Postoperative adjuvant transarterial chemoembolization for participants with hepatocellular carcinoma: a meta-analysis
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CRD summary
This review concluded postoperative adjuvant transarterial chemoembolisation seemed promising for hepatocellular carcinoma (liver cancer) patients with risk factors (multiple nodules over 5cm or vascular invasion), but these results should be interpreted with caution given limitations in data quality; further research is needed. Data quality limits the reliability of the pooled results, which the authors acknowledged and reflected in their conclusions.

Authors' objectives
To determine the efficacy and safety of postoperative adjuvant transarterial chemoembolisation for participants with hepatocellular carcinoma.

Searching
EMBASE, MEDLINE, Web of Science, the Cochrane Library, and the China Journal were searched from January 1990 to March 2010 for articles in any language. Search terms were reported. Reference lists of retrieved articles were scanned. Five trial registries were searched and experts were contacted to identify additional studies.

Study selection
Randomised controlled trials (RCTs) that compared hepatectomy plus adjuvant transarterial chemoembolisation versus hepatectomy alone in patients with primary hepatocellular carcinoma were eligible for inclusion. Chemotherapeutic drugs could be used in both treatment groups. Patients with any stage of hepatocellular carcinoma were eligible, but they had to have no previous management, no distant metastasis, good or moderate liver function, and no contraindication for laparotomy. Trials had to report on at least one primary outcome. Trials were excluded if they did not use lipiodol or embolic agent, or if they involved intravenous, portal vein or oral chemotherapy, or immune treatment.

Primary outcomes included mortality, disease free survival rate, tumour recurrence, or median survival. Secondary outcomes included adverse events.

The included trials studied transarterial chemoembolisation with lipiodol dose ranging from 2 to 20 mL, in combination with one to five courses of chemotherapy (less than two weeks to 12 weeks postoperative) in patients with hepatocellular carcinoma. The type of chemotherapy included adriamycin, carboplatin, cisplatin, doxorubicin, epirubicin, 5-fluorouracil, or mitomycin. Most of the included patients underwent curative or radical resection, but palliative resection was also included. Participants primarily had stage IIIa disease; the proportion of patients with cirrhosis ranged from 72 to 85% (where reported). In most patients, the diameter of the tumour was over 5cm; some patients had portal vein or hepatic vein invasion.

Two reviewers independently performed study selection and disagreements were resolved by discussion.

Assessment of study quality
Two reviewers independently assessed trial quality using the Cochrane Handbook and the criteria by Wu. Quality factors such as blinding, randomisation, withdrawals, and allocation concealment were assessed. Disagreements between reviewers were resolved by discussion.

Data extraction
Two reviewers independently extracted data on mortality, disease free survival rate, tumour recurrence, and median survival. The data were used to calculate relative risks (RRs), with 95% confidence intervals (CIs). Data on adverse events were also extracted. Where additional information was required, attempts were made to contact the authors of the included trials.
Methods of synthesis
A fixed-effects meta-analysis was undertaken to calculate pooled relative risks, and 95% confidence intervals. Random-effects meta-analysis was used when significant statistical heterogeneity was detected. Statistical heterogeneity was assessed using the $X^2$ and $I^2$. Sensitivity analysis was undertaken on the basis of quality. A narrative synthesis was presented for adverse event data.

Results of the review
Six trials were included in the review (n=590 participants, as reported in table 2). The quality of the included trials was variable; two trials were deemed high quality, two trials moderate quality, and two trials were low to very low quality. The main quality issues were a lack of blinding and allocation concealment.

Mortality: Compared with control, transarterial chemoembolisation had a statistically significantly lower risk of one-year mortality (RR 0.48, 95% CI 0.35 to 0.65; $I^2=41%$; four RCTs) and three-year mortality (RR 0.76, 95% CI 0.64 to 0.90; $I^2=48%$; four RCTs), but there was no difference for five-year mortality. Sensitivity analysis (removing the very low quality trial) resulted in three-year mortality no longer showing a statistically significant difference.

Tumour recurrence: Compared with control, transarterial chemoembolisation had a statistically significantly lower risk of one-year post-operative tumour recurrence (RR 0.68, 95% CI 0.55 to 0.84; $I^2=44%$; five RCTs). Sensitivity analysis (removing the very low quality trial) did not alter the significance of results.

Adverse events: Transarterial chemoembolisation was associated with transient fever (86%), nausea and vomiting (26 to 66%), deterioration of liver function (16 to 53%), and ascites (32%).

Authors' conclusions
Postoperative adjuvant transarterial chemoembolisation seemed promising for patients with hepatocellular carcinoma with risk factors (multiple nodules of over 5cm or vascular invasion), but the results should be interpreted with caution due to limitations in data quality; further research is needed.

CRD commentary
Inclusion criteria for the review were clearly defined. Several relevant databases were searched, with no language restrictions. Publication bias was not assessed; the authors acknowledged that it could not be ruled out. Attempts were made to reduce reviewer error and bias throughout the review process.

Trial quality assessment was undertaken using a standard tool, which indicated the variable quality of the included trials. Trials were pooled using fixed-effects and random-effects meta-analysis (as required) and statistical heterogeneity was assessed, which was appropriate.

Overall, concerns with data quality limits the reliability of pooled results, which the authors appropriately acknowledged and reflected in their conclusions.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further research needs to be conducted on transarterial chemoembolisation in hepatocellular carcinoma to overcome the data limitations of the included trials. Trials need to have adequate follow-up and sample sizes. Studies should also aim to assess quality of life, duration of hospital stay and costs.

Funding
Not stated.

Bibliographic details
Zhong JH, Li LQ. Postoperative adjuvant transarterial chemoembolization for participants with hepatocellular

**PubMedID**
20887328

**DOI**
10.1111/j.1872-034X.2010.00710.x

**Original Paper URL**

**Indexing Status**
Subject indexing assigned by CRD

**MeSH**
Carcinoma, Hepatocellular; Chemoembolization, Therapeutic; Humans; Postoperative Period

**AccessionNumber**
12010007373

**Date bibliographic record published**
26/01/2011

**Date abstract record published**
13/07/2011

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.