Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials

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Authors’ objectives
To assess the effectiveness and safety of transarterial chemoembolisation in unresectable hepatocellular carcinoma.

Searching
MEDLINE and Cancerlit were searched from 1980 to 2000; the search terms were specified. The authors also checked reference lists for additional studies. Abstracts and full reports of studies published in English were eligible.

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

Specific interventions included in the review
Studies were eligible for inclusion if they compared chemoembolisation with controls receiving a non-active treatment, or if they compared different transarterial therapies. The studies in the review included one or more of the following treatments: conservative therapy, transarterial chemotherapy, transarterial chemoembolisation, transarterial embolisation. The authors did not define each regimen in detail.

Participants included in the review
Studies were eligible for inclusion if they included people with unresectable hepatocellular carcinoma. The percentage of women in the included studies ranged from 0 to 30%. The mean ages, where reported, ranged from 41 to 67 years.

Outcomes assessed in the review
Studies that included 2-year mortality as an outcome were eligible for inclusion. The outcomes in the review were overall survival, tumour growth and safety. Two-year survival was the primary outcome. If crude rates of overall mortality were not reported, the authors used actuarial probabilities reported in the text or extrapolated from figures. When assessing tumour growth, complete response was defined as no evidence of neoplastic disease using computed tomography at the end of treatment. Partial response was defined as a reduction in total tumour size of more than 50%.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors assessed methodological quality according to allocation concealment and the handling of withdrawals. Trials were classified as being of a high quality if they had adequate concealment of treatment allocation and adequate handling of withdrawals. Three authors assessed trial quality independently. Any discrepancies were resolved by consensus.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data were extracted on sample size, participant characteristics, treatment characteristics and outcomes. When overall mortality was not reported, it was calculated according to intention-to-treat methods. The authors calculated survival odds ratios (ORs) for each trial.
Methods of synthesis
How were the studies combined?
The authors combined the ORs from five RCTs with a non-active treatment group using a random-effects model. They also calculated 95% confidence intervals (CIs) for all estimates and tested for significance using a Mantel-Haenszel chi-squared test. Meta-regression analysis was used to combine and analyse all other trials.

How were differences between studies investigated?
The authors used meta-regression analysis with a logistic model to explore heterogeneity in the results of all 18 trials. The analysis examined age, gender, publication year, sample size, treatment regimen, treatment allocation concealment and the handling of withdrawals. Univariate and multivariate analyses were conducted.

Results of the review
Eighteen RCTs with 2,466 participants, 178 of whom received non-active treatment, were included.

Chemoembolisation reduced overall mortality at 2 years in comparison with non-active treatment (5 trials, 424 participants; OR 0.54, 95% CI: 0.33, 0.89, P=0.015). There was no statistically significant heterogeneity between study results.

Overall mortality was lower in people receiving transartrial embolisation than in those receiving transarterial chemotherapy (OR 0.72, 95% CI: 0.53, 0.98, P=0.039). There was no evidence that transarterial chemoembolisation was more effective than transarterial embolisation (OR 1.007, 95% CI: 0.79, 1.27, P=0.95).

Fourteen randomised trials contained sufficient data about complete and partial response. In 9 trials there were no complete responses, whereas in the remaining 5 trials the complete response rates ranged from 0.007 to 30% (mean 6%). The mean partial response rate was 32.7% (range: 5 to 68).

The three most frequent complications from chemoembolisation were liver failure, sepsis and gastrointestinal bleeding. The mean rate of severe adverse effects after treatment was 5.6% (range: 0 to 50). The percentage of treatment-related deaths within 30 days ranged from 0 to 10%.

Cost information
No

Authors’ conclusions
In people with unresectable hepatocellular carcinoma, chemoembolisation improves overall survival at 2 years compared with non-active treatment, but the size of the benefit is relatively small.

CRD commentary
This review had a defined research question and pre-specified inclusion criteria. The search strategy was described, but the authors limited their search to published English language studies found via two databases. This might have introduced publication bias and language bias. The authors described the methods used to select and assess the quality of the studies. A formal process for assessing study quality was used, although it was relatively simplistic. However, only RCTs were included in the analysis.

The rationale and methods used to pool the data appear appropriate in general terms, although some of the specifics have been critiqued by another commentator (see Other Publications of Related Interest). The authors noted that there was some heterogeneity between the studies, but formal heterogeneity tests were not statistically significant. The authors argued that differences in the baseline characteristics of the participants and treatment regimens were accounted for using a random-effects model.

The authors estimated some data when it was not available from the original studies. These estimates might have introduced additional bias.
The authors acknowledge that their analysis was limited by differences in baseline severity of illness and chemoembolisation procedures, lack of information about potential confounding factors, and the inability to fully compare different chemoembolisation procedures. However, overall, the data presented support the authors' conclusions.

**Implications of the review for practice and research**

**Practice:** The authors stated that the chemotherapeutic agents currently used for transarterial chemoembolisation are no more effective than transarterial embolisation alone. They emphasised the need for more effective anticancer drugs.

**Research:** The authors stated that further RCTs comparing transarterial chemoembolisation versus no treatment should use quality assurance measures to document adherence to treatment, and assign participants according to Child-Pugh class, the number and size of lesions, and the presence of portal vein thrombosis.

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