Therapy for unresectable hepatocellular carcinoma: review of the randomized clinical trials - I: hepatic arterial embolization and embolization-based therapies in unresectable hepatocellular carcinoma

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CRD summary
The review investigated hepatic arterial embolisation-based therapies in unresectable hepatocellular carcinoma. The main conclusion was that hepatic artery chemoembolisation is associated with survival benefit in comparison with embolisation without antineoplastic agents. The authors' conclusions seem appropriate and they highlight the limited evidence available for some of the treatments. However, relevant studies might have been missed and the quality of the included studies was unclear.

Authors' objectives
To review randomised trials in unresectable hepatocellular carcinoma (HCC).

Searching
MEDLINE was searched from inception to December 2002 for studies published in the English language; the search terms were reported. Two previous review papers and textbook chapters were also screened.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies assessing a therapeutic anticancer treatment for HCC were eligible for inclusion. Interventions such as supportive care or for the prevention of HCC were not eligible. This review specifically reported on hepatic arterial embolisation-based therapy. The authors have conducted two related reviews (see Other Publications of Related Interest nos.1-2). The included studies compared the following: transarterial embolisation (TAE) and transarterial chemoembolisation (TACE) with supportive care or non-beneficial systemic therapy; different chemotherapeutic agents for TACE; TACE with hepatic artery chemotherapy; different methods of hepatic artery embolisation; and TACE with and without local immunotherapy.

Participants included in the review
Studies of patients with unresectable HCC were eligible for inclusion. The included studies were of diverse patient groups with different types of liver disease: in some studies the majority of patients had hepatitis B virus, while in others the majority had hepatitis C virus, Child-Pugh class A or B liver dysfunction, Okuda I, and Okuda II.

Outcomes assessed in the review
Studies reporting survival data were eligible for inclusion. The included studies reported survival at 1 and 2 years; some reported 3-year survival.

How were decisions on the relevance of primary studies made?
Two reviewers independently screened studies for inclusion and any discrepancies were resolved by discussion.

Assessment of study quality
The authors did not state that they assessed validity.
**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data on the percentage survival at 1 and 2 years and, where reported, 3-year survival, were extracted.

**Methods of synthesis**
**How were the studies combined?**
The studies were grouped according to intervention and discussed in a narrative synthesis.

**How were differences between studies investigated?**
Differences between the studies were reported in tables and also discussed.

**Results of the review**
Eighteen RCTs (n=2,618) were included.

Seven of the 18 studies reported that the sample size was based on a power calculation.

Chemoembolisation versus supportive care or non-beneficial therapy (7 RCTs, 546 patients).

The two most recently published studies provided evidence that arterial embolisation is beneficial in carefully selected patients with unresectable disease, and that chemoembolisation may be more effective than embolisation without antineoplastic agents. One of these trials compared TAE, TACE and supportive care; the 1-, 2- and 3-year survival rates were 82%, 63% and 29%, respectively, with TACE compared with 63%, 27% and 17% for the supportive care group (P=0.009). Survival rates at 1, 2 and 3 years with TAE were 75%, 50% and 29%, respectively. The second of these trials compared TACE with supportive care; the 1-, 2- and 3-year survival rates were 57%, 31% and 26%, respectively, with TACE compared with 32%, 11% and 3% in the supportive care group. A third earlier trial reported statistically significantly better 1-year survival rates in patients receiving TAE compared with 5-fluorouracil, but the difference was not statistically significant at 2 years. The other four trials showed no statistically significant benefit of TACE or TAE over the control treatment.

Different chemotherapy agents for TACE (5 RCTs, 1,301 patients).

None of the included studies reported a power calculation. Untoward effects, treatment duration and length of follow-up were poorly reported. Four of the five studies showed no statistically significant difference in 1- and 2-year survival based on the type of chemotherapeutic agent used: TACE using doxorubicin versus TAE; TACE using farmorubicin versus TACE using doxorubicin; and TACE using cisplatin versus TAE. One trial comparing high- and low-dose lipiodol in conjunction with epirubicin and mitomycin reported improved survival with high-dose lipiodol in patients with Child-Pugh Class A liver function.

TACE versus hepatic artery chemotherapy (2 RCTs, 324 patients).

One trial showed no statistically significant difference between the two treatments in low-risk patients, though in high-risk patients TACE was associated with inferior survival rates compared with arterial chemotherapy and lipiodol without embolisation (7% and 0% for the TACE group at 1 and 2 years, respectively, compared with 28% and 14%; P<0.05). In the second trial, in which almost half of the patients had unifocal HCC at presentation, chemotherapy and lipiodol without embolisation was statistically significantly inferior to TACE with and without lipiodol.

TACE with different embolisation methods (2 RCTs, 206 patients).

One trial showed that embolisation with bletilla striata was associated with statistically significantly improved survival at 1, 2 and 3 years in comparison with embolisation with gelfoam particles. In the second trial, there was no statistically significant difference in survival when autologous clot was compared with gelfoam.

TACE with and without local immunotherapy (2 RCTs, 241 participants).
In one trial, TACE and low-dose radiotherapy with the addition of a bacterial vaccine was associated with statistically significantly improved survival at 1 year, but not 2 and 3 years, compared with TACE and radiotherapy alone. In the second trial, the addition of immunotherapy to TACE was associated with improved survival.

Authors’ conclusions
There is a significant survival benefit associated with TACE for unresectable HCC, particularly for those with relatively preserved hepatic function, modest tumour burden and preserved performance status. A limited number of trials have suggested that TACE may be more effective than TAE. For patients with portal vein thrombosis, Child-Pugh Class C liver dysfunction or diffuse tumour, embolisation is potentially harmful and such patients should be considered for arterial therapy without embolisation. Based on a limited number of trials, embolisation-based therapy is of greater benefit than hepatic artery chemotherapy without embolisation. In recent studies where TACE was associated with a survival benefit, sequential treatments and combinations of lipiodol and cisplatin or doxorubicin were used. Data available on the optimal material for embolisation, treatment schedules and chemotherapy doses are limited. The addition of immunotherapy to hepatic artery-based treatments has demonstrated potential benefit in a small number of studies.

CRD commentary
The review addressed a clear research question using defined inclusion criteria. Relevant studies might have been missed since only one database was searched for studies and there was limited reference checking. The review was restricted to English language studies and there were no specific attempts to find unpublished studies; there is therefore a risk of language and publication bias. Appropriate methods were used to minimise reviewer error and bias in the study selection process, although similar methods do not appear to have been used for the data extraction. Study quality was not assessed.

The reasons for conducting a narrative synthesis rather than a meta-analysis were not discussed, although the decision to conduct a narrative appeared appropriate. The studies were appropriately grouped for the narrative synthesis, and similarities and differences between the studies were considered. The authors’ conclusions seem appropriate and they highlight the limited evidence available for some of the treatments. However, they may not be reliable as relevant studies might have been missed and the quality of the included studies was unclear.

Implications of the review for practice and research
Practice: The authors implied a number of implications for practice in their detailed conclusions.

Research: The authors stated that the addition of immunotherapy to hepatic artery-based therapy is a promising area for future research.

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Other publications of related interest
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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.