapy and hepatic artery embolisation. 5-fluorouracil 1000–1250 mg; cisplatin 70–90 mg; adriamycin 50–60 mg; peripheral embolisation with iodine oil emulsion and central embolisation with gelfoam Treatment group: 3–5 courses of TACE with 1-month interval; 3-DCRT delivered 1–2 weeks after the last course of TACE if liver function tests were normal. Radiotherapy: Varian23EX linear accelerator used to deliver 6 MV high-energy X-ray radiotherapy. Sum of radiation doses received by each participants ranged from 40 Gy to 66 Gy (median 55 Gy) with 2–2.5 Gy/day, radiation administered in 20–33 sessions
Outcomes	According to RECIST, treatment efficacy divided into CR, PR, SD, and PD Response rate was the sum of CR+PR

Liao 2010 *(Continued)*

- 1- and 3-year survival rates
- Toxic effects
- Death rate and cause

Notes	Source of funding: Project of Quzhou Science and Technology Bureau No information on the compliance and ITT/PP analysis Attempted to contact the first author, without success

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization was performed by drawing lots."
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported for all outcomes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported for all outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	There were postrandomisation dropouts and all relevant outcomes were reported for only 45 participants (i.e. 23 in treatment and 22 in control group).
Selective reporting (reporting bias)	High risk	1 predefined outcome (serious adverse events) not reported. Protocol not available
Other bias	Low risk	No other potential source of bias identified, baseline characteristics comparable

Ning 2009

Methods	Study design: parallel randomised clinical trial Study duration: March 2002 to March 2005 Duration of follow-up: not reported
Participants	Country: China Setting: inpatient, 1 centre People with HCC; Karnofsky score ≥ 70; no cirrhosis, jaundice, or ascites; no severe illnesses except HCC; no history of liver radiotherapy; no contraindications for chemotherapy or radiotherapy; adequate bone marrow, renal, and cardiac function; expected survival > 3 months Number: treatment group 34; control group 32 Mean age (range): 56.5 (37–72) years

Ning 2009 *(Continued)*

	Sex (M/F): 46/20
Interventions	Control group: 4 courses of TACE with 1-month interval. TACE comprised hepatic arterial infusion chemotherapy and hepatic artery embolisation. 5-fluorouracil 1000–1250 mg; hydroxyl radical 20 mg; cisplatin 60 mg; mitomycin 14 mg; peripheral embolisation with 10 mL iodine oil emulsion and central embolisation with 1–2 mm gelfoam Treatment group: 2 courses of TACE with 1-month interval; 3-DCRT delivered 4 weeks after the last course of TACE if liver function tests were normal. Radiotherapy: a precise linear accelerator used to deliver 6 MV high-energy X-ray radiotherapy. The sum of the radiation doses received by each participant ranged from 45 Gy to 55 Gy with 2–5 Gy/day
Outcomes	According to RECIST, treatment efficacy divided into CR, PR, SD, and PD Response rate was the sum of CR+PR AFP • 1- and 3-year survival rates • Quality of life • Toxic effects
Notes	Source of funding: not reported Baseline characteristics comparison not presented Attempted to contact first author, without success

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned to a treatment group and to a control group." Comment: random allocation method not mentioned
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported for all outcomes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported for all outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 66 participants included in main analysis of all relevant outcomes
Selective reporting (reporting bias)	High risk	1 predefined outcome (serious adverse events) not reported. Protocol not available
Other bias	Unclear risk	Demographic and baseline characters not presented in either group

Shang 2007

Methods	Study design: parallel randomised clinical trial Study duration: May 2003 to March 2007 Duration of follow-up: > 6 months
Participants	Country: China Setting: inpatient, 1 centre People with HCC liver function Child-Pugh class A or B; tumour size < 6 cm; liver and kidney function normal; no portal vein tumour thrombus; no intratumour dissemination or distant metastasis; no ascites; expected survival > 3 months Number: treatment group 40; control group 36 Median age (range): treatment group 52 (36–68) years; control group 54 (38–70) years Sex (M/F): treatment group 24/16; control group 24/12 Tumour size: treatment group < 3 cm, 26, 3–6 cm, 14; control group < 3 cm, 20; 3–6 cm, 16 Mean AFP: treatment group 834 µg/L; control group 630 µg/L HBV (+/–): treatment group 32/8; control group 30/6 Stage (I/II): treatment group 28/12; control group 22/14
Interventions	Control group: 3 courses of TACE with 1-month interval. TACE comprised hepatic arterial infusion chemotherapy and hepatic artery embolisation. 5-fluorouracil 1000 mg; cisplatin 40–60 mg; adriamycin 60 mg, or mitomycin C 10–20 mg; peripheral embolisation with iodine oil emulsion 5–20 mL and central embolisation with gelfoam Treatment group: 2 courses of TACE with 1-month interval; 3-DCRT delivered 3 weeks after the last course of TACE if liver function tests were normal. Radiotherapy: the sum of the radiation doses received by each participant was ≤ 30 Gy with 2 Gy/day, 1 session/day, 5 days/week, total course: 4–6 weeks
Outcomes	According to RECIST, treatment efficacy divided into CR, PR, SD, and PD Response rate was the sum of CR+PR • 1-, 2-, and 3-year survival rates • Toxic effects
Notes	Source of funding: not reported No information on the compliance and ITT/PP analysis Attempted to contact the first author, without success

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned to a treatment group and to a control group." Comment: random allocation method not mentioned
Allocation concealment (selection bias)	Unclear risk	Not reported

Shang 2007 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported for all outcomes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported for all outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information on whether the analysis included lost data
Selective reporting (reporting bias)	High risk	1 predefined outcome (serious adverse events) not reported. Protocol not available
Other bias	Low risk	Demographic and baseline characters similar in both groups

Xiao 2008

Methods	Study design: parallel randomised clinical trial Study duration: January 2002 to June 2006 Duration of follow-up: > 6 months
Participants	Country: China Setting: inpatient, 1 centre People with I–IIIa stage of primary liver cancer without celiac lymph nodes or distant metastasis; with liver function Child-Pugh class A or B; Karnofsky score ≥ 70; WBC ≥ 3.0×10^9/L, PLT ≥ 5.0×10^{12}/L; imaging examination can confirm pathological lesions and surgical resection could not be performed Number: treatment group 30; control group 30 Mean age (range): treatment group (16–75 years); control group (17–78 years) Sex (M/F): treatment group 22/8; control group 23/7 Tumour size: treatment group 2.8–14.5 cm; control group 2.5–16 cm Child-Pugh class (A/B): treatment group 19/11; control group 20/10 Stage (I/II/III): treatment group 10/12/8; control group 12/13/5
Interventions	Control group: 2 courses of TACE with 1-month interval. TACE comprised hepatic arterial infusion chemotherapy and hepatic artery embolisation. 5-fluorouracil 1000–1250 mg; cisplatin 100 mg; adriamycin 50–100 mg; peripheral embolisation with iodine oil emulsion 10–30 mL and central embolisation with gelfoam 1–2 mm. Treatment group: 2 courses of TACE with 1-month interval; 3-DCRT delivered 1–3 weeks after the last course of TACE if liver function tests were normal. Radiotherapy: Varian23EX linear accelerator used to deliver 6 MV high-energy X-ray radiotherapy. The sum of the radiation doses received by each participant was 55 Gy, 5 Gy/session, 5 sessions/week
Outcomes	According to RECIST, treatment efficacy divided into CR, PR, SD, and PD Response rate was the sum of CR+PR

Xiao 2008 *(Continued)*

- 1-, 2-, and 3-year survival rates
- Toxic effects

Notes	Source of funding: not reported How to deal with several adverse reactions (e.g. fever, abdominal pain) not mentioned No information on compliance and ITT/PP analysis Attempted to contact the first author, without success

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to a treatment group and to a control group by random number table."
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported for all outcomes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported for all outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 60 participants included in main analysis of all relevant outcomes
Selective reporting (reporting bias)	High risk	1 predefined outcome (serious adverse events) not reported. Protocol not available
Other bias	Low risk	Demographic and baseline characters similar in both groups

Xiao 2011

Methods	Study design: parallel randomised clinical trial Study duration: January 2008 to December 2010 Duration of follow-up (mean): 2 years
Participants	Country: China Setting: inpatient, 1 centre People with primary liver cancer; normal blood examinations; renal and cardiac function; no portal vein tumour thrombus; no intratumour dissemination or distant metastasis; no ascites; expected survival > 3 months Number: treatment group 40; control group 40 Median age (range): treatment group 40 (20–72) years; control group 39 (25–63) years

Xiao 2011 *(Continued)*

	Sex (M/F): treatment group 29/11; control group 28/12 Tumour size: treatment group ≤ 5 cm, 25; > 5 cm, 15; control group ≤ 5 cm, 23; > 5 cm, 17 Mean AFP: treatment group ≤ 400 µg/L, 22; > 400 µg/L, 18; control group ≤ 400 µg/L, 25; > 400 µg/L, 15 Tumour number (single/multiple): treatment group 31/9; control group 29/11 Stage (III/IV): treatment group 34/6; control group 35/5
Interventions	Control group: 1 or 2 courses of TACE with 1-month interval. TACE comprised hepatic arterial infusion chemotherapy and hepatic artery embolisation. Cisplatin 60–120 mg; adriamycin 30–100 mg; peripheral embolisation with iodine oil emulsion 10–30 mL, and central embolisation with gelfoam Treatment group: TACE with 3-DCRT. 3-DCRT delivered by 6 MV high-energy X-ray radiotherapy. The sum of the radiation doses received by each participant ranged from 50 Gy to 60 Gy, 2 Gy/day, 5 days/week
Outcomes	According to RECIST, treatment efficacy divided into CR, PR, SD, and PD Response rate was the sum of CR+PR • 0.5-, 1-, and 3-year survival rates • Toxic effects
Notes	Source of funding: not reported Cases of "lost to follow-up" reported, but no information on ITT/PP analysis mentioned Attempted to contact the first author, without success

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization was performed by random number table."
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported for all outcomes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported for all outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information on whether the analysis included lost data
Selective reporting (reporting bias)	High risk	1 predefined outcome (serious adverse events) not reported. Protocol not available
Other bias	Low risk	Demographic and baseline characters similar in both groups

Zhao 2006

Methods	Study design: parallel randomised clinical trial Study duration: January 1998 to April 2000 Duration of follow-up: > 6 months
Participants	Country: China Setting: inpatient, 1 centre People with primary liver cancer; Karnofsky score ≥ 70; normal liver function; tumour size < 6 cm; no portal vein tumour thrombus; no intratumour dissemination or distant metastasis; no ascites Number: treatment group 49; control group 47 Median age (range): treatment group 53 (32–70) years; control group 52 (36–69) years Sex (M/F): treatment group 32/17; control group 28/19 Tumour size: treatment group < 3 cm, 28; 3–6 cm, 21; control group < 3 cm, 25; 3–6 cm, 22 AFP ≥ 400 ng/mL: treatment group 42; control group 42 Stage (I/II): treatment group 36/13; control group 31/16
Interventions	Control group: 4 courses of TACE with 1-month interval. TACE comprised hepatic arterial infusion chemotherapy and hepatic artery embolisation. 5-fluorouracil 750 mg; hydroxyl radical 15 mg; cisplatin 40 mg Treatment group: 2 courses of TACE; 3-DCRT delivered 3 weeks after the last course of TACE. Radiotherapy: Varian23EX linear accelerator used to deliver 3-DCRT. The sum of the radiation doses received by each participant was 45–55 Gy, 4–5 Gy/session, every other day
Outcomes	According to RECIST, treatment efficacy divided into CR, PR, SD, and PD; CR and PR considered as objective response Response rate was the sum of CR+PR • Serum AFP • 1-, 2-, and 3-year survival rates • Toxic effects
Notes	Source of funding: not reported Cases of "lost to follow-up" reported, but no information on ITT/PP analysis mentioned Attempted to contact the first author, without success

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned to a treatment group and to a control group." Comment: random allocation method not mentioned
Allocation concealment (selection bias)	Unclear risk	Not reported

Zhao 2006 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported for all outcomes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported for all outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information on the distribution of lost data or whether the analysis included the lost data
Selective reporting (reporting bias)	High risk	1 predefined outcome (serious adverse events) not reported. Protocol not available
Other bias	Low risk	Demographic and baseline characters similar in both groups

3-DCRT: three-dimensional conformal radiotherapy; AFP: alpha fetoprotein; CR: complete response; ECOG PS: Eastern Cooperative Oncology Group performance status; F: female; HCC: hepatocellular carcinoma; ITT: intention to treat; M: male; NCI-CTC: National Cancer Institute Common Toxicity Criteria (now known as Common Terminology Criteria for Adverse Events (CTCAE)); PD: progressive disease; PLT: platelets; PP: per protocol; PR: partial response; RECIST: response evaluation criteria of solid tumours; SD: stable disease; TACE: transcatheter arterial chemoembolisation; WBC: white blood cell count.

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

Study	Reason for exclusion
Chia-Hsien 2001	Not a randomised clinical trial and the control group was not 3-DCRT.
Chung 2006	Not a randomised clinical trial
Guo 2005	Not a randomised clinical trial, but a retrospective study
Koo 2010	Not a randomised clinical trial
Liang 2005	Not a randomised clinical trial, but a retrospective study
Lu 2015	Not a randomised clinical trial, but a retrospective study
Shim 2005	Not a randomised clinical trial, but a retrospective study
You 2007	Not a randomised clinical trial, but a retrospective study
Zeng 2004	Not a randomised clinical trial, but a retrospective study
Zhang 2009	Not a randomised clinical trial, but a retrospective study

3-DCRT: three-dimensional conformal radiotherapy.

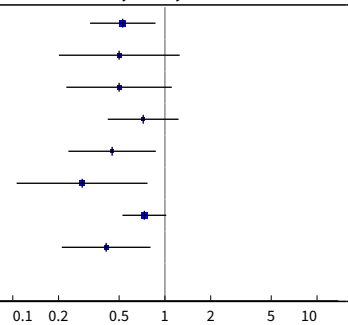
DATA AND ANALYSES

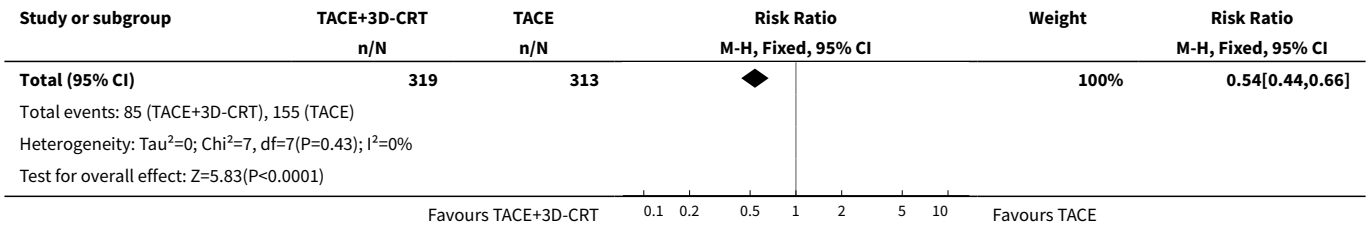
Comparison 1. Transcatheter arterial chemoembolisation (TACE) followed by three-dimensional conformal radiotherapy (3-DCRT) versus TACE alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality: at 1 year	8	632	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.44, 0.66]
2 All-cause mortality: at 2 years	7	584	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.60, 0.78]
3 All-cause mortality: at 3 years	7	552	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.73, 0.88]
4 Proportion of participants without complete and partial tumour response	8	632	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.39, 0.61]
5 Proportion of participants with leukopenia	5	438	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.92, 1.34]
6 Proportion of participants with serum transaminases elevation	4	280	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.66, 4.27]
7 Proportion of participants with total bilirubin elevation	2	172	Risk Ratio (M-H, Fixed, 95% CI)	2.69 [1.34, 5.40]
8 All-cause mortality: at 1 year (sensitivity analysis)	3	284	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.37, 0.74]
9 All-cause mortality: at 2 years (sensitivity analysis)	3	284	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.58, 0.88]
10 All-cause mortality: at 3 years (sensitivity analysis)	3	284	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.74, 0.94]
11 Proportion of participants without complete and partial tumour response (sensitivity analysis)	3	284	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.33, 0.68]

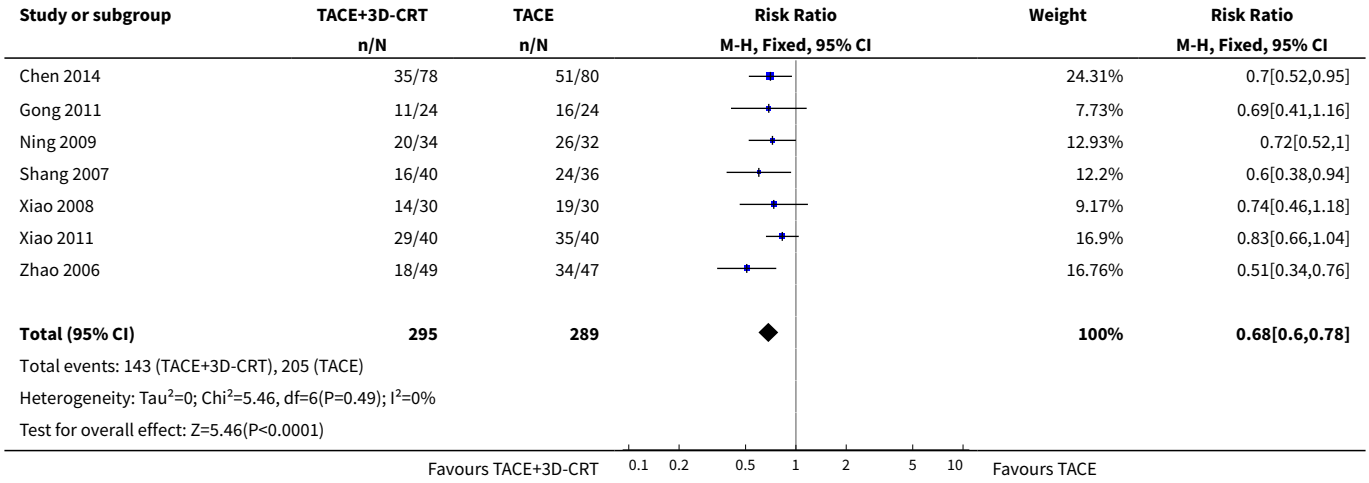
Analysis 1.1. Comparison 1 Transcatheter arterial chemoembolisation (TACE) followed by three-dimensional conformal radiotherapy (3-DCRT) versus TACE alone, Outcome 1 All-cause mortality: at 1 year.

Study or subgroup	TACE+3D-CRT n/N	TACE n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Chen 2014	17/78	33/80		20.82%	0.53[0.32,0.87]
Gong 2011	5/24	10/24		6.39%	0.5[0.2,1.25]
Liao 2010	6/24	12/24		7.67%	0.5[0.22,1.11]
Ning 2009	13/34	17/32		11.19%	0.72[0.42,1.23]
Shang 2007	9/40	18/36		12.11%	0.45[0.23,0.87]
Xiao 2008	4/30	14/30		8.95%	0.29[0.11,0.77]
Xiao 2011	22/40	30/40		19.17%	0.73[0.53,1.02]
Zhao 2006	9/49	21/47		13.7%	0.41[0.21,0.8]

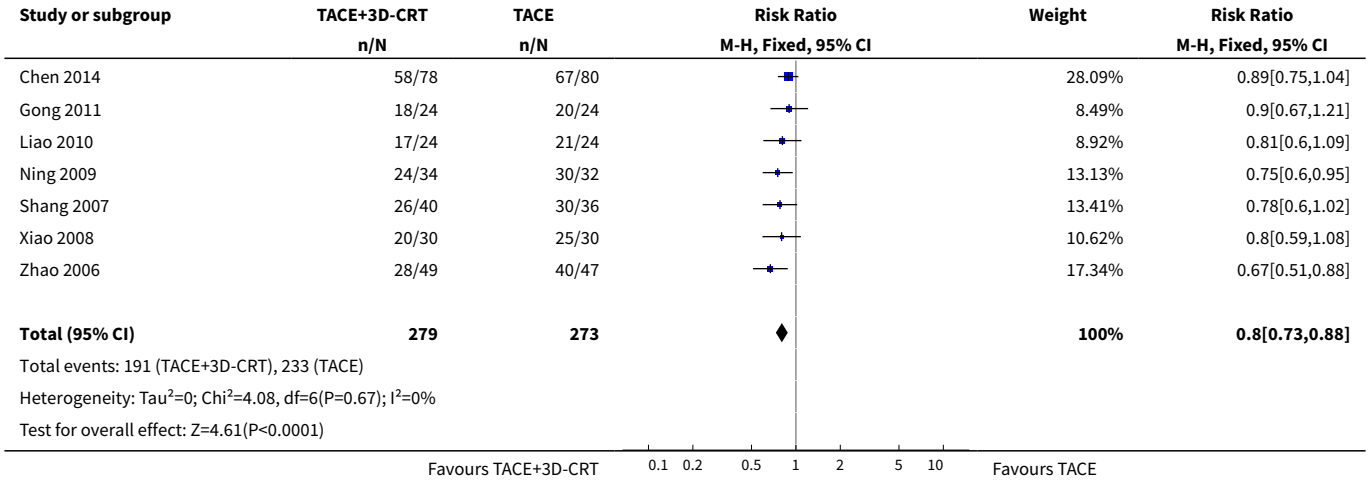




Analysis 1.2. Comparison 1 Transcatheter arterial chemoembolisation (TACE) followed by three-dimensional conformal radiotherapy (3-DCRT) versus TACE alone, Outcome 2 All-cause mortality: at 2 years.

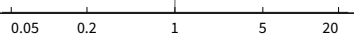


Analysis 1.3. Comparison 1 Transcatheter arterial chemoembolisation (TACE) followed by three-dimensional conformal radiotherapy (3-DCRT) versus TACE alone, Outcome 3 All-cause mortality: at 3 years.



Analysis 1.4. Comparison 1 Transcatheter arterial chemoembolisation (TACE) followed by three-dimensional conformal radiotherapy (3-DCRT) versus TACE alone, Outcome 4 Proportion of participants without complete and partial tumour response.

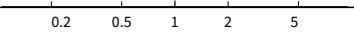
Study or subgroup	TACE+3D-CRT n/N	TACE n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Chen 2014	20/78	37/80		23.34%	0.55[0.36,0.87]
Gong 2011	7/24	11/24		7.03%	0.64[0.3,1.36]
Liao 2010	5/24	12/24		7.67%	0.42[0.17,1]
Ning 2009	8/34	17/32		11.19%	0.44[0.22,0.88]
Shang 2007	10/40	17/36		11.43%	0.53[0.28,1]
Xiao 2008	3/30	11/30		7.03%	0.27[0.08,0.88]
Xiao 2011	10/40	22/40		14.06%	0.45[0.25,0.83]
Zhao 2006	14/49	28/47		18.26%	0.48[0.29,0.79]
Total (95% CI)	**319**	**313**		**100%**	**0.49[0.39,0.61]**
Total events: 77 (TACE+3D-CRT), 155 (TACE)					
Heterogeneity: Tau^2=0; Chi^2=2.06, df=7(P=0.96); I^2=0%					
Test for overall effect: Z=6.32(P<0.0001)					



Favours TACE+3D-CRT Favours TACE

Analysis 1.5. Comparison 1 Transcatheter arterial chemoembolisation (TACE) followed by three-dimensional conformal radiotherapy (3-DCRT) versus TACE alone, Outcome 5 Proportion of participants with leukopenia.

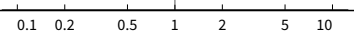
Study or subgroup	TACE+3D-CRT n/N	TACE n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Chen 2014	11/78	4/80		2.7%	2.82[0.94,8.48]
Liao 2010	9/24	7/24		4.72%	1.29[0.57,2.89]
Shang 2007	37/40	32/36		32.39%	1.04[0.9,1.2]
Xiao 2008	30/30	29/30		36.73%	1.03[0.94,1.13]
Zhao 2006	39/49	31/47		23.46%	1.21[0.94,1.55]
Total (95% CI)	**221**	**217**		**100%**	**1.12[0.92,1.34]**
Total events: 126 (TACE+3D-CRT), 103 (TACE)					
Heterogeneity: Tau^2=0.02; Chi^2=12.25, df=4(P=0.02); I^2=67.35%					
Test for overall effect: Z=1.14(P=0.25)					



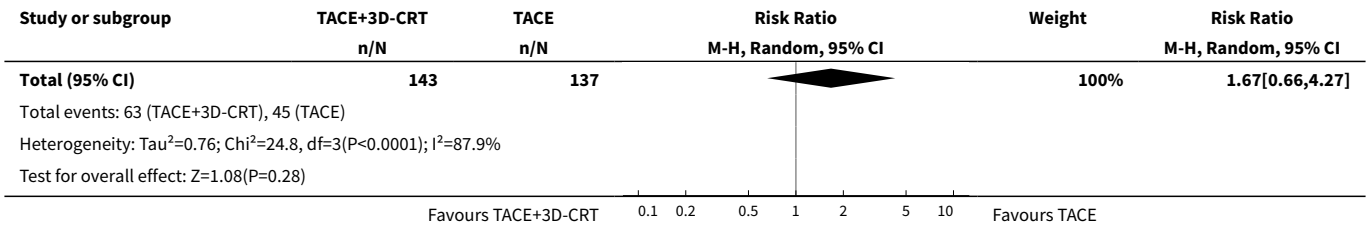
Favours TACE+3D-CRT Favours TACE

Analysis 1.6. Comparison 1 Transcatheter arterial chemoembolisation (TACE) followed by three-dimensional conformal radiotherapy (3-DCRT) versus TACE alone, Outcome 6 Proportion of participants with serum transaminases elevation.

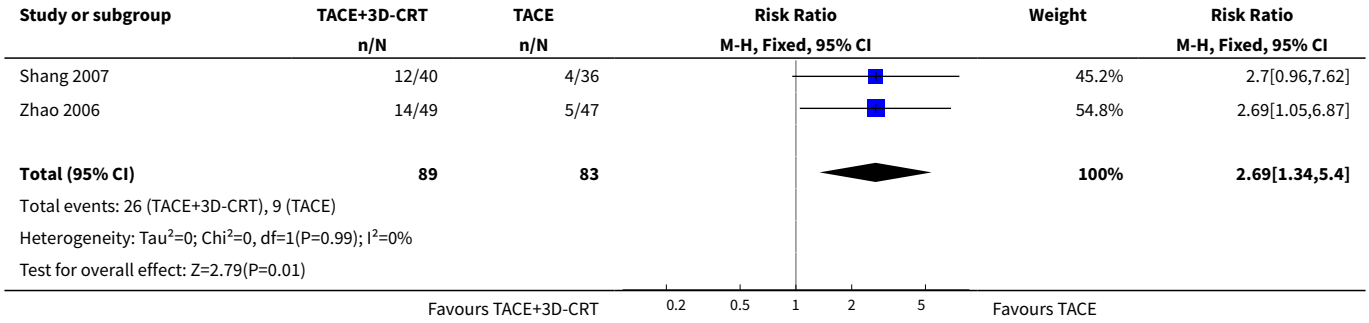
Study or subgroup	TACE+3D-CRT n/N	TACE n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Liao 2010	11/24	9/24		26.08%	1.22[0.62,2.4]
Shang 2007	12/40	4/36		22.01%	2.7[0.96,7.62]
Xiao 2008	26/30	28/30		29.88%	0.93[0.78,1.1]
Zhao 2006	14/49	4/47		22.03%	3.36[1.19,9.47]



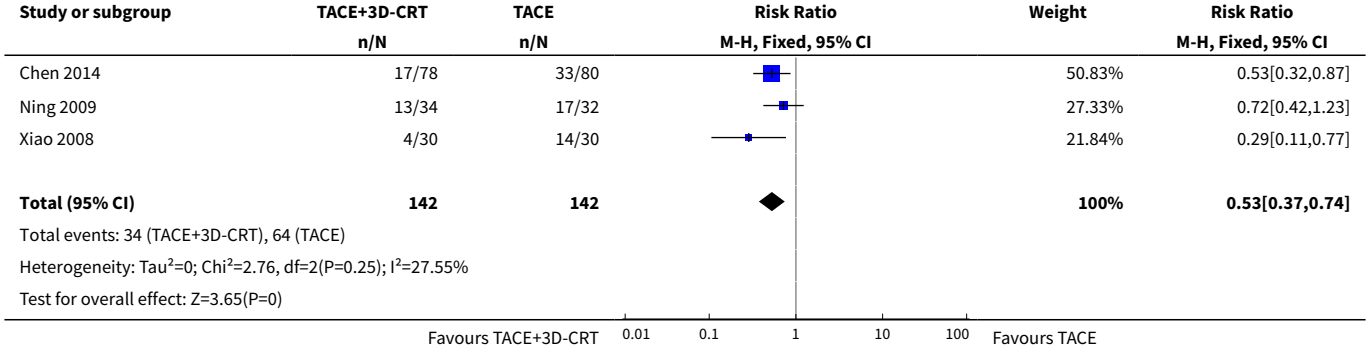
Favours TACE+3D-CRT Favours TACE



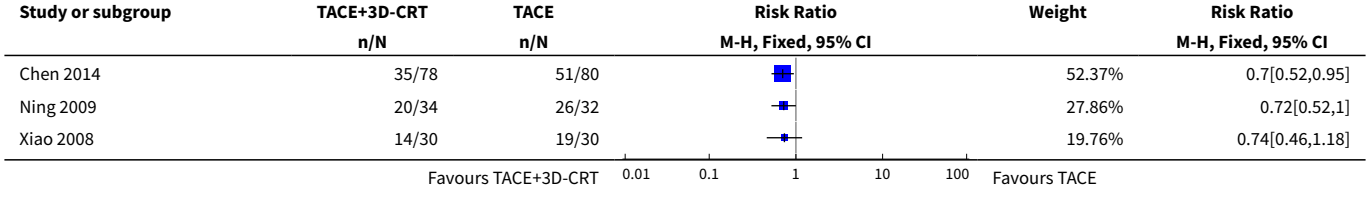
Analysis 1.7. Comparison 1 Transcatheter arterial chemoembolisation (TACE) followed by three-dimensional conformal radiotherapy (3-DCRT) versus TACE alone, Outcome 7 Proportion of participants with total bilirubin elevation.

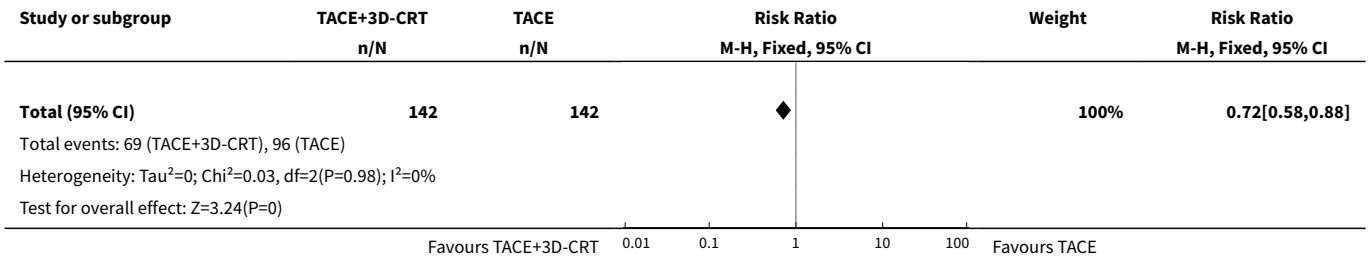


Analysis 1.8. Comparison 1 Transcatheter arterial chemoembolisation (TACE) followed by three-dimensional conformal radiotherapy (3-DCRT) versus TACE alone, Outcome 8 All-cause mortality: at 1 year (sensitivity analysis).

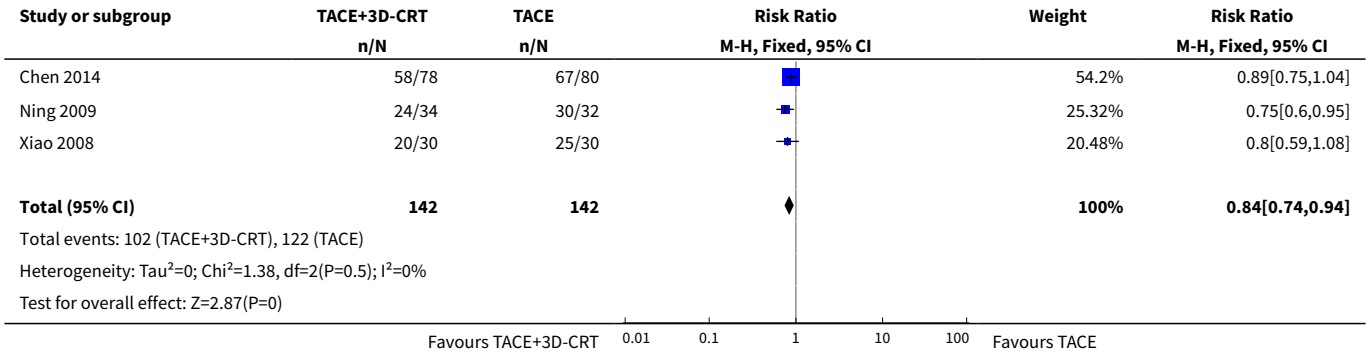


Analysis 1.9. Comparison 1 Transcatheter arterial chemoembolisation (TACE) followed by three-dimensional conformal radiotherapy (3-DCRT) versus TACE alone, Outcome 9 All-cause mortality: at 2 years (sensitivity analysis).

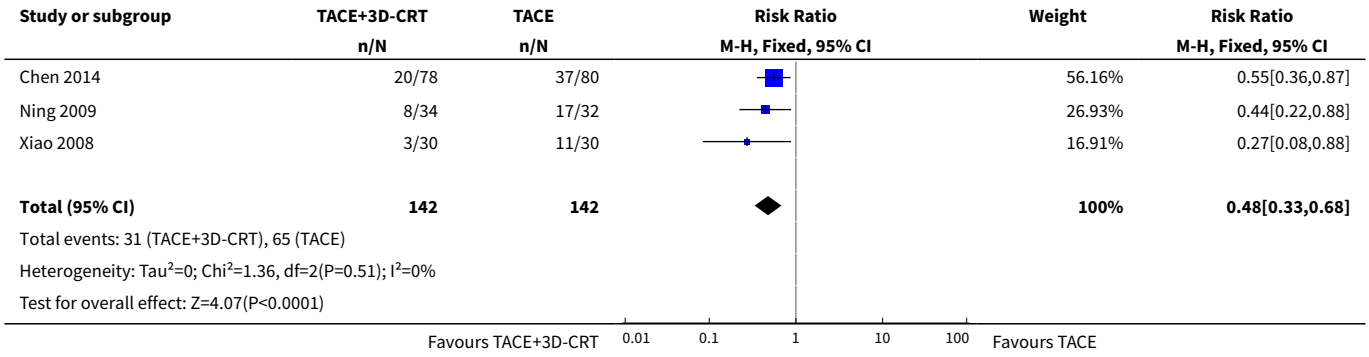




Analysis 1.10. Comparison 1 Transcatheter arterial chemoembolisation (TACE) followed by three-dimensional conformal radiotherapy (3-DCRT) versus TACE alone, Outcome 10 All-cause mortality: at 3 years (sensitivity analysis).



Analysis 1.11. Comparison 1 Transcatheter arterial chemoembolisation (TACE) followed by three-dimensional conformal radiotherapy (3-DCRT) versus TACE alone, Outcome 11 Proportion of participants without complete and partial tumour response (sensitivity analysis).



ADDITIONAL TABLES

Table 1. Non-serious adverse events

Outcomes/ studies	TACE followed by 3-DCTRT						TACE						Both groups
	0	I	II	III	IV	N1	0	I	II	III	IV	N2	Total
Leukopenia													
Chen 2014	—	—	—	3		11	—	—	—	2		4	15
Liao 2010	—	—	9	—	—	9	—	—	7	—	—	7	16
Shang 2007	—	36		1	—	37	—	30		2	—	32	69
Xiao 2008	0	4	17	8	1	30	1	5	15	7	2	30	60
Zhao 2006	—	39		—	—	39	—	31		—	—	31	70
Serum transaminases elevation													
Chen 2014	—	—	—	—	—	—	—	—	—	—	—	—	9
Liao 2010	—	—	11			11	—	—	9			9	20
Ning 2009	—	—	—	—	—	—	—	—	—	—	—	—	16
Shang 2007	—	10		2	—	12	—	3		1	—	4	16
Xiao 2008	4	12	5	6	3	30	2	17	9	2	0	30	60
Zhao 2006	—	12		2	—	14	—	4		0	—	4	18
Nausea and vomiting													
Xiao 2008	0	6	6	18	0	30	0	7	7	16	0	30	60
Total bilirubin elevation													
Shang 2007	—	—	—	—	—	12	—	—	—	—	—	4	16
Zhao 2006	—	—	—	—	—	14	—	—	—	—	—	5	19

Table 1. Non-serious adverse events *(Continued)*

Radiation hepatitis													
Gong 2011	—	—	—	—	—	3	—	—	—	—	—	—	3
Liao 2010	—	—	—	—	—	1	—	—	—	—	—	—	1
Fever													
Chen 2014	—	—	—	—	—	15	—	—	—	—	—	15	30
Thrombocytopenia													
Shang 2007	—	4		2	—	6	—	6		3	—	9	15

'0 to IV' indicated different degrees of severity for adverse effects; 'N1' indicated the number of participants in the transcatheter arterial chemoembolisation (TACE) followed by three-dimensional conformal radiotherapy (3-DCRT) group, 'N2' indicated the TACE alone group, and 'Total' indicated both groups.

APPENDICES

Appendix 1. Search strategies

Database	Period of search	Search strategy
The Cochrane Hepato-Biliary Group Controlled Trials Register	May 2018	(conformal radiotherap* or 3DCRT or 3D-CRT) AND (((transarterial or transcatheter or therapeutic or artificial) and (chemoemboli* or emboli*)) or TACE or TAE) AND (((liver or hepatic or hepatocellular or hepato-cellular) and (carcinom* or cancer* or neoplasm* or malign* or tumo*)) or HCC)
Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	May 2018	#1 MeSH descriptor: [Radiotherapy, Conformal] explode all trees #2 conformal radiotherap* or 3DCRT or 3D-CRT #3 #1 or #2 #4 MeSH descriptor: [Embolization, Therapeutic] explode all trees #5 ((transarterial or transcatheter or therapeutic or artificial) and (chemoemboli* or emboli*)) or TACE or TAE #6 #4 or #5 #7 MeSH descriptor: [Carcinoma, Hepatocellular] explode all trees #8 MeSH descriptor: [Liver Neoplasms] explode all trees #9 ((liver or hepatic or hepatocellular or hepato-cellular) and (carcinom* or cancer* or neoplasm* or malign* or tumo*)) or HCC #10 #7 or #8 or #9 #11 #3 and #6 and #10
MEDLINE Ovid	1946 to May 2018	1. exp Radiotherapy, Conformal/ 2. (conformal radiotherap* or 3DCRT or 3D-CRT).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. 1 or 2 4. exp Embolization, Therapeutic/ 5. (((transarterial or transcatheter or therapeutic or artificial) and (chemoemboli* or emboli*)) or TACE or TAE).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 6. 4 or 5 7. exp Carcinoma, Hepatocellular/ 8. exp Liver Neoplasms/ 9. (((liver or hepatic or hepatocellular or hepato-cellular) and (carcinom* or cancer* or neoplasm* or malign* or tumo*)) or HCC).mp. [mp=title, abstract,

(Continued)

		original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 10. 7 or 8 or 9 11. 3 and 6 and 10
Embase Ovid	1980 to May 2018	1. exp computer assisted radiotherapy/ 2. (conformal radiotherap* or 3DCRT or 3D-CRT).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 3. 1 or 2 4. exp artificial embolism/ 5. (((transarterial or transcatheter or therapeutic or artificial) and (chemoemboli* or emboli*)) or TACE or TAE).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 6. 4 or 5 7. exp liver cell carcinoma/ 8. exp liver tumor/ 9. (((liver or hepatic or hepatocellular or hepato-cellular) and (carcinom* or cancer* or neoplasm* or malign* or tumo*)) or HCC).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 10. 7 or 8 or 9 11. 3 and 6 and 10
LILACS (Bireme)	1982 to May 2018	(conformal radiotherap$ or 3DCRT or 3D-CRT) [Words] and (((transarterial or transcatheter or therapeutic or artificial) and (chemoemboli$ or emboli$)) or TACE or TAE) [Words] and (((liver or hepatic or hepatocellular or hepato-cellular) and (carcinom$ or cancer$ or neoplasm$ or malign$ or tumo$)) or HCC) [Words]
Science Citation Index Expanded (Web of Science)	1900 to May 2018	#4 #3 AND #2 AND #1 #3 TS=(((liver or hepatic or hepatocellular or hepato-cellular) and (carcinom* or cancer* or neoplasm* or malign* or tumo*)) or HCC) #2 TS=(((transarterial or transcatheter or therapeutic or artificial) and (chemoemboli* or emboli*)) or TACE or TAE) #1 TS=(conformal radiotherap* or 3DCRT or 3D-CRT)
Conference Proceedings Citation Index – Science (Web of Science)	1990 to May 2018	#4 #3 AND #2 AND #1 #3 TS=(((liver or hepatic or hepatocellular or hepato-cellular) and (carcinom* or cancer* or neoplasm* or malign* or tumo*)) or HCC) #2 TS=(((transarterial or transcatheter or therapeutic or artificial) and (chemoemboli* or emboli*)) or TACE or TAE) #1 TS=(conformal radiotherap* or 3DCRT or 3D-CRT)

CONTRIBUTIONS OF AUTHORS

LL: designed, codeveloped, and drafted the protocol and review; identified studies, extracted data, assessed risk of bias.
ZJ: designed, codeveloped, and drafted the protocol and review; identified studies, extracted data, assessed risk of bias.
WZ: provided overall guidance and supervision, and contributed to the revision of the review; resolved disagreements regarding identified studies.
CT: provided overall guidance and supervision, and contributed to the revision of the review.
NX: provided overall guidance and supervision, and contributed to the revision of the review.

All review authors approved the final version of this review for publication.

DECLARATIONS OF INTEREST

LL: none
ZJ: none
WZ: none
CT: none
NX: none

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- Change in review title: during the review process, we observed that in most trials, participants underwent two courses of TACE or more with a one-month interval, and 3-DCRT was delivered one week to four weeks after the last course of TACE when liver function tests were normal. So, for greater accuracy, we changed the original title "Combination of three-dimensional conformal radiotherapy and transcatheter arterial chemoembolisation versus transcatheter arterial chemoembolisation for primary hepatocellular carcinoma" into "Transcatheter arterial chemoembolisation followed by three-dimensional conformal radiotherapy versus transcatheter arterial chemoembolisation alone for primary hepatocellular carcinoma in adults."
- We added two new authors (CT and NX) at the review stage as they provided overall guidance and supervision, and contributed to the revision of the review.
- We changed the order of the secondary outcomes as follows: "health-related quality of life; non-serious adverse events; and proportion of participants without serum AFP normalisation". Previously, the order of the outcomes was: "proportion of participants without serum AFP normalisation; health-related quality of life; and non-serious adverse events". We changed the order of the outcomes as health-related quality of life and non-serious adverse events are more important to people with hepatocellular carcinoma than the outcome 'proportion of participants without serum AFP normalisation'.

INDEX TERMS

Medical Subject Headings (MeSH)

*Radiotherapy, Conformal [adverse effects]; Carcinoma, Hepatocellular [metabolism] [mortality] [*therapy]; Cause of Death; Chemoembolization, Therapeutic [adverse effects] [*methods]; Combined Modality Therapy [adverse effects] [methods]; Liver Neoplasms [metabolism] [mortality] [*therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Adult; Aged; Female; Humans; Male; Middle Aged; Young Adult